HIV Vaccines in Canada: Legal and Ethical Issues

A Backgrounder

HIV Vaccines in Canada: Legal and Ethical Issues A Backgrounder

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EXECUTIVE SUMMARY

Why a Paper on HIV/AIDS and Vaccines?

Current prevention efforts – including education about safer sex and provision of condoms, making sterile injection equipment available to people who inject drugs, peer counselling, providing HIV treatments to reduce mother-to-child transmission, and making blood supplies safer – have slowed the spread of HIV but have not stopped it. The best long-term hope for controlling AIDS is the development and widespread distribution of a safe, effective, and affordable preventive vaccine.

Research aimed at developing a preventive HIV vaccine is accelerating. Over the coming decade, Canadians will likely be involved in vaccine clinical trials both here and abroad. In fact, HIV vaccine trials in Canada have already begun. The existing trials, the likelihood of further trials, and the potential impact of a preventive HIV vaccine on HIV prevention programs all raise a number of legal and ethical issues that need to be addressed.

About this Background Paper

This background paper is designed to provide a detailed analysis of the major legal and ethical issues related to the development and delivery of an HIV vaccine in Canada. For a shorter and more accessible examination of the topics discussed in this paper, readers should consult *HIV Vaccines in Canada: Legal and Ethical Issues: An Overview* or the series of info sheets on HIV Vaccines in Canada (see box).

The Overview Document and Series of Info Sheets

For a shorter, more accessible version of the background paper, see:
HIV Vaccines in Canada: Legal and Ethical Issues: An Overview (an updated, 50-page summary of this paper, with 34 recommendations to governments, trial organizers, the pharmaceutical industry, researchers, and community organizations)
the series of eight info sheets on HIV Vaccines in Canada (based on the Overview, these info sheets provide even more accessible information and a summary of the most important recommendations).

Both these documents are also available in French, and are on the Legal Network's website (www.aidslaw.ca/Maincontent/issues/vaccines.htm).

The paper deals with HIV vaccines in Canada, but many of the issues it raises also apply to other developed countries, and some of them will resonate with people working on vaccine issues in developing countries. It focuses primarily on HIV preventive vaccines; however, the issues with respect to therapeutic vaccines are very similar.

What Are the Issues?

Among the many legal and ethical issues discussed in this paper are the following:

- Why should Canada increase its investment in HIV vaccines development and delivery, and develop a formal HIV vaccine plan?
- What is required to ensure that the consent obtained for participation in an HIV vaccine clinical trials is both informed and comprehending?
- What information about an HIV vaccine trial needs to be disclosed as part of the informed consent process?
- Could compensation provided for taking part in an HIV vaccine trial become an undue incentive to participate?
- What legal recourses are available if consent is improperly obtained?
- Is participation in an HIV vaccine trial a right or a privilege?
- Is it ethical to exclude particular sub-populations, such as injection drug users or pregnant women, from HIV vaccine trials?
- Should researchers be obligated to contribute to the development of the communities in which the HIV vaccine trials will be taking place?
- To what extent are researchers obligated to provide prevention counselling to participants in an HIV vaccine trial?
- What level of medical care should be provided to participants who become HIV-positive during the course of an HIV vaccine trial?
- Should participants in an HIV vaccine trial who suffer a vaccine-related injury be entitled to compensation?
- If an efficacious HIV vaccine is developed, would a mandatory vaccination program be appropriate for the general population or for specific sub-populations?

Activities Undertaken

Work on this project started in 1999, in partnership with the Centre for Bioethics of the Clinical Research Institute of Montréal. Activities have included:

- David Thompson presented preliminary findings on 17 September 1999 at a seminar held in conjunction with the Legal Network's 1999 Annual General Meeting, and at other events, including a meeting at the Canadian AIDS Society office on 24 November 1999 and a number of presentations and skills building seminars held in 2000 and 2001.
- On 19 and 20 September 2000, the Legal Network held a workshop on the legal, ethical, and human rights issues raised by the development and eventual availability of a vaccine for HIV/AIDS. Participants from across Canada provided input into the first draft of this paper.
- After the workshop, the paper was revised, taking the comments received into account, and the overview document and series of info sheets were prepared.
- In addition to the work undertaken in Canada, the Legal Network has also done extensive work on international aspects of vaccine development and delivery. For more information, see the Network's website (at www.aidslaw.ca/Maincontent/issues/vaccines.htm).

What Does this Paper Contain?

This paper focuses on the legal and ethical issues related to the research and delivery of a preventive HIV vaccine in Canada.

The **Introduction: Lessons from the History of Vaccines** considers several lessons from history that are relevant to our ethical and legal reflection on anti-HIV vaccine research and development.

Part One: Preparatory Phase of Vaccine Research examines issues that need to be addressed before clinical trials are launched. It discusses the legal and ethical dimensions of questions such as whether resources should be invested in HIV vaccine research, which candidate vaccines should be selected for clinical trials, and what type of clinical trials should be conducted. Part One also looks at whether researchers should be able to shop around in different countries to obtain regulatory approval for their clinical trials. It analyzes the impact of personal and population risk on the decision to participate in a clinical trial and on the ethically acceptable risks of such trials. Part One concludes with an overview of the regulatory framework in Canada as it pertains to HIV vaccine clinical trials.

Part Two: Clinical Trials examines the legal and ethical issues that arise during the design, planning and implementation of a vaccine clinical trial. Part Two is divided into three sections. Section I focuses on the importance of involving communities throughout the clinical trials process, and on the role of community advisory boards. Section II discusses issues that arise prior to and during the recruitment process, including the need for researchers to work with the community to facilitate recruitment. This section also examines issues that are specific to three sub-populations: street involved youth, injection drug users and women. Section III reviews issues that arise when participants consent to participate in a clinical trial, including the need for such consent to be informed, voluntary and comprehending. It discusses the obligation of researchers to fully disclose pertinent information about the trial. This section also looks at what standard of care should be provided in the event that participants acquire HIV infection during the course of the trial; the need to provide participants with preventive counselling; the risks of discrimination against participants; and whether participants should be compensated for vaccine-induced injury.

Part Three: Vaccine Delivery explores legal and ethical issues that arise during the delivery of a vaccine that has been shown to be efficacious. It highlights the complicated interplay between a number of key variables that will ultimately determine the utility of vaccination from a public health perspective and from the perspective of the individual. It reviews the lessons to be learned from experience with other vaccines, including attempts to deliver these vaccines to marginalized communities; examines whether a coercive approach to vaccine delivery is appropriate; and discusses the need for an HIV vaccine delivery plan in Canada, outlining what should be included in that plan. This part of the paper also examines various mechanisms that could be put into place in order to accelerate vaccine delivery, increase people's willingness to be vaccinated, and increase overall coverage of an HIV vaccine.

Canada is the primary locus for this paper on the legal and ethical issues associated with clinical research for a prophylactic HIV vaccine. In reality, however, a great deal of clinical vaccine research is likely to take place in developing nations where seroincidence rates are high and risks associated with litigation are low. Throughout this paper, reference is made to international law instruments and universal ethical guidelines that help situate vaccine trials both domestically and internationally within a universalist approach to research. Such a universalist analysis insists that

the trials provide for adaptation and input to procedures on the local level, to account for cultural, demographic, and epidemiological complexities.

The final sections of the paper explore Canada's potential contribution to several mechanisms that might facilitate delivery of HIV vaccines internationally.

This paper is designed to identify issues and stimulate discussion. Where possible, it will provide some practical suggestions for the pursuit of basic strategies that one hopes will allow Canada to become an international standard of reference for excellence in the legal and ethical analysis, planning, and conduct of HIV vaccine clinical trials.

Next Steps

The overview document and series of info sheets will be sent to a broad range of individuals and organizations with an interest in HIV vaccine issues, including to all those to whom recommendations are directed. Both documents and this paper will also be made available on the Legal Network's website. Those who receive the documents will be asked for their comments, and their views on how best to ensure action on the recommendations. The Network will follow up on the issues raised in the documents, focusing in particular on efforts to ensure that Canada will develop a Canadian HIV Vaccine Plan.

For Further Information …

Contact the Legal Network at info@aidslaw.ca or 514 397-6828. Further copies of this paper, the overview, and the series of info sheets can be retrieved at the website of the Canadian HIV/AIDS Legal Network at www.aidslaw.ca/Maincontent/issues/vaccines.htm or ordered through the Canadian HIV/AIDS Clearinghouse (email: aids/sida@cpha.ca).

INTRODUCTION

Lessons From The History Of Vaccines

Vaccine is a word that elicits strong reactions: feelings of hope, enthusiasm, and sometimes of fear and mistrust. The emotions of hope and enthusiasm spring from the recent historical record of several mass public health vaccination campaigns against significant infectious diseases during the past two centuries. In many societies that have employed vaccination as a primary preventive tool supporting public health, infant mortality rates have declined; epidemics have been eliminated, prevented, or curtailed; life expectancies have lengthened; and important economies in health-care costs have been realized.

The history of vaccination holds several important lessons for ethical reflection on research and development of an anti-HIV vaccine. Key among these lessons are:

- discovery of a vaccine does not necessarily translate into effective vaccine delivery;
- vaccine science can make a major contribution to public health;
- prejudice, stigmatization, and discrimination are the handmaidens of epidemic; and
- without a legal and ethical framework, vaccine research can ride roughshod over the human rights of its subjects.

Discovery Does Not Necessarily Translate into Effective Delivery

Edward Jenner developed the cowpox vaccine against smallpox in 1796. Within two decades, millions of people had been vaccinated and the disease was extinguished wherever massive vaccination campaigns took place and subsequent boosting dosages were administered. Yet it was difficult to maintain public vigilance in order to continuously sustain public vaccination and "vaccination readiness." High levels of coverage were necessary in an increasingly mobile world in which vaccination was unevenly applied and progress against the epidemic was thus variable. In 1885-86, nearly a century after the advent of the smallpox vaccine, the city of Montréal lost 1.89 percent of its population to disease.[1] This was the last major uncontrolled resurgent epidemic of smallpox in Canada, and it clearly demonstrated that discovery does not always equal delivery. During a 15-month period, almost 20,000 deaths were registered in Québec[2] until "the epidemic began to die down in the autumn of 1885 as the smallpox ran out of unvaccinated hosts.... Every one of these deaths could have been prevented."[3] In 1886, as a direct result of the epidemic, the Québec legislature created its Provincial Board of Health on a permanent basis.[4]

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[1] M Bliss. *Plague: A story of smallpox in Montreal*. Toronto: Harper Collins, 1991, at 259.

[2] Ibid.

[3] Ibid, at 261-262.

[4] Ibid, at 263.

"When smallpox reappeared in the province in 1888, boards of health were more alert and the public more willing to be vaccinated and isolated."[5]

Vaccine Science Can Make a Major Contribution to Public Health

Smallpox subsequently ebbed and flowed in various locations around the world as rates of vaccination varied in tandem with civil unrest, government lack of interest, and outright war. Building on an expanding base of national vaccination campaigns, the World Health Organization launched a vaccination drive in 1966 to eradicate smallpox. "In sagas of authentically uplifting drama, which were the greatest, most satisfying events of their lives for many of the people involved, the WHO's smallpox fighters tracked down, cornered, and stamped out the disease village by village, province by province, country by country.[6] Smallpox was driven from South America in 1970, Indonesia in 1972, and India and Bangladesh in 1975. Africa was the last battleground in the late seventies. Finally, "after intense [action and] scrutiny, the World Health Organization announced the global eradication of smallpox on December 9, 1979."[7]

At the beginning of the 21st century, we now possess vaccines against 21 infectious diseases, some bacterial, others viral. Included in this list are anthrax, diphtheria, hepatitis A and B, influenza, Japanese encephalitis, Lyme disease, measles, mumps, pertussis, rabies, rubella, polio, tetanus, tuberculosis (BCG), typhoid, varicella, and yellow fever.[8] Several of these vaccines confer high levels of protective immunity. This is the case with the polio vaccines and we are now on the verge of eliminating this disease worldwide. Other vaccines confer only partial immunity or succeed in rendering only a portion of those vaccinated immune. Examples include the BCG vaccine against tuberculosis, which is somewhat effective in preventing tuberculosis in the brain, particularly if administered to young children in populations where the disease is pervasive. Yearly influenza vaccines are yet another example of a vaccine that may only confer protective immunity on a portion of those immunized and partial post-infection immunity on others.

Prejudice, Stigmatization, and Discrimination Are the Handmaidens of Epidemic

Like many other diseases, the HIV epidemic in Canada is disproportionately present among minority populations and marginalized subgroups distant from the seats of economic and political power. The potential target populations for vaccine clinical trials experience difficulties in accessing health care, relatively high rates of comorbidities, and economic and social deprivation that render health promotion complex and difficult. Vaccine research will have to meet with these communities and engage them in interactions that are attentive, respectful, empowering, and collaborative. Clinical trials of candidate HIV vaccines may be well positioned to offer or at least facilitate the development of some long-term tangible benefits for targeted communities.

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5 Ibid, at 264.

6 Ibid, at 269.

7 Ibid, at 270-71.

8 MA Gerber (ed). *The Jordan Report 2000*: *Accelerated Development of Vaccines*. Bethesda MA: National Institute of Allergy and Infectious Diseases, National Institutes of Health, at iii, 145-146.

Without a Proper Legal and Ethical Framework, Research Can Ride Roughshod over the Human Rights of Its Subjects

Unfortunately, a history of medical research from around the world (some of it vaccine research and, in particular, research conducted in the 19th and 20th centuries) reveals a significant minority of unethically constituted cohorts in which people recruited from marginalized communities have been subjected to non-consensual experimentation, including terminal patients, psychiatric patients, prisoners, prisoners condemned to death, juvenile delinquents in detention, ethnic minorities, Aboriginal peoples, soldiers, and prisoners of war.[9]

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[9] The Nuremberg Code. The Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law 10(2). Nuremberg, October 1946-April 1949. Washington DC: USGPO, 1949. See also HK Beecher. Ethics and Clinical Research. The New England Journal of Medicine 1966; 274(24): 1354-60, and National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report. Bethesda, MA: US Government Printing Office, 18 April 1979. Available as DHEW Publication no (OS) 78-0013 and no (Os) 78-0014, and SM Reverby. History of an apology: from Tuskegee to the White House. Research Nurse 1987; 3(4): 1-9, and T Lemmens. In the name of national security: Lessons from the final report on the human radiation experiments. European Journal of Health Law 1999; 6(1): 7-23.

Part 1: Preparatory Phase of Vaccine Research

Although HIV vaccine research has been ongoing for many years, the arrival of the Phase III clinical trial of the VaxGen Inc AIDSVAX B/B Gp 120 experimental vaccine in Canada in 1999 has demonstrated that scientists and communities have much work to do to prepare properly for trials of HIV vaccines in this country.

Vaccine research will target persons who are at high personal risk for HIV infection and will generally seek to recruit participants from communities that are socially vulnerable to HIV infection. Vaccine research may impact upon the assumption of risk by the trial participants themselves and also by others within targeted communities. It may affect HIV prevention activities as well as community relations and development. Preparing an infrastructure capable of supporting repeated clinical trials would ideally require development of a productive, trusting, and collaborative relationship between scientific researchers and the participants in clinical trials and their communities. Collaborative partnerships and networks need to be established and consultative exchanges need to take place so that researchers can better understand the concerns of targeted communities and social groups and vice versa.[10]

This part will examine seven critical issues that should be addressed before initiating a clinical trial of an anti-HIV experimental preventive vaccine on human subjects. The issues are as follows:

1. Should resources be invested in HIV vaccine research?
2. Which candidate vaccines should be chosen for clinical trials?
3. What type of clinical trials should be conducted? How can a balance be maintained between obtaining results speedily and protecting human subjects in these clinical trials?
4. Should researchers dissatisfied with a regulatory refusal in one country be permitted to solicit approval for the same protocol in another country?
5. Does a personal or population risk of HIV infection raise the threshold of ethically tolerable risk in an HIV trial?
6. Would a correlation between personal risk and the willingness to accept a heightened risk of adverse events induced by an experimental vaccine constitute an ethical criterion influencing participation in a clinical trial?

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10 Joint United Nations Programme on HIV/AIDS. Ethical considerations in HIV preventive vaccine research: Guidance Document. Geneva: UNAIDS, May 2000, at Guidance Points 2, 3, 5. See also R Strauss et al. Willingness to Volunteer in Future Preventive HIV Vaccine Trials: Issues and Perspectives from Three US Communities. Abstract no 817. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000, and S Kippax et al. New Antiviral Therapy and the Promise of Vaccines: a Challenge to HIV Prevention for Social Sciences. Plenary paper presented at the IXth Annual Meeting of the Canadian Association for HIV Research, Montréal, 29 April 2000, and C Weijer, EJ Emanuel. Protecting Communities in Biomedical Research. In Policy Forum: Ethics. Science 2000; 289(5482): 1142-44.

This part will conclude with an analysis of the regulatory framework in Canada as it pertains to submissions to conduct clinical trials on candidate vaccines.

I Critical Issues

A. Should Resources Be Invested in HIV Vaccine Research?

This first of the questions to be discussed in this section is not rhetorical, but rather identifies a central controversy. This controversy, although rooted in scientific matters, reaches into the domains of research ethics, clinical ethics, and social ethics. Issues of justice as well as professional and social responsibility are prominent, as will become clear as we review the reasons that are advanced in favour of and against the conduct of HIV vaccine research.

1. Reasoning in Support of HIV Vaccine Research

The need to conduct HIV vaccine research and to develop a safe and effective HIV vaccine is obvious when one considers that HIV now poses an alarming threat to the health of human beings across the world.

In May of 1999, HIV surpassed tuberculosis as the world's leading cause of death by infectious disease.[11] As of December 2000, approximately 36,100,000 people were living with HIV/AIDS and there were approximately 15,000 new infections per day.[12] HIV is now present in virtually every nation and has reached epidemic proportions in sub-Saharan Africa and in parts of Southeast Asia. There is a risk of serious epidemic in the Indian subcontinent, and in the Caribbean. HIV is increasingly prevalent in Russia and parts of Eastern and central Europe as well as in Latin and South America. HIV is also present in East Asia and the Pacific. Although prevalence rates are as yet relatively low in the latter region, UNAIDS notes that conditions such as commercial sex trade, wide use of illicit drugs, and migration and mobility across borders in parts of this region of the world mean that there is a lot of room for expansion.[13] In North America, HIV continues to make inroads in an increasing number of specific and highly vulnerable communities. In view of this tragic situation, humanity requires an HIV vaccine.

In both developed and developing countries, HIV insidiously attains endemic and epidemic proportions in marginalized communities and vulnerable social groups. This is the case in Canada, where the proportion of Aboriginal people among those contracting HIV is increasing.

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[11] Vaccine Briefs: AIDS now world's most deadly infectious disease. IAVI Report 1999; 4(3): 2.

[12] Joint United Nations Programme on HIV/AIDS. World TB Day 2001: Access to TB Cure A Human Rights Imperative: TB and HIV Linked, Joint Efforts Needed. Geneva: UNAIDS Press Release of 22 March 2001. See also Joint United Nations Programme on HIV/AIDS. Report on the global HIV/AIDS epidemic. Geneva: UNAIDS, June 2000, and Joint United Nations Programme on HIV/AIDS/World Health Organization. AIDS Epidemic Update. Geneva: UNAIDS/WHO, December 2000.

[13] Joint United Nations Programme on HIV/AIDS/World Health Organization. Supra, note 12, at 7.

Aboriginal people are infected at a younger age than non-Aboriginal Canadians, are more likely to be women, and injection drug use is an important mode of transmission.[14]

Among gay and bisexual men in Canada, HIV seroincidence rates have declined from those observed five to ten years ago at the height of the epidemic. However, as treatments improve the numbers of gay men living with HIV are increasing. Recent trends observed in both the US and some Canadian cities suggest that transmission rates are on the rise again.[15] In Canada, men who have sex with men still account for the largest group affected by the epidemic. In many cities in North America, seroincidence rates in this population are particularly high in the subsets comprised of injection drug users and gay youth.[16]

The HIV epidemic is a serious problem among injection drug users in Canada in both urban and rural settings. Studies indicate that seroincidence rates are extraordinarily high, and the risks of exposure to HIV are even greater within certain sub-populations within this group, notably among prisoners, Aboriginal injection drug users, and men who have sex with men.[17]

Women in Canada are also increasingly becoming infected with HIV, especially those who use injection drugs and those whose partners are at increased risk for HIV infection.[18]

Among Canadian youth, HIV prevalence and incidence data show that the highest risk is among street youth, young men who have sex with men, and injection drug users.[19]

Within the communities most affected by HIV in Canada, the highest risks of exposure to HIV exist within groups of people who are both marginalized and stigmatized. The need for effective preventive solutions within these communities and subgroups is acute. Precariousness of income and housing, mobility, and a lack of consistent access to medical and social support mean that long-term medical treatment of HIV in these settings presents a considerable challenge and requires specific targeted interventions. In these difficult environments, vaccination could offer a much-needed preventive solution.

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[14] Health Canada. HIV/AIDS Epi Update: HIV and AIDS Among Aboriginal People in Canada. Ottawa, April 2000.

[15] K JP Craib et al. Relationship between HIV optimism and sexual risk behaviour in a cohort of gay men in Vancouver: Evidence of Complacency? 10th Annual Canadian Conference on HIV/AIDS. Toronto, 31 May-3 June 2001. Abstract no 323. See also Thomas J Coates. Prevention among MSM when AIDS is no longer so deadly. Speech presented in Plenary Session, Epidemiology & Public Health Track C, at the 10th Annual Canadian Conference on HIV/AIDS, Toronto, 1 June 2001.

[16] Health Canada. HIV/AIDS Epi Update: HIV and AIDS among men who have sex with men. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, April 2000. See also JA Catania et al. The Continuing HIV Epidemic Among Men who Have Sex with Men. American Journal of Public Health 2001; 91(6): 907-914.

[17] Health Canada. HIV/AIDS Epi Update: HIV and AIDS among injection drug users in Canada. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, April 2000. See also J Bruneau et al. Gender-Specific Determinants of HIV infection among injection drug users in Montreal. Canadian Medical Association Journal 2001; 164(6): 767-773, and J Bruneau, E Franco. Re: High rates of HIV infection among injection drug users participating in needle exchange programs in Montreal: Results of a cohort study. Letter to the editor. American Journal of Epidemiology 1999; 150(3): 326.

[18] Health Canada. HIV/AIDS Epi Update: HIV and AIDS among women in Canada. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, April 2000.

[19] Health Canada. HIV/AIDS Epi Update: HIV and AIDS among youth in Canada. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, November 1999.

In many developing countries, particularly those in sub-Saharan Africa, the HIV epidemic has become so pervasive that it affects all levels of society, mainstream and marginal.[20]

The case in favour of developing an effective preventive HIV vaccine grows in strength when one considers that today's antiretroviral treatments ("ART") are unable to cure the disease or eliminate the virus from the body. This situation is unlikely to change in the near future. Moreover, treatment regimens result in variable and less than perfect efficacy in suppressing retroviral replication. HIV remains viable in the immune system's "long term memory cells" and rates of suppression can vary in viral reservoirs corresponding to different "compartments/systems" of the body.[21] Treatment is costly and lifelong, requiring extreme compliance accompanied by specialized test-intensive clinical follow-up.

People taking antiretroviral therapies experience adverse effects in varying degrees. These are the result of: toxicity, difficulties of metabolism, deleterious interactions with other medications and/or with illegal street drugs, and of genetic intolerance.[11] The ability of HIV to mutate means that the probability of treatment failure increases over time as drug-resistant strains of HIV emerge ("virologic failure"). Second line "salvage" therapies have relatively low levels of efficacy. In countries where treatments are readily available, the development and spread of multi–drug resistant HIV is now becoming a public health concern requiring access to sophisticated resistance testing.[22]

However, when they are successful, therapies can reduce viral load (an indirect measure of replication) to extremely low levels in the blood and even in semen. This stabilization of viral reproduction can also stabilize morbidity and sometimes even reverse disease progression for an indeterminate period of time. When treatments work, they prolong life. They also appear to have a significant role to play in reducing rates of transmission.[23]

But HIV infection is disproportionately present in countries where health budgets do not permit widespread access to patented anti-HIV drugs. Ninety-five percent of people with HIV live in developing countries and 92 percent of people with HIV have access to only eight percent of the world's AIDS budget.[24] Accessibility to ART is not merely a function of costs but is also

[20] Joint United Nations Programme on HIV/AIDS. Supra, note 12.

[21] PF Barroso et al. Effect of antiretroviral therapy on HIV shedding in semen. Annals of Internal Medicine 2000; 133(4): 280-4.

[22] JP Routy et al. Transmission of Dual and Triple-Class Drug Resistant Viral Variants in Primary / Early HIV-1 Infection (PHI) in Montreal. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Abstract no 567. See also H Salomon et al. Prevalence of HIV-1 resistant to antiretrioviral drugs in 81 individuals newly infected by sexual contact or injecting drug use. *AIDS* 2000; 14: f17-f23, and N Loder. Drug-resistant HIV shows a worrying increase in the UK. *Nature* 2000; 07(6801): 120, and Deronde et al. Establishment of new transmissible and drug-sensitive human immunodeficiency virus type 1 wild types due to transmission of nucleoside analogue-resistant virus. *Journal of Virology* 2001; 75(2): 595-602, and DA Cooper, S Emery. Latent reservoirs of HIV infection: Flushing with IL-2? *Nature Medicine* 1999; 5(6): 611-612.

[23] TC Quinn. Viral load and heterosexual transmission of human immunodeficiency virus type 1. New England Journal of Medicine 2000; 342(13): 921-929. See also CJ Carpenter et al. Antiretroviral Therapy in Adults Updated Recommendations of the International AIDS Society: USA Panel Consensus Statement. Journal of the American Medical Association 2000; 283 (3): 381-390, and AS Fauci et al. Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents. Panel on clinical practices for treatment of HIV infection convened by the US Department of Health and Human Services and the Henry J Kaiser Family Foundation, ATIS, April 2001.

[24] A Forbes. Beyond Condoms: Reducing risk during sex without condoms. Presentation from Harm Reduction Coalition's 3rd National Conference, Communities respond to drug related harm: AIDS, hepatitis, prison, overdose and beyond. Miami, 22-25 October 2000. See also: B Gellman. Death Watch: The Global response to AIDS in Africa: World shunned signs of the coming plague. Washington Post 5 July 2000; A01, and R Voelker. Poor Nations

dependent upon HIV testing facilities, clinical medicine, and laboratory testing technology. The vast majority of people with HIV and those vulnerable to HIV today will not live to see the health benefits nor the positive impact upon prevention that will be consequent upon lower viral loads brought about by either accessible efficacious treatments or by future preventive vaccines with post infection endpoints.

A vaccine is likely to be more accessible than current or future therapeutic treatments. In developed countries a preventive vaccine administered in a single dose or with relatively few boosters will be cost-effective when compared with the monetary and material requirements of lifelong chronic treatments. A vaccine will be cost-effective if optimal levels of efficacy, safety, and coverage can be achieved with minimal deleterious impact upon risk assumption in target populations, and hence upon rates of transmission. In the long term, a preventive vaccine should also be cost-effective in developing nations when compared to the cost of treatments and the loss of human resources resulting from the epidemic. The development and distribution of an HIV vaccine for prevention or for infectiousness may be the primary, if not the only, hope for public health in developing nations.[25] A vaccine with a post-infection set point attenuating disease morbidity and symptoms and significantly reducing infectiousness could also help to reduce health costs in developed nations.

The above reasoning in favour of investing in the development of a preventive HIV vaccine gathers force when we consider the realities of prevention. If used according to instructions, the efficacy of consistent condom use is approximately 98 percent; similar rates can be achieved in injection drug use by the use of sterile needles.[26] These are far higher efficacy rates than any vaccine is ever likely to confer. Yet the apparent simplicity of these statements is deceiving. The causes of human behaviour are multifactorial, involving complex interactions among various influences that are environmental, social, religious, cultural, economic, resource-based, educational, and psychological in nature. HIV prevention work must convince people to alter behaviour in the most personal and intimate circumstances of their lives. In Canada, people at risk are often found in communities or groups that are socially vulnerable to HIV infection. Marginalized from political and economic power, they may lack the resources and infrastructure to support HIV prevention.[27]

Ravaged by AIDS Need the Right Resources. Journal of the American Medical Association 1999; 282: 1992-1994, and M Angell. Investigators' Responsibilities for Human Subjects in Developing Countries, New England Journal of Medicine 2000; 342(13): 967-968, and SS Forsythe. The Affordability of antiretroviral therapy in developing countries: What policy makers need to know. United States Agency for International Development (USAID), Family Health International's AIDS Control and Prevention (AIDSCAP) Project (623-0238-A-00-4031-00), and D Farah. Seeking a Remedy for AIDS in Africa: Continent's woes limit reach of cheaper drugs. The Washington Post 12 July 2001.

25 N Letvin et al. Prospects for vaccines to protect against AIDS, tuberculosis and malaria. Journal of the American Medical Association 2001; 285(5): 606-611 at 606. See also L Garrett. Back to basics: Most AIDS experts aren't happy with the current crop of vaccine candidates -- and they want efforts to return to fundamental question. Newsday 5 June 2001, and V Zonana. Commonwealth leaders urge greater support for AIDS Vaccines; Blair announces UK£14 million grant to IAVI. IAVI Report 1999; 4(5).

26 A Saracco et al. Man-to-Woman transmission of HIV: Longitudinal study of 343 steady partners of infected men. Journal *of Acquired Immune Deficiency Syndromes* 1993*;* 6: 497-502. See also I De Vincenzi. Heterosexual Transmission of HIV in European Cohort of Couples. European Centre for the Epidemiological Monitoring of AIDS, Paris, 1993. Abstract no WS-C02-1; 1: IXth International Conference on AIDS / IVth STD World Congress, Berlin, 9 June 1993. Reported in Update: Barrier protection against HIV infection and other sexually transmitted diseases. *Morbidity and Mortality Weekly Report* 1993; 42 (30): 589-591, at 597.

27 T de Bruyn. *HIV/AIDS and Discrimination: A* Discussion Paper. Montréal: Canadian HIV/AIDS Legal Network & Canadian AIDS Society, 1998.

Discussion of HIV raises cultural, religious, and political taboos surrounding issues such as sexuality, homosexuality and homophobia, sex trade work, substance use, the role of women in society, the place of Aboriginal peoples, the rights of incarcerated criminals, racism, etc.[28] To work with these subjects, HIV prevention requires cultural sensitivity, needs assessments, careful planning, evaluation, and adjustment. Community support is required throughout the process. It is labour intensive and must be sustained and precisely targeted. Results may be slow to germinate and difficult to maintain over the long haul.

Absent a preventive vaccine or a medical cure, the need for prevention would not diminish until such time as consistently high levels of preventive behaviour are achieved in targeted populations and among people in the epidemic's core groups and networks of transmission. This behaviour modification must be maintained for a period that is long enough to break the cycle of transmission and reduce overall levels of seroprevalence (eg, perhaps as long as a generation or more). Thus, the challenge of achieving widespread and durable changes in behaviour in any given community is formidable. Even if such success could be achieved within communities vulnerable to HIV in Canada, the global nature of the pandemic will condemn Canadians to eternal vigilance on both the public health and community levels.

In the year 2001, it is apparent that behaviour modification prevention efforts have been effective in slowing transmission in specifically targeted communities, but that on a global scale the spread of HIV has outpaced prevention.[29] Recognition of the limits and difficulties inherent in HIV prevention makes a strong case for support of a parallel stream of resources dedicated to development of an eventual HIV vaccine.

2. Why HIV Vaccine Research Is Questioned

We focus attention here on five reasons that have been brought forward to question the wisdom of embarking upon the research required to develop a preventive HIV vaccine.

The first reason emphasizes the scientific uncertainties of vaccine research. The precise molecular mechanisms by which HIV overcomes the very immune system a vaccine would seek to stimulate are still only partially understood.[30] Then there is a possibility, perhaps even a likelihood, that a variety of vaccines would have to be developed against the multiple genetic types of HIV called "clades," which are unevenly distributed around the world.[31] Moreover, if HIV vaccination were to require repeated booster doses in order to maintain durable immunogenicity, delivery of the vaccine and compliance would become serious problems.

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[28] Ibid.

[29] Joint United Nations Programme on HIV/AIDS/World Health Organization. Supra, note 12.

[30] N Letvin et al. Supra, note 25. See also L Garrett. Supra, note 25, and J Stephenson. US AIDS Research Office Chief: Intensify Vaccine, Prevention Research. Journal of the American Medical Association 1998; 280(14). And cf. M Merson. The Search for an AIDS Vaccine and an Effective Global Response, rev. of Shots in the Dark: The Wayward Search for an AIDS Vaccine by J Cohen, The New England Journal of Medicine 2001; 344(23): 1801-1802.

[31] R Mestrel. Hope for Vaccine Rises. Los Angeles Times 4 June 2001. See also: J Gouldsmith. Viewpoint: Do HIV Clades Really Matter? IAVI Report 1999; 4(4), and J Flores and Bradac. Rational Choice of HIV strain(s) for AIDS vaccines. Discussion held at Bethesda MD, 17 June 1997. Available through the NIAID Division of AIDS Resources at www.niaid.hih.gov/daids/vaccine/meetings/rational.htm.

Second, development of an experimental HIV vaccine is a lengthy process. It could take up to nine years or more from pre-clinical research through Phase III testing in order to develop a successful vaccine. Data interpretation, licensing approval, and delivery of the vaccine to market could take another 10 years. Experience with a wide variety of vaccines against other diseases demonstrates that absent a concerted international effort, the populations in developing countries will not see a vaccine, if at all, until much later than the profit-generating pharmacies of industrialized nations.[32]

As of the winter of 1999-2000, the majority of scientific HIV vaccine research had not yet progressed to clinical trials in humans (Phase I, II, or III). The year 2000 edition of *The Jordan Report* into accelerated development of vaccines lists 118 candidate HIV vaccines undergoing research and development. Thirty-eight percent of these are in Phase I trials, four percent in Phase II trials, and two percent in Phase III trials.[33] Most commentators agree that we are still at least five to 10 years away from the first licensed vaccine products – something that has been repeated at every major AIDS conference since the mid-1980s!

Third, there is a fear that vaccine research might divert resources away from care, treatment, and support for people with HIV. Critics of vaccine research claim the process is too long and uncertain to warrant diversion of resources from existing prevention campaigns, treatments, and therapeutic research. In countries where a substantial proportion of the population is already infected, such as South Africa, people are looking for access to antiretroviral treatments, basic treatment of opportunistic infections, palliative care, prevention of vertical transmission, and intensive development of prevention and information services. South Africa has in fact embarked on an ambitious program of vaccine development, but it will be politically difficult to drain scarce resources away from treatments, care, and services to provide for vaccine research.[34] Ideally, vaccine research should be supported from new sources of funding so as not to play off the interests of those already infected against those, often in future generations, who are uninfected. Vaccine research should not inadvertently facilitate a schism in communities severely challenged by HIV/AIDS.

Fourth, some would argue that it is unwise to embark on costly and lengthy HIV vaccine research when existing knowledge in HIV prevention has not been fully applied. Recognizing that prevention has not been able to contain the epidemic does not mean that it is ineffective. The battle against AIDS will require a multidisciplinary approach drawing upon all available and effective means, and some believe that with appropriate investments over a sustained period, prevention could curb incidence rates significantly. They point to prevention programs that have been shown to significantly reduce transmission rates in targeted communities.[35]

Advocates argue that prevention has never been allowed to achieve its full potential because of lack of investment and commitment. They suggest that the first priority for the allocation of scarce resources needs to be given to familiar techniques shown to be potentially effective. News articles in 1999 pointed to a persistent shortage of affordable condoms of good quality in South Africa and in other nations as an example of practical obstacles that must be urgently

[32] R Widdus. AIDS Vaccines for the World: Preparing now to assure access. New York: International AIDS Vaccine Initiative, July 2000.

[33] MA Gerber (ed). Supra, note 8, 149-54.

[34] P Kahn. Vaccines at Durban: A closer look. IAVI Report 2000; 5(4). See also K Birmingham. SAAVI Awards First AIDS Vaccine Grants. Nature Medicine 1999; 5(11): 1220.

[35] Joint United Nations Programme on HIV/AIDS/World Health Organization. Supra, note 12. See also M Merson. Supra, note 30.

overcome.[37] Faced with epidemic levels of seroprevalence and incidence, communities may interpret vaccine research as a speculative venture with a significant opportunity cost.

The fifth consideration brought forward to question the wisdom of HIV vaccine development centres on economics, in that there is relatively little economic incentive to invest in the comparatively high-risk venture of vaccine development as opposed to development of therapies requiring chronic repetitive consumption over a very long-term course of disease.

The battle against tuberculosis serves as an interesting analogy. Approximately one-quarter of the world's population is infected with TB, and eight million more people are infected annually.[36] Only five percent (400,000) of annual infections occur in people who reside in nations affluent enough to pay the predicted market price of a new vaccine. Even within developed countries, many at risk for TB are poor and have difficulty accessing medical care. TB is the world's second-ranking cause of death by infectious disease, yet vaccine research is sporadic and too limited relative to the number of people TB kills. Without government incentives, the 400,000 "affluent" people infected annually do not constitute a sufficiently large market threshold to justify the risk of investment in TB vaccine development.[37]

In the case of HIV, however, it is possible that (i) the forces of competition, (ii) the fact that the disease is incurable and ultimately fatal; and (iii) elements of academic and corporate pride, will combine with (iv) government incentives and (v) public pressure to facilitate vaccine development.

Recent history, however, suggests that even a successful vaccine may never be appropriately delivered to the developing world. There are existing treatments and cures for several severe tropical diseases that are neither manufactured nor distributed because of a lack of paying customers and technical infrastructure for their distribution. Tuberculosis is an infection that is preventable and treatable, yet treatments are often inconsistent, non-compliant, and inappropriately administered.[38] Critics of HIV vaccine research point to the TB experience and argue that funding would be better invested in prevention, which requires human resources but fewer expensive and specialized technical resources than vaccine distribution.

3. HIV Vaccine Research: A Position Statement

When the above arguments for and against vaccine research are weighed, one fact repeatedly comes to the fore – the current distribution of prevention and treatment resources is not achieving success in the global fight against AIDS.[39] If the present system is losing the war, then new strategies – particularly vaccine research and development –must be urgently explored.

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[36] N Letvin. Supra, note 25, at 607-9. See also Joint United Nations Programme on HIV/AIDS/World Health Organization. HIV Causing tuberculosis cases to double in Africa. Geneva: Joint UNAIDS / WHO Press release of 23 April 2001, and World Health Organization. WHO Report 2001: Global Tuberculosis Control. Geneva: World Health Organization Communicable Diseases Department, 2001.

[37] M Bulard. La Nécessaire définition d'un bien public mondial. Le Monde Diplomatique. janvier 2000: 8-9.

[38] World Health Organization. Supra, note 36.

[39] M Angell. The Pharmaceutical Industry - To whom is it accountable - Editorial. *New England Journal of Medicine* 2000; 342(13): 1902-1904; M. Angell. Investigators' Responsibilities for human subjects in developing countries - Editorial. *New England Journal of Medicine* 2000; 342(13): 967-969.

The case for HIV vaccine research is also bolstered by international law. International covenants and treaties on human rights, when read in light of the ever-growing threat HIV poses to human life, health, and security, require that HIV preventive efforts be intensified. These texts may even be interpreted as implying that a refusal to conduct HIV vaccine research would be equivalent to a serious neglect of human rights. Examples of instruments and other documents that could support such a point of view include:

(i) *The Universal Declaration of Human Rights*;[40]

(ii) various resolutions adopted by the UN Commission on Human Rights;[41]

(iii) *The Convention on the Rights of the Child;* [42]

(iv) *The Vienna Declaration* and Programme of Action, World Conference on Human Rights, June 1993;[43]

(v) the International Guidelines on HIV/AIDS and Human Rights;[44] and

(vi) *UNAIDS Guidance Document – Ethical Consideration in HIV Preventive Vaccine Research.*[45]

HIV vaccine research need not be seen as being in a directly antagonistic and competitive position vis-à-vis other prevention efforts or research for new therapies. An "either/or" interpretation can be avoided for the following reasons.

Vaccine research advances basic science

Research efforts designed to develop new therapeutic treatments or to develop vaccines (whether preventive or therapeutic), will draw upon many of the same initial sources of basic science. Moreover, subsequent discoveries re immune correlates made in the course of applied research in the search for either therapeutics or vaccines may potentially be of interest to researchers in either field. This symbiotic relationship means that HIV vaccine research has indirect

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40 The General Assembly of the United Nations (United Nations High Commissioner for Human Rights). Universal Declaration of Human Rights. Adopted 1948. See Preambule, arts. 1, 3, & 25.

41 UN Commission on Human Rights. Report of the Secretary-General. 53rd session, Second International Consultation on HIV/AIDS and Human Rights. Geneva, 23-25 September 1996. See also Committee on Economic, Social and Cultural Rights. The Right to the Highest Attainable Standard of Health: 2000/04/07. E/C.12/2000/4, CESCR General Comment 14.

42 United Nations General Assembly. Convention on the Rights of the Child. 61rst Plenary meeting, 20 November 1989. UNGA Doc A/RES/44/25. New York, 12 December 1989, at art. 3, 6, 19, 24. Note: Canada has ratified and adopted this document and it therefore has binding legal force here.

43 The Vienna Declaration and Programme of Action. World Conference on Human Rights, Vienna: June 1993. A/CONF. 157/24 (Part 1), ch III.

44 Office of the United Nations High Commissioner for Human Rights and the Joint United Nations Programme. HIV/AIDS and Human Rights: International Guidelines. Second International Consultation. Geneva, 23-25 September 1996. New York: UNAIDS and OHCHR, 1998. See also Joint United Nations Programme on HIV/AIDS, Inter-Parliamentary Union. Handbook for Legislators on HIV/AIDS, Law and Human Rights. Geneva: UNAIDS, Inter-Parliamentary Union, 1999, at 24-8. Note: This document lists key human rights, with examples of their specific application in the HIV/AIDS context including; inter alia: "the right to health (eg. ensuring equal and adequate access to the means of prevention, treatment and care, such as for vulnerable populations with lower social and legal status (e.g. [in many societies] women and children); [and …] sharing in scientific advancement and its benefits, e.g. ensuring equal access to […] universal infection control protocols or treatment drugs; [….]."

45 Joint United Nations Programme on HIV/AIDS. Supra, note 10, at guidance points 2, 3, 4, 5, 7, 10, 17, 18.

therapeutic benefit for people living with HIV via the potential development of therapeutic vaccines and of new techniques of immune reconstruction.[46]

Vaccine research facilitates other AIDS efforts

Phase III clinical trials of HIV vaccines require very large numbers of participants over long periods. The establishment of a long-term relationship with these participants offers other people working in the field of HIV/AIDS services a rare inroad into some of the most marginal communities that are highly affected by HIV and AIDS. Vaccine clinical trials can thus form a network infrastructure that could in turn be used to facilitate the simultaneous provision of a wide variety of services to researchers, participants, and involved communities. Potential services include: (i) contributions to HIV prevention work, both for participants and for people in the targeted communities; (ii) access to HIV testing and treatments; (iii) diagnoses and treatment of HIV-related opportunistic infections; and (iv) community skills-building and development, including the development of community-based expertise in HIV vaccination.[47] It could also be possible to use clinical trials as a means of furthering development of a local medical infrastructure for HIV testing and treatment. With informed consent and ethical procedures, the vaccine trials may provide a framework for the conduct of both qualitative and quantitative psychosocial research for use by epidemiologists in the development of effective HIV prevention campaigns and strategies for eventual delivery of future HIV vaccines.

Vaccine research facilitates other health promotion efforts

During Phase III clinical trials it may be possible to administer vaccines against other infectious diseases. It may also be possible to diagnose and treat other health conditions, notably sexually transmitted diseases. These health promotion activities may help to reduce vulnerability to HIV infection.

Economic obstacles can be overcome

The spread of the pandemic and its threat to human health and economies require (i) an increase in the resources dedicated to fighting AIDS, and (ii) a commensurate reordering of global health priorities and not merely reallocation within pre-existing AIDS budgets. Some of these additional resources can be used to sustain vaccine research in the form of multiple, large-scale, longitudinal trials.

Given the inherent limitations of free-market economic forces, there will have to be a rebalancing of economics through a concerted and persuasive system of incentives, planning, and commitment dedicated not only to basic research but also to proactive planning for eventual vaccine delivery. This effort must involve industry, government regulators, charities,

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[46] J Stephenson. AIDS Researchers explore new drug options. Journal of the American Medical Association 2000; 283(9): 1125. See also A Rachel et al. Fusion-Competent vaccines: Broad neutralisation of primary isolates of HIV. Science Magazine 1999; 283(5400): 357-62, and D Blakeslee. HIV Antibody Vaccines: A second chance. Special report posted on the website of the Journal of the American Medical Association. 25 August 1999. Available at http://www.ama-assn.org/special/hiv/newsline/special/jamadb/newabvac.htm, and D Blakeslee. Fusion and Fusion Inhibitors: A background briefing posted on the website of the Journal of the American Medical Association. 19 January 1999. Available at www.ama-assn.org/special/hiv/newsline/briefing/fusion.htm

[47] J Cohen. Shots in the Dark: The Wayward search for an AIDS vaccine. New York: Norton, 2001. See also C Schaper et al. Statistical issues in the design of HIV vaccine trials. Annual Review of Public Health 1995; 16(1): 1-22.

international agencies, and non-governmental and community organizations, backed by forceful public, political, and social pressure.[48]

Position

We believe that it is ethically imperative to launch and sustain HIV vaccine research, particularly considering:

•the scale of human suffering in the HIV pandemic, including illness, disability, loss of life, the orphaning of children, loss of productivity, etc; and

•the threat that AIDS poses to the political, economic, and social security of many parts of the world;[49]

and considering that:

•the uninterrupted spread of HIV will increase the overall pool of mutating viral genes;[50]

•HIV interacts on an individual and collective level to exacerbate the threat posed by another epidemic, tuberculosis, and vice versa;[51]

•the permanent presence of HIV would require unending vigilance and expense in public health, prevention, and health care in both the developed and developing worlds; and

•in many nations, the impact of AIDS has the potential to curtail and even reverse progress in the development of human culture, health, and economies;[52]

A decision not to pursue HIV vaccine research today would mean continue to witness the epidemic spread of HIV without investigating the rich potential of a branch of science that has successfully prevented or reduced the scope of other epidemics,

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48 R Widdus. Supra, note 32. See also W Vandermissen. Global Public Goods in Health: Developing AIDS, Malaria & Other Priority Vaccines. Slide notes from a speakers' presentation to the World Bank Human Development Week session on the economics of an HIV vaccine, February 2000.

49 K Birmingham. UN acknowledges HIV/AIDS as a threat to world peace. Nature Medicine 2000; 6: 117.

50 TA Kerns. Ethical Issues in HIV Vaccine Trials. Seattle, Washington: St Martin's, 1997 at 4.

51 Joint United Nations Programme on HIV/AIDS/World Health Organization. Supra, note 36. See also Markowitz et al. Incidence of Tuberculosis in the United States among HIV-infected persons. Annals of Internal Medicine 1997; 126: 123-32, and C Perronne. Tuberculosis, HIV infection and malnutrition: an infernal trio in central Africa. Nutrition 1999; 15(4): 321-2.

52 C Hackett. Statement made by the chief of the Caribbean division of RBLAC/UNDP at a meeting on HIV/AIDS in the Caribbean. Barbados, 11-12 September 2000. Available at: www.undp.org/hiv/policies/12_9_00.html. See also J Jeter. AIDS Sickening African Economies; farms are idle, jobs unfilled. The Washington Post 12 December 1999: A1, and Africa's "future is frightening" because of HIV. Canadian Medical Association Journal 2000; 162(5): 683, and Reuters Medical News. AIDS is eroding the educational system in Africa. Reuters Health Information 28 April 2000, and KA Sepkowitz. AIDS: The first 20 years. The New England Journal of Medicine 2001; 344(23): 1764-72 and, MS Gottlieb. AIDS Past and future. The New England Journal of Medicine 2001; 344(23): 1788-91, and D Bueckert. AIDS epidemic slows world population growth: report. The Calgary Herald 30 September 1999. Reporting on: LR Brown, B Halweil. Breaking out or breaking down. World Watch. Washington DC: Worldwatch Institute, September-October 1999.

sometimes by entirely eliminating infectious diseases. The current state of the HIV/AIDS epidemic makes such a refusal ethically indefensible.

No other branch of science holds out such promise for HIV prevention at such potential economies of delivery. While we acknowledge the uncertainties, concerns, and difficulties that arise in vaccine development, our challenge is to ensure that the research takes place in rational ways that respect scientific principles while incorporating legal and ethical guidelines serving to protect the rights of individuals, communities, and collectivities involved in the research.[53]

In conclusion, we believe that governments, funders, and industry in Canada should make a firm commitment to facilitating a sustained program of HIV vaccine pre-clinical and clinical research in Canada. The program should reflect objectives set out in a national HIV vaccine plan and should explicitly acknowledge that HIV vaccine development and delivery is of fundamental strategic importance to:

- **the future delivery of health care within many disadvantaged and vulnerable communities in Canada;**
- **Canada's international development interests;**
- **Canadian interests in the emergence of a global economic order;**
- **national and global security interests; and**
- **respect for human rights and the safeguarding of international ethical standards in experimentation on human subjects.**

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53 TA Kerns. Supra, note 50 at 205-8. See also C Levine et al. Building a new consensus: Ethical principles and policies for clinical research on HIV/AIDS. IRB: A Review of human subjects research 1991; 13(1-2): 1-17, and C Weijer, EJ Emanuel. Supra, note 10.

B. Which Candidate Vaccines Should Be Chosen for Clinical Trial?

With the decision to proceed with research, a second question immediately arises: How do we choose which candidate vaccines to test in human subjects? This central question gives rise to the following issues, an issue being a question that is generating debate or controversy. First, what degree of confidence and consensus should exist regarding the basic science underlying HIV vaccine hypotheses before one proceeds to clinical trials? Second, what degree of probability of a confirmation of that hypothesis should exist before initiating vaccine trials in human beings? Third, at what threshold of risk to participants do HIV vaccine trials become ethically unjustifiable?

These issues lead to the two following questions:

- Should one choose to test a less risky experimental vaccine that is less likely to demonstrate efficacy over a riskier candidate that is more likely to be efficacious? and
- Should one proceed rapidly to clinical trials even though the basic science has not evolved to the point where it can provide a full definition of immune correlates nor much prediction of the probability of efficacy?

The risk-benefit analyses inherent in these issues and questions are illustrated in the decision to proceed with a Phase III clinical trial of a Gp 120 bivalent vaccine in North America versus the much greater caution exercised with respect to research into live-attenuated HIV vaccines.

1. The Phase III Clinical Trial of the VaxGen Inc. AIDS VAX BB Gp120 Vaccine

(i) Description

The AIDSVAX B/B experimental vaccine is produced by VaxGen Inc, a relatively small biotech company based in California. VaxGen Inc is a subsidiary of Genetech Inc, a much larger "life sciences" enterprise.

The candidate vaccine is comprised of a recombinant (meaning genetically engineered) glycoprotein designed to resemble that found on the outside surface of the protein envelope surrounding the human immunodeficiency retrovirus. It is a "bivalent" vaccine, meaning that it contains two subtypes of the HIV clade B currently prevalent in sexually transmitted HIV infection in North America. One is a laboratory subtype and the other resembles a naturally occurring subtype seen in primary isolates in the field.[54]

This is the first Phase III clinical trial of an experimental HIV vaccine in Canada and the United States. It is a double-blind, randomized, placebo-controlled trial, with two-thirds of participants

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[54] Testing a vaccine designed to help curb the devastating toll of HIV in the developing world. CDC Update. HIV/AIDS Prevention Centres for Disease Control and Prevention and the National Centre for HIV, STD and TB Prevention. 18 August 2000, at 2. See also CDC Update. HIV AIDS Prevention Centres for Disease Control and Prevention and the National Centre for HIV, STD and TB Prevention, 28 August 2000, at 2, and L Santiago. Large HIV Vaccine Trial Begins. GMHC Treatment Issues 1998; 12(10): 2.

receiving the experimental vaccine and one-third receiving placebo. There is also an arm of the cohort in Thailand that uses a different clade of Gp 120. This Phase III trial will last for three years and full data analysis will require at least another year following the end of the trial. If there is clear evidence of efficacy demonstrated at the midpoint in the trial, participants receiving placebo will be offered the vaccine and the company will proceed to apply to the FDA for licensing. [55]

In North America this is a multi-centre trial, with more than 50 cities cumulatively recruiting approximately six thousand HIV seronegative homosexual and bisexual men and some of their female sexual partners. Incidence rates among this subpopulation is approximately one and one-half percent. There are three test sites in Canada: Vancouver, Toronto, and Montréal. There is also one site in Amsterdam. Given the nature of the subtypes used (eg, both derived from clade B), the trial is designed to produce immunity against mucosal infection and is therefore not open to people who have injected drugs during a three year period prior to enrolment. Given the epidemiology of HIV in Canada, this is something that merits ethical questioning with respect to access to both clinical trials and to the benefits of the science. [56] This subject will be further explored in Part Two of this paper, which deals with legal and ethical issues arising during the recruitment of human subjects to vaccine clinical trials.

In the research arm in Thailand, VaxGen Inc is using a B/E bivalent test vaccine delivering a protein common to the E clade of HIV prevalent among injection drug users in Southeast Asia. This branch of the study, which again uses a double-blind, randomized, placebo-controlled format, involves approximately two thousand five hundred HIV-seronegative people, most of whom attend treatment centres for injection drug use. Half the participants receive the B/E candidate vaccine and the other half form the placebo control group. A smaller number of participants is required in Thailand, due to the higher incidence rates among injection drug users there (four and one-half per cent).[57]

(ii) Background

In the early 1990s, Phase I and II clinical trials of Gp 120 vaccines demonstrated acceptable levels of safety. These early studies did not, however, provide strong evidence of neutralizing antibodies. Of approximately four hundred seronegative participants who entered the Phase II trial and who had a record of "at risk" behaviour, 11 became infected with HIV. A study of those who became HIV infected ("breakthrough infections") failed to detect a significant difference in

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[55] An interview with Don Francis. IAVI Report 1999; 4(3), at 12. See also V Popovic. VaxGen's Experience in development and evaluation of an HIV preventive vaccine, AIDSVAX(r). Oral presentation given at the Xth Annual Canadian Conference on HIV/AIDS Research. Toronto, 1 June 2001.

[56] Exclusion criteria: Consent form to the phase III trial to determine the efficacy of Bivalent AIDSVAX B/B vaccine in adults at risk of sexually transmitted HIV-1 infection in North America and Europe (VAX004): Centre de recherche du Centre hospitalier de l'Université de Montréal, January 2000. See also K Harrison et al. Medical eligibility, comprehension of the consent process, and retention of injection drug users recruited for an HIV vaccine trial. Journal of Acquired Immune Deficiency Syndrome Human Retrovirology 1995; 10(3): 386-90, and E Oscapella, R Elliott. Injection Drug Use and HIV/AIDS: Legal and ethical issues. Montréal: Canadian HIV/AIDS Legal Network, 1999: 62-72.

[57] An interview with Don Francis. Supra, note 55, at 8.

the immune response of those who had received the test vaccine from those who received the placebo. In 1994, the National Institutes of Health ("NIH") refused to fund a Phase III trial.[58]

VaxGen then argued that pre-clinical study in vitro and in monkeys had demonstrated good immunogenicity. It also pointed out (correctly) that Phase I and II trials involving small numbers of participants are not designed to detect efficacy. They are primarily designed to determine dosage and safety. The company studied people with "breakthrough" infections from Phase II. They first eliminated those from this study who had been infected prior to entry. Of the remaining 11 people, three had not completed the full course of experimental vaccination and the majority of the others "were infected by viruses whose Gp 120 proteins were structurally different from that used in the vaccines". This latter observation suggested that "Gp 120 vaccines could be effective if they include proteins from more than one HIV strain."[59]

VaxGen returned to the laboratory and produced "bivalent" candidate vaccines containing two subtypes of Gp protein designed to elicit a broader immune reaction and thereby hopefully prevent "breakthrough" infections. The safety of the bivalent model of test vaccine was reconfirmed in Phase I and II trials. VaxGen raised private venture capital for a Phase III clinical trial. Given the demonstrated safety record and the new "bivalent" theory, the US National Institute of Allergy and Infectious Diseases (NIAID) – Vaccine Working Group and the Scientific Review Committee of the World Health Organization recommended in the spring of 1998 that the Phase III trial proceed. Health Canada approved the trial on 25 March 1999.[60]

Thus, it is important to realize that the current AIDSVAX B/B trial represents a hypothesis built upon a hypothesis: the first being that a Gp 120 vaccine is capable of generating a sustained and significant immune response; the second being that a bivalent (or multivalent) envelope protein immunogen can be designed to elicit a broader immunogenicity that can specifically target and hopefully prevent infection by different clades of HIV and by a wider range of mutant subvariations within either clade B or E.

(iii) The Scientific and Ethical Controversy Over the Gp 120 Trial

Controversy has surrounded this Gp 120 Phase III trial since its inception, and persists to this day. The ethical dimensions of the controversy are intimately linked to the scientific issues.[61]

Critics claim that the decision to test Gp 120 in a Phase III clinical trial is unsound for a number of reasons. However, the core of their criticism is their belief that a vaccine containing Gp 120 proteins alone will not elicit a sufficiently broad-based immune response to confer protective immunity. Gp 120 does not appear to incite the immune system to produce a large cytotoxic lymphocyte response ("CTL response") to HIV infection, rather it mostly induces antibodies.

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[58] B Snow. Vaxgen: Pushing the envelope. In: B Snow (ed). HIV Vaccine Handbook: Community perspectives on participating in research, advocacy and progress. Washington DC: AIDS Vaccine Advocacy Coalition, 1999, at 195-9. An adaptation of an article from Bay Area Reporter January 1998 and radio KALW interview, June 1998. See also J Stephenson. AIDS Vaccine moves into phase 3 trials. Journal of the American Medical Association 1998; 280(1): 7-9, and An interview with Jack Nunberg. IAVI Report 1999; 4(3): 11-13 at 12.

[59] Consent form to the phase III trial to determine the efficacy of Bivalent AIDSVAX B/B vaccine in adults at risk of sexually transmitted HIV-1 infection in North America and Europe (VAX004). Montréal: Centre de recherche du Centre hospitalier de l'Université de Montréal, January 2000, at 5-6.

[60] Ibid. See also B Snow. Supra, note 58.

[61] An interview with Neal Nathanson. *IAVI Report* 1999; 4(1): 5.

Nor does this type of antigen elicit antibodies capable of targeting all the components of HIV thought to play an important role in disabling the immune system (eg, TAT proteins).[62] In the past, small-scale trials of various experimental vaccines (preventive and therapeutic) consisting of Gp proteins have not provided a clear indication of probable success.[63] These vaccines are expected to elicit antibodies but not much of a CTL response.[64] The scientific basis for proceeding with a relatively large-scale efficacy trial (Phase III) is thus questioned.[65]

The critics maintain that it would be ethically very dubious to enrol so many participants in a trial of a candidate vaccine that will likely fail to bestow immunity to HIV upon a significant proportion of participants. A trial that is likely to yield results that do not show efficacy imperils confidence in the HIV vaccine endeavour and it squanders limited and precious resources.

> Running these studies ties up volunteers; it makes them ineligible for further studies once a better immunogen is developed; and it ties up government and media attention.[66]
>
> We have to recognize that there are limitations to the number of trials we can do simultaneously, and perhaps sequentially. Each trial requires a large number of participants so we have to plan and choose wisely because there are limited resources - not just monetary but also community, [government, and media] resources - in terms of willingness to participate and actual numbers of people who are vaccine-naïve.[67]

Of course if clinical efficacy trials are conducted in sub-Saharan Africa, potential human volunteers will not be in short supply, although communities might nevertheless rapidly become

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62 S Cohen et al. Pronounced acute immunosuppression in vivo mediated by HIV Tat challenge. *Proceedings of the National Academy of Sciences USA* 1999; 96(19): 10842-7.

63 RC Desrosiers. Strategies used by human immunodeficiency virus that allow persistent viral replication. *Nature Medicine* 1999; 5(7): 723-5 at 724. See also FD Goebel et al. Recombinant gp 160 as a therapeutic vaccine for HIV-infection: results of a large randomized clinical trial. *AIDS* 1999; 13: 1461-9, and PF Wright. Immunization with envelope MN rgp 120 vaccine in human immunodeficiency virus infected pregnant women. *Journal of Infectious Diseases* 1999; 180: 1080-8. And cf. D Blakeslee. HIV Antibody Vaccines: A second chance. Special posting on the website of the *Journal of the American Medical Association* HIV/AIDS Information Center. Available at www.ama-assn.org/special/jamadb/newabvac.htm

64 F Frankel et al. Attenuated Listeria monocytogenes: Expressing HIV Gag or Nef elicit-human HIV-specific CD4 and CD8 T cell responses. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Abstract no 806.

65 B Snow. Supra, note 58. See also Laboratory Purists and Renegade Empiricists Duke it out over how to proceed with vaccine development efforts: current products "certain to fail". *The Body* 1998; 5(1). Available at www.thebody.com/tag/jan98.html, and JP Moore. Back to primary school. *Nature* 1995; 376: 115, and D Blakeslee. HIV and Antibodies. A background briefing posted on the website of the HIV/AIDS Information Centre of the *Journal of the American Medical Association* 11 May 1999. Available at www.ama-assn.org/special/hiv/newsline/briefing/antibody.htm, and RI Connor et al. Immunological and virological analyses of persons infected by human immunodeficiency virus type 1 while participating in trials of recombinant gp 120 subunit vaccines *Journal of Virology* 1998; 72(2): 1552-76.

66 An interview with Jack Nunberg. Supra, note 58, at 12.

67 Studying the volunteers who make HIV vaccine trials possible: An interview with Susan Buchbinder. *IAVI Report* 1999; 4(4): 8-9, 15 at 9.

cynical if numerous clinical trials each requiring considerable mobilisation of human and material resources, repeatedly do not demonstrate vaccine efficacy.[68]

Those who support the Phase III clinical trial of the Gp 120 experimental vaccine, and who advocate generally for a more iterative and empirical approach to testing experimental vaccines, maintain that a trial is useful even if the experimental vaccine does not work.[69] In the worst-case scenario, it will at least allow us to eliminate these Gp 120 envelope proteins from the list of possible candidates.[70]

The Phase III trial will allow VaxGen Inc to study the immune response to a Gp immunogen and this knowledge may possibly allow for development of a second- generation candidate vaccine that elicits better antibody response. Such a future product might be tested as a primary vaccine or as a booster to be used in combination with some other technology (eg, DNA vaccination).

It will also allow university and professional researchers in a number of cities to acquire basic experience with a vaccine clinical trial. It may also help maintain pharmaceutical industry interest in vaccine research and catalyze the overall research process. If for instance the AIDSVAX vaccines do demonstrate 30 per cent efficacy or more, they may effectively become the standard of care and hence the minimal threshold to be administered in both arms of subsequent clinical trials. This would substantially increase either the numbers of participants required for efficacy trials or the length of those trials. This prospect may be inciting competing companies to accelerate their research in order to get candidate vaccines into efficacy trials and to complete those studies before the Gp 120 vaccine crystallizes into the ethically required and politically expected standard of care in vaccine clinical research.

The current AIDSVAX B/B trial will permit important psychosocial quantitative and qualitative research to take place, investigating the impact that the presence of a vaccine trial may have upon personal risk management among participants and among people in targeted communities.

Through the present clinical trial, VaxGen Inc can establish the requisite network of professional and community contacts for conducting a large Phase III trial. This network could continue to exist after the end of the trial and could serve other clinical trials as well as other HIV/AIDS-related interventions. Indeed, VaxGen will acquire and perfect an expertise in mounting a multicentre clinical trial and this knowledge will be marketable either as a consulting expertise or by acting as an agent for other companies wishing to test their experimental vaccines.[71]

Demonstrating that a candidate vaccine is inefficacious against HIV is not a failure. “It is important to understand that a successful trial is one that asks important research questions and answers those questions definitively, [eg, it either proves or disproves the hypothesis] not necessarily one that leads to a licensable vaccine.”[72] Thus, a trial that demonstrates that a

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[68] DJ DeNoon (ed). Conference Coverage: UNAIDS decries AIDS exceptionalism. *AIDS Weekly Plus* 19 April 1999. Available at www.aegis.com/pubs/aidswkly/1999/AW990407.html

[69] Transcript of testimony given by Dr. Jonathan Mann before the Presidential Advisory Council on HIV/AIDS. Washington DC, 15 March 1998.

[70] B Snow. Supra, note 58, at 199. See also M Balter. AIDS Research: Impending AIDS vaccine trial opens old wounds. *Science Magazine* 1998; 279(5351): 650.

[71] An interview with Don Francis. Supra, note 55, at 8.

[72] B Snow. Efficacy Trials. *Bay Area Reporter* April 1996. Reproduced in B Snow (ed). Supra, note 58, at 49. See also *Scientific blueprint for AIDS vaccine development.* New York: International AIDS Vaccine Initiative, 1998, at 30.

candidate vaccine is ineffective allows us to set aside further research in that direction and turn our attention to other hopefully more promising candidate vaccines. Hence, well run, scientifically sound efficacy trials do not necessarily lead to a licensable vaccine.[73]

Thus, while the AIDSVAX B/B clinical trial continues, so does the controversy concerning the timing and scientific foundations of the trial.[74] The ethical issues are of major importance. If there is a strong probability that Gp 120 will not be efficacious as a vaccine, then it is ethically highly dubious to set up a Phase III trial of this vaccine when the only likely ouctomes are the accumulation of the knowledge and infrastructures needed to do a very good Phase III trial when a more promising candidate vaccine is designed. If this were indeed the case, then at the very least, participants and involved communities should be fully informed that this is the principal objective of the trial.

It is essential at this point to recall the Nuremberg Code. The Code requires that experiments be designed to yield fruitful results that justify their performance.[75] This requirement finds an echo in many other international covenants, national guidelines, and principles of good clinical practice.[76] These provisions establish that a study that is scientifically flawed, (such as one that is unable or unlikely to generate a statistically significant and definitive answer to the hypothesis) is unethical and thus that scientific soundness is one of the necessary prerequisites to ethical clinical research.

Equally important is the issue of informed consent (which will be discussed in greater detail in Part Two). Are the persons invited to participate in the AIDSVAX trial fully cognizant of the controversy surrounding this trial? Consent is vitiated if the information given to potential participants is too narrow and effectively blinds them to the true nature of the clinical trial presented to them.[77]

2. Live-Attenuated Vaccines

A review of the recent history surrounding live-attenuated HIV vaccine research also serves as an excellent example of the difficult ethical and scientific decisions to be made when selecting a vaccine for testing. In contrast to the Gp 120 bivalent experimental vaccine, health authorities at the Food and Drug Administration in the United States have resisted considerable pressure at

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[73] ML Clements-Mann. Challenges in HIV Vaccine Development: Institutional Roles and Response. Conference given at the First Annual Conference on Vaccine Research, Symposium 1, Issues in Clinical and Field Trials: design, execution and analysis. Bethesda MD, 30 May-1 June 1998.

[74] For a thorough overview of the debate concerning the initial proposal (and subsequent refusal) to allow monovalent Gp 120 phase III clinical trials to proceed in the United States, consult Transcript of the NIAID HIV Vaccine Working Group Meeting, 21-22 April 1994. Available at: www.aegis.com/hivinfoweb/library/vaccines/1994vwg.html

[75] *The Nuremberg Code*. Supra, note 9, at 181-2.

[76] Medical Research Council of Canada, National Science and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. *Tri-Council Policy Statement: Ethical conduct for research involving humans*. Ottawa: August 1998, at Section C2 art. 1.5. See also Joint United Nations Programme on HIV/AIDS. Supra, note 10, at Guidance Point 4.

[77] DJ Roy et al. *Bioethics in Canada*. Scarborough, Ontario: Prentice Hall, 1994, at ch 13.

various times in the past brought to bear by a minority of researchers who have wanted to proceed with small-scale human trials of a live-attenuated strain of HIV.

(i) Background

By 1997, a group of researchers known as the International Association of Physicians in AIDS Care ("IAPAC") had gained notoriety as a group lobbying to proceed rapidly with clinical research involving experimental live-attenuated HIV vaccines. They announced that some members of the group were willing to vaccinate themselves and indicated that hundreds of people had volunteered for Phase I and II trials.[78] A few researchers proposed that terminal cancer patients also be recruited to Phase I clinical trials.[79]

When United States officials appeared reluctant to approve clinical trials of live-attenuated vaccines, IAPAC suggested that volunteers in overseas nations might still be willing to participate clinical trials of live attenuated vaccines even if trials the United States did not sanction the tests.[80] In the final analysis, approval to proceed with clinical trials in the US was withheld in the face of mounting evidence suggesting these vaccines might not be safe. Pre-clinical basic science suggested that live-attenuated vaccines presented too many uncertainties and too many potentially serious risks to both individual and to public health to permit testing in human subjects in the late 1990s.[81]

(ii) A Brief Analysis

"[L]ive-attenuated vaccines, such as those used against measles, mumps or polio, have achieved the most effective and longest-lasting protection against a wide range of infectious organisms."[82] This successful track record would suggest that the probability of benefit in terms of bestowal of immunity could be quite high. This would argue in support of conducting clinical trials of live-

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[78] K Birmingham. AIDS Vaccine Trial. *Nature Medicine* 1997; 3(10): 1055. See also CF Farthing. A Call to physicians. Vaccine volunteer registration form. Available at www.iapac.org/vaccines/vaccineform.html and T Beardsley. Lives in the Balance: Researchers plan to modify HIV and try it as a live AIDS vaccine. *Scientific American* 1998; 279(4): 17, and J Cohen. Weakened SIV vaccine still kills. *Science* 1997; 278: 24-5.

[79] T Beardsley. Supra, note 78. See also Laboratory purists and renegade empiricists duke it out over how to proceed with vaccine development efforts: current products "certain to fail." Supra, note 65.

[80] D Gold. Proposed Live HIV Vaccine Trials Face Safety, Production Hurdles. *IAVI Report* 1997; 2(3): 1. See also WL Heyward et al. Obstacles and progress toward development of a preventive HIV vaccine: With 40 phase I trials, only one for phase 2, and none for phase 3, the term "HIV vaccine development pipeline" may be a misnomer. *Journal of the International Association of Physicians in AIDS Care* 1997; August.

[81] J Cohen. Supra, note 78, at 24. See also D Brown. Live HIV vaccine's safety doubted: monkey, human cases suggest mediocre protection, eventual illness. *The Washington Post* 3 July 1998: A03, and JI Mullins, LM Frenkel. Summary Report from the 1999 Keystone Symposia on AIDS. Ringing out an old AIDS vaccine approach. *Medscape HIV/AIDS* 1999; 5(1): 3-4 (available at: www.medscape.com/Medscape/HIV/journal/1999/v05.n01/mha0202.mull/mha0202.mull), and TC Greenough et al. Declining CD4 T-cell counts in a person infected with nef-deleted HIV. Letter to the editor. *The New England Journal of Medicine* 1999; 340(3): 236-7, and JC Learmont. Immunologic and virologic status after 14 to 18 years of infection with an attenuated strain of HIV-1: A Report from the Sydney blood bank cohort. *The New England Journal of Medicine* 1999; 340(22): 1715-22.

[82] D Blakeslee. A Live HIV Vaccine: Hope and Questions. Briefing posted on the HIV-AIDS Newsline website of the *Journal of the American Medical Association* 20 January 1997, at 1. Available at www.ama-assn.org/special/hiv/newsline/special/reports/live.htm. See also WL Heyward et al. Supra, note 80.

attenuated HIV candidate vaccines in human beings. Why should we stay away from testing this possibly "most promising" idea along the spectrum of hypotheses concerning how to achieve an effective long-lasting immune defence against HIV?[83]

Unfortunately, the risks of harm with respect to gravity and possibly also with respect to probability of occurrence are not minimal. Live-attenuated strains of HIV used as candidate vaccines remain permanently viable in the body. If successful, a preventive vaccine should stimulate the immune system to hold the live-attenuated vaccine strain permanently in check as well as to repel infection by an acquired strain of the virus. But even if weakened by multiple deletions of gene sequences, or partial deletions of genes, pre-clinical studies in monkeys suggest that the strains of HIV used as vaccine may remain virulent, capable of reproduction and possibly of pathogenesis. This risk is called "residual pathogenesis". In such a case, what would happen when the immune system of the human subjects who have been vaccinated weakens in times of stress or illness or with advancing age?[84]

Moreover, there is also a possibility that in the process of replication, the strains of HIV used in live-attenuated vaccines may be able to repair deleted or truncated genes with available amino acids and become more virulent than the original vaccine. This is called a "retroversion to virulence." [85] Careful study of the natural history of infection in 13 individuals in the Sydney Blood Bank Cohort who were infected by a naturally occurring nef-depleted attenuated HIV indicates that:

> some people infected with attenuated virus have immunologic and virologic signs of disease progression, though their disease is less aggressive than that caused by viral strains that are not attenuated. […. This] provides another cautionary note with respect to the use of live attenuated strains as vaccines. If large populations of uninfected person were given this virus, there would almost certainly be unacceptable risks. On the other hand, if the virus could be further attenuated without loss of immunogenicity, this approach might still be feasible.[86]

In either of the two scenarios – "residual pathogenesis" or "retroversion to virulence" – the consequences for individuals receiving the experimental vaccine could be tragic. Their health could be severely compromised and they might be in danger of transmitting new strains of HIV to others. The evaluation of a trade off between the safety and efficacy of live attenuated strains of HIV will also be affected by background rates of sero-incidence as well as the impact of vaccination upon behaviour - notably whether vaccination results in an increase in unprotected

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83 Making the case for the live attenuated approach: An interview with Ronald Desrosiers. *IAVI Report* 1997; 2(2).

84 J Cohen. Supra, note 78. See also B Berkhout et al. Genetic Instability of Live Attenuated Human Immunodeficiency Virus Type-1 Vaccine Strains. *Journal of Virology* 1999; 73(2): 1138-45, and C Grady. *The Search for an AIDS Vaccine: Ethical issues in the development and testing of a preventive HIV vaccine*. Indianapolis: Indiana UP, 1995, at 12–13.

85 B Berkhout et al. Supra, note 84. See also R Björn et al. Evidence for recombination of live, attenuated immunodeficiency virus vaccine with challenge virus to a more virulent strain. *Journal of Virology* 1999; 74(8): 3537-42.

86 K Collins, G Nabel. Naturally Attenuated HIV: Lessons for AIDS vaccines and treatment. Editorial. *The New England Journal of Medicine* 1999; 340(22): 1756-7. See also JC Learmont et al. Immunologic and virologic status after 14 to 18 years of infection with an attenuated strain of HIV-1. *The New England Journal of Medicine* 1999; 340(22): 1715-22.

sexual and needle sharing relations.[87] If ever the live attenuated vaccine were to become sexually transmissible, then many further ethical issues would be raised involving informed consent and compensation for damages. Moreover, there is now evidence that HIV, like many other retroviruses, is carcinogenic.[88]

In view of the preceding, it might be possible that vaccine induced adverse effects from live-attenuated vaccines might not develop until many years following the date of vaccination. Hence with this kind of experimental vaccine it will be necessary to determine very precise surrogate markers of immunity - in order to be able to detect any weakening of immunity in its the earliest stages. These vaccines would also require implementation of a very sophisticated and accurate system of long-term post marketing surveillance and a sustained ability to re-contact participants many years after the end of the trial. Federal government regulations of clinical trials scheduled to take effect in September 2001 will require pharmaceutical sponsors to keep the participants' files for a period of 25 years to "allow for patient follow-up throughout the subsequent stages of drug development, assessment and marketing."[89] But record keeping is not pro-active surveillance.

Guidance Point 9 of the UN Guidance Document, *Ethical Considerations in HIV Preventive Vaccine Research*, suggests a high standard of care and compensation for vaccine-induced adverse effects:

> The nature, magnitude, and probability of all potential harms resulting from participation in an HIV preventive vaccine trial should be specified in the research protocol as fully as can be reasonably done, as well as the modalities by which to address these, including provision for the highest level of care to participants who experience adverse reactions to the vaccine, compensation for injury related to the research, and referral to psycho/social and legal support, as necessary.[90]

But a high level of care and treatment of research subjects who sustain a vaccine-induced injury resulting from live-attenuated trials could well end up creating long-term obligations that industry acting in developing countries would find unacceptable or requiring organized systems of treatment delivery that would surpass the present capacities of governments in developing countries. Offering even the possibility of lifelong treatment of vaccine-induced or breakthrough infections to trial participants recruited from a target population where seroincidence is extremely high and treatments are otherwise unavailable could constitute undue incentive and inducement for countries, communities and individuals to participate in vaccine clinical

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87 S Blower et al. Live attenuated HIV vaccines: predicting the trade-off between efficacy and safety. *Proceedings of the National Academy of Sciences (US)* 2001; 98(6): 3618-23. See also S Blower. Live attenuated HIV vaccines: predicting the trade-off between efficacy and safety. Abstract of a presentation to the Mathematical Biology Session of the Annual meeting of the Canadian Applied and Industrial Mathematics Society. Victoria, Bc, 8 June 2001.

88 D Blakeslee. HIV: A cancer virus as well? Briefing Paper covering 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Available at: www.ama-assn.org/special/hiv/newsline/conferen/retro00/db0203.htm. And cf. MA Wainberg. Live Attenuated AIDS Vaccines: Let's keep the research moving forward. *IAVI Report* 2000; 5(1): 12-13.

89 Regulatory Impact Analysis Statement. Regulations Amending the Food and Drug Regulations. (1024: Clinical Trials). SOR/2001-203. *Canada Gazette Part II* 2001; 135(13): 1129-52 at 1150.

90 Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Point 9.

research.[91] The risk is that these treatments may be looked to as a surrogate (but primary) means of developing medical infrastructure and of gaining access to therapy.

And finally, given the demonstrated ability of some live-attenuated strains of simian immunodeficiency virus (SIV) to induce illness in chimpanzees, there are some people, including a coalition of AIDS researchers, primatologists, and animal conservationists, who are urging vaccine researchers not to inject chimps with recently discovered strains of HIV that might cause AIDS-like disease in these animals.[92]

Basic scientific research into attenuated strains of HIV is continuing.[93] In the face of such potentially serious risks and onerous structural requirements, there is currently no clinical research underway involving human beings receiving an experimental live-attenuated HIV vaccine.

Unless the basic science can demonstrate that (i) the potential benefits of such a vaccine significantly surpass those of any other type of experimental vaccine, and (ii) that it is possible to reduce the probability of vaccine-induced health problems; it is unlikely that research in humans will receive approval in North America. For the time being, the testing of live-attenuated vaccines will best be limited to large and lengthy animal cohorts.

Some, however are not pleased with this constraint. They argue that the urgency of finding an inexpensive preventive strategy in the face of high rates of seroincidence and acute human suffering should militate in favour of testing the vaccine potential of live, multiply-attenuated strains of HIV, particularly on persons at high risk of becoming infected by HIV. Proponents of conducting at least phase I clinical trials of attenuated vaccines argue that this research should be allowed to proceed with subjects who are terminal cancer patients with competent immune systems.[94] They also argue in favour of conducting research with volunteers who are extremely well informed, understand all of the attendant risks and uncertainties, and freely and voluntarily consent to be subjects for this research.[95]

Since the announcement of disease progression in primates vaccinated with live attenuated vaccines and the announcement of disease progression in members of the Sydney Blood Bank Cohort, pressure to proceed with clinical trials of attenuated HIV vaccines in human subjects has decreased appreciably. Fundamental research is now proceeding cautiously, focusing on ways to genetically alter viral genes both in HIV itself and in vaccine vectors in order to control the development of virulence in live-attenuated vaccines.[96]

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[91] Joint United Nations Programme on HIV/AIDS. Supra, note 10, Notes to Guidance Point 16, at 42.

[92] A Prince, L Andrus. AIDS Vaccine trials in Chimpanzees. Letter to the editor. *Science Magazine* 1998; 282: 2194d. See also J Cohen. Researchers urged not to inject virulent HIV strain into chimps. *Science Magazine* 1999; 282: 1090-91, and cf. N Letvin. Response to Letter by A Prince and L Andrus: AIDS Vaccine Trials in Chimpanzees. *Science Magazine* 1998; 282: 2194d, and LR Sibal, KJ Samson. Nonhuman Primates: A critical role in current disease research. *Institute for Laboratory Animal Research Journal* 2001; 42(2).

[93] S. Comeau. In conversation with Dr. Mark Wainberg. *McGill News* 2001, Spring: 1. See also D Blakesley. Global perspective from International AIDS Society President Mark Wainberg. *Journal of the American Medical Association* 1998; 280(21): 1811.

[94] T Beardsly. Lives in the balance. *Scientific American* 1998; 279(4): 17.

[95] AJ Pinching. Live attenuated vaccine trials in medically informed individuals: a special case? *The Journal of Medical Ethics* 2000; 26: 44-46.

[96] J Whitney et al. The M184V mutation of SIV RT delays reversion of live-attenuated SIV containing deletions in the noncoding region. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2

In an opinion addressed to the research community, Dr Mark Wainberg stated in early 2000:

> It would be foolish to argue that the development of a live, attenuated HIV vaccine is not fraught with biological and ethical problems. On the other hand, would it be ethical to stop or delay research into such a product if other, safer approaches fail and we then have a world with 100 million HIV-infected people instead of the 35 - 40 million we now have?
>
> The safety problems with live attenuated HIV vaccines to date should not lead to complete pessimism over the prospects for this approach, or to abandonment of research. The need for a safe, effective vaccine against HIV is simply too urgent to overlook any potentially promising approach. While we all hope that the current strategies based on recombinant gp120, viral vectors such as canarypox, adenovirus and other vectors, or naked DNA will be successful, the reality is that we must have fallback positions if they fail.
>
> It will be at least 5 - 10 years until the world is ready to attempt Phase I vaccination studies with a live attenuated form of HIV. But let's continue basic research in this important area and be ready with a product that will have at least passed safety studies in animals, in the event that the approaches now rightly receiving top priority fail to yield an effective vaccine.[97]

It is likely, however, that live-attenuated experimental vaccines will always pose a greater index of uncertainty and hence of risk to human subjects relative to other types of candidate vaccines. Thus, the risk-benefit analysis outlined above is not a definitive discussion. Instead, it will reoccur with a potentially altered ratio of risks to benefits whenever newer and better-designed experimental live-attenuated vaccines are proposed for testing.

C. What Type of Clinical Trials Should Be Conducted?

Difficult issues arise in evaluating when to proceed with Phase I, II and particularly Phase III trials. Science and communities must strike an uneasy balance between (i) an empirical approach to research and (ii) a desire for the relative certainty and security that could be gained through an exhaustive pre-clinical science. Can this balance be tipped by the urgency of the pandemic?

Only larger trials conducted with human subjects can generate data with a sufficient degree of statistical certainty to evaluate vaccine efficacy. This means that rapid deployment of Phase III trials becomes an objective for those seeking to accelerate scientific inquiry and the eventual production of an HIV vaccine. Interest in rapid vaccine development, testing, and implementation runs high in nations that do not have the health budgets required to offer

February 2000. Abstract no 820. See also T Matano et al. Protection by a confined live vaccine against simian immunodeficiency virus challenge. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Abstract no 810.

97 MA Wainberg. Live Attenuated AIDS Vaccines: Let's keep the research moving forward. *IAVI Report* 2000; 5(1): 12-13 at 13.

expensive combination therapies to people infected with HIV.[98] The desire to proceed expeditiously with clinical trials is also rooted in a "history of empirical risk taking" in the field of vaccine research.[99] In Canada, a strong desire for an efficient vaccine can be reasonably anticipated in those communities where prevention efforts have been unable to attain and sustain the levels of safer sexual and needle-sharing behaviours necessary to arrest the progression of the epidemic or to eliminate it.[100] Even in communities where infection rates have stabilized, an efficient vaccine would be a progressive step in fighting the epidemic.

However, premature resort to clinical trials of ultimately risky candidate vaccines could adversely affect the lives of thousands of volunteers and strike a blow at future research and vaccination. Concerns have also been expressed that standards of ethical conduct of clinical trials and respect for the human rights of participants might suffer in a headlong rush to test vaccines.

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98 Proceeding of AIDS Vaccine Development for Africa, Session Rt04. XIIIth International AIDS Conference, Durban, South Africa. 11 July 2000. See also: World Bank will lend more $ to India for AIDS. *Nature Medicine* 1998; 4(7): 750, and J Esparza et al. HIV Vaccine development: From basic research to human trials. *AIDS* 1996; 10 (Supl. A): S123-S132 at S131.

99 J Esparza et al. Supra, note 98, at S131. See also TA Kerns. *Jenner on Trial*: *An ethical examination of vaccine research in the age of smallpox and the age of AIDS.* Lanham, MD: UP of America, 1997, at 74, 77-8. Note: On page 74 Kerns states: "It is not always necessary to fully understand the inner workings of a process in order to make significant discoveries about that process." Further, on page 78 he notes: "Whether the disease be plague, smallpox, […] AIDS, […] or any other of the dread infectious diseases new or old, that can make life on earth so difficult and fragile, let us hope that we, in the midst of our own epidemic diseases, recognise what is at stake. May we realize that our humanness is being challenged at least as much as our science is being challenged. And may we acquit ourselves well."

100 Health Canada. *HIV/AIDS Epi Update: HIV/AIDS Among injecting drug users in Canada*. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, May 2001. Available at www.hc-sc.gc.ca/hpb/lcdc/bah/epi/idus_e.html. See also Health Canada. *HIV/AIDS Epi Update: Risk behaviours among injecting drug users in Canada*. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, May 2001. Available at www.hc-sc.gc.ca/hpb/lcdc/bah/epi/drugr_e.html, and J Bruneau et al. Supra, note 17, and S Martindale. Increased rate of new HIV infections among young gay and bisexual men in Vancouver, 1995-99 vs 2000. 10th Annual Canadian Conference on HIV/AIDS. Toronto, June 2001. Abstract no 329, and R Voelker. Losing sight of HIV prevention: What the San Francisco increase in HIV infections might foretell. *International Associations of Physicians in AIDS Care Journal*, November 2000.

1. Accelerated HIV Vaccine Research

(i) One Version of a Dilemma

International and national standards for ethical research involving human beings consistently require that research be grounded in scientific soundness.[101] In *Ethical Issues in HIV Vaccine Trials*, Thomas A Kerns eloquently framed the debate concerning accelerated HIV vaccine research in an ethics-centred discourse. The following statements, taken from his text, serve to underline the pivotal relationship between science and ethics in vaccine research:

The thesis statement

> In the face of so much growing personal tragedy associated with HIV infection and in the face of such a rapidly spreading epidemic bringing with it immense human, social and economic costs, we must quickly move on to large scale efficacy trials as soon as it is scientifically, politically and ethically feasible.

The antithesis statement

> We must, under no circumstances, begin Phase I, II or III HIV vaccine trials until we can ensure that the individual rights and well-being of all those who volunteer for the trials will be protected to the fullest extent possible, as required by The Nuremberg Code and the WHO/CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects. Anything short of full compliance with these guidelines would be wrong, would be a violation of internationally accepted ethical codes, and would endanger any potential successful outcome of these trials.[102]

This debate about when to go to trial is rooted in the process and methodology of the scientific investigation itself. It is not restricted to proposals to test potentially "higher risk" experimental vaccines such as live-attenuated candidates, but rather affects proposals to test virtually every experimental vaccine in humans. Kerns initially sets out these statements as though they represent opposing viewpoints. He does so for dramatic effect, but proceeds to nuance his analysis by exploring the possibilities for satisfying both the urgent drive for vaccine research and the ethical need to fully protect participants and communities in the process.[103]

(ii) Reasoning in Favour of Accelerated Multi-Phase Empirical HIV Vaccine Research

[101] Regulations Amending the Food and Drug Regulations. (1024: Clinical Trials). SOR/2001-203. *Canada Gazette Part II* 2001; 135(13): 1116-29 at 1123. See also Medical Research Council of Canada. Supra, note 76, at Ch. 7 s. A., and Joint Programme of the United Nations. Supra, note 10, Guidance Point 4 (and notes), and World Medical Association. *The Declaration of Helsinki*. Adopted by the 18th WMA General Assembly, Helsinki Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, October 1975; 35th WMA General Assembly, Venice, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd WMA General Assembly, Edinburgh, October 2000, at Art. 11.

[102] TA Kerns. Supra, note 50, at 2-3.

[103] Ibid, at 209-10, 216-17.

In 1998, the late Dr Jonathan Mann spoke to the US Presidential Advisory Council on HIV/AIDS and indicated that "the National Institutes of Health was violating human rights by failing to move on wide-scale clinical trials of AIDS vaccines."[104] Dr Mann supported an approach that would see several parallel large-scale trials of experimental vaccines proceed simultaneously. In his presentation to the Advisory Council, he was scrupulously careful not to refer to "Phase III" trials, but rather used the term "wide-scale." His proposed approach thus admits of the possibility to blur the lines between Phase II and III trials in favour of using many intermediate-sized trials as a means of pushing research forward.

Dr Mann's comments were not aimed at promoting any one specific candidate vaccine. His presentation focused upon four principal points:

- **Speed:** The need to move rapidly to clinical trials;
- **Quantity:** The need to test more experimental vaccines (eg, several simultaneous trials);
- **Empiricism:** Overlooking the basic scientific explanation of how a potential vaccine might work and relying instead upon field-generated observational data to confirm efficacy; and
- **Human rights:** That, on balance, human rights considerations favour an empirical approach to vaccine research.

Dr Mann noted that it is possible today to use Phase I and II trials to determine that some existing experimental vaccines are indeed safe and do generate at least partial immune responses. Once pre-clinical research and Phase I and II trials have cleared these two important hurdles, he would support proceeding to large-scale trials as quickly as possible even if the correlates of immunity are not yet identified.

Dr Mann was not alone in advocating for large-scale efficacy trials prior to determination of the correlates of immunity. His point of view was and continues to be shared by many other prominent researchers who feel that only through iterative resort to large-scale trials will we be able to draw conclusions about immune correlates.[105] It also raised considerable controversy and fears that politics and political correctness might unduly supplant science in the clinical investigative process.[106] In many respects the current Phase III trial of the AIDSVAX B/B Gp 120 experimental vaccine reflects just such an approach. Phases I and II have demonstrated safety and a partial immune response. The trial has proceeded despite considerable controversy as to whether it is likely to confer protective immunity in humans.[107] Company officials emphasize that the trials will generate useful scientific data concerning immune response even if the candidate vaccine should prove to be inefficacious.

Such a research strategy will have implications for the ultimate delivery of licensed vaccines. Dr Neal Nathanson, director of the Office of AIDS Research at the US National Institutes of Health

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104 Transcript of a presentation given by Dr. Jonathan Mann to the Presidential Advisory Council on HIV / AIDS. Washington DC, 15 March 1998. Available at www.hsph.harvard.edu/hai/resources/pacha/mannpacha-transcript.html.

105 TA Kerns. Supra, note 50, at 209.

106 L Garrett. A Life Mission: HIV researchers urgently pursue elusive vaccine. *Newsday* 15 June 1988: A07. See also AIDS Vaccine Research Committee (NIH). AIDS Vaccine Development: Letter to the Editor. *Science Magazine* 1998; 280(5364): 803c.

107 One Trial, Many Opinions. *IAVI Report* 1998; 3(4).

was interviewed on this subject in 1998 by the *Journal of the American Medical Association*. He stated:

> My view is that the urgency is so great that we need to go into the field with the first product that comes along and looks like it might be even partially effective in terms of protection.... I imagine a wave of vaccines coming along, where the first thing that is fielded is not the final product.[108]

The history of the polio vaccine also suggests that one should not let the possibility of a better vaccine "preclude a potentially lifesaving one now."[109]

> By 1949, John Enders and his colleagues had grown the polio virus in test tubes, a critical step in vaccine development…. Then Salk applied this discovery by developing a killed whole-virus vaccine. Eminent polio researchers, however, including Enders and Albert Sabin, opposed field trials of the Salk vaccine. At that time, orthodox science dictated that ideal vaccines for viral diseases required living but weakened [eg, "attenuated"] virus strains.…
>
> Fortunately, polio research was then funded by the March of Dimes campaign [with private foundation funding]…. Undeterred by the lack of consensus among scientists … the March of Dimes committed to widespread public distribution of the vaccine, even if it proved to be only 25 percent effective. Thus, the Salk vaccine was tested among over half a million children before the summer polio season of 1954.
>
> On April 12, 1955, the results of the vaccine trials were broadcast to an expectant world: the vaccine worked. In comparing the subsequent incidence of paralysis among children who had received the vaccine with those who had received placebo shots, the rate of paralysis was found to be 72 percent lower among vaccine recipients. A better vaccine – Sabin's oral vaccine – was not introduced for another seven years. In that time, Salk's vaccine saved tens of thousands of lives and prevented hundreds of thousands of lifelong disabilities. The critical lesson: Do not let a better vaccine of the future preclude a potentially lifesaving one now."[110]

Hindsight is perfect, but the Salk vaccine demonstrated a high level of efficacy (70 percent). Would commentators have judged this empirical approach differently if its efficacy had only been 10 percent? This was an extraordinarily large clinical trial. If the vaccine had failed to provide protection in 450,000 vaccinated children, would the public have been willing to support a Phase III trial of the next experimental vaccine?[111]

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[108] J Stephenson. Supra, note 30, at 1211.

[109] R Marlink. Lessons from the March of Dimes. *Harvard AIDS Review* 1997; Spring. Available at www.aids.harvard.edu/publications/har/spring_1997/index.html

[110] Ibid.

[111] Ibid. See also TA Kerns. Supra, note 50, at 113-14. Note: Kerns points out that the Salk whole killed polio vaccine did in fact cause 79 out of more than 400,000 persons vaccinated in the efficacy trial to contract polio presumably because the process used to kill the virus "may have been imperfect." A further 125 persons became infected through contact with those vaccinated. In the end, society judged these risks to be acceptable as the number of lives saved far exceeded the number of fatalities (11) which resulted from vaccination.

(iii) Accelerated Vaccine Research in the Context of Human Rights

Dr Mann founded his human rights arguments in favour of accelerated multi-trial empirical research upon the notion that the value of human rights is vastly undermined if people do not have the basic health required in order to exercise, enjoy, and enforce those rights.

> Human rights are particularly relevant to this discussion because, as you know, human rights in the first instance involves a relationship between the state and the individual....

Speaking of the American government's role in funding basic science and research for therapeutics, Dr Mann stated:

> […] the federal government's failure to proceed to AIDS vaccine field trials, while it has contributed institutionally and financially to field trials of other vaccines which met essentially similar vaccine development criteria - - in other words, human safety and immune response - - without prior knowledge of the correlates of immunity, this failure of the government to proceed represents a clear violation of the human rights of American citizens. We don't even have to talk about citizens in other countries. The human rights of Americans are being violated [….]
>
> This is underscored by the fact that the vulnerable population in the United States, ... the 40,000 or so new infections this year are already people who are marginalized and discriminated against within our society. Therefore, the failure to proceed with development of this vaccine exacerbates existing and pre-existing patterns of societal discrimination.[112]

The propensity of the HIV epidemic to disproportionately affect marginalized, disadvantaged, and minority populations in the US is well documented. Figures released by the Centers for Disease Control and Prevention for the years 1998 and 1999, show that 57 percent of new HIV infections in the US occurred among the black population even though African Americans account for just 13 percent of the total US population.[113]

In the US, within the minority of men who have sex with men (MSM), differences in HIV epidemiology along lines of race and ethnicity are pronounced. Non-Hispanic black and Hispanic men who have sex with men have higher levels of HIV incidence and contract HIV at a younger age than is the case among white MSM. They also exhibit higher rates of morbidity (progression to AIDS) and mortality, indicating that they benefit less from treatments than their white counterparts.[114]

"Race/ethnicity is not a risk factor for HIV infection; however, among racial/ethnic minority MSM, social and economic factors, such as homophobia, high rates of poverty and unemployment, and limited access to health care, are associated with high rates of HIV risk

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[112] Transcript of testimony given by Dr. Jonathan Mann. Supra, note 69.

[113] Centres for Disease Control and Prevention. *Trends in the HIV & AIDS Epidemic,* 1998, at 3.

[114] Centres for Disease Control and Prevention. HIV/AIDS Among racial / ethnic minority men who have sex with men: United States, 1989-1998. *Morbidity and Mortality Weekly Report* 2000; 49(1): 4-11. See also Clarification. *Morbidity and Mortality Weekly Report* 2000; 49(4): 91, and Centres for Disease Control and Prevention. National data on HIV prevalence among disadvantaged youth in the 1990s: Most compelling evidence to date of the continued impact of HIV on young African-American women. *CDC Update* September 1998.

behavior."[115] In addition, rates of HIV infection among Hispanic Americans and African Americans are generally higher than among whites. Further socio-economic factors such as language and cultural diversity, poverty, and substance use, may also correspond with vulnerability and hence increased risk of contracting HIV.[116]

Patterns of racial, ethnic, and minority disparities in AIDS are also emerging in Canada, where in 1990, 88.7 percent of declared AIDS cases were among "white" people; but by 1999, "whites" accounted for only 65.6 percent of the declared AIDS cases in this country.[117] This discrepancy has narrowed somewhat over the past year; however, it has not disappeared and ethnic minorities continue to be over-represented among reported AIDS cases in Canada.

Aboriginal people in Canada contract HIV at a younger age and progress more rapidly to AIDS than non-Aboriginal people. They now represent a disproportionately high percentage of people with AIDS in Canada.[118] Reported AIDS cases in Canada's black population are also now disproportionately high.[119] As is the case everywhere, race and ethnicity in Canada are certainly not risk factors in contracting HIV. Instead, race and ethnicity in this country correlate with a multiplicity of barriers to accessing services. They are a locus of discrimination, and that correlates with factors of social, economic, and political marginalization. This in turn creates conditions of vulnerability to HIV infection because significant difficulties arise in accessing the information, resources, services and support necessary to address, encourage and sustain preventive behaviours.

Gay men also continue to account for a disproportionately high percentage of HIV infections in Canada and they comprise the largest number of people living with HIV.

Dr Mann foresaw that a vaccine might have the potential to help break the endless repetition of these familiar patterns of disparity within the HIV epidemic in North America. His call for vaccine research in the name of human rights increasingly finds support in documents produced by UNAIDS. The United Nations recognizes that the HIV pandemic expresses itself along the lines of economic and resource disparities already present in the world. UNAIDS promotes the human right to enjoy the benefits of scientific progress and its applications, including the importance of assuring that those societies, communities, and people who support and bear the burden of vaccine research also rapidly access its ultimate benefit (i.e.- an eventual vaccine).[120]

Guidance Point 1 of the UNAIDS *Ethical Considerations in HIV Preventive Vaccine Research* states:

> Given the severity of the HIV/AIDS pandemic in human, public health, social, and economic terms, sufficient capacity and incentives should be developed to

[115] Centres for Disease Control and Prevention. HIV / AIDS Among Hispanics in the United States. *CDC Update* 31 January 2001. See also Centres for Disease Control and Prevention (US). Supra, note 114.

[116] Centres for Disease Control and Prevention. Supra, note 115.

[117] Health Canada. *HIV/AIDS Epi Update: AIDS/HIV Ethnicity in Canada*. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, May 2001, at 2, 4.

[118] Health Canada. *HIV/AIDS Epi Update: HIV/AIDS Among Aboriginal Persons in Canada Remains a Pressing Issue.* Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, May 2001.

[119] Health Canada. Supra, note 117, at 2, 4.

[120] Office of the United Nations High Commissioner for Human Rights and the Joint United Nations Programme. Supra, note 44, and also Joint United Nations Programme on HIV/AIDS, Inter-Parliamentary Union. Supra, note 44, at 81, 82 and 84, and Health as a Human Right. World Health Organization, 1998. Available at www.who.int/archives/who50/en/human.htm.

> foster the *early and ethical development* of effective vaccines.[121] [emphasis added]

One of Dr Mann's most significant contributions to the battle against AIDS was to startle people into understanding the necessary connection between human rights and health, and – correspondingly – between human rights, ethics, and science. He used this connection to attempt to rattle the scientific community out of its focused quest for laboratory perfection and to re-situate HIV vaccine research in the context of the "real world."[122]

The ability to accelerate vaccine research, development, and delivery, will depend not merely upon basic science, but also upon available resources, and private and public initiatives designed with a concerted strategy of moving forward with vaccine clinical research whenever safety and reasonable but imperfect science suggests it is appropriate to do so. The ability to draw maximum benefit from an HIV vaccine will also depend upon efforts made to ensure that research and delivery take place in an ethical manner respecting the dignity and the human and collective rights of target populations, volunteers in vaccine trials, and vaccinated individuals. These latter factors of budget, strategy, and ethical guidance are inevitably somewhat political. Dr. Mann quite rightly pointed out that the enormous human suffering caused by the world-wide pandemic must weigh in this balance.

His call for critical, and continual re-evaluation of scientific progress "serves to remind us that solutions to the diverse and often competing global health challenges require a rare clarity of vision based on the dignity and value of human life."[123] It also encourages a multitude of key players to deconstruct professional and virtual fences in order to work together in a multi-disciplinary, multi-faceted approach to accelerating vaccine development and delivery.

(iv) Accelerated Vaccine Research: Key Advantages

In summary, there are many potential advantages of moving rapidly to empirical efficacy testing of a multiplicity of candidate vaccines. Included among these are the following:

- the fact that if a vaccine was even minimally efficacious (30 percent or more), it could potentially save many lives in countries where an epidemic is emerging and seroincidence is high;[124]
- even if the vaccine is only partially efficacious, important information concerning correlates of immunity will be garnered from a phase III clinical trial. Indeed this may be the only source for such information;[125]

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121 Joint United Nations Programme on HIV/AIDS. Supra, note 10, at 11.

122 Transcript of testimony given by Dr. Jonathan Mann. Supra, note 69.

123 G Nary. About Jonathan Mann. *Journal of the International Association of Physicians in AIDS Care* 1996; October.

124 RM Anderson, GP Garnett. Low-efficacy HIV vaccines: potential for community-based intervention programmes. *The Lancet* 1996; 348(9033): 1010-12.

125 J Esparza et al. Supra, note 98.

•this information would be used to develop subsequent generations of potentially more effective candidate vaccines;

•conducting vaccine clinical trials provides an opportunity for researchers and governments to collaborate in developing infrastructure for a wide variety of HIV related services including prevention, testing, treatment, and eventual vaccine delivery; and

•people participating in clinical trials will receive an important personal benefit if counselling, education, support and referrals are built into the research process. [126]

(v) Accelerated Vaccine Research: Potential Drawbacks

An empirical approach might misuse resources

A rush to test experimental vaccines is not without potential drawbacks. Budgets for vaccine research represent a relatively modest proportion of overall funding dedicated to pharmaceutical research on HIV/AIDS. Testing a wide range of candidates without taking additional laboratory time to try to identify the most promising among them could amount to a waste of scarce resources. History might have judged the Salk vaccine trial differently if the determined efficacy had been significantly lower.

Could this represent a shift in research ethics?

The move to an empirical basis for Phase III trials might represent a subtle but important shift in scientific methodology whereby the principal purpose of several large-scale trials in humans becomes the furthering of scientific knowledge as opposed to the determination of efficacy. This argument was advanced by Dr. John McNeil, director of the Department of Defense (U.S.)HIV/AIDS vaccine development program at the Walter Reed Army Institute speaking to a panel of experts convened by the Advisory Council on AIDS in April 1997. The purpose of this meeting was to provide expert commentary concerning proposed recommendations designed to implement a strategy for accelerating and encouraging vaccine development. Dr. McNeil stated:

> We view that development and basic research are interdependent and should occur concurrently with each other. Each informs the other. In fact, clinical research in the realm of HIV and many other diseases where we don't know the correlates of immunity for the disease or we don't have adequate animal models must be viewed as primary scientific-generating information. [….] Some people are uncomfortable with this concept […].[127]

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[126] Harvard AIDS Institute. *Designing Efficacy Trials*: *HIV Vaccines for developing countries*. Symposium series on vaccine solutions for developing countries. Boston, Mass, 20-23 October 1996, at 4. Note: For further information on this debate consult A Fauci et al. Development and evaluation of a vaccine for Human Immunodeficiency Virus (HIV) infection. *Annals of Internal Medicine* 1989; 110(5): 373-85 at 374. See also C Grady. Supra, note 84, at 58, 82-5, 93-9, 106-13, and ML Clements-Mann. Supra, note 73, and DJ DeNoon (ed). Conference Coverage: 1999 State of the AIDS Vaccine: Good, Not Great. *AIDS Weekly Plus* 19 April 1999. Available at www.aegis.com/pubs/aidswkly/1999/AW990404.html, and DJ DeNoon (ed). Supra, note 68, and Transcript of testimony given by Dr. Jonathan Mann. Supra, note 69.

[127] Transcripts of a U.S. Government Sponsored AIDS Vaccine Panel Discussion convened by the Presidential Advisory Council on AIDS. Washington DC, 7 April 1997. Available at: www.aegis.com/hivinfoweb/library/misc/Pach0407.html.

Any shift away from using large scale trials primarily for the purpose of determining efficacy towards other more diffuse scientific objectives, would have some impact upon the analysis of burdens and benefits for potential volunteers trying to decide whether or not to enrol. It would certainly have an impact upon the informed consent process and, more specifically, upon the requisite information to be communicated to both participants and communities where recruitment takes place. As Christine Grady has noted in her seminal work on ethical issues in the development and testing of a preventive HIV vaccine: "[I]f the goal is to learn something about human immune responses, the trials should not be called vaccine efficacy trials, but should honestly be presented as efforts to learn about protective immune responses […]."[128]

This Might Stifle Development of a Subsequent "Better" Vaccine

Some people believe that ethics, economics, and the very human demand for immediate assistance will combine forces to make Dr Nathanson's prediction of a series of marketed vaccine products highly unlikely. If the rush to clinical trials results in identification of a low-efficacy vaccine, it will be delivered only in communities with very high levels of seroincidence.[129]

But if this vaccine becomes the standard of care, the ethical principle of "do no harm" as expressed through the procedural practice of "clinical equipoise" will put an end to "placebo" control arms in subsequent clinical trials. The control group will henceforth be vaccinated with the "standard of care" vaccine plus a placebo. Participants in the other arm would receive the standard-of-care vaccine and the new experimental vaccine together.[130] The partial protection offered by the existing "compassionate release" vaccine and the potential for a synergistic interaction between the two products would significantly increase the number of participants required to determine the comparative efficacy of the newer product at the same time as it would make a significant number of people unwilling to participate in a trial which only offered placebo in the control arm. This implies higher research costs. If those costs become prohibitive, societies might unwittingly sacrifice a higher-quality product (that never gets tested) in favour of the earlier arrival offering lower efficacy. Over the long term, this decision could cost many lives. [131]

Thus, some researchers, afraid that there may be only one or two chances for developing an HIV vaccine, prefer to adopt a prudent approach that would only put to clinical trial those products for which laboratory research has suggested a clear possibility of success. Balancing the lives to be saved by accelerated testing and delivery of a possibly low-efficacy vaccine against the lives that could be lost if the low-efficacy vaccine slows development of subsequent products, is a difficult and complex exercise.

The risks that the experimental vaccine is unsafe may increase

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128 C Grady. Supra, note 84, at 110.

129 B Mirken. AIDS Clinical Trials: Why they have recruiting problems. *AIDS Treatment News* 1995; 217. See also WL Heyward et al. Obstacles and Progress Toward Development of a Preventive HIV Vaccine. *International Association of Physicians in AIDS Care Journal* 1997; August. See also RM Anderson, GP Garnett. Supra, note 124.

130 Joint United Nation Programme on HIV/AIDS. Supra, note 10, at Guidance Point 11.

131 By way of analogy see G Kolata, K Eichenwald. Hope for sale: A special report; Business thrives on unproven care, leaving science behind. *The New York Times* 3 October 1999.

In theory, Phase I and II trials should screen out unsafe candidates. Close monitoring and regularly scheduled interim analysis during the trial should also permit rapid interruption of the protocol if problems emerge.[132]

But HIV has already made a substantial impact upon how medications are brought to market in Canada. The resulting record is not entirely unblemished. Pressure from patients faced with a terminal disease has increased the "therapeutic" role of clinical trials of new drugs, particularly for those who have exhausted other treatment options. The early release of medications on a compassionate basis has figured prominently in AIDS pharmacology. This has benefited many people. Similarly, the recently adopted amendments to the *Food and Drug Act Regulations* governing clinical trials in Canada represents an effort to streamline approval of research in future. But the true extent of a number of important adverse effects related to antiretroviral therapies (and possible genetic intolerance thereto) has been detected only after the drugs were marketed. Some of these side effects include lipodystrophy,[133] pancreatitis,[134] insulin resistance,[135] osteonecrosis,[136] liver toxicity,[137] interaction affecting methadone maintenance doseages,[138] and birth defects.[139] Given the urgency of the world-wide HIV pandemic, there is considerable pressure to compress the timelines of research and to move products forwards into testing and hopefully marketing as soon as is scientifically and logistically possible. Given this tendency, effective Phase IV post-marketing surveillance of HIV vaccines will be very important.

Unlike experimental treatments, preventive vaccines are tested on healthy, uninfected volunteers and therefore have no potential therapeutic value for the volunteers. In this context, the same level of adverse effects observed in antiretroviral therapy would not likely be accepted by seronegative persons recruited to participate in a large-scale clinical trial of an experimental vaccine in Canada.

Care must be taken to ensure that the candidate vaccines to be tested are in fact as safe as practically possible. The calculated levels of anticipated risk and the resulting risk - benefit ratios must be ethically acceptable to warrant proceeding with a trial using human research subjects.

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132 Regulations amending the Food and Drug Regulations. Supra, note 101, 1116-29. See also Regulatory Impact Analysis Statement. See also Regulatory Impact Analysis Statement. Regulations Amending the Food and Drug Regulations. (1024: Clinical Trials). *Canada Gazette Part II* 2001; 135(2): 1129-52.

133 C Flexner. Fat City: Understanding HIV Lipodystrophy. *The Hopkins HIV Report* 1998; September.

134 Bristol-Meyers Squibb extends warning on ddI-related pancreatitis. *Reuters Health Information* 23 November 1999.

135 C Vigouroux et al. Diabetes, insulin resistance and dyslipidaemia in lipodystrophic HIV infected patients on highly active antiretroviral therapy (HAART). *Diabetes Metab* 1999; 25(3): 225-32. See also Food and Drug Administration (US). Diabetes & protease inhibitors, Health advisory for newest class of AIDS drugs: Letter to physicians of 11 June 1997.

136 NIH Study Demonstrates Surprising Complication in HIV Infection. *NIH News Release* 8 September 2000.

137 MS Sulkowski et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *Journal of the American Association* 2000; 283(1): 74-80. See also JS James. Liver toxicity, ritonavir, and Hepatitis C: new data published. *AIDS Treatment News* 2000; 335. Available at www.aegis.org/pubs/atn/2000/atn33502.html, and Boehringer Ingelheim Roxane Laboratories. Important drug warning re: Severe, life-threatening and fatal cases of hepatotoxicity with Viramune. Letter to physicians. November 2000.

138 P Robinson. Viramune (nevirapine) / methadone interaction. Letter addressed to physicians from Boehringer Ingelheim Roxane Laboratories. 30 July 1999.

139 J Cadman. Efavirenz Pregnancy Warning. *Treatment Issues* 1998; 12(3). Available at: www.aegis.org/pubs/gmhc/1998/gm120305.html.

Questions concerning the provision of treatment and compensation for any future injuries caused by the experimental vaccine must be resolved and understood by recruits before they consent.[140] The challenge is to be able to consistently conduct this careful analysis and then obtain truly informed and comprehending consent all the while streamlining research timelines and blending empiricism with scientific rationalism in our approach to HIV vaccine research.

The impact upon community willingness to be involved in research

The supply of potential volunteers in a country such as Canada is limited.[141] Imagine that we adopt a more iterative approach to vaccine clinical research, conducting multiple simultaneous tests of experimental vaccines for which we have little understanding of the immune correlates or of their potential efficacy. If these empirically driven trials are likely to generate data useful for future research but do not demonstrate vaccine efficacy, then we must also carefully consider the potential impact of such results upon public confidence in both vaccines and in the scientific research process itself. Shifting the emphasis in "rational empiricism" towards the empirical side of the equation will require a public awareness campaign (at least in communities likely to be targeted for recruitment to trials) in order to promote an understanding of this shift. This in turn will help to facilitate: i) long-term public support, ii) a willingness to volunteer for future research, and iii) avoidance of undue optimism.

2. Accelerating HIV Vaccine Research: Multiple Smaller Trials

At the present time, a combination of factors appear to be tipping the balance in favour of the empirical approach advocated by Jonathan Mann. These factors include:

- increased government interest and funding for research;
- deadline-objective dates for "success" set by governments providing funding[142];
- certain not-for-profit foundations that provide risk venture capital for research in exchange for a guaranteed delivery of any resulting successful vaccine at a reasonable cost to people in developing nations [143]; and
- the fact that extremely high rates of seroprevalence in sub-Saharan Africa underline that time is of the essence.

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140 *Halushka* v *University of Saskatchewan* (1965), 53 DLR (2d) 436 (Sask. CA). See also Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Points 9 & 12.

141 Studying the volunteers who make HIV vaccine trials possible: An interview with Susan Buchbinder. Supra, note 67, at 15.

142 M Puls. Clinton calls for AIDS vaccine in next decade. *The Detroit News* 19 May 1997. See also). National Institute of Allergy and Infectious Diseases. Status of AIDS vaccine research at the National Institutes of Health (NIH). Press release of 18 May 1999. Available at www.niaid.nih.gov/newsroom/NIHvacc.htm, and D Shelton. AIDS vaccine: Rhetoric or reality? Special report posted on the internet site of the *Journal of the American Medical Association* 18 August 1997. Available at: www.ama-assn.org/special/hiv/newsline/special/amnews/amn0818.htm, and cf. National Vaccine Information Center. National consumer advocate organization says Clinton administration is playing politics with the AIDS vaccine. Press release of 18 May 1997. Available at www.909shot.com/presiden.htm, and ME Watanabe. Science, Policy Issues put AIDS vaccine on slow track. *The Scientist* 1997; 11(22): 1.

143 P Kahn. World Bank, EC meetings explore ways to stimulate AIDS vaccine development. *IAVI Report* 1999; 4(2): 9-10 at 10. See also IAVI. International AIDS Vaccine Initiative Targeted Genetics Corporation and Children's Research Institute to collaborate to develop AIDS vaccine. Press release of 15 February 2000. Available at www.iavi.org/press/11/targen.htm.

When Jonathan Mann made his presentation to the Presidential Advisory Council, fewer than 40 candidate vaccines had already been tested in Phase I trials, and fewer than five had proceeded to Phase II trials. The VaxGen Phase III trials of the AIDSVAX Gp 120 vaccines were about to be approved and plans were underway for three more Phase III trials over the coming years.[144] Despite the ongoing debate between theorists and empiricists, virtually everyone involved in vaccine research at the time concurred that this effort was far too modest.

By the end of 1999, research was investigating approximately one hundred and eighteen experimental vaccine products around the world. The proportion involved in clinical trials in humans (Phase I, II or III) is as yet relatively modest (46 percent), and only two of these – the two AIDSVAX bivalent vaccines – are currently in Phase III trials.[145] But this is more than at any time in the past, and several other products are poised to move into clinical trials in the near future.

Key funders and facilitators of HIV vaccine research, including UNAIDS, are attempting to move the debate between science and empiricism forward by advocating for progress and for compromise:

> There is an urgent need to move forward on HIV vaccine research. In the absence of a full understanding of the pathogenesis of HIV/AIDS and of immune correlates of protection, it is unlikely that vaccine trials will be conducted with full consensus of the scientific community. It is necessary to maintain an appropriate balance between the theoretical and the empirical approach to vaccine development, after careful analysis of risk/benefit, scientific, logistical and public health considerations. And it is essential that vaccine research, and particularly trials, be conducted to the highest scientific and ethical standards and with respect for human rights.[146]
>
> Unless major advances are made in our understanding of the nature of protective immune responses to HIV-1 in humans, that information will only be obtained through the conduct of phase III field efficacy trials. However, in view of the rate of progression of the HIV pandemic, especially in developing countries, it would not be ethical to wait in the hope that such advances will occur soon […]. In fact these trials, conducted in parallel or sequentially, may represent our best chance to enhance our basic knowledge of the nature of protective immune responses to HIV infection.

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144 WL Heyward et al. Supra, note 80. See also P Fast, W Snow. HIV Vaccine Development: An Overview. Available through the *Journal of the American Medical Association* 25 March 1997. Available at www.ama-asn.org/special/hiv/treatment/updates/vacessay.htm, and J Esparza et al. Supra, note 98, and M Langan, C Collins. *Paving the Road to an HIV Vaccine*: *Employing tools of public policy to overcome scientific, economic, social and ethical obstacles*. San Francisco: Centre for AIDS Prevention Studies, AIDS Research institute, University of California, 1 December 1998, at 10-11, and AIDS Vaccine Advocacy Coalition. *9 Years and Counting: Will we have an HIV vaccine by 2007?* Chicago: May 1998, at Appendix C: HIV preventive vaccines in clinical trials under IND status by the US Food & Drug Administration.

145 MA Gerber (ed). Supra, note 8, Appendix C: AIDS Vaccine Candidates in Development, 149-70.

146 Joint United Nation Programme on HIV/AIDS. *Summary Booklet of Best Practices (Vaccines)*. Geneva: UNAIDS, 2000.

> Thus, […] there is no other choice but to effectively integrate further basic research with the initiation of large-scale efficacy trials in the process of HIV vaccine development.[147]

Esparza published the above-cited passage in the journal *AIDS* in 1996. Since that time, basic science has improved our knowledge of immune responses to HIV infection and there is evidence pointing towards some of the likely correlates of immunity. However, our knowledge is still incomplete and Esparza's assessment remains as pertinent today as it was so many years ago. The positions of theorists and empiricists are not irreconciliable, but rather potentially synergistic. Considerations of public health and of human rights have their just place in this debate.

(i) Conducting Multiple Trials Simultaneously

Echoing her husband's call for an accelerated research agenda, the late Mary Lou Clements-Mann called for simultaneous development of many HIV vaccine concepts in many large-scale clinical trials including intermediate-sized "Phase 2.5" trials. To support this position, she championed a re-examination of preconceptions concerning vaccine research and development. In a presentation made to the First Annual Conference on Vaccine Research in Bethesda, Maryland in 1998, she drew the following conclusions:

- a vaccine need not prevent infection to be effective. Attenuating and slowing pathogenesis might be enough;
- a vaccine might still be useful even if it only generates temporary immunity;
- it may not be necessary, nor even possible to demonstrate protective immunity in animal models before human efficacy trials can begin;
- vaccine-induced immune responses might still be effective even though they do not match those seen in natural infection;
- many efficacy trials will be needed; and
- trials that "fail" [i.e. that succeed in demonstrating that the candidate vaccine is not efficacious] need not set back research.[148]

The idea of conducting multiple "intermediate-sized" investigations between Phase II and Phase III clinical trials reflects a decision to trade off the statistical certainty of efficacy in favour of a reduction in costs and thus an increase in the number of experimental vaccines to be examined. This could accelerate progress in vaccine development. The proposal takes the earlier arguments advanced by Jonathan Mann and extends them one step further. While Dr Mann argued for rapid large-scale testing of products that have been determined to be "safe" and to generate some immune response, this proposal would alter the basic methodology of investigation.

Intermediate-sized ("Phase II.5") trials would not always recruit a sufficient number of people to allow researchers to conclude with scientific certainty that an experimental vaccine under study is in fact efficacious. If the vaccine is extremely efficacious, the smaller sample size will still

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147 J Esparza et al. Supra, note 98.

148 ML Clements-Mann. Supra, note 73.

predict efficacy, but medium levels of efficacy will be suggested but not proven. In this latter case, the difference in the number of breakthrough infections observed in vaccinated participants and the number of infections among people in the placebo control arm would be too small to constitute conclusive evidence of efficacy. Thus, results obtained with smaller studies may not justify licensing for widespread distribution but merely signal the way toward further study. A more limited interim "compassionate" distribution might be offered to people at very high risk of contracting HIV in communities, social groups, and populations that are vulnerable to HIV and AIDS.

(ii) The Benefits of Using Smaller Trials

Researchers envisage using intermediate-sized trials as a screening device that will signal the most promising candidates and eliminate the least (i.e.- those exhibiting less than levels thirty per cent efficacy) from the competition.[149] The identified "promising" candidates would then be moved into full-size Phase III trials. Using extensive epidemiological and psychosocial profile data collected from participants during an American HIVNET vaccine preparedness study from 1995 through 1997, researchers calculated that an intermediate-sized trial of 1500 participants per arm followed over just 18 months could be used to identify candidate vaccines that are reasonably effective (i.e. 60 percent efficacy or greater) and to screen out products with no or low efficacy (less than 30 percent) in a population with an annualized background rate of seroincidence as low as two percent.[150] This compares favourably with the costs of conducting a full sized Phase III trial in that same population which would require 3000 people per arm over a three-year period to generate a 90 percent capacity to evaluate vaccine efficacy between 30 to 60 percent.[151]

Thus, at first glance, the intermediate-sized approach appears to be an attractive proposition. Lower costs would facilitate a multi-trial, multi-candidate approach, permitting scientists to leave no reasonable stone unturned, and thereby facilitating an empirical approach to research. Fewer numbers of participants should also reduce logistical difficulties and make it easier to keep higher-quality (more-detailed) field notes.[152] Such trials would postpone the difficult decision about which vaccines to choose for Phase III study, until more data becomes available. Researchers can use these smaller trials to advance their scientific knowledge of immune response to vaccination. The observational database they generate will increase the index of scientific confidence in the few candidates ultimately selected for Phase III testing.[153]

Intermediate-sized trials have also been suggested for experimental vaccines with a possible post infection endpoint. "Given the large variability in CD4 count and its relatively modest average decline in the year after infection, a slower decline in CD4 count among infected vaccinees would not be detectable."[154] Researchers would have to use the comparatively expensive plasma "viral load" test to detect differences between infected vaccinees and infected

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149 AS Fauci. HIV Vaccine Research: Considerations for the new millenium. Lecture given at the 32nd National Immunization Conference. Atlanta GA, 22 July 1998. See also M Langan, C Collins. Supra, note 144, at 14, and W Snow. How to find out if an HIV vaccine works: Designing vaccine efficacy trials. *Bay Area Reporter* 15 April 1996.

150 *NIH AIDS Research Program Evaluation: Findings and Recommendations*. Vaccine Research & Development Area Review Panel, 1998, at 60. See also W Snow. Supra, note 149.

151 R Hoff. Transcripts of a presentation made to the Joint meeting of the AIDS Subcommittee of the National Advisory Allergy and Infectious Diseases Council and the AIDS Research Advisory Committee. Bethesda MD, 17 June 1994. Available at www.aegis.com/hivinfoweb/library/vaccines/1994arac2.html#hoffagenda. See also W Snow. Supra, note 149, and US Congress, Office of Technology Assessment. *Adverse Reactions to HIV Vaccines: Medical, Ethical, and Legal Issues*. Washington DC: USGPO, September 1995. OTA-BP-H-163, and WN Rida et al. Some statistical issues in HIV vaccine trials. *Statistics in Medicine* 1994; 13: 2155-2177.

152 C Grady. Supra, note 84, at 122. See also S Self. An intermediate size trial design for HIV vaccine trials. Conference given at the Biostatistics seminar, University of California, San Francisco, 25 August 1998. Available at www.biostat.uscf.edu/events_old.html, and S Self. Strategies for efficacy evaluation of HIV vaccines. Conference given at Emory University, Atlanta GA, 3 April 1999.
Available at www.emory.edu/WHSC/YERKES/VRC/VDC/speakers.html.

153 AIDS Vaccine Advocacy Coalition. Supra, note 144.

154 W Rida et al. Intermediate-size trials for the evaluation of HIV vaccine candidates: a workshop summary. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* 1997; 16(3): 195-203.

people from the control group. With limited resources, in order to reduce costs, intermediate-sized trials and endpoints defined in terms of a post infection reduction in viral load set points could be used to significantly advance vaccine research.[155]

(iii) The Risks in Reducing the Size of Trials

The danger, however, is that reducing the number of participants in order to suggest (as opposed to confirm) efficacy might so severely compromise statistical certainty that the trial will not be of much predictive value at all. This danger is particularly present in HIV vaccine trials because of the high rate of genetic mutation in the retrovirus as well as the potential for behaviour modification within the cohort and hence fluctuations of seroincidence and seroprevalence.

If, for instance, participants utilize post exposure prophylaxis (PEP) or early infection treatment, and if these interventions succeed in reducing HIV incidence in the cohort and succeed in reducing viral load in persons experiencing breakthrough infections, then it is not at all clear that even viral load measurements would be a valid surrogate marker of vaccine effect. In such a setting, substantially larger (rather than smaller) sample sizes would be required to assess vaccine efficacy.[156]

Large-scale vaccine efficacy trials in humans work best in an environment in which:

- background rates of seroincidence are high and relatively uniform across society and are well understood in advance of the trial and during the course of the trial;
- rates of co-morbidities are low and consistent throughout the length of the trial;
- the genetic composition of the virus targeted by the vaccine is consistent and does not mutate;
- there is a relatively uniform susceptibility to infection and thus few natural variations in resistance to the virus;
- the measures (correlates) of effective immunity are well understood in advance; and
- there are relatively few, if any, actions (behavioural, environmental, or medical) that can be implemented to change the course of the epidemic.[157]

Unfortunately for vaccine scientists, HIV fails to meet most of these ideal preconditions. Numerous factors influence HIV seroincidence prior to and during the course of a clinical trial. Rates of seroincidence are in dynamic flux during an HIV epidemic. They vary over time according to a number of social and environmental factors, including: multiple political influences; the effectiveness of current prevention campaigns; the degree to which the culture has understood and assimilated the prevention and harm reduction messages, accurately assessed risk, and is culturally prepared to support, exercise and sustain safer behaviours.[158] The effect of

[155] C Collins. Using viral load as an endpoint in HIV vaccine trials: New HIV treatments likely to impact vaccine studies. *IAVI Report* 1998; 3(2). See also C Schaper et al. Supra, note 47, and N Nathanson. *National Institutes of Health Fiscal Year 2002 Plan for HIV-Related Research*. Bethesda MD: Office of AIDS Research: National Institutes of Health, June 2000, at 99-104 and 123. Available at www.nih.gov/od/oar.

[156] C Collins. Supra, note 155.

[157] C Grady. Supra, note 84, at 107, 121-3, 130-31. See also C Levine et al. Supra, note 53, at 4, 5-8.

[158] S Kippax et al. Supra, note 10. Re: emerging trends and variations in HIV epidemiology in Canada, see also M Alary et al. Faint light on the horizon? Trends in HIV prevalence, incidence and needle borrowing among injection

the preventive counselling provided to participants during the clinical trial may also have a considerable impact upon trends in seroincidence during the trial.[159] The stage of development in the epidemic (ie, is it nearing a saturation point?) will also impact upon background rates of seroprevalence and seroincidence.

Given these multiple variables, a prior and continuing knowledge of this epidemiology will be essential to determining what levels of vaccine efficacy can be predicted by a given clinical trial designed with a given number of participants, in a given target population, over a prescribed period of time. Ultimately, these same high levels of surveillance and understanding will also be necessary in order to precisely determine whether a vaccine with a demonstrated level of efficacy is suited for distribution in an epidemic at a given stage of its development.[160]

High rates of fluctuation in both the basic epidemiology of HIV and in the human factors that influence it mean that there will be a greater propensity for significantly large interpretative margins of error whenever a decision is made to conduct HIV vaccine research with statistically suboptimal sample sizes. Clinical trials embarking upon such a course would have to compensate with better vaccine preparedness study data, more complex and hence costly detailed modeling and design, close attention to emerging trends in epidemiological data throughout the duration of the trial, and cross referencing to data generated in parallel and bridging cohorts.

The AIDSVAX B/B clinical trial seems to be at the minimum size level required to detect approximately 30 percent efficacy via a phase III clinical trial among men who have sex with men in North America. The number of participants was already revised upward during the recruiting process from 5500 to 6300. This increase was partially due to the fact that seroincidence rates were falling among North American gay men during 1997 and 1998, (the period of recruitment) necessitating an adjustment in the cohort's parameters. VaxGen may also be able to use some of the data generated from the trial in Thailand to infer reinforcing hypotheses of efficacy in the North American environment.

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drug users participating in the survUDI study. Oral presentation to the Xth Annual Conference of the Canadian Association for HIV Research. Toronto, 1 June 2001. Abstract no 315, and TJ Coates. Supra, note 15, and K JP Craib et al. Supra, note 15, and L Calzavara et al. Risk factors for recent HIV infection among men who have sex with men (MSM): Results from the Polaris HIV seroconversion study. Oral presentation to the Xth Annual Conference of the Canadian Association for HIV Research. Toronto, 2 June 2001. Abstract no 325, and P Braitstein et al. Closer to the edge: History of sexual assault strongly associated with high risk behaviours and adverse outcomes among a cohort of injection drug users (IDU): Poster presentation to the Xth Annual Conference of the Canadian Association for HIV Research. Toronto, June 2001. Abstract no 352, and RS Remis et al. Increased HIV prevalence among women undergoing abortion in Montreal: Evidence for increasing heterosexual transmission? Poster presentation to the Xth Annual Canadian Conference on HIV/AIDS Research. Toronto, 31 May-3 June 2001. Abstract no 360P, and E Tharao et al. A strategy to address HIV issues faced by people in Ontario from HIV endemic countries. Poster presentation to the Xth Annual Conference of the Canadian Association for HIV Research. Toronto, June 2001. Abstract no 443P, and S Strathdee. HIV infection and risk behaviours among young gay and bisexual men in Vancouver. *Canadian Medical Association Journal* 2000; 162(2): 21-5, and SA Strathdee. Determinants of sexual risk-taking among young HIV-negative gay and bisexual men. *Journal of Acquired Immune Deficiency Syndrome and Human Retroviruses* 1998; 19: 61-6.

[159] J Baeten et al. Rapid decline in risk of HIV-1 acquisition after enrolment in a vaccine preparedness cohort of Kenyan prostitutes: implications for the design of HIV-1 vaccine efficacy trials. Oral presentation to a vaccine preparedness workshop at the XIIIth International AIDS Conference. Durban, South Africa, 10 July 2000. Abstract no MoORC128. See also RS Remis et al. Trends in high risk sexual behaviour among homosexual men participating in the AIDSVAX B/B vaccine trial in Canada: results to 12 months. Oral presentation to the Xth Annual Conference of the Canadian Association for HIV Research. Toronto, 2 June 2001. Abstract no 305.

[160] S Blower et al. Supra, note 87.

If a program of intermediate-sized trials permits scientists to rapidly identify a vaccine with an efficacy for sterilizing immunity in excess of sixty percent, then all Canadians will benefit from such a strategy. But if an experimental vaccine has an efficacy of less than sixty percent, then resorting to intermediate-sized trials may very well turn out to be a double-edged sword. These smaller trials would attain the highest predictive degree of probable efficacy if conducted among populations where seroincidence is particularly high. This means that the various communities that are the most affected by and vulnerable to HIV infection (populations which in Canada are often also the most socially marginalized), may be asked to bear the burden of a research methodology that is not statistically capable of determining levels of efficacy below 30 percent. There is considerable irony in this situation since even a very low-efficacy preventive vaccine might theoretically be of considerable public health benefit if it could be widely distributed within a population with very high rates of transmission.[161] But by screening out experimental vaccines that have an efficacy rate between nil and 30 percent, intermediate-sized trials will reject candidates that might have been useful for the target populations, if not the mainstream of Canadian society. The proposed methodology might end up denying those most at risk of contracting HIV access to a potentially useful vaccine.

If this modified research methodology identifies one or two potentially promising candidates (with potential efficacy somewhere between thirty and sixty percent), there will be enormous public pressure to deliver a vaccine to vulnerable populations on a "compassionate" basis. But the trial results motivating this demand will not be statistically significant. It is theoretically possible that the vaccine could be distributed to thousands of people, only to discover several years later, upon completion of a full scale Phase III trial, that it does not work. The emotional and political impact of such a "failure" could be considerable. It might engender a deeply rooted public mistrust of scientific research. If public health authorities were to embark upon such a compassionate distribution of an unproven vaccine, great care would have to be taken to educate the targeted populations about the high degree of uncertainty still associated with the product. Significant resources would have to be dedicated to the informed consent process and to concurrent efforts aimed at reinforcing sustained preventive behaviours.[162]

Given the uncertainty associated with the compassionate release product's efficacy, it might be difficult to attain the levels of coverage in the target population required in order to achieve optimal results. Conversely, once the promising but unproved product is widely released into vulnerable communities on a compassionate basis, it might become very difficult to recruit people into a Phase III confirmatory trial. No one would want to risk receiving the placebo. This could significantly delay the research.[163]

Moreover, if a second candidate vaccine is developed and put into a Phase III efficacy trial there would be a demand for the people in the control arm to receive the "compassionately released" earlier vaccine.[164] If that earlier vaccine conferred even minimal protection, this would affect the end results of the Phase III trial of the newer candidate. Under such conditions, the trial would have to recruit a much larger number of participants in order to prove the efficacy of the newer experimental vaccine with statistical certainty.

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161 Ibid.

162 By way of analogy see G Kolata, K Eichenwald. Supra, note 131.

163 Ibid.

3. Accelerated Vaccine Research and Vaccine Preparedness Studies

The desire to accelerate a research agenda should not leave communities with the impression that there is no time to hear their concerns and no possibility to effect changes to research methodology in order to take into account factors particular to individual sites in a multi-centred trial. One way to avoid this problem is to conduct preparatory work with target populations. Vaccine preparedness studies (VPS) recruit potential participants well in advance of clinical trials. Information is distributed, preventive counselling takes place, and periodic HIV testing is conducted to determine seroincidence data.[165] This work can be conducted by government, private charitable foundations, public health agencies, or private industry. Such studies began in the United States long before any candidate vaccines were available for Phase III testing.[166] In Uganda, VPS financed by the US National Institutes of Health took place for nine years before a Phase I clinical trial began in 1999.[167]

A VPS serves at least six principal goals:

i. recruitment of participants for future clinical trials,

ii. facilitating a thorough pre-trial education and better-quality informed consent, as well as offering an opportunity to evaluate the durability of this comprehension;

iii. gathering information re willingness of people within the target community to consent to participate in vaccine clinical research and identification of the barriers to enrolment;

iv. dissemination of HIV prevention information to potential participants offering an opportunity to evaluate the quality and effectiveness of supportive counselling and accompanying referrals thus allowing counsellors to improve their work before a vaccine trial actually commences;

v. periodic HIV testing within the context of a VPS will generate information on the in situ epidemiology, as well as information concerning the natural history of early HIV infection within members of the target population;[168] and

vi. establishing productive and mutually reinforcing links between researchers and targeted communities.[169]

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164 Joint United Nations Program on HIV/AIDS. Supra, note 10, Guidance Point 11: Control group, 31-2.

165 ARS Périssé et al. Willingness to participate in HIV vaccine trials among men who have sex with men in Rio de Janeiro, Brazil. *Journal of Acquired Immune Deficiency Syndromes* 2000; 25(5): 459-63. See also BA Koblin et al. Readiness of high-risk populations in the HIV Network for Prevention Trials to participate in HIV vaccine efficacy trials in the United States. *AIDS* 1998; 12: 785-93, and BA Koblin et al. Willingness to participate in HIV-1 vaccine efficacy trials and the effect of media events among gay and bisexual men in New York City. *Journal of Acquired Immune Deficiency Syndrome* 1997; 15(2): 165-71, and GR Seage III. Are US populations appropriate for trials of human immunodeficiency virus vaccine? *American Journal of Epidemiology* 2001; 153(7): 619-27.

166 Studying the volunteers who make HIV vaccine trials possible: An interview with Susan Buchbinder. Supra, note 67, at 8.

167 Uganda: A long, rocky path to Africa's first HIV vaccine trial: An interview with Roy Mugerwa. *IAVI Report* 1999; 4(4): 4-5.

168 CL Celum et al. Early human immunodeficiency virus (HIV) infection in the HIV Network for Prevention Trials vaccine preparedness cohort: risk behaviors, symptoms, and early plasma and genital tract virus load. *Journal of Infectious Diseases* 2001; 183(1): 23-5.

These studies gather data that is critical to the design, conduct and interpretation of clinical research. For instance, a VPS should gather background information on emerging trends in epidemiology and on seroprevalence and seroincidence rates. Evidence of how a given community accesses medical services such as antiretroviral therapies and post-exposure prophylaxis can also be gathered.[170]

These studies identify variations within the targeted populations so that researchers can adjust their research methodologies and therefore more effectively communicate the information needed to promote comprehending informed consent.[171] For instance, interviews conducted during VPS studies in the United States identified significant differences between young gay men and older gay men. The former were found to have a lower level of baseline knowledge about clinical trials. In comparison to their older counterparts, they also exhibit a statistically significant propensity to engage in risk behaviours; unblind their study participation (by being tested outside the cohort); and take more risks if they suspect that they have received the experimental vaccine as opposed to the placebo.[172] Thus, researchers need to approach targeted populations at each site with as few assumptions as possible and use site-specific preparedness studies to acquire required background data.[173]

Vaccine clinical trials can potentially involve partnerships linking psychosocial qualitative research to quantitative evaluations of efficacy. If HIV preventive counselling and referrals to other services are to be effective during the course of the trial, it is essential to gather information about the cultural context of health behaviours within communities. This will help researchers ensure that appropriate language and methodology is used when addressing sensitive issues such as sexuality. In Canada, a VPS would evaluate baseline levels of knowledge of clinical trials

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169 AIDS Vaccine Advocacy Coalition. *HIV Vaccine Preparedness Study*. Bethesda MD: Office of Communications, National Institute of Allergy and Infectious Diseases, March 1995. Available at www.avac.org/sciences/vps.html. See also Studying the volunteers who make HIV vaccine trials possible: An Interview with Susan Buchbinder. Supra, note 67, and G Seage et al. The HIV network for efficacy trials (HIVNET) vaccine preparedness study (VPS): goals and current status. Presentation at the 3rd Conference on Retroviruses and Opportunistic Infections. 28 January-1 February 1996.

170 B Snow. Vaccine Preparedness Studies: Bill Snow Interviews Susan Buchbinder. In B Snow (ed.). Supra, note 58, 55-60. See also KL Goldenthal et al. Preventive HIV type 1 vaccine clinical trials: a regulatory perspective. In Joint United Nations Programme on HIV/AIDS, World Health Organization HIV Vaccine Initiative. *Future Access to HIV Vaccines: Report from a WHO-UNAIDS Consultation* 2-3 October 2000. Geneva: WHO / UNAIDS, at 5-7.

171 R Strauss et al. Supra, note 10. See also ARS Périsse et al. Supra, note 165, at 459, and HIV Vaccine research communications: The current environment. Bethesda, MD: The National Institutes of Allergy and Infectious Diseases: Division of AIDS, 2 March 2001. Available at www.niaid.nih.gov/daids/vaccine/vacrpt.htm.

172 S Buchbinder et al. USCF Researchers find risk factors for HIV infection among men who have sex with men. News release of 30 June 1998, Geneva; Centre for AIDS Prevention Studies, University of California. See also WR Lenderking et al. The influence of changes in knowledge of vaccine trial concepts on willingness to participate in HIV vaccine trials over 18 months follow-up in the vaccine preparedness study of the HIVNET. Abstract no P30. Presentation to the Second Annual Conference on Vaccine Research, 28-30 March 1999, and S Scheer et al. Feasibility and suitability of targeting young gay men for HIV vaccine efficacy trials. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1999; 20: 172-78. And cf. SA Strathdee. Feasibility of HIV vaccine trials among high-risk cohorts in Vancouver. Poster presentation at the 11th Annual BC AIDS Conference, Vancouver, July 1998.

173 S Buchbinder et al. The feasibility of conducting preventive HIV vaccine trials in gay men in the United States. XIth International AIDS Conference. Vancouver, 7-12 July 1996. Abstract no Mo. C. 1592. See also S Buchbinder et al. Predictors of seroconversion in vaccine preparedness studies of gay men. IXth International AIDS Conference. Berlin, 7-12 Agust 1994; 10(1):87. Abstract no 301C.

(placebos, randomization, phases, risks, etc). It will also evaluate background rates of literacy and of computer literacy.[174]

A VPS can thus serve not only the purpose of acquiring background information but also the purpose of disseminating information in order to encourage informed debate in target communities that will hopefully lead those communities to lend their support to clinical vaccine research. The Department of AIDS of the National Institutes of Allergy and Infectious Diseases in the United States has recently assessed the communications challenges facing researchers and concludes:

> Awareness of vaccine research issues in general, and of AIDS vaccine research in particular, is very low. The lack of information and awareness extends from the general public, to medical professionals, and the media. Leaders of national AIDS organizations, who frequently comment in public on a variety of AIDS-related issues, have acknowledged a low level of awareness on AIDS vaccine research issues. Influential policy makers and elected officials have also made misinformed public statements that have endangered support for vaccination and vaccine research. The consequences are most evident in stable or decreasing vaccination rates and media coverage of vaccine research issues that understates their value and overstates their risks.[175]

In addition, the influence of culture upon HIV prevention and access to research and treatments should not be under-estimated in a multi-cultural society such as Canada. Epidemiology in both Canada and the United States demonstrates that race and ethnicity can correlate with systemic barriers to understanding information, reducing harm, and accessing care.[176] A properly designed vaccine preparedness study with accompanying community relations activities can help to overcome some of these challenges. A well designed VPS could help researchers, target communities and individuals to overcome cultural barriers to HIV related research and more broadly to HIV prevention within the target communities.

If a vaccine clinical trial targets people from ethnic communities in a city such as Vancouver, a VPS could help researchers to forge links with people from the urban Aboriginal population as well as with people who adhere to the Sikh, Muslim, and Hindu religions. Such a study could also establish preparatory links with a wide variety of South Asian and Southeast Asian communities where languages such as Punjabi, Hindi, Urdu, Gujarati, and Chinese are spoken. In

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174 DS Metzger et al. Randomized controlled trial of audio computer-assisted self-interviewing: utility and acceptability in longitudinal studies. HIVNET Vaccine Preparedness Study protocol team. *American Journal of Epidemiology* 2000; 152(2): 99-106.

175 HIV Vaccine research communications. Supra, note 171.

176 Centres for Disease Control and Prevention (US). Supra, note 114. See also M Radhakrishnan. HIV/AIDS and discrimination in South Asian communities: an ethnocultural perspective. *Canadian HIV/AIDS Policy & Law Newsletter* 1999; 4(4): 54-5, and HIV/STD Knowledge, attitudes, and risk behaviors among Hmong-American adolescents. *School Health Opportunities and Progress Bulletin* 2000; 4(23), and BE Robinson et al. HIV/STD Knowledge, attitudes and risk behaviors among Hmong-American adolescents: an unstudied population. *Journal of Sex Education and Therapy*; 24(1&2): 37-46, and P DeCarlo et al. What are Latinos' HIV prevention needs? Fact Sheet. Center for AIDS Prevention Studies, University of California. Available at www.caps.ucsf.edu/latinotext.html , and LF O'Sullivan et al. Mother-Daughter Communication about sex among urban African-American and Latino families. *Journal of Adolescent Research*; 16(3): 269-92.

Montréal by contrast, the focus would be upon the urban Aboriginal population as well as the Latin American, Arab, and Haitian communities.[177]

VPS work can evaluate the willingness of communities to participate in the design and conduct of clinical trials. The influence of the family can be an important factor in determining an individual's decision not to participate in vaccine research and this holds true even within cohorts of gay men.[178] Customs of communication within families vary according to cultures and traditions. An understanding of these traditions will help scientists determine the best means of recruiting people into a vaccine cohort, and how best to ensure that consent is voluntary and comprehending.

In addition, if ever a vaccine efficacy trial is conducted with a post infection endpoint, there may be a need to design the trial to include retrospective contact tracing. This tracing would serve to obtain information concerning the rate of infection among the sex partners of trial subjects who experienced breakthrough infections. This information will help to calculate vaccine efficacy for infectiousness.[179] Such a study would require contacting and interviewing spouses and steady sexual partners as well as testing these people for HIV infection. This in turn requires tact, cultural sensitivity and a thorough understanding of attitudes towards sex, and risk behaviours within the target community.

Interactions with communities will raise debate concerning:

•the risk of reinforcing existing stigma and prejudice against targeted communities;

•funding for prevention initiatives;

•accountability;

•methodology; and

•ownership and use of the research results and maintenance of the scientific integrity of that research.[180]

Vaccine preparedness studies are lengthy and risk being sacrificed to the urgency of an accelerated research agenda. Private financing of research is a risk investment. Investors seek to maximize returns within the shortest possible time. In Montréal, researchers were asked in March 1999 to participate in the Phase III trial of the AIDSVAX B/B Gp 120 experimental vaccine. The recruiting process had to be finished by mid September, the start-up date for the North American trial. Contrary to the situation in the United States, where the preparatory period was longer, it was decided that in Montréal time would not permit the recruitment of women who are sexual partners of gay or bisexual men.

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177 *Ethnocultural Communities and HIV/AIDS: Inventory of targeted programs and services*. Ottawa: Canadian AIDS Society, March 1998, at 1-3, 14-15. See also City of Vancouver, Social Planning: Multiculturalism & Diversity. Available at www.city.vancouver.bc.ca/commsvcs/socialplanning/initiatives/multicult/multi&diver.

178 Studying the volunteers who make HIV vaccine trials possible: An interview with Susan Buchbinder. Supra, note 67 at 9.

179 DC Barth-Jones. Monte Carlo simulation experiments for analysis of HIV vaccine effects and vaccine trials design. *Proceedings of the 2000 Winter Simulation Conference* 1985-94. See also AL Adams et al. Simulations to evaluate HIV vaccine trial designs. *Simulation* 1998; 71(4): 228-41.

180 B Snow. Working with Communities: 1991. Speech delivered to a meeting of National Co-operative Vaccine Development Group for AIDS, Ottawa, 1991. In B Snow (ed). Supra, note 58, at 11-16. See also B Snow. Supra, note 170.

No VPS work had been conducted in the Montréal target communities and given the tight launching schedule, none was undertaken. Considerable seroincidence and seroprevalence data was however available to vaccine researchers due to the presence of a large pre-existing longitudingal seroincidence cohort in that city – (the Oméga Cohort). In contrast to the situation at some American sites (eg, Boston), where preparedness studies had been ongoing for years, funds in Montréal were allocated to community-directed vaccine education only after the trial was announced. Community forums and press conferences have been held, articles published in the local press, and pamphlets distributed.

The results are difficult to interpret. There were reports in the press that some US sites of this multi-centre trial had difficulties recruiting their contingent of participants despite extensive VPS work and significant media promotion.[181] Montréal succeeded in rapidly recruiting 99 people for the trial. Some studies conducted in the United States have shown that willingness to participate actually decreases somewhat as volunteers are apprised of the full spectrum of risks and uncertainties associated with clinical research.[182] Could it be that recruitment in Montréal was relatively easy because the community was uninformed about the many ethical issues inherent in vaccine research? Or did other factors, such as hard work by local staff, universal medical care, and a relatively cohesive self-identifying gay "community" make it easier to recruit people here?

The people recruited to the Montréal site do not represent a cross-section of Montréal's gay population. With only four anglophone participants and one hispanophone participant in the cohort, both linguistic minorities are under-represented. Would a VPS have corrected this imbalance? The quality of the research data and its relevance to vaccine delivery in targeted Canadian communities will be improved if preparation for trials permits clinical researchers to ensure that the cohort is indeed representative of the populations where vaccination will be required.

The community advisory board in Montréal suggested several changes to the consent process, including the addition of supplemental information and a reallocation of emphasis to certain key points. The process to revise the contents of consent took several months and the hospital REB adopted the vast majority of the suggested revisions. Participants were informed of these changes at the moment of enrolment (verbally and on a written sheet). However, the final revised consent form was available only after many participants had received their first injection. At that time, participants were given the option of (i) staying with the original consent form, (ii) signing the revised version, or (iii) dropping out of the trial. Revising the consent form once administration of the experimental vaccine (or placebo) has already begun was a highly unorthodox procedure. It might have been avoided if the start-up period been longer and the community better prepared for the advent of vaccine research.

A VPS can help to provide the advanced training necessary to permit a target community to more rapidly assess research proposals, to make known matters of local concern and to identify its requirements for development of a community based response to HIV prevention that includes a place for prophylactic vaccines. But despite the understandable interest in accelerating research, there are practical limits to the capacity to compress the time required for this community education prior to and during a clinical trial.

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[181] AE Cha. Company will test AIDS vaccine: Subjects sought in South Bay. *San Jose Mercury News* 12 December 1998. See also L Richardson. Rolling up their sleeves, Volunteers take on killer. *The New York Times* 21 December 1998.

[182] BA Koblin et al. Readiness of high-risk populations in the HIV Network for Prevention Trials to participate in HIV vaccine efficacy trials in the United States. Supra, note 165. See also S Scheer et al. Supra, note 172.

Moreover, in facilitating the development of a strong and lasting partnership with communities, vaccine preparedness studies may help researchers and sponsors to garner public and political support for eventual delivery of an efficacious vaccine. A decade ago, Bill Snow delivered a speech to vaccine researchers and advocates, in which he described why researchers should work closely with communities when conducting clinical research in the United States. In that speech he noted:

> Everyone needs a vaccine for AIDS, but "everyone" isn't a constituency. It is people known to be at high risk, those with the same demographics as the epidemic, who will benefit most immediately and most directly from your vaccine if they will take it, and if they can get it. [….]
>
> It's not news that we live in a country where we can't [always] educate freely about safe sex, or give out condoms and clean needles without a fight. There is no reason to believe you'll be able to give your vaccine freely either, if those in political power think it will promote promiscuous sex, homosexuality, freer drug use, or teenage sexuality.[183]

Ten years later in Canada, the need for community support and solidarity remains integral to mobilizing public and political support for HIV vaccine research, development and delivery. This support must encourage strong leadership capable of battling stereotypes, stigma associated with HIV and AIDS, institutional inertia and beleaguered budgets.

4. Conclusion

The rush toward an empirical model of clinical research can generate some unexpected consequences that could damage the very communities the research is trying to benefit.

Unless the trials are carefully managed and supported with increased and intensive complementary resources (education, prevention, community involvement, etc), it is not immediately clear that an acceleration to large-scale empirical clinical trial research or a reduction in trial size to an intermediate level will achieve the purported goal – that is, getting an effective vaccine more quickly to those that need it most.

Intermediate-sized trials would require a greater investment in vaccine preparedness studies, careful modelling and design by trained statisticians, greater attention to the informed consent process, increased efforts for volunteer retention, and intensive community education campaigns. Without these ancillary supports, modifying the basic methodology of scientific research risks doing more harm than good.

D. Shopping for Regulatory Approval

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[183] B Snow. Supra, note 180, at 13-14.

Should researchers dissatisfied with a regulatory refusal in one country be permitted to solicit approval for the same protocol in another country? This ethical (and potentially legal) controversy arises out of the following facts:

- vaccine research would be easiest and most beneficial in populations with high HIV seroprevalence and low availability of HIV treatment; and
- high-prevalence populations are predominately in developing countries, while groups conducting vaccine research are mostly based in developed countries.

The ethical challenge is to avoid a "race to the bottom" that could occur if nations compete against each other for research projects by seeking to offer paths of least ethical resistance.

The UN draft guidance document entitled *Ethical Considerations in HIV Preventive Vaccine Research* proposes principles of guidance pertinent to this issue.[184] The general and non-binding language used in the draft reflects differences of opinion present among parties to the proceedings. Nevertheless, at least four of the principles are of interest:

> ***Guidance Point 3:*** Strategies should be implemented to capacitate host countries and communities so that they can practice meaningful self-determination in vaccine development, can ensure the scientific and ethical conduct of vaccine development, and can function as equal partners with sponsors and others in a collaborative process.
>
> ***Guidance Point 6:*** HIV preventive vaccine trials should only be carried out in countries and communities that have the appropriate capacity to conduct independent and competent scientific and ethical review.
>
> ***Guidance Point 7:*** Where relevant, the research protocol should describe the social contexts of a proposed research population (country or community) that create conditions for possible exploitation or increased vulnerability among potential research participants, as well as the steps that will be taken to overcome these and protect the dignity, the safety, and the welfare of the participants.
>
> ***Guidance Point 9:*** The nature, magnitude, and probability of all potential harms resulting from participation in an HIV preventive vaccine trial should be specified in the research protocol as fully as can be reasonably done, as well as the modalities by which to address these, including provision for the highest level of care to participants who experience adverse reactions to the vaccine, compensation for injury related to the research, and referral to psycho/social and legal support as necessary.[185]

While legislation can provide a normative, instrumental, and positivist structure for clinical research, ethical principles can provide support extending well beyond a legal framework. Ethics provides guidance to researchers in order to safeguard the integrity of the scientific process through the protection of the human rights and interests of the subjects of the research and of the people in the communities from which those subjects are recruited. If law and ethics are to be effective, they must exist against a background of knowledge, competence, and resources facilitating their respect and implementation.

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184 Joint United Nations Programme on HIV/AIDS. Supra, note 10.

185 Ibid, Guidance points 3, 6, 7 and 9.

Not surprisingly, the UNAIDS guidance document places considerable importance upon the building of skills, capacities, and infrastructures necessary to support clinical trials of experimental HIV vaccines. This development can help to level the playing field and reduce the risk that human rights could be sacrificed in the competition for research resources and for rapid results. This in turn will deter "shopping" for a convenient forum. The notes to Guidance Point 6 state:

> Proposed HIV vaccine research protocols should be reviewed by scientific and ethical review committees that are located in, and include membership from, the country and community where the research is proposed to take place. This process ensures that the proposed research is analysed in scientific and ethical concerns by individuals who are familiar with the conditions prevailing in the potential research population.
>
> Some countries [and communities] do not currently have the capacity to conduct independent, competent and meaningful scientific review. If the country's capacity for scientific and ethical review is inadequate, the sponsor should be responsible for ensuring that adequate structures are developed in the host country for scientific and ethical review prior to the start of the research.[186]

This issue of community development is not restricted to developing nations. It also has application in Canada. For example, the need to devote resources to minimizing the deleterious impacts upon preventive behaviours that may result from the publicity surrounding a vaccine trial will require a community response wherever a trial takes place. Competition for scarce research funding exists in every environment. Sponsors financing multi-site vaccine efficacy trials can use competitive bidding by awarding research contracts to the first centres to complete ethical review and respond to their calls for tenders. This increasingly common practise in clinical research might result in decreased protection for research subjects and their communities if the resources allocated are insufficient to permit a thorough ethical review within extremely short time constraints. The consistent application of ethical principles to research protocols and to procedures of informed consent with the resources required to back them up will help prevent a "race to the bottom" in the developed world and in the developing world.

In Montréal, the AIDSVAX B/B Gp 120 Phase III clinical trial is devoting 10 percent of the site's overall budget to community development. This developmental mandate finances work in the following fields:

- HIV prevention which takes into consideration the impact of vaccine research and potential delivery in the target community;
- community education concerning experimental vaccines and vaccine trials;
- a community advisory board charged with reviewing and monitoring consent processes, the execution of the cohort, and aiding participants who may have concerns or complaints;
- development of a community knowledge base (expertise) surrounding the ethical issues in clinical trials of HIV vaccines; and
- a legal defence fund reserved for participants who may test positive on ELISA tests as a result of their vaccination.

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[186] Ibid, Notes to Guidance Point 6 at 21-22.

These issues were identified by community researchers, volunteers, and organizations as priorities particular to the gay community in Montréal. But the principle of setting aside a proportion of clinical trial funding for the express purpose of facilitating community education, skills building, and development is something that can be applied in a multiplicity of environments where clinical trials of vaccines occur.

But what if Montréal were the only city in which the host community consistently imposes a local development initiative upon HIV vaccine research? Would this place the city at a competitive disadvantage for future research cohorts? And if so, would this disadvantage not inadvertently and perversely penalize a community that has worked hard to develop a community presence in HIV prevention? In order to avoid a disorganized and uneven playing field, it may be necessary to engage in a national and international consensus building around the principle of community development as an integral part of vaccine research. This subject will be covered in greater detail in Part 2 of this paper.

E. Does a Personal or Population Risk of HIV Infection Raise the Threshold of Ethically Tolerable Risk in an HIV Vaccine Clinical Trial?

Highly vulnerable people from communities with high seroincidence form subsets of the population that are of particular interest to researchers and they will be a priority target for recruitment to clinical trials and for the eventual delivery of any future licensed vaccine.

Certain experimental HIV vaccines might carry significantly higher levels of risk of adverse events and yet still prove to be useful for public health in communities where the epidemic is spreading rapidly. The difficult issues that arise when deciding when and how to test experimental vaccines on such a population have been described by Dr Ronald Desrosiers of the New England Regional Primate Research Centre. “Ultimately,” he says, “it really turns into a risk/benefit equation of what is acceptable. An attenuated HIV vaccine should only be offered to people who are at high risk of becoming infected by the virus. This vaccine is not for babies. … Is it ever going to be absolutely 100% safe? Forget it. It will never be. If you put it into enough people, there will be problems. That is true of every live, attenuated vaccine.” But, he says, the question boils down to what the likelihood is of the person becoming naturally infected by HIV versus becoming injured by the vaccine: “We’re never going to know until we put it into humans, and that’s why people have different best guesses.”[187]

This willingness to vary what one considers to be the ethically tolerable threshold of risk also reflects the reality of the global pandemic. Time is of the essence and pressure is exerted upon scientists to proceed more rapidly, to adopt a more empirical, less strictly scientific approach, and to embark upon a more risk-tolerant course of research.

G. Correlation Between Personal Risk and Willingness to Accept Heightened Risks of Adverse Events

Individuals living in a community with high rates of seroprevalence and of HIV incidence and who consider themselves to be at high personal risk for contracting HIV might express a higher threshold of acceptance for a vaccine offering relatively lower levels of efficacy and presenting relatively higher risks of adverse events.

Would a correlation between personal risk and the willingness to accept heightened risks of adverse events induced by an experimental vaccine constitute an ethical criterion influencing participation in a clinical trial?

The Canadian Tri-Council Policy Statement requires that experimentation of higher-risk products on people at "higher risk" must be subject to rigorous ethical review and monitoring. But Dr Desrosier's argument (cited above) suggests that in circumstances of extreme probability of HIV infection, particularly in situations where treatments and prevention materials are not accessible, people will more readily enrol in vaccine clinical trials because they have "nothing to lose." Hence, even vaccine trials presenting significant risks of vaccine-induced harm and/or low probabilities of efficacy might be preferable to nothing at all.[188] Are these two positions compatible with each other?

One potential problem is that the Desrosiers line of reasoning seems to assume that high levels of personal risk assumption are inevitable and that the factors influencing this behaviour are immutable. However, there are a multitude of factors that can influence an individual's ability to assess, manage, assume, or decline risk. Examples include: domestic violence; threats of physical violence; the balance of power in a sexual relationship; illegal substance use; the balance of power in a drug-using relationship; self-esteem; education; economics; culture – its values, confrontations, and denials; discrimination and related stigma, shame, and prejudice; mental health; homelessness; lack of sustainable social networks; grief; lack of access to material resources; fatigue; stress; etc.[189] To ignore this psychosocial context of HIV epidemiology, and to use the existing risk levels as justification for embarking upon higher-risk experimentation might mean that science becomes complicit in (or at least chronically dependent upon) the persistence of antisocial, anti-health conditions in society.

At the very least, prevention efforts targeting fundamental health promotion and the social determinants of health should continue in tandem with vaccine research. Otherwise, the research

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187 J Cohen. Supra, note 78, at 25.

188 Ibid at 25.

189 The Centres for Disease Control and Prevention (US). HIV/AIDS among racial / ethnic minority men who have sex with men: United States, 1989-1998, and CDC Editorial note. *Journal of the American Medical Association* 2000; 238(8): 995. See also A Vassal et al. *Gay and Lesbian Issues and HIV/AIDS: A discussion paper.* Montréal: Canadian HIV/AIDS Legal Network & Canadian AIDS Society, 1997, and T de Bruyn. Supra, note 27, 11-86, and C Schuler. One woman's crusade against rape in South Africa. *Christian Science Monitor* 12 April 2000: 1, and Office of the United Nations High Commissioner for Human Rights and the Joint United Nations Programme on HIV/AIDS. Supra, note 44, and B Donovan, M Ross. Preventing HIV: determinants of sexual behaviour *The Lancet* 2000; 355: 1897-1901 at 1898 et ss, and P DeCarlo et al. What are Homeless People's HIV Prevention Needs? Center for AIDS Prevention Studies, AIDS Research Institute, University of California. Available at www.caps.ucsf.edu/homelesstext.html, and Centres for Disease Control and Prevention (US). Supra, note 114, and D Willms et al. Participatory aspects in the qualitative research design of phase II of the ethnocultural communities facing AIDS study. *Canadian Journal of Public Health* 1996; 87(Suppl. 1): S15- S25.

rests upon ethically dubious grounds suggestive of a potential for exploitation of participants' vulnerabilities and the creation of sharp community divisions along lines of class and of health.

The point here is not to prescribe a pre-set program of "community development taxation" destined for use in HIV prevention, to be imposed upon pharmaceutical sponsors and governments involved in vaccine research. The actual procedures to be employed may vary widely from nation to nation and from one community to another. Instead, the important point is that choosing to conduct higher-risk experimentation upon human subjects who are themselves at relatively "higher" risk implies that researchers have already taken cognizance of the risk and have identified the people subject to it. In this circumstance, the ethical directives that can be universally applied to clinical trials of experimental HIV vaccines (do no harm, maximize benefits, reduce consequential harms, apply distributive justice to the sharing of burdens and benefits) require that research contribute to HIV prevention and that it address underlying causes of risk behaviours both for trial participants and for their community.

It is essential to emphasize that "at risk" individuals cannot look for some degree of protection from an experimental product of undetermined efficacy. This would be scientifically inaccurate and dangerous to public health, as it blurs the distinction between experiment and therapy. It must be kept in mind that vaccine efficacy (whether for susceptibility or infectiousness) is not confirmed until after completion of the Phase III trial and the analysis of the data it generates. This is all the more important in that trials will involve a placebo arm and are double-blind. All participants must be advised of the necessity of continuing to practise "safer" preventive behaviours.

It is also essential to emphasize that the benefits of participation in a clinical trial of a preventive vaccine are much less personal in nature than the benefits that might accrue from participation in a clinical trial of an experimental therapeutic drug. In the latter case, the pre-existing standard of care (if one exists) is available in both the test and placebo control arms of the study. The experimental therapy is merely incrementally added to the test arm such that both arms potentially offer considerable therapeutic benefit against an illness afflicting the research subjects.

In contrast, the less personal benefits available to participants in a clinical trial of a prophylactic HIV vaccine would include:

- helping to advance basic scientific knowledge;
- contributing to the eventual development of an HIV vaccine;
- making a positive contribution to development of community health infrastructures; and
- accessing periodic prevention services and other health promotion initiatives (eg, hepatitis vaccines).

Even the possibility of helping to develop an eventual successful vaccine provides relatively little immediate or direct benefit to the participants. Phase I through III clinical trials can take place over a period of 10 years or more. Data analysis, government approval, manufacturing and marketing, and provincial government/public health decisions determining what segment of the population will be vaccinated may require at least another three to five years. Thus, the next generation will reap the benefit of a successful vaccine, but it is the participants in the clinical trial today who are at risk of contracting HIV and are in immediate need of preventive support.

Awareness of one's own personal risk factors for HIV infection and of the impact that the epidemic is having on one's community may provide a strong motivation to volunteer for a vaccine clinical trial. However, care must be taken to separate the understandable but unrealistic desire for immediate protection from the more realistic desire to advance science and community knowledge. The latter may facilitate the future development of a vaccine that may someday help to alleviate one's own personal level of risk. Scientific integrity will be protected by emphasizing that clinical trial participation cannot be looked to for a protective advantage. Moreover, the legal and ethical requirements of free and informed consent will require that this point be made clear at the moment of recruitment and throughout the trial. It will also require that risks, including the relatively "higher" levels of risk associated with some candidate vaccines in comparison with others, be fully disclosed.

II The Canadian Regulatory Framework As It Pertains to Submissions to Conduct Clinical Trials on Candidate Vaccines

Could a clinical trial of an experimental HIV vaccine present any real risks of harm if conducted in Canada? Can we count upon governmental and professional authorities, research ethics boards, and upon market forces to screen out any research project that would potentially subject research subjects to unethical risks of harm? In this section, we examine the present systems that were conceived to protect research subjects from undue harm.

A. Approving Clinical Trials: The Current State of Federal Law

In Canada, all clinical trials of drugs (including trials of preventive vaccines) must be submitted for pre-approval to the Therapeutic Products Program ("TPP") of Health Canada pursuant to the *Food and Drugs Act*[190] and its accompanying Regulations.[191] The TPP is charged with ensuring that clinical trials are properly designed and undertaken and that participants are not exposed to "undue" risk.[192] The TPP currently reviews the safety, efficacy, and quality data submitted by the sponsor and approves the distribution of the experimental drug or vaccine to the investigator. The TPP may authorize the trial if the protocol is scientifically sound and the drug or vaccine would not pose "unacceptable risks" to the trial participants.[193]

At the time of the writing of this paper, the Regulations do not require research ethics board ("REB") approval prior to the conduct of clinical trials in human subjects, although the TPP certainly encourages pharmaceutical companies sponsoring research to obtain such prior approval. Under the current federal legislation and regulations, there is no national system for accrediting REBs and no statutory recognition of the role of REBs.[194] This lack of definition means that Health Canada has no direct quality assurance with respect to REB monitoring of

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190 *Food and Drug Act*, RSC 1985, c. F-27 as amended.

191 *Food and Drug Regulations*. CRC 1978, ch. 870, as amended.

192 Regulatory Impact Analysis Statement. Regulations Amending the Food and Drug Regulations (1024: Clinical Trials). *Canada Gazette Part 1* 2000; 134(4): 227-60 at 227.

193 Ibid at 229.

194 Ibid at 229.

clinical trials. It should be noted, however, that some provincial laws, regulations, and policies have defined REB composition, and some of their roles, powers, and responsibilities.[195]

In addition, the current *Food and Drugs Act* Regulations do not incorporate defined rules of generally accepted good clinical practice for the conduct of clinical trials in this country. Health Canada has merely a suggestive power in this sense. Nor is there any standard mechanism for routine powers of inspection of clinical trial sites to ensure that good clinical practice is in fact being applied. The Auditor General of Canada recently issued reports expressing concerns about the lack of a such an inspection system.[196] Much of this however is about to change with the adoption of new regulations scheduled to take effect in the fall of 2001.[197]

B. New Federal Regulations and Their Impact on Vaccine Clinical Trials

Amendments to the Regulations of clinical trials under the *Food and Drugs Act* were proposed in early 2000, then reviewed, amended and finally adopted in June 2001. These are the first important substantive amendments to the regulation of clinical trials in this country in 40 years. The new regulations take effect on 1 September 2001. Included among the revisions are:

- All clinical trial applications (phases I, II and III) will be evaluated under a 30-day default system. The TPP will implement a seven day administrative target for phase I trials, however prophylactic vaccines will not be included in this administrative target. Under the 30 day default, approval of a drug for clinical trial is automatically presumed if the TPP has not analyzed and refused the application within that delay.

- The incorporation of standards of good clinical practice into the design and conduct of clinical trials as well as into the ethics review of the protocol and informed consent;

- An inspection system to permit on-site examination of clinical trials to ensure that they are respecting standards of good clinical practice and complying with the approved scientific protocols ; and

- A legislative definition of the role to be fulfilled by REBs in the approval of clinical trials extending to them a limited legal authority of review and ultimate approval of the ethical

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195 *Civil Code of Québec*, art. 21 which requires ethics committee approval when an experiment is to be conducted upon subjects who are "groups of minor persons or incapable persons of full age." See also A Jean et al. *Éthique de la recherche et en integrité scientifique*. Québec: Ministère de la Santé et des Services sociaux, 1998.

196 M Barrados et al. Other Audit Observations: National Defense and Health Canada: Non-compliance with conditions and inadequate monitoring with respect to the pre-licensing use of an anti-malarial drug. *Report of the Auditor General of Canada*. Ottawa: Government of Canada, April 1999. See also Implementing Health and Safety Regulatory Programs. In *Report of the Auditor General of Canada.* Ottawa: Government of Canada, December 2000, at ch 24: Special Insert.

197 Regulations Amending the Food and Drug Regulations. (1024: Clinical Trials). SOR/2001-203. *Canada Gazette Part II* 2001; 135(2): 1116-29, at Art. C.05.001: 1117.

content and standards of both scientific protocols and consent forms *prior* to commencement of clinical research. Requirements concerning the composition of an REB are also set out and they include provision for at least "one member knowledgeable in ethics," one member knowledgeable in Canadian laws relevant to the research proposed, and one member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the sponsor or the site where the clinical trial is to be conducted.[198]

1. Role of REBs

REB approval of vaccine clinical trials will now be recognised in legal regulations. Under the new regulations, REB approval will not be required prior to applying to the TPP for scientific review, but it is required prior to commencing all clinical trials (Phase I, II and III). Consequently, TPP review can proceed concurrently with an REB review.

Initial proposals to require REB approval prior to submission of an application to the TPP have been dropped. Thus, although REB approval will be a necessary pre-condition to clinical vaccine research, its relative independence from regulatory scientific review is preserved. Spokespersons for REBs seem to have interpreted this carefully preserved chronology (TPP first, REB second) as preventing an undesired transfer of legal regulatory responsibility to the shoulders of REBs. Industry stakeholders also objected to any proposal to first obtain REB approval before submitting protocols to the regulator. [199]

But this legal demarcation is potentially troublesome and somewhat tenuous. Until now, ethics committees have normally exercised a review and monitoring function, reporting to the Board of Directors of the research institution in which the trial is carried out. Ultimate legal approval rested with the TPP. Under the new regulations, the REB receives official federal regulatory recognition as "a body that is not affiliated with the sponsor, and the principal mandate of which is to *approve* the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to *ensure* the protection of their rights, safety and well-being…" [emphasis added][200]

The new regulations also require the ethics board to provide the sponsor with signed attestations to the effect that they will uphold standards of generally accepted principles of good clinical practice in their deliberations. The sponsor is required by regulation to ensure that these undertakings are obtained. REBs now have a regulatory authority to "approve" scientific protocols and consent forms; research cannot proceed without this approval. The law rarely accords such privileges of power without also exacting correlative obligations and responsibility. Henceforth, it may be unwise to assume that REBs can shelter behind the civil responsibility of

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198 ID. Note: For a complete understanding of the amendment process, the reader should consult the first version of the proposed amendments published in Regulations Amending the Food and Drug Regulations. (1024: Clinical Trials). *Canada Gazette Part I* 2000; 134(4): 227-60. And cf. this with the final approved version of the amendments to take effect on 1 September 2001, published in: Regulations Amending the Food and Drug Regulations. (1024: Clinical Trials). SOR/2001-203. *Canada Gazette Part II* 2001; 135(2): 1116-29.

199 Regulatory Impact Analysis Statement. Supra, note 132, at 1146.

200 Regulations Amending the Food and Drug Regulations. Supra, note 197, at Art. C.05.001: 1117.

the boards of directors which appoint them and the professional responsibility of the principal investigator.

This prescribed chronology leaves the REB to interact independently with the pharmaceutical sponsor and principal investigator. This will place considerable pressure on the REB to rapidly complete its ethics review without requesting too many changes, since it will be the last remaining gate keeper along the path leading to the start-up of clinical research.

This may not be the best way of proceeding given that the testing of an HIV vaccine raises extraordinarily complex ethical issues. While ethical and scientific review are generally conducted independently of one another, they should not exist in a vacuum. Science can inform ethics and vice versa. Refusal is the most extreme form of REB reaction to a proposed protocol and consent form. But many areas of concern can be identified by an REB which can then issue recommendations to the sponsor and to the principal investigator to subtly adjust their study in order to take into account specific local factors and to minimise the harms and risks to participants and to maximise their benefits. The amended regulations suggest that the TPP will not accord indicative value to the ethics review process, but will only retroactively consider REB refusals to permit the research to go forward.[201]

A further troubling point lies in the fact that the amended regulations compress ethical review of research into a simple review of the scientific protocol and of the consent form – as though the latter in and of itself represented consent. This may reflect a legalistic view of the consent form as something designed primarily to shelter the sponsor and the principal investigator from civil liability. Ethics, however, takes a much broader view of the consent process, and the amended regulations do not reflect this.

The new regulations which proscribe experiments with candidate drugs that have the potential of "seriously endangering the life, health or safety of participants or other persons" – are sufficiently vague and flexible to allow room for a continued lively debate concerning the testing of "higher risk" experimental vaccines on participants who are themselves at relatively "higher risk" for contracting HIV. While the amended regulations will aid industry and REBs to find ethically appropriate standards of risks and benefits, the debate surrounding their application will remain critical to HIV vaccine research in Canada.

At this point in time, several key questions remain unanswered: How will REBs deal with the exercise of accentuated legal powers and the commensurately increased degree of civil responsibility potentially implicit in the exercise of their functions under new federal regulations? Where will the funding, resources, training, insurance and time be found in order to support REBs in the exercise of these newly recognised legal powers? How are REBs to conduct periodic reviews of on-going research? Will these changes ensure that the ethical and health interests of participants in HIV vaccine trials are well protected?

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[201] Regulations Amending the Food and Drug Regulations. (1024: Clinical Trials). *Canada Gazette Part I;* 134(4): 245-60, at Art. C.05.008 (d): 252. See also Regulatory Impact Analysis Statement. Supra, note 132, at 1146.

2. Role of Generally Accepted Principles of Good Clinical Practice

As indicated above, the new regulations require that generally accepted principles of good clinical practice be the standard of practice in the design and conduct of a clinical trial. Initial proposals to define good clinical practice with respect to international or domestic codes of ethics were struck from the final version of the regulations. Instead, the principles of good clinical practice (as set out in the accompanying Regulatory Impact Analysis Statement) are now sufficiently broadly framed to allow for a continued debate concerning the evaluation of clinical trials of candidate HIV vaccines and in particular those that might present potentially elevated risks.[202]

Given the preventive as opposed to therapeutic purpose of a prophylactic vaccine, it is somewhat difficult to apply principles developed for research within the framework of the clinical practice of medicine to a clinical trial of such an HIV vaccine. Nevertheless, some of the principles of good clinical practice outlined in the new regulations and analysis statement are particularly pertinent to the risk-benefit analysis in a proposed vaccine trial. These principles are as follows:

- Clinical trials must be conducted in accordance with good clinical practices and the applicable regulatory requirement(s);[203]
- Before a trial is initiated, foreseeable risks and inconveniences must be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks;[204]
- The rights, safety and well-being of the trial subjects are the most important considerations and must prevail over interests of science and society; [….];[205]
- The clinical trials must be scientifically sound and clearly described in a protocol;[206]
- The clinical trial is conducted, and the drug [vaccine] must be used, in compliance with the protocol; and [the regulations];[207]
- For each clinical trial site, the approval of a research ethics board is obtained before the clinical trial begins at the site;[208]
- Written informed consent, given in accordance with the applicable laws governing consent, is obtained from every person before that person participates in the clinical trial but only after that person has been informed of

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202 Regulations Amending the Food and Drug Regulations. Supra, note 197, at Arts. C.05.001, C.05.010: 1117, 1123. See also: Regulatory Impact Analysis Statement. Supra, note 132, at 1132-33.

203 Regulations Amending the Food and Drug Regulations. Supra, note 197, at Art. C.05.010: 1123-24. See also Regulatory Impact Analysis Statement. Supra, note 132, at 1132-33. Note: The RIAS describing the first version of the proposed amendments to the regulations defined GCP with reference to *the Declaration of Helsinki*, whereas the adopted amendments contain no such reference to an external code of ethical conduct.

204 Regulatory Impact Analysis Statement. Supra, note 132, at 1132.

205 ID.

206 Regulations Amending the Food and Drug Regulations. Supra, note 197, at Art. C.05.010 (a): 1123.

207 Ibid, at Art. C.05.010 (b): 1123.

208 Ibid, at Art. C.05.010 (d): 1123.

(i) the risks and anticipated benefits to his or her health arising from participation in the clinical trial, and

(ii) all other aspects of the clinical trial that are necessary for that person to make the decision to participate in the clinical trial;[209] and

- The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.[210]

One problem, however, is that there is a considerable discrepancy between the content of the Regulatory Impact Analysis Statement and the new Regulations. The standards of good clinical practice defined in the actual legal text are not nearly as extensive or as rigorously defined as those outlined in the analysis statement.[211] Relying upon the interpretative notes instead of the actual text of the Regulations to define these applicable standards is a relatively weak legal solution at best.

C. The Tri-Council Policy Statement

Other sources of guidance potentially applicable to a risk-benefit analysis of a request to conduct a vaccine clinical trial can be found in federal and provincial policies governing ethical review of research in Canada.[212]

In 1999, the National Science and Engineering Research Council of Canada, the Medical Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada, jointly issued a statement setting guidelines for research involving human subjects. Known as the Tri-Council Policy Statement, it sets out a broad framework of universal rules governing the ethical conduct of research involving humans.[213] This statement is a policy and does not have the force of law. Written for three broadly different disciplines, it has been criticized as being so general as to lack substantive content. Nevertheless, it attempts to set out threshold ethical guidelines that must be met before funding can be obtained from any of the nationally funded councils.[214]

Pertinent extracts from the Tri-Council Policy Statement concerning individual risks and participation in clinical research are set out below:

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[209] Ibid, at Art. C.05.010 (h): 1124.

[210] Regulatory Impact Analysis Statement. Supra, note 192, at 230.

[211] Regulations Amending the Food and Drug Regulations. Supra, note 197, at Arts. C.05.001, C.05.010: 1117, 1123. See also Regulatory Impact Analysis Statement. Supra, note 132, at 1132-33.

[212] Medical Research Council of Canada. Supra, note 76. See also A Jean et al. Supra, note 195.

[213] Medical Research Council of Canada. Supra, note 76.

[214] Ibid, at Goals of the Policy; Context of an Ethics Framework; Section 1: Ethics Review (A) Research Requiring Ethics Review (Art. 1.1).

> **Article 1.1a** All research that involves living human subjects requires review and approval by an REB in accordance with this Policy Statement, before the research is started….
>
> The standard of minimal risk is commonly defined as follows: if potential subjects can reasonably be expected to regard the probability and magnitude of possible harms implied by participation in the research to be no greater that those encountered by the subject in those aspects of his or her everyday life that relate to the research, then the research can be regarded as within the range of minimal risk. Above the threshold of minimal risk, the research warrants a higher degree of scrutiny and greater provision for the protection of the interests of prospective subjects.
>
> **Article 1.6** The REB should adopt a proportionate approach based on the general principle that the more invasive the research, the greater should be the care in assessing the research.
>
> **Article 2.4** Researchers shall provide, to prospective subjects or authorised third parties, full and frank disclosure of all information relevant to free and informed consent. Throughout the free and informed consent process, the researcher must ensure that prospective subjects are given adequate opportunities to discuss and contemplate their participation.… [R]esearchers or their qualified designated representatives shall provide prospective subjects with the following: […]
>
> **c.** A comprehensive description of reasonably foreseeable harms and benefits that may arise from research participation….[215]

The Canadian research councils are not risk adverse, but they do attempt to circumscribe and manage risk. The required evaluation of "minimal" risk is linked to the probability and the magnitude of potential harm that participants encounter in those aspects of their everyday life that relate to the subject matter of the research. At first glance, then, acute levels of personal risk of contracting HIV appears to be a relevant factor in defining acceptable levels of risk for approval of a vaccine trial.

However, HIV vaccine research must be distinguished from clinical therapeutic research. The risk of contracting HIV is rooted in behaviour, and behaviour can be changed. Risk-taking sometimes reflects underlying psychosocial factors and pre-existing medical conditions (eg, mental health, substance use, etc.), but these too can be addressed. Therefore, care must be taken to ensure that a vaccine trial provides participants with risk-reduction counselling and, where indicated, with referrals to health and social services. If effective, these interventions can be expected to reduce the risk of contracting HIV in everyday life. This in turn must be taken into consideration when evaluating the upper level of "minimal risk" acceptable in a vaccine trial.

HIV vaccine trials recruit from particular communities and social groups. They pose potentially unique psychosocial risks to the participants (eg, discrimination on multiple fronts, positive testing for vaccine immune response, false positive interpretation of testing for HIV antibodies, etc). Given that the correlates of successful immune protection are not yet fully defined and that

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[215] Ibid.

some of the most promising vaccine technologies are new, there will also be uncertainty surrounding the potential for medical risks to participants' health. Certain experimental vaccines may present a higher than "minimal" probability of medical and psychosocial adverse events. According to Article 1.1(a) of the Tri-Council Policy Statement set out above, when risks arising from clinical trial participation exceed "minimal" levels, the research must be subject to much more rigorous scientific and ethical scrutiny and monitoring. Given the new technologies used to make many candidate vaccines, it is very likely that HIV vaccine clinical research will almost always involve more than minimal risk. The funders also require that the protocol contain express provisions (eg, support and compensatory mechanisms) dedicated to the protection of the participants.

Section 7 of the Statement endorses the need to respect the principle of equipoise as a prerequisite to clinical research. The principle requires that clinical trials, at their point of departure, maintain "the genuine uncertainty about the comparative therapeutic value of each arm" (i.e.- placebo vs experimental drug in a clinical trial). But it also holds that people "should not be disadvantaged as a result of their participation in the research."[216] This means that people in both arms of the trial must have access to the existing standard of care.

The therapeutic element is largely absent from a clinical trial of a preventive vaccine. But the prominence given to the principle of equipoise in the Policy Statement nevertheless implies that rigorous, state-of-the-art, effective counselling for HIV risk reduction must be available to participants in both arms (vaccine and placebo) of a trial. For all practical purposes, in matters of HIV prevention, this is the current clinical standard of care. This work naturally includes an assessment of the subjects risk and at least some preliminary identification of the factors contributing to that risk. This in turn may lead to an identified need for referrals to ancillary health and social services. These services are particularly important in a vaccine cohort because people are recruited precisely because they are at relatively high risk for contracting HIV and because the consent form requests that they access HIV testing through the cohort and refrain from seeking testing elsewhere. In the context of a trial of a "higher risk" candidate vaccine where the subjects are recruited because they are at commensurably "higher" levels of personal risk, the obligation to provide counselling and referrals with adequate follow-up is simply more acute. In phase III efficacy trials, statistical compensation for the resulting risk reductions will have to be found by increasing the size of the cohort.

D. Risk, the Design of Vaccine Clinical Science, and Its Regulation: Conclusion

The ethical need to minimize harms to participants and maximize the benefits of research implies a dynamic and correlative relationship between ethical principles and the procedures that actualize them. Thus, as potential risks to participants increase, so should the efforts deployed to protect them and to contain and compensate for harm should it occur.

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[216] Ibid, at Section 7, Clinical Trials, sub-Section A: Clinical Equipoise. See also World Medical Association. Supra, note 101, at Arts. 5 and 29.

In matters of HIV vaccine research, the index of uncertainty with respect to potential harms will be greatest in Phase I trials, where protocols should undergo rigorous scientific review. However, Phase II and III trials are not devoid of risks. Evaluation of the safety of the experimental preventive vaccine is an important objective in every phase of research. The ethical analysis of risks and benefits must take place before each and every phase of clinical research. Moreover, Phase I, II and III vaccine clinical trials will involve human subjects who are HIV-seronegative and usually fairly young. With such a cohort, the quantity of damages, should they arise, is potentially larger than would be the case in a cohort of older patients involved in clinical trial research for a therapeutic drug. Moreover, the countervailing "benefits" of participating in a vaccine clinical trial are relatively weak, given the non-therapeutic objectives of preventive vaccine research. Subsequent sections of this paper will discuss how researchers can use creative means to partially redress this potential imbalance in the risk benefit ratio.

Regulators at Health Canada are working under very strict time constraints that are about to become even stricter. Although clinical experiments of HIV vaccines are exempted from 30-day default approval, it is likely that the regulator's culture of accelerated approvals will have some impact on the approval of vaccine trials. Steps have been taken to incorporate ethical approval, and the procedures of good clinical practice through which ethical principles can be applied, into the legal requirements for the assessment, approval, and conduct of clinical trials in Canada. However, the statutory definition of the substantive content that the law ascribes to this ethical analysis remains nebulous. It will have to be interpreted with reference to the record of common law and civil law jurisprudence, doctrine and ethical guidelines surrounding questions of human experimentation and voluntary, free, informed, and comprehending consent thereto.

When the new regulations are implemented in September 2001, research ethics boards will receive legally delegated responsibilities by which they will become a kind of legal gatekeeper to research. Given the highly competitive world of research funding, the increasing partnerships between industry and academic researchers, and the relative lack of resources, time, and training facing Canadian REBs, one can legitimately wonder how effective the REBs will be at exercising this new legal power. Leaders in communities targeted for HIV vaccine research will want to develop an expertise in interpreting protocols and consent procedures. Communities will need to develop working relationships with ethicists and patient advocates who are members of REBs in order to ensure that their unique cultural viewpoints are considered and understood. This understanding will help facilitate a better quality of risk-benefit analysis.

PART 2: CLINICAL TRIALS

I Working with Target Communities

This section analyzes an important element of vaccine clinical research, namely the involvement of communities in clinical trials and the mutually beneficial relationship between community-based HIV prevention and vaccine clinical science. It states the case for development of a close relationship through which both communities and researchers understand and support each other's work.

The section then proceeds to examine one model for community involvement, namely the Community Advisory Board (CAB). It highlights the strengths and weaknesses of this model with reference to the missions of CABs currently operating in Montréal and in Vancouver for the AIDSVAX B/B Gp 120 Phase III clinical trial. Brief mention is made of some of the other measures vaccine researchers employ in order to facilitate community involvement. The section concludes with basic recommendations designed to encourage strong partnerships between clinical researchers and target communities.

A Why Is Community Participation Important and Imperative in All Phases of Vaccine Trials?

There are four central arguments in favour of building collaboration between community-based HIV prevention and vaccine clinical science:

- The first considers the potential for vaccine trials to generate an undue optimism and premature confidence in the community. This might inadvertently lead to a de-emphasis of the real risk HIV poses to the community's public health.
- The second argument is founded upon the ability of community involvement in a given clinical trial to help develop a lasting capacity among researchers (including, potentially, researchers drawn from within the community) to review and conduct ethical vaccine research. Moreover, such expertise will inevitably be of help in future, when the time comes to meet the daunting challenges of vaccine delivery.
- The third acknowledges the rich potential for a supportive and mutually reinforcing relationship between vaccine clinical research and community-based research initiatives.

- The fourth argument in support of community involvement in vaccine clinical research is an extension of the previous two. In essence, it points to the ability of a clinical trial to act as a catalyst for overall community development.

These arguments will be examined in detail below.

1. Why is Community Involvement Important?

Stating a broad general principle of community involvement in research, Dr Charles Weijer, bioethicist at Dalhousie University, Halifax, noted in a presentation made to Health Canada in May 1999 that community participation in all phases of research is important and imperative:

> [R]esearch often does not take into account that individuals are part of a large community or family.... [Rather, it] embraces an atomistic view of the person with little or no reference in policy to the individual's relationship to others or members of communities. This oversight leads to the need for a moral principle: "Respect for Communities." This principle confers upon the researcher an obligation to respect the values and interests of the community wherever possible and protect the community from harm. This principle is supported in arguments that people do not view themselves atomistically, but rather as members of communities that constitute their values and self understandings.[217]

This cultural and community contextualization of clinical research is even more imperative in the particular case of clinical trials of HIV preventive vaccines. The special circumstances of vaccine research that warrant increased community involvement are as follows: (i) volunteers are uninfected when they are recruited; (ii) aside from testing, the clinical trial offers no direct HIV-related clinical benefits; (iii) the timespan necessary in order to test a vaccine, identify and confirm its efficacy, and get it licensed, manufactured, and marketed is very long; and (iv) the trials will recruit participants from within communities where people at high personal risk of contracting HIV can be found.

Beyond issues of recruitment, community involvement in vaccine clinical trials implies numerous educational activities. Community leaders, journalists and HIV service organizations need to be informed about vaccine research. Those working in the specific field of HIV prevention will need to modify messages to acknowledge the existence of vaccine research in their community and to inform the public that clinical research today does not signify a proximate cure. They will also need to emphasize the necessary and synergistic relationship between a future licensed vaccine and sustained harm-reducing behaviours.

2. What Do We Mean By "Community"?

[217] C Weijer, EJ Emanuel. Supra, note 10. See also C Weijer. Protecting Communities in Research: Ethical Issues to the Continuing Education and Communication committee HIV / AIDS Policy, Coordination and Programs Division Health Canada. Unpublished summary of presentation. 29 May 1999.

This is one of the thorniest questions that researchers will face when organizing large-scale efficacy trials. While a persuasive case can be made for community involvement at every phase of the trial, defining that community, the extent of its collective interests, and its role in vaccine research can be problematic.

> The term "community" delineates a wide variety of human associations, from tribes to municipalities to religious adherents. A single set of regulations to fit all types of communities is doomed to failure. What is needed are morally relevant criteria that distinguish communities. Characteristics of particular importance and relevance to communities in biomedical research can be identified.[218]

As evidenced by the citation above, authors Weijer and Emanuel propose a Cartesian analysis in which different communities are classified by characteristics relevant to biomedical research.[219] "Communities can be arrayed along a spectrum of cohesiveness, from those that have all the characteristics to those that have only a few."[220] The authors then present community involvement in research as a kind of ethical protection of the legitimate interests of the collectivity, including the community's culture, dignity, and public health. Protections for communities thus depend on their characteristics. Weijer and Emanuel believe that "three general regimes of protection can be delineated, based on the specific protections appropriate to the distinct types of communities: (i) community consent and consultation; (ii) community consultation alone, and (iii) no added protections."[221] According to this plan, those communities with the highest degree of cultural cohesion will merit the greatest degree of "protective" involvement in clinical research.

One difficulty with this analysis, however, is that it implies that strong communities with strong institutions of community leadership and democracy merit protection, while weaker ones do not. Yet there are many communities currently struggling to emerge from an oppressive environment or history that have yet to develop a full spectrum of specific political and cultural institutions. Ironically, it is these latter nascent communities that may be in a much more fragile position and in greater need of research skills building and overall development. Partial community development is characteristic of many of the communities affected by HIV and AIDS in Canada that are likely to be targeted by recruitment campaigns for vaccine trials. Moreover, Weijer and Emanuel's approach seems to downplay the potential role for clinical research to help protect the weakest and most vulnerable communities and to contribute to their development.

Communities can be delineated according to a multitude of different criteria, including language, ethnicity, common health concerns, or even participation in a given type of clinical trial. We will return to this difficult question in greater detail when we examine the meaning ascribed to the word "community" in "community advisory board." At this point, we merely ask the reader to

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218 C Weijer, EJ Emanuel. Supra, note 10.

219 Ibid at 1142. Note: The characteristics chosen by Weijer and Emanuel for types of communities in biomedical research are: common culture and traditions, canons of knowledge and shared history; comprehensiveness of culture; health-related common culture; legitimate political authority; representative group/individuals; mechanism for priority setting in health care; geographic localization; common economy/shared resources; communications network; and self-identification as community.

220 Ibid.

221 ID.

keep in mind that benefiting a community through research will run up against problems of definition, leadership, and finding common interests.

3. What Do We Mean By "Community Involvement"?

Care should be taken to differentiate between community information, review, and involvement.

Whereas *community information* is a passive process of collective information dissemination concerning HIV vaccines (eg, a media strategy for diffusion), *community review* can range from little more than informal dialogue between researchers and members of the study population to negotiation of a formal agreement between researchers and the study population. A defining feature of community review is that it actively involves members of a study population in the evaluation of proposed research.[222] *Community involvement* is a mobilization of a community-wide response. This response advocates for HIV vaccine research; supports and values clinical trials; monitors and evaluates the impact of such research upon HIV prevention; gives voice to community priorities and preconditions for participation in clinical research; strives to ensure the protection of vulnerable subjects and their communities; and takes steps to plan for the delivery of an eventual vaccine.

Community involvement has been proposed as a supplemental protection of human research subjects.[223] This is because representatives of the target population can act as key informants helping researchers identify and minimize risks of harm specific to the community and also those applied against the community by external forces.

4. The Relationship Between Vaccine Clinical Trials and Collective Risk Assessment

The principle of community involvement in HIV prevention as well as in the fields of care, treatment, and support for people with HIV was established long before the advent of HIV vaccine clinical trials. In North America, this principle partially results from the early engagement of volunteerism within relatively marginalized communities, such as gay men. This volunteerism filled gaps in services that were initially slow to respond and hesitant in the face of an unknown and therefore feared pathogen. Drawing upon the experience of the civil rights movement, early advocacy on behalf of people living with and affected by HIV and AIDS was closely allied with the fight for civil rights for gay people.[224]

Beyond these historical roots, community involvement in HIV work must attempt to keep in step with the evolving epidemiology in North America if it is to remain relevant and influential. HIV infection is largely determined along networks of people engaging in risk behaviours (sexual

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[222] RR Sharp, MW Foster. Involving Study Populations in the Review of Genetic Research. *The Journal of Law, Medicine & Ethics* 2000; 28(1): 41-51.

[223] Human Genome Diversity Comittee. *The Human Genome Diversity Project: Summary Document*. London: Human Genome Organisation, 1994. Note: the document recommends that participation of study populations be a mandatory supplement to existing human subjects protections.

[224] C Levine et al. Supra, note 53, at 4.

relationships and needle sharing). Within these networks, high levels of risk assumption can occur for a variety of reasons. In addition to the obvious factor of seroprevalence, there are a number of conditions specific to communities and social groups (eg, cultural, urban, environmental, social, economic, and legal conditions) that can act cumulatively to increase vulnerability to infection.

HIV prevention is focused upon trying to induce sustained preventive behaviour modification and harm reduction within these widely diverse communities. But to support and sustain individual behaviour modification, prevention must also induce change on a collective level. Here, the objective is to incite community awareness so that an accurate collective risk assessment results. Thus, prevention works with both HIV-positive and HIV-negative people seeking to inculcate collective non-discriminatory values of mutual support and responsibility.

HIV vaccine trials and eventual delivery of a vaccine might influence not merely the research subjects but also their communities. Quantitative epidemiology can identify changes in collective risk assessment and assumption. Already preliminary inquiry at the Oméga research cohort in Montréal has shown than that ten percent of respondents report that the availability of a relatively efficient vaccine could incite them to abandon safer sex.[225]

Qualitative psychosocial research is however needed to identify the factors motivating such changes and their relative importance. One key challenge will be to measure the influence (if any) that a generalized optimism (induced at least in part by the existence of vaccine-trials) might exert upon collective cultural support for preventive behaviours. In attempting to answer these questions, researchers are looking at the impact of present day HIV treatments on risk assessment and assumption as a close analogy.[226] Information presented at the XIII International AIDS Conference held in Durban, South Africa in July 2000 failed to demonstrate "clear and universal trends" (at least on a global scale) concerning potential revisions in risk assessment among gay and homosexually active men, hypothetically resulting from treatment optimism and information concerning vaccine trials.[227]

But in specific cities in the developed world, including some in Canada, clear evidence of recent increases in seroincidence among men who have sex with men is beginning to emerge. This is despite relatively high levels of basic HIV/AIDS awareness.[228] Researchers will want to investigate many hypotheses that might explain this observed phenomenon:

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[225] J. Vincelette et al. Croyances des participants de la cohorte Oméga au sujet de l'essai vaccinal du AIDSVAX B/B. IXth Annual conference of the Canadian Association for HIV Research. Abstract no 332P. Montréal, May 1998. Published in *Canadian Journal of Infectious Diseases* 2000; 11(Suppl. B): 62b.

[226] S. Kippax et al. Supra, note 10.

[227] P Aggleton. Rapporteur's Report. Track D, Social Science, of the XIIIth International AIDS Conference. Durban, South Africa. 14 July 2000.

[228] LA Balleroy et al. HIV Prevalence and Associated Risks in Young Men Who Have Sex with Men. *The Journal of the American Medical Association* 2000; 284(2): 198-204. See also S Russell. San Francisco's long-feared and often predicted new wave of HIV infection is here. *The San Francisco Chronicle* 30 June 2000; A summary of a report released by the San Francisco Department of Public Health reporting that 11 public health surveillance indicators point to increasing rates of HIV infection from 1997 through 1999, and RS Hogg et al. Increasing incidence of HIV infections among young gay and bisexual men in Vancouver. *AIDS* 2001; 15(10): 1321-22.
And, Health Canada. *HIV/AIDS Epi Update: Recent data indicate HIV infections are rising in Canada among men who have sex with men.* Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, November 2000, and R Voelker. Supra, note 100, and D Brown. HIV on rise in young gay men: Black males infection rate especially high in possible "resurgent epidemic." *The Washington Post* 1 June 2001: A01.

•In some settings, it might be the result of accumulated "AIDS fatigue," manifested by relapses to higher frequencies of unsafe behaviours and a cumulative fatalism over time.

•Relapses to higher frequencies of unsafe behaviours may mean that what Susan Kippax terms the commonly used "precisely gauged strategies" [of negotiated harm reduction] do not reflect a statistically sound assessment of risk.[229]

•In some settings, increasing seroincidence may reflect the inability to encourage health promotion and harm reduction among "difficult to reach" subsets of the population.

•Increasing seroincidence among men who have sex with men may also reflect a subconscious but common perception that HIV is less threatening because treatments render AIDS less visible. Antiretroviral therapies delay the onset of opportunistic infections and attenuate disease morbidity, prolonging life. Prior to 1996, HIV was already a disease with a long asymptomatic phase. Therapies have potentially lengthened the delay between initial infection and clinical onset of disease to the point where it now spans more than a generation. Better treatments and prophylaxis of opportunistic infections as well as basic hormonal therapies have helped to postpone and diminish the visible indications of AIDS (eg, Kaposi's sarcoma, wasting syndrome). As AIDS extends its timeline, it becomes less sudden, less surprising, and less visibly stark.

•When successful, antiretroviral therapy lowers viral load in blood. The quantity of virus present in seminal fluids also declines in approximately 60 percent of patients who experience a lower viral load in the blood. This may lead some HIV-positive individuals to conclude that they are less infectious and therefore that the need for preventive behaviours is less urgent.[230]

•Moreover, HIV-positive people who respond well to treatment are living longer and in better health. Overall seroprevalence in the community therefore increases. Thus, "in the context of at least some continued risk behaviour, [this] would result in greater chance of encountering an infected partner, and hence becoming a sero-converter."[231]

•Finally, antiretroviral therapies, post-exposure prophylaxis, and vaccine research may collectively send a message to vulnerable populations that a cure or at least a chronic control of HIV disease is just around the corner. Undue optimism and false hope may encourage people to be less cautious because the probability of infection will be underestimated and the consequences of AIDS will be perceived as less severe.[232]

Reports of HIV transmission rates in North America among gay men and young gay men in 1999 and 2000, now provide increased co-incidental evidence to suggest a possible cause and effect

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229 S Kippax et al. Supra, note 10.

230 SJ Misovich et al. Belief in a Cure for HIV Infection Associated with Greater HIV Risk Behaviour Among HIV Positive Men Who Have Sex With Men. *The Canadian Journal of Human Sexuality* 1999; 8(4): 241-8.

231 L Calzavara et al. Increasing HIV incidence among MSM repeat testers in Ontario, Canada, 1992-1998. Oral Presentation at the XIII International AIDS Conference. Durban, South Africa, 13 July 2000. Abstract no ThOrC718.

232 K JP Craib. Supra, note 15.

relationship between the introduction of protease inhibitors in combination therapies and a subsequent reduction in vigilance by gay men in some cities. At the very least, research exists in Canada which demonstrates that the existence of therapies has the capacity to encourage a greater number of persons to believe that AIDS will eventually become a chronic disease.[233]

Information presented at the XIII International AIDS Conference in Durban, South Africa suggests that there is a continued need for careful *local* monitoring of sexual practices and a further need for sharing of information concerning successful prevention techniques.[234] Thus, the issue of how to motivate populations to not only engage in effective harm-reduction behaviours but also how to sustain such behaviours over the long term, particularly in the face of news concerning new therapies is a subject that warrants in-depth and on-going investigation.

Similarly, we must inquire as to whether publicity for successive waves of vaccine efficacy trials might also engender substantial optimism and whether this optimism will in fact concretely weaken the collective's assessment of risk. And what would be the impact of the announcement of the discovery of a vaccine – even one that is only partly efficacious? If safer sexual and injection behaviors are no longer perceived as important, desired, expected and caring norms, then individuals may very well engage in higher risk activities. If the initial generations of HIV vaccines are only partially efficacious, the result of higher risk behaviours could be disastrous for public health.

In the meantime, clinical trials of HIV vaccines should proactively anticipate the problem and work closely with local prevention agencies to minimize such adverse feedback. Vaccine clinical trials should not and cannot ethically isolate themselves from these larger community issues. Instead, if appropriately structured, they can facilitate the community-based research that will help to answer some of the questions, thereby contributing to better HIV prevention.

In conclusion, there are widely divergent communities in Canada (many existing along the social, political, economic, and health-care margins of society) that will be targeted for vaccine research. Recent seroincidence studies in cities such as Toronto,[235] Vancouver,[236] and San Francisco [237] demonstrate that gains in prevention are tenuous, fragile, reversible, and subject to a wide variety of influences. Vaccine researchers must collaborate with the community to pre-emptively prevent nefarious impacts arising as a result of false or ill-informed optimism generated by the publicity surrounding their clinical trials. In order to accomplish this, as well as to secure popular ongoing support for vaccine research, development, and delivery, key

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233 J Otis et al. Sex between men in Montreal: The Omega Cohort: a report from the front. Conference given 9 November 2000. Concordia University lecture series on HIV/AIDS. Citing R Lavoie et al. Attitudes towards new HIV therapies among bisexual and gay men of a cohort study in Montreal: a longitudinal perspective. IXth Annual Canadian conference on HIV/AIDS research. Abstract no 470p. Montréal, April 2000. Published in *The Canadian Journal of Infectious Diseases* 2000; 11(Suppl. b): 88b.

234 P Aggleton. Supra, note 227.

235 L Calzavara et al. Supra, note 231. See also: Subsequent data produced by The Polaris Seroconversion Study. Supra, note 231.

236 K JP Craib. Supra, note 15. See also: RS Hogg et al. Supra, note 228.

237 W McFarland et al. Implications of highly active antiretroviral treatment for HIV prevention: the case of men who have sex with men in San Francisco. San Francisco Department of Public Health presentation at the XIIIth International AIDS Conference. Durban, South Africa, July 10 2000. Abstract no MoPpD1127. See also: R Voelker. Supra, note 100.

stakeholders must proactively and expansively involve community representation in every step of the timeline.

5. Vaccine Clinical Trials Can Also Serve to Build Research Capacity

There is already precedent in research guidelines for the notion that both sponsors and researchers may have some obligation to contribute to the development of the host community. Such guidelines generally highlight the need to develop an on-site capacity to conduct scientific research. In particular, they emphasize as a fundamental point of departure, an ability to undertake scientific and ethical review of research protocols.

For example, guidance point three of the UNAIDS Guidance Document *Ethical considerations in HIV preventive vaccine research* notes:

> Capacity building: Strategies should be implemented to build capacity in host countries and communities so that they can practise meaningful self-determination in vaccine development, can ensure the scientific and ethical conduct of vaccine development, and can function as equal partners with sponsors and others in a collaborative process.[238]

The notes accompanying this point identify a wide variety of factors that may lead to disparities in the balance of power and, hence, undue influence in the relationship between the host country and the sponsor. The notes propose that "development of an HIV vaccine will require international co-operative research transcending in an ethical manner such disparities" so that the ultimate relationship between host country (or community) and the pharmaceutical sponsor is a "collaboration among equals." The notes stop short, however, of assigning specific proportionate responsibility (eg, among sponsors, sponsor countries, research institutions, governments of host countries, communities, etc) for implementing the capacity-building strategies required to overcome these disparities.[239]

But disparities in the capacity to understand, review, and undertake clinical research do not only exist between pharmaceutical sponsors and target communities in developing countries. There also exists considerable developmental disparity within the developed North. In Canada, serious disparities in economic development, education, technical infrastructure, and health services are manifest when one compares disadvantaged minorities with the middle class. There are also geographic and structural impediments to accessing services and infrastructure when and where they do exist. These disparities divide along geographic, economic, racial, legal, and other lines. They have the potential to pose real barriers to the implementation of vaccine clinical trials. Canadian rural communities, geographically remote Aboriginal and First Nations reserves; the homeless populations of the central streets of our largest cities, are all examples of communities

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238 Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Point 3, at 15.

239 Issues of disparity include: weaknesses in the local economic capacity; underdevelopment of health services infrastructure; lack of community and cultural experience with research and a commensurate understanding of scientific research; lack of local political support for HIV vaccine research; underdevelopment of in situ technical supportive infrastructure; the absence of personnel and technical capacity for HIV prevention as well as for HIV health care and treatment.

where practical access to HIV prevention, research, and sophisticated health care is often sub-optimal.

In Canada, language is also an important factor influencing the speed with which influential multi-centre trials can induce research capacity within communities. Didactic materials, recruitment campaigns, retention strategies, dissemination of results, and concomitant prevention will all require translation and cultural adaptation if they are to be equally successful in French- and English-speaking Canada, in numerous Aboriginal communities, and in targeted ethnocultural communities.

However, care must be taken to prevent infrastructure and economic disparities from becoming an automatic and perpetual barrier to research. As discussed in the subsequent section of this paper detailing the legal and ethical issues pertinent to recruitment for vaccine trials, many of the barriers posed by such disparities are surmountable.

Guidance Point 6 of the UNAIDS ethical considerations states:

> HIV preventive vaccine trials should only be carried out in countries and communities that have the capacity to conduct appropriate independent and competent, scientific review. [240]

Here, however, the notes to the above point clearly point to an active developmental role for the sponsor:

> If the country's capacity for scientific and ethical review is inadequate, the sponsor should be responsible for ensuring that adequate structures are developed in the host country for scientific and ethical review prior to the start of the research.[241]

Clinical trials of HIV vaccines should take place in an environment in which capacity exists to comprehend, support, and conduct ethical and scientific clinical research. Partnerships must be formed between sponsors and host countries that facilitate mutual understanding and respect for different cultures and allow for development of in situ scientific and ethical competence. In this way, the parties involved in clinical research will overcome disparities through capacity building. A primary objective of such partnership should be sustainable development. In other words, the resulting structures (laboratories, human resources, etc) should be developed to provide durable community support and a permanent infrastructure capable of renewal, serving not merely the clinical trial at hand, but also subsequent research cohorts.

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[240] Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Point 6 at 21.

[241] Ibid, Notes to Guidance Point 6, at 21.

6. HIV Vaccine Trials Can Facilitate General Community Development

Here we look beyond contributions made for the specific purpose of developing the capacity to undertake scientific and ethical review of clinical vaccine research. We consider something that is more basic and much broader in scope – the development of general infrastructure capable of supporting community health services.[242] According to this perspective, one of the objectives of a clinical trial would be to attempt to leave the community in a better overall state than when it arrived. This philosophy is not merely founded upon the general arguments in favour of community involvement set out at the beginning of this section, but also upon certain key characteristics particular to HIV vaccine clinical research.

First, as mentioned above, vaccine research may inadvertently influence, on a conscious and subconscious level, both individual and collective risk assessment and assumption.

Second, to scientists, a clinical trial is a "success" if it can accurately prove or disprove the proffered hypothesis (eg, whether *or not* a candidate vaccine is safe and efficacious). Moreover, even if a Phase III clinical trial does not result in a licensable vaccine, it will at least generate a better understanding of safety, immunogenicity, and how to measure efficacy. Some of this information will foster the development of new and better therapies for people with HIV. However, the primary hope of the common citizen in the targeted community will be for development of a vaccine that can be delivered within the community. Unfortunately, this is by no means a certain outcome. We must anticipate the possibility of not finding a vaccine for years to come or – even worse – never finding an efficacious vaccine.[243] Given the as yet comparatively high index of uncertainty associated with the potential outcome of vaccine research, both researchers and communities will want to strenuously examine means of maximizing more immediate, tangible, and consistent benefits for all concerned, including target communities.

Third, unlike clinical trials of experimental therapeutic medication, vaccine trials cannot offer therapeutic pharmaceutical clinical benefits. Instead, they can offer their participants condoms, needles, counselling, and referral to ancillary medical and social services – things that in Canada should already be accessible elsewhere by publicly funded health care. Providing support for community development may therefore compensate for the relative paucity of options for direct benefits to cohort participants.

Fourth, the more organized and structured target communities in Canada will likely expect some tangible benefit in return for their support for vaccine research. It also makes sense for sponsors and researchers to build alliances with HIV-affected communities in lobbying for research subsidies. In return, communities will look for an invitation to invest (eg, time, energy,

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[242] Note: This could include contributions to such diverse factors as: physical infrastructure that will directly and indirectly improve public health (eg, the provision of clean drinking water), health promotion information and activities, harm reduction; HIV prevention; care, treatment and support for people living with HIV / AIDS; construction of laboratories and medical facilities; training of community leaders and health care professionals, work to promote the human rights of people living with HIV; etc.

[243] Note: Let us recall that the outcome of vaccine research is far from certain and delivery to a particular population at a particular point in time is even more difficult to predict. Vaccine development and delivery face a number of potentially important obstacles including: the diversity of HIV clades; the mutability of HIV; the epidemiology of HIV infection (in particular the potential interplay between seroincidence and vaccine efficacy); and the economics regulating distribution of health resources.

resources, media and support) in the research process, in order to determine how will the research benefit the community?

> This process of engagement will differ across communities and studies and goes beyond delivery of objectives and data to communities. Attention to process and inclusion will be key to a successful and genuine partnership […].[244]

Fifth, if the prevailing systems distributing health care, health promotion, and HIV-related services remain unchanged, then HIV epidemics may, in some nations (and in some communities within Canada), run a mostly uninhibited course. Given the amplitude of the problem HIV poses, and its potential to grievously affect populations in many parts of the world, it makes sense to use a variety of governmental, charitable, and community incentives and subsidies to promote a vigorous program of vaccine research.

Sixth, an important way to meet these expectations is to collaborate with communities in providing incremental improvements to local HIV prevention and health promotion. Given the long and imprecise timelines for vaccine research, development, and delivery, the generation of persons in the communities participating in clinical research today is unlikely to be the primary beneficiary of an ultimate vaccine. Host communities struggling with high seroincidence and an emerging epidemic will be interested in examining vaccine clinical research not merely for its ability to generate an eventual vaccine, but also for its potential to develop or enhance resources needed in the present-day war on HIV.

But what kinds of benefits could be put into place? Care must be taken to avoid the temptation to have recourse to consent-deforming personal incentives to compensate for a lack of direct benefits accruing from the scientific research. Hence, with collaboration between all key players, clinical trials might, in a tangential fashion, provide a framework for community development. Here the community should play a key role in defining its needs. One response permitting researchers to respect the principle of beneficence may be to use the opportunity provided by the clinical trial as a means of promoting overall HIV prevention. This is one obvious area where the expertise and resources of vaccine clinical researchers accord relatively well with needs in the community.

In a "developed" country such as Canada, community development efforts could focus upon matters such as: (i) vaccination campaigns; (ii) diagnosis and referrals to treatment of other morbidities, including STDs; (iii) HIV prevention; (iv) harm reduction, (v) health promotion; (vi) outreach to specific vulnerable communities; and (vii) increasing access to specialized health care – particularly for marginalized populations such as street-involved injection drug users.

In theory, clinical trials of experimental HIV vaccines may be able to contribute not merely a framework for development but also some of the required resources. This does *not*, however, imply that the role of clinical investigative science should be deflected from its principal purpose of conducting statistically credible, verifiable, reproducible, and useful scientific research. Clinical trials should not become "urban development agencies." They cannot, in and of themselves, provide a solution to the complex problems of health promotion, HIV prevention, and access to medications in developing nations. However, in making a meaningful and

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[244] S. Kirkendale. HPTN Approach to ensuring Community Involvement in Research. An unpublished draft document. North Carolina: HIV Prevention Trials Network, Family Health International, August 2000.

proportionate contribution to advance the cause of development, through the realization of reasonable, community-directed, attainable, socially sustainable and reproducible development goals, they can at least ethically position themselves to provide some immediate (as well as longer-term) benefits to affected populations.[245]

Holding HIV vaccine research to a standard whereby it contributes incrementally to the realization of "small attainable development goals" conforms to the grass-roots nature of community involvement. Moreover, acting on a modest, practical scale will prevent the issue of community development from becoming an inducement that deforms the free and voluntary nature of consent. This may be a particularly important consideration in cultures that place importance on the collective decision-making process.

7. Clinical Trials of Vaccines Can Facilitate Community Research Initiatives

Phase III vaccine trials recruit HIV-negative individuals vulnerable to HIV infection within targeted communities where seroincidence is relatively high. During the course of the trial, the participants undergo periodic testing for HIV antibodies, accompanied by pre- and post-test counselling. The clinical trial also conducts regular interviews with participants concerning risk behaviour during the periods between tests. When necessary, referrals are made to other health services.

In the event of seroconversion, prompt referrals to treatment are made, initial pre-treatment viral load is measured, and subsequent viral load may be monitored over an extended period.

Depending upon the specificity of the criteria used in the recruitment process, and if conducted with a sufficiently large number of participants on site, a vaccine trial could open a potential window to interesting psychosocial research into risk behaviours (assessment, assumption, motivations, and management) and related social conditions within different subsets of the cohort.

For example, because there exists a "popular" (but likely to be erroneous) initial public perception that an HIV vaccine will be a "cure" (eg,, a completely effective prophylaxis), clinical trials of HIV vaccines may tend to attract people who have hitherto been unable to effect harm-reducing behaviour modification. Vaccine trials may be well positioned to break new ground in developing an understanding of such difficult-to-reach segments of affected communities. The knowledge generated by the vaccine trial may enable local prevention agencies and health-care providers to establish links for service delivery to such subsets of the community. In multi-centre efficacy trials, however, this will only be possible if each site has a sufficiently large number of participants to generate representative and, ideally, statistically significant qualitative research data.

Phase III vaccine trials will also generate a potential cohort for research into the immune reaction during the primo-infection period. In addition, although pre- and post-test counselling and referral services should encourage volunteers to achieve and maintain harm-reducing behaviours, the vaccine trial may nevertheless (once unblinded) reveal a small cohort of people who received

[245] T Barnett. HIV/AIDS in Africa: Implications for "development" and major policy. XIIIth International AIDS Conference. Durban, South Africa, 10 July 2000. Abstract No. MoPeD502.

placebo, were repeatedly exposed to HIV, and yet remained uninfected. Scientists will be interested in this subset of the cohort for the study of rare inherent immunity against HIV.

If the participants' legal rights, ethical interests and, especially, informed consent are well respected, all of the above "sub-cohorts" should be of interest to affected communities. Community based research ["CBR"] involves studies initiated by and for community interests.[246] Community-based researchers may wish to use the opportunity and the underlying infrastructure generated by the vaccine trial to "add on" further research projects analyzing the determinants of risk in specific subsets of the cohort. The resulting increase in knowledge may be useful in generating better preventive interventions.

The relationship between community-dependent research and vaccine research can become a two-way opportunity. A number of disparate factors present in HIV and AIDS work in Canada today should come together to encourage both community researchers and vaccine clinical scientists to open further research opportunities to each other.[247] Integration of community-based psychosocial research into vaccine clinical trials may help the former overcome difficulties currently experienced in accessing scientific and ethical review of CBR protocols and consent procedures.[248]

This opportunity will, however, be substantially reduced if multi-centre trials involve so many sites that the participants recruited in each individual city are numerically too small to be able to generate statistically significant social science data. The Phase III clinical trial of the AIDSVAX B/B Gp 120 candidate vaccine counts between 87 and 105 people at each of the three Canadian sites (Montréal, Toronto, Vancouver).[249] These cohorts are too small to generate much useful information on their own. The differences in the gay and bisexual populations and the differences in the socio-economic conditions and sub-cultures that exist between each of these geographically distant cities will somewhat reduce the value of information generated by pooling data. Extending the pool even further to include US cities where politics, language, culture, economics, racial and ethnic composition, and health services are substantially different from that found in any of the three Canadian cities will further weaken the applicability of the results.

Finally, whenever it is proposed to overlay a new community research project on the pre-existing framework of a vaccine cohort, care would have to be taken to obtain the free and informed consent of vaccine trial participants, as well as the support of the community. If two research projects are to begin recruiting at the same, and if both are focused upon closely related objectives, it may be ethically acceptable to merge the two into the same consent process. Before

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246 T Trussler et al. *Knowledge from Action: Community-based Research in Canada's HIV Strategy*. Vancouver: AIDS Vancouver & Health Canada, 1998, at 5.

247 T Meyers. Advancing Science Through Community-Based HIV Research. Presentation at The Social Sciences and Humanities in HIV/AIDS Research: International Summer Institute Part Five. 26 May-5 June 1997, at 2. Meyers cites factors such as: (i) the multi-disciplinary nature of the study of HIV epidemiology in Canada; (ii) the concordant multi-disciplinary preventive responses via strategies of community health promotion and empowerment; (iii) the increasing involvement of minority groups in HIV/AIDS work; (iv) the diversity of issues, and (v) the relative scarcity of research funds, etc.

248 R Marchand et al. Community based research ethical review: overcoming the structural barriers of community based research. Oral Presentation to a session on the Ethics of Research, at the XIIIth International AIDS Conference. Durban, South Africa, 12 July 2000. Abstract no WeOrA602.

249 J Vincelette et al. Canadian participation in the first phase III trial of a preventive HIV vaccine (AIDSVAX). Presented at the 9th Annual Conference on HIV/AIDS Research, Montrél, 27-30 April 2000.

arriving at such a conclusion, however, representatives of the target community or communities should be consulted in order to help researchers determine whether their potential subjects see the projects in the same light and would be equally inclined to participate in either study. And finally, a refusal to participate in an additional community research project should not prohibit entry into the base vaccine trial or have negative consequences upon the individual's continued participation.

8. Conclusion: Why Is Community Involvement Important?

As noted above, there are a number of factors unique to clinical trials of experimental HIV vaccines that weigh in favour of strong community involvement in the research process. Not the least of these is the need to ensure that the community is well informed in order to prevent undue optimism and yet still be able to foster grass-roots political support for long term research, development and eventual vaccine delivery. The proposed UNAIDS Guidance Document, *Ethical considerations in HIV preventive vaccine research*, reserves a prominent role for community involvement and, to a lesser extent, community development ("capacity building") in HIV preventive vaccine research. The principle of community involvement is codified in guidance point 5 of the document, which states:

> To ensure the ethical and scientific quality of proposed research, its relevance to the affected community, and its acceptance by the affected community, community representatives should be involved in an early and sustained manner in the design, development, implementation, and distribution of results of HIV vaccine research.[250]

Notes in the document also indicate that community support is seen as interconnected and key to the securing of political, economic, and scientific support for vaccine research, development, testing, and eventual delivery.

HIV vaccine clinical research itself, as well as community-based research, are both in relatively embryonic stages of development in Canada. Some of the most vulnerable and affected communities demonstrate a potential to divide along lines of serostatus in which HIV prevention uneasily straddles the fence. Despite the above-cited arguments pointing to an essential long-term role for community involvement in vaccine research, the link is also embryonic and will require careful nurturing. The full extent of the role reserved for community and community-based research remains controversial. The rapporteur for the social science track at the XIII International AIDS Conference noted that:

> the importance of vaccines in prevention is not contentious, but the role of social research in relation to vaccine trials remains at issue. Among other issues, social research is needed to monitor the impact and trialing of vaccines on communities, as well as individual trial participants. Why is it that social research has to beg for a place at the vaccines table?[251]

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[250] Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Point 5 at 19.

[251] P Aggleton. Supra, note 227.

The theme of community involvement in every stage of vaccine work is central to the successive of vaccination as a long term public health initiative and we will return to this theme throughout the analysis presented in subsequent sections of this paper.

B Community Advisory Boards: A Means to Promote Community Participation and Development

The notes accompanying UN guidance point 5 emphasize that research is a trust-building partnership involving all relevant parties. The drafters of the UN Guidance Document foresee the need for *formal* structural recognition of this important relationship:

> There should be established a continuing forum for communication and problem-solving on all aspects of the vaccine development programme from phase I through phase III and beyond, to the distribution of a safe, effective, licensed vaccine. All participating parties should define the nature of this ongoing relationship.[252]

One structure frequently resorted to in order to create a forum in which community concerns can be aired is the Community Advisory Board (hereinafter the "CAB"). In its usual form, the CAB is a relatively informal and non-corporatist committee of motivated individuals who volunteer from the target community or communities to provide representative advice to researchers.[253]

CABs can help researchers to better comprehend targeted communities. In cultural settings where the discussion of HIV is still the subject of shame and taboo, a CAB can draw upon the experience of local HIV community prevention work to help the researchers identify where the target population is found (both in terms of urban and human geography) and how that population addresses the difficult issues of sexuality, injection drug use, homosexuality and illness.[254]

CABs also provide researchers with advice on how to foster retention of research subjects, undertake community relations, disseminate information, conduct preventive counselling for trial participants, and engage in community prevention and development.[255] Indeed, if engaged sufficiently in advance of the recruitment process, the CAB, working in collaboration with other stakeholder organizations in HIV prevention, can assume a leadership role in the design of risk-reduction methods, information campaigns, the informed consent process, etc. [256]

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[252] Joint United Nations Programme on HIV/AIDS. Supra, note 10, Notes to Guidance Point 5, Community Participation, at 19.

[253] B Snow. Community Advisory Boards: An institutional mechanism for community participation. Reprinted from *The Bay Area Reporter* October 1998, in B Snow (ed). Supra, note 58, at 149-53.

[254] Note: Community involvement in the research process can help researchers target a wide variety of extremely specific subsets in communities. Examples include: Native and Aboriginal populations (and subsets thereof), male and female sex trade workers and their clients, injection drug users, ethnic communities with cultural and immigration ties to regions of the world where HIV is endemic; specific professions; etc.

[255] M Peterson, S Gonzales. VaxGen Memo. Unpublished document addressed to Local Community Advisory Boards in the AIDSVAX B/B Gp 120 clinical trial. Brisbane, California: Co-chairs of the National Community Advisory Board-VaxGen, 29 September 1999.

[256] R Levine. The Ethics of HIV Vaccine Trials. Keynote Oral Presentation at the HIV Vaccine Trials Symposium: Ethics. XIIIth International AIDS Conference. Durban, South Africa. 13 July 2000. Abstract no ThOr95.

CABs can inform researchers about how best to recruit potential research subjects in light of the community's cultural attitudes toward sexuality, family, health, and religion.[257] It can also attempt to engage the community in a critical reflection and dialogue concerning the community's culture and its impact upon public health and attitudes to participation in vaccine clinical trials. In some of the cultures that place a high importance on a collective process of decision-making, there may nevertheless be strong undercurrents of highly individualistic insistence upon autonomous informed consent. Thus, by sharing their knowledge of the community with scientists, a CAB can help researchers to identify such subtleties, thereby recognizing the dangers of stereotypes.[258] In this way, the CAB may help researchers obtain a "collective acceptance and support" of the clinical trial, all the while protecting the process of individual, voluntary, informed, and comprehending consent.

During the trial, the CAB can also provide a forum in which trial participants and people at risk of contracting HIV can voice issues or concerns.

The current AIDSVAX B/B Gp 120 candidate Phase III vaccine trial taking place in North America has convened a National Community Advisory Board in the United States to monitor issues of concern to both the target population and the participants. It oversees implementation of site-specific CABs. Its publicly stated objective is to ensure that a CAB be struck at all participating sites – an objective that has largely been met. If one considers that this is the first Phase III clinical trial of an experimental HIV vaccine and that it is principally privately funded, then the successful attainment of this goal may represent a significant precedent. Through support for CABs, the company has taken a step that implicitly recognizes the importance of the ethical principle of "respect for the community" prescribed by Dr Weijer above.

Each of the three Canadian cities involved in the trial has struck such a committee. Not surprisingly, however, the missions, mandates, and activities of these boards vary considerably. This reflects local variations in approaches to HIV prevention and it conforms to the UNAIDS Guidance Document, which notes that it is the responsibility of all participating parties to define their ongoing relationship.

When a multi-centre trial spans several nations or even continents, the potential for variations in epidemiology, medical services, legal structures, culture, language, definitions of "community," etc is enormous. But Canada is a country so large that considerable variations in human geography, culture, and provincial health laws and services exist. From one city to another there are substantial variations in HIV epidemiology, ethnicity and cultures, community organization, patterns of socialization, media resources, patterns of legal and illegal substance use, delivery of health services, etc. Considerable variation can also occur from one community to another within even the same city. CABs can provide invaluable assistance to researchers by helping them to understand these variations. This support will be particularly important in cities where extensive vaccine preparedness studies have not taken place.

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[257] M Watson. Does culture matter in HIV/AIDS prevention in Zimbabwe? XIIIth International AIDS Conference. Durban, South Africa, 10 July 2000. Abstract no MoPeD2627, and T Liverpool. The impact of HIV/AIDS in the Caribbean and how culture has affected the epidemic. XIIIth International AIDS Conference. Durban, South Africa, 10 July 2000. Abstract no MoPeD2619.

[258] G Lindegger, L Richter. Cross-cultural issues in the implementation of informed consent in HIV vaccine trials in South Africa. An oral presentation at the XIII International AIDS Conference. Durban, South Africa, 13 July 2000. Abstract no ThOrE653. See also: R Macklin. *Against Relativism: Cultural Diversity and the Search for Ethical Universals in Medicine*. New York: Oxford University Press, 1999.

1. How the Word "Community" in "Community Advisory Board" Is Defined

The manner in which the word "community" is defined, including how "community leaders" are identified, is a controversial subject. Sharp and Foster, supra, describe various degrees of community review, ranging across a full spectrum from simple dialogue to structured consultation to contractually required collective approval to a formal partnership with the community leadership. They note:

> Formal community approval ... requires that there be authorities empowered to speak for the study population at large. Similarly, community consultation assumes the existence of shared communal interests and values. Culturally heterogeneous populations may not possess such shared interests, and thus may not be able to reach consensus about the most salient research-related risks.[259]

Establishing effective community representation whether in the form of a CAB or in some other form presupposes the existence of defined community leadership. A CAB will function best where there is a pre-existing and well-defined community structure of HIV prevention and HIV-related services.

In some instances, in situ community organization by people in the targeted community has simply not developed for want of resources or because the local culture is hostile to or ambivalent about their interests. For instance, in many nations of the world where the criminal law sanctions behaviours associated with potential vulnerability to HIV transmission (eg, persons who are HIV-positive and unable to practise safer sex; prostitution; homosexuality; injection drug users), the law may deter potential leaders, advocates, and representatives in target populations from stepping forward to assume a leadership role in a CAB. It may also deter governments, sponsors, and researchers from responding to community initiatives and becoming involved in community development.[260] In these environments, community involvement in decisions affecting research and the formation of a CAB will be difficult, although not necessarily impossible.

In providing comment upon Sharp and Foster's model of "community review," Eric Juengst has noted:

> But what sort of study populations enjoys the ability to legitimize this sort of collective representation? ....

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[259] RR Sharp, MW Foster. Supra, note 222.

[260] A Zuyderduin. Linking Health and Human Rights to Advance the Wellbeing of the gays, lesbians and bisexuals of Botswana. An oral presentation at the XIIIth International AIDS Conference. Durban, South Africa, 13 July 2000. Abstract no ThOrD735. Note: In Botswana, homosexuality is punishable by 7 years imprisonment. In this presentation, the speaker related that when men who have sex with men have presented themselves to health care nurses charged with HIV prevention, they have been refused condoms, been told to "go away and only return with their girlfriends". In such an environment, it would be difficult to imagine forming a community advisory board for a clinical trial recruiting men who have sex with men.

> It may be that only real communities, in the end, [eg, those with representative institutions and leadership] have the moral standing to participate in "community review" processes, and that the concern over the interests of larger "socially identified groups" will have to be foregone as well-intended, but misplaced.[261]

There is still considerable controversy as to whether a "community" can be built along themes such as: (i) a "shared illness – or threat of illness"; or (ii) a common adversity resulting from legal sanctions and discrimination. Nowhere is this controversy more acute than in the case of injection drug users. Witness the following statements from Fabrice Olivet, President of the French group Self Support and Harm Reduction Among Drug Users:

> An experiment that may qualify as "communitarian" has worked as part of the response against AIDS: gay men efficiently mobilized together against the devastation caused within their community. But can drug users follow the same path in their fight against discrimination? ....
>
> Many drug users disagree because the pseudo-community of drug users is above all a by-product of repression. Illegality leads to the development of common codes, semi-secret signs ... testifying to a shared proximity with criminality. It's not enough to constitute a "community," is it?
>
> Drug use remains a solitary and brief act. It does not necessarily involve a relation to others ... the only relation involves a person and a product. So to draw out the boundaries of that "community" would be quite difficult ... as they might as well include the whole of humanity.... Community building may be an appropriate answer to systematic oppression of a clearly identified group ... but it becomes problematic when it appears that the criteria defining membership into [sic] that group are very, very subjective....
>
> Instead of imagining that drug users form a coherent group, we should acknowledge for good that drug use affects everyone.[262]

The evident desire for a conceptual rapprochement of all humanity around issues of drug use reflects a political strategy employed by those promoting harm reduction as a means of furthering HIV prevention. By defining drug use as a universal phenomenon spanning a continuum of products and intensity, advocates seek to overcome the social, cultural, and legal sanctions that constructively and often physically separate the identified illicit drug user from the rest of society.[263] Hence, for some, avoiding a specific community-based approach may be seen as the best strategy for generating support for harm reduction and health promotion.

However, one should not jump to conclusions. Indeed, even Olivet recognizes that "when implementing health programmes to fight the undesirable consequences that are related to drug

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261 ET Juengst. What "Community Review" Can and Cannot Do. Commentary. *Journal of Law, Medicine & Ethics* 2000; 28(1): 52-54.

262 F Olivet. Did you say "community?" *Change: Coalition of HIV and AIDS Non-Governmental Organisations in Europe* 2000; 3: 8.

263 Note: The full spectrum of drug use in society includes licit drugs such as caffeine and tobacco, as well as the use and abuse of prescription drugs, and the use and abuse of a wide variety of illicit drugs.

use, it's obviously useful to implicate individuals who have first-hand experience of the products targeted." In Vancouver, community-based advocacy for injection drug users has emerged with the formation of the Vancouver Area Network of Drug Users and the BC Association of People on Methadone. In Australia, substance users have been able to develop a strong community voice despite the official criminal prohibition of illegal substance use.[264] One of the key factors to success in HIV prevention among injection drug users in Australia and in other nations has been the ability to intervene with needle exchanges reinforced by diverse harm reduction programs at early stages of the epidemic and to intervene among young and occasional injection drug users.[265] A society that adopts a harm-reduction public health oriented approach to drug use may allow its drug users to feel more secure in organizing politically around their demands for better access to health services, including access to clinical trials and the benefits of vaccine research.

But in other cities, cultures and countries where a strong network of not-for-profit community-based AIDS service organizations does not exist, it is public health officials or local health professionals and local health care institutions who step forward to assume the "community" role in vaccine research. Occasionally, this is vigorously contested by militants for community AIDS service development (both within and outside the country), who will question the democracy and representative quality of such surrogate representation.[266] One of the chief concerns voiced with respect to surrogate representation is the apprehended risk of corruption in the appropriation of resources dedicated for local community health development and corruption of the free and voluntary qualities of the informed consent process.

Sharp and Foster, for instance, do not consider such surrogate representation as community involvement. They state:

> A defining feature of community review is that it actively involves members of a study population in the evaluation of proposed research.[267]

In Vancouver, membership in the CAB for the AIDSVAX B/B Gp 120 Phase III clinical trial is drawn exclusively from trial participants. The CAB at that trial site has selectively limited the definition of its "community" base to the clinical trial participants themselves and their sexual partners. Information forums jointly convened by the investigators and the CAB are limited to this particular constituency. The meetings are held to develop and reinforce awareness of the health and prevention issues inherent in HIV vaccine clinical research. These meetings also serve to develop a sense of camaraderie, volunteer appreciation, and community – all centered around

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264 DC Des Jalrlais. Maintaining low HIV seroprevalence in populations of injecting drug users. *Journal of the American Medical Association* 1995; 274(14): 1226-31. See also L McLachlan, A Hunter. Innovative approaches to reach intravenous drug users: Summary of presentations made at Session E15. XIIIth International AIDS Conference. Durban, South Africa, 12 July 2000, and L McLauchlan et al. Involving injectors in reducing needle stick exposure from discarded injecting equipment: a model for poor communities. On the Sweeps Project: Brisbane Youth Service in Fortitude Valley (Australia). XIII International AIDS Conference. Durban, South Africa, 11 July 2000. Abstract no TuPpE1284.

265 DC Des Jalrlais. Supra, note 264.

266 Note: At the XIIIth International AIDS Conference in Durban, South Africa, some "activists" from Australia vigorously contested the definition of "community" leaders and the degree of community involvement incorporated into the AIDSVAX B/E phase III clinical trial in Thailand. These activists criticised what they perceived to be a lack of strong representive participation by the participants in overseeing the clinical trial and shaping its community interactions in matters of recruitment, informed consent, and protection of participants' rights.

267 RR Sharp, MW Foster. Supra, note 222.

the actual act of participation. The CAB meetings are also open to all cohort participants, who receive advance notice, agendas, and minutes of same by mail.[268]

In Montréal, by contrast, the CAB reserves one half of its membership for trial participants but also draws members from the community at large. In defining its mission the board has favoured an approach that provides for extensive education aimed at the target community as a whole. Collaboration with the local community-based HIV prevention agency has been essential to this process.

The Vancouver approach offers several advantages that the Montréal model, oriented toward the entire gay community, cannot – notably:

- The CAB is able to legitimately assert its role as a democratic representative of the constituency of cohort participants. This is probably the biggest advantage to a participant-centred approach.
- It should permit the CAB to focus its energies and work on protecting the rights and interests of a very sharply defined constituency, thereby avoiding dilution of energy and scarce resources.
- The participant-centred mandate may prove useful in cohorts where problems with retention (higher levels of drop-out) are anticipated or develop.

In the Vancouver model, the role of community education concerning HIV vaccine trials would more likely fall to public health, provincial health authorities, and pre-existing community AIDS prevention agencies.

Eric Juengst proposes just such a trial-specific approach as a means of defining "new forms of community" that more easily accommodate community review so that researchers will be able to make "respect for diversity more than just a matter of rhetoric."[269]

> [T]his interpretation of "study population" would not require that the prospective participants already be members of one pre-existing political "community" capable of speaking for their interests: for the purpose of this group's "community review" their eligibility as research subjects would be their membership card, and the community to which they belong would be the community of research subjects they create in collaboration with the researchers. Community review in this context becomes a process of community construction, rather than community reaction, encouraging prospective research cohorts to think of themselves collectively as a self-defined group with common interests, rather than either as isolated individuals on the one hand or as merely a reflection of other communities and socially identified population on the other.[270]

This is essentially the approach adopted by long-term vaccine preparedness studies. There are, however, a number of practical disadvantages. This definition of "community" does not recognize the larger pre-existing community's interest in promoting and maintaining generally

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[268] Telephone Interview with R G, a member of the Community Advisory Board for the AIDSVAX B/B Gp120 Clinical Trial, Vancouver Site. 20 April 2000.

[269] ET Juengst. Supra, note 261, at 54.

[270] Ibid, at 54.

low levels of HIV risk behaviour. Nor does it take into account the potential for permeable overlapping relationships between the "community" of research subjects and those with a similar profile who choose not to participate. Indeed, sexual and needle-sharing networks will extend well beyond the community of research subjects and can even reach beyond the limits of the officially targeted community. This "volunteers are community" model either: (i) ignores the impact of potential harms affecting people beyond the cohort and therefore deems these harms to be acceptable as a kind of "collateral damage"; or (ii) it relegates responsibility for education of the larger community to other actors. It thus ignores the potential for coalition building between diverse elements of the targeted community. It also ignores the potential for vaccine clinical trials to stimulate community based research initiatives related to HIV vaccine research and delivery.

To be successful, vaccination with an eventual licensed vaccine should attain the highest practical levels of coverage in all communities where seroincidence is sufficiently high to warrant vaccination. As such, the "community" of people interested in vaccination and vaccine research extends well beyond the limited number of potential research subjects.

Juengst himself acknowledges this potential concern, noting:

> This approach to involving study populations would also fail to provide larger population groups with any significant protections, since the decision of these cohort-communities could still pose risks to other members of the population groups that they statistically (but not politically represent).[271]

Additionally, this approach seems to deny the authenticity and the potential of communities to develop politically in the face of adverse social conditions. In so doing, the ethical obligation of researchers to make a lasting contribution to development of the larger community conveniently falls by the wayside.

The number of people with HIV in Canada has been increasing due to longer life expectancies and to variable incidence rates that sustain the epidemic in some communities and augment its severity in others. The market for antiretroviral therapies is thus a growing one. People with HIV have a strong common interest in the development of treatments that are easier to take (compliance), offer higher levels of durable efficacy, cause a minimum of adverse events, and do not permit resistant mutations of the retrovirus to develop. To achieve these goals, the pharmaceutical industry will have to engage in a sustained program of pre-clinical and clinical research for many years to come. It is reasonable to predict that this process will require numerous clinical trials. In such an environment, it may be possible to engage in community building based upon the interest and probable participation of a critical mass of people with HIV in a large number of prospective cohorts.

We could therefore expect look to the recent record of the involvement of people with HIV and AIDS and their community representatives in clinical research in Canada as a role model for community involvement in HIV vaccine clinical trials. People with HIV and representatives of community-based organizations offering care and support have played an important role in treatment advocacy, ethical review of scientific protocols, information dissemination, lobbying for access to treatments, and post-marketing surveillance.

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[271] Ibid.

On the other hand, this model can only be stretched so far. The schedule of future vaccine research is likely to be much more muted, sporadic, and unpredictable. Relative to the potential for conducting large-scale vaccine efficacy trials in developing nations, industry may perceive that Canada is too costly an environment in which to operate. If we act alone in imposing community standards, industry may simply decide that Canadian ethical standards and demands for community involvement as well as contributions to development are too exacting and uncompetitive. In short, at least a broad international consensus is probably required concerning the need for an energetic and well-resourced program of vaccine research striking a balance between the need to ensure respect for universal ethical standards and an obligation to accommodate local needs.

Barring such a consensus, community building based even partly upon the defining characteristic of probable participation in vaccine clinical research would be an uphill battle. At most, it would likely be restricted, along the lines of Juengst's analysis, to the transitory time-spans of individual trials. Vaccine preparedness studies can help to bridge the gap between sporadic cohorts, but ultimately Canada will have to act on a multiplicity of fronts (national and international) if its communities are to be consistently recognized and protected through the process of HIV vaccine research.

2. The Role of People with HIV on Community Advisory Boards

How will CABs be able to promote understanding and support of vaccine research in their communities? This question is not posed in a vacuum but rather arises in the face of perceived competing demands for scarce resources in both the national and provincial AIDS strategies. If, as is the case with the AIDSVAX B/B Gp 120 trial, populations are targeted in which both seroprevalence and seroincidence are at relatively high levels, then collaboration and support from people with HIV will be essential to ensure full community support for vaccine research and development. In such environments, some seroconversions during efficacy trials are inevitable. One role of the CAB will be to make recommendations so that the protocol and operations of the vaccine trial ensure that people testing HIV-positive rapidly access the information, support, and services they need.

Resources in Canadian AIDS service organizations (hereinafter "ASOs") are scarce and staff turnover is high. Hence, the typical ASO will have many other interests that take priority over involvement in HIV vaccine research. In this environment of diverse and urgent demands, it will be necessary for stakeholders to include people working in such organizations in the community response to vaccine research. It is important that vaccine research not be perceived as a threat to pre-existing programs and services. Ideally, new resources should be forthcoming in order to allow staff to assimilate this new element into their work in the field of HIV prevention.

It has become routine to state that HIV-positive people must be consulted and involved at every stage of HIV community-based work. Within the context of a clinical trial of a preventive vaccine, the challenge is to give substance rather than mere "appearance" to this assertion. There are a number of compelling reasons that favour involving HIV-positive people in the design and implementation of HIV vaccine clinical trials. For example, the message that clinical trials of experimental vaccines do not mean that a cure is near should not only be addressed to HIV-

negative individuals, but also to people living with HIV. Transmission, after all, involves both HIV-negative and HIV-positive people. Recognizing this obvious fact implicitly acknowledges that both can have a role to play in prevention. Indeed, in terms of benefits to public health, the strength and vitality of communities and the human relationships those communities foster, it seems self-evident that both the HIV positive person and the HIV negative person have mutually reinforcing ethical interests in promoting HIV prevention - and thus vaccine research.

Effectively including vaccine-related information into secondary prevention campaigns targeting HIV-positive individuals will require input from HIV positive people. People living with HIV, and indeed all persons affected by or vulnerable to HIV infection will need to understand the difference between preventive and therapeutic vaccines, the implications of medium to low vaccine efficacy, and the significance of post infection endpoints in vaccines designed to demonstrate efficacy for infectiousness. People living with HIV will also have an implicit interest in ensuring that an eventual licensed preventive vaccine is made accessible to their sexual partners (eg, to HIV-negative partners in serodiscordant couple or "regular" relationships). Pursuing such inclusive policies will help to stimulate interest in CAB volunteerism and enhance the breadth of the CAB's perspective and thus the legitimacy of its informative and representative functions.

Some researchers are inquiring whether there is a growing rift within the Canadian gay population between HIV-positive and HIV-negative gay men, manifested by social, economic, structural, and political divisiveness. Some have gone so far as to suggest that HIV-positive status may become a social identity that, by virtue of the allocation of scarce community resources to HIV/AIDS services, becomes "the defining element of gayness."[272] HIV positive persons experience discrimination within the gay community and in society at large. There is some evidence generated from Canadian psychosocial research involving HIV-negative gay and bisexual men suggesting a perceived split in community along lines of serostatus.[273]

In western nations, people are working to target prevention messages through programs specific to HIV-negative individuals and other programs specifically conceived for HIV-positive persons. In so doing they adopt a comprehensive approach to HIV prevention.[274] Concern about the potentially divisive impact of vaccine clinical research and delivery is worthy of consideration

[272] MR Botnick. Self-Esteem and Development in the Gay Community. Workshop PRV62. Canadian AIDS Society Skills Building Workshop. Winnipeg, 12-15 November 1999.

[273] This may be indirectly inferred but not conclusively shown by information gathered by the Oméga Cohorte. See R Noël et al. OMEGA participants under the magnifying glass (at http://omega.gre.ulaval.ca/english/20c.htm); J Otis. How do gays assess risk? Available at http://omega.gre.ulaval.ca/english/13c.htm; J. Cox. The new HIV therapies: a cautious optimism for seronegative gay men. / Nouvelles thérapies anti-VIH et attitudes des HARASAH face au sida (available at: http://omega.gre.ulaval.ca/francais/20f.htm).

[274] Combating complacency in HIV prevention. *Body Positive*: *An AIDS and HIV information resource 2001*; XIV(2). Available at: www.thebody.com/bp/feb01/complacency.html. See also W Senterfitt. The Complicated relationship between disclosure of HIV status and practise of safer sex, part I. *Being Alive.* West Hollywood Ca, May 2001. Available at: www.beingalivela.org/, and W Senterfitt. Disclosure of HIV status and practise of safer sex, part II. *Being Alive.* West Hollywood Ca, June-July 2001. Available at http://www.beingalivela.org/, and W Senterfitt. Is the rate of new HIV infections rising? The San Francisco controversy and its lessons for Los Angeles and the US. *Being Alive*. West Hollywood Ca, October 2000. Available at www.beingalivela.org/, and The Aims of Gay Men Fighting AIDS. GMAF (An HIV prevention agency working in the metropolitan London (UK) region organised by gay men for gay men). Available at www.demon.co.uk/gmfa/gmfa/aims.htm, and George House Trust (a voluntary organisation for the North West of England). Secondary prevention campaign launch: Major new education campaign aimed at HIV+ gay men. Press release of 1 October 1998. Available at www.georgehousetrust.org.uk.

and merits proactive planning. Unless access to effective treatments and care can be guaranteed, the development and delivery of an efficacious preventive vaccine could potentially create a schism in the community between those who are already infected and those who are not.

But long before delivery, practical concerns about the allocation of scarce research and prevention resources may also be voiced. Such is already the case in developing countries, where people question the wisdom of investing resources in a technology (vaccines) that is unlikely to yield results for several years, when the most basic resources for prevention (condoms, youth education, prophylaxis for pregnant women, testing, and treatments for those already infected) are lacking. Moreover, if history were to someday perceive that vaccine development occurred at the expense of advances in therapeutic treatments, then history will look to those responsible for promoting the vaccine research to also account for the human consequences of this choice. It will therefore be important for communities and scientists to ensure that vaccine research and development does not occur as an exclusive and isolated endeavour. It should not be, nor should it be perceived to be, an either/or choice in relation to research for new therapies.

It is in the best long-term interests of all stakeholders, including HIV positive people, to ensure that the allocation of resources dedicated to vaccine research and related community work does not unduly detract from the provision of care, treatment, and services for people with HIV. As a concrete example, the current CABs operating in Canada may want to take care to inform people that the primary funding for the AIDSVAX B/B Gp 120 Phase III clinical trial comes from the private rather than public sector. Ideally, funding for future vaccine research, development and delivery should be part of a new budgetary envelope dedicated in part to long term aleviation of the epidemics in Canada and the pandemic overseas.

People will also be interested to learn that pre-clinical research has the potential to generate information useful for development of both preventive and therapeutic vaccines. Clinical trials will take place using candidate vaccines as one element of "multiple prevention strategies" designed to block transmission from mothers to newborns.[275] Such research should help to develop delivery systems that support compliance. Moreover, clinical vaccine research will also yield data concerning the correlates of immunity and this will be useful for research in the fields of immune reconstruction and clinical therapies. Indeed, each stream of research (vaccines and therapies) has the potential to generate information of mutual benefit to researchers working in the other. People with HIV will be particularly interested in participating in the design and monitoring of vaccine trials in order to advocate for wide dissemination of the scientific information that is generated concerning the correlates of immunity.

Finally, the involvement of people with HIV in vaccine research will enable the community to speak with a strong, united voice, lobbying for a continuous stream of research and development and for the highest ethical standards in vaccine research specifically, and in all types of clinical research generally.

3. The Montréal Experience: One Model for a Community Advisory Board

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[275] HIV Vaccine and Prevention Research at NIAID: An Interview with Peggy Johnston. *IAVI Report* 2000; 5(3): 8-11 at 12.

In Montréal, the AIDSVAX CAB is comprised of approximately ten people, half of whom are participants in the clinical trial. The committee was chosen by election of volunteers at a community information forum organized by researchers before recruitment began. The committee is charged with renewing its membership. If seats become vacant during the trial, a call for volunteers is sent out to participants (and, when applicable, to the community at large). Board members conduct interviews before a final selection is made.

Members of the committee in Montréal include a physician with an HIV practice, a lawyer with some professional experience in bioethics, and an employee of a local community-based HIV prevention organization. The people from these fields expressed their own interest in participating and are volunteers who do not officially represent their employers. This kind of professional experience is useful to a CAB, particularly at the beginning of its mandate.[276] With proper didactic materials and a solid working relationship with the investigator, the members drawn from a lay background can learn the basic principles of vaccine clinical research. It is true that a CAB requires knowledge or input from those who have knowledge from many different fields including: the terminology and acronyms of vaccines; the basic principles of vaccination; the basic principles of clinical investigative research; clinical research ethics; vaccine delivery, and HIV epidemiology, etc.[277] Although this may seem a daunting task, training a CAB in such matters will involve many of the same processes (albeit in greater detail) that are used when informing participants about the experimental vaccine and the trial for the purpose of obtaining informed, voluntary, and comprehending consent.

The Montréal board contains representation from people with HIV and specific efforts have been made to see that the CAB's composition reflects a diversity in ethnicity, educational levels and backgrounds, and age. In and of itself, however, such representation does not guarantee that the views of specific subsets of the target population will be taken into consideration or addressed. These issues need to be more formally addressed in the board's agenda and workplan.

In Montréal, the CAB has defined its primary mission to include: (i) promotion of the best interests of the participants in this vaccine clinical trial; (ii) promotion of the best interests of the gay community with respect to this present and any future vaccine research; and (iii) facilitation of a transfer of knowledge to the gay community and also to other communities that are likely to be targeted for future vaccine research.

The Mandate of the Montréal CAB

Act as a consultative body – offering a kind of "sober second thought" to researchers. The CAB exercises no decision-making powers and has very low risk of incurring legal liability;

Exercise a reviewing function by providing counsel and advice to researchers with respect to the

[276] Note: In Montréal, three members of the CAB are employed in field related to HIV/AIDS and are able to dedicate some employment hours to supporting the CAB. These members are thus particularly well placed to develop skills and detailed knowledge concerning HIV vaccine research. They can thus act as a source of information to others in the CAB and in the community.

[277] B. Snow. Supra, note 253, at 149.

following matters:

- Informed consent methodologies, procedures and documents;
- Information distributed to participants;
- Retention strategies;
- Presentation of data and cohort results to community forums, community media, etc.
- Future research projects to be grafted onto the existing cohort or that propose to use data (especially psycho-social) data generated by the cohort.
- Strive to be representative of the spectrum of community interests and concerns recognising the limitations inherent in the fact that it is not a democratically elected body accountable to any constituency in the community;
- Assist participants who have complaints; and
- Set rules for the administration of a legal defence fund for participants who may suffer discrimination as a result of their participation in this clinical trial.

Much of this CAB's initial work focused upon extensive revision of the consent procedures and forms as well as revision of the participant's information guide. During this process, the CAB recommended that additional risks associated with trial participation be identified and that others be reprioritized. The CAB suggested that information given to participants be revised to include mention of local health services (eg, the availability of post-exposure prophylaxis). As a result of CAB advice, a list of local community-based services was added to the documents provided to participants; time limits built into the consent process were lengthened; the language of the written materials was occasionally simplified; and the visual presentation of schedules and of participant's obligations were improved. The CAB also expressed concern about the use of the clinical trial as a means to collect and bank DNA tissue samples for future research. It recommended that limitations be imposed upon the future uses of the collected samples in order to reflect perceived community-specific research priorities, taking into consideration potential matters of controversy.

As a result of this revision and consultation process, the consent and information documents were exhaustively rewritten and resubmitted to the REB, which in turn approved the vast majority of the proposed changes. Hence, the CAB was able to play an informative role not merely for researchers and the community but also (indirectly) for the university research institute's ethics review board, whose members may have had comparatively little prior understanding of the target community.

Additionally, the CAB in Montréal requested that cohort nursing staff undertake a periodic evaluation and revision of individual counselling techniques – with the goal of keeping up to date and encouraging long-term quality control of this important process.[278] This matter is

[278] Joint United Nations Programme on HIV/AIDS. Supra, note 10. Guidance Point 14 prescribes: "Appropriate risk-reduction counselling and access to prevention methods should be provided to all vaccine trial participants, *with new methods being added as they are discovered and validated*" [emphasis added]. Guidance Point 15 prescribes: "Monitoring informed consent and interventions: A plan for monitoring the initial and continuing adequacy of the informed consent process and risk-reduction interventions, including counselling and access to prevention methods, should be agreed upon before the trial commences. Note: The CAB can strive to encourage the research cohort to ensure that the spirit of Guidance Points 14 and 15 is respected. It can require that cohort managers and investigators report periodically on the methodologies used to evaluate and up date counselling techniques and the results of their evaluation. The board should insist that pre and post-test counselling during the trial conforms to the highest available standards and that it be periodically subject to review, revision and updating. In Montréal, the vaccine

discussed in greater detail in Section III of this part of the paper, where we discuss informed consent and counselling during the clinical trial.

The CAB is working with the researchers and local prevention specialists to attempt to foresee and attenuate the possible negative impacts that the arrival of the vaccine cohort might have upon community perceptions of risk and risk management.[279] The researchers have set aside approximately ten percent of the site's total budget for education of the target population concerning vaccine trials and the concomitant need to maintain harm-reducing preventive behaviours. The major part has been granted to Action Séro-Zéro, a community-based, not-for-profit, non-governmental HIV prevention agency working in the community. The agency has conducted a preliminary small scale community evaluation of knowledge and attitudes concerning vaccine research and development. It has produced didactic materials, media interventions, and several community information forums. It will assume a leadership role in commenting upon vaccine efficacy results and contextualising this information within a framework promoting harm reducing behaviours and prevention.

Future plans include hosting an intensive skills-building workshop aimed at developing community expertise in vaccine clinical research. The hope is that this will lead to development of a critical mass of trained people who can be recruited to community advisory boards in future trials. This skills-building exercise will therefore also be open to key representatives from other communities where people are likely to be targeted for future vaccine research (eg, young injection drug users, male sex trade workers, urban Aboriginal people, prisoners, etc). In addition, as the clinical trial progresses, the Montréal CAB will invite a community health worker who works with young or new injection drug users to attend the committee's meetings as an observer again with the goal of facilitating a transfer of information.

The CAB is able to serve as a political buffer between the private interests of the pharmaceutical sponsor and the public interests of the local community prevention agency. It helps the prevention agency not only to effectively maintain its independence from commercial interests but also to maintain an all-important public appearance of this independence. In turn, the Montréal board also strives to maintain a certain degree of independence from the cohort in order to protect its mandate to be representative of the community.[280]

Thus, the work in Montréal is an informal tripartite arrangement in which the CAB, cohort researchers, and the local not-for-profit HIV prevention agency collaborate to raise collective

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trial's nursing staff takes part in a periodic professional development exercise involving health care workers from many of the city's principal HIV testing sites.

[279] Note: Among the important messages that the CAB, researchers and local HIV prevention agencies must communicate to the local target community are the following: (i) The importance of maintaining continued support for future vaccine research even if this particular clinical trial proves that its experimental vaccine is inefficacious; (ii) Why increased scientific knowledge concerning the correlates of immunity constitutes a significant advancement warranting the vaccine research; (iii) Why an eventual low -efficacy vaccine might be delivered to people in communities or nations where seroincidence is very high, but not in others where transmission rates are lower; (iv) The essential relationship between clinical trials of candidate vaccines and continued sustained preventive behaviours; and (v) The essential relationship between delivery of an eventual medium to low efficacy vaccine and continued sustained preventive behaviours.

[280] Note: In Montréal, CAB members are not paid, but rather are volunteers. The CAB meetings are attended by the cohort's office co-ordinator and the principal investigator, but neither vote. CAB members maintain a right to communicate directly with the media, although the cohort wishes to exercise a right of scientific review with respect to communicated information.

awareness concerning HIV vaccine research – its promise and its limitations. This partnership recognizes and accommodates the inherent strengths and limitations of the CAB, some of which are described at the end of this section. Without supportive partnerships, the CAB will be in danger of becoming just a "rubber stamp" – providing the appearance of community consultation and involvement without substantive content, serving instead to shield the research from the community.

4. The Need for Notes for Posterity

Whatever form CABs ultimately take, this information and their experience needs to be summarized and kept for posterity in a format that can be easily distributed to community advisory boards in future vaccine trials. Moreover, this exercise should not be undertaken by CABs acting in isolation. In theory, each CAB may have much to learn from the collective expertise of others performing similar functions at each site of a multi-centre trial. An organizational structure permitting an independent network of communication between CABs in cities across regions, countries, and even continents may be useful.

Ultimately, the CAB experience may stimulate community discussions at a higher "political" level, aimed at elaborating principles for minimal standards for community development contributions and community involvement in vaccine clinical science.

5. A Summary of the Strengths of the CAB Model

The CAB model has many strengths and several weaknesses. It is not a panacea for the problems of infrastructure development or for the inequalities in global and regional distribution of health-related services. CABs are but one element of a coordinated approach to HIV vaccine research, which in turn is but one element of a coordinated response to HIV/AIDS.

- CABs have the advantage of being comprised of volunteers and thus involve individuals motivated to contribute to their respective communities. For the research cohort, this means that the CAB is a relatively inexpensive structure to maintain.
- If a CAB can maintain a close interface with local community-based HIV prevention agencies, it can facilitate access to a network of resources for the cohort researchers. As such, a CAB is a flexible instrument, allowing researchers to understand local conditions, needs, and priorities.
- A CAB can provide researchers with detailed insight into their target community's cultural beliefs, popular medical beliefs, HIV risk assessments and management.
- A CAB can provide an essential buffer between the private commercial interests of the sponsor and the more public mandate of community-based organizations working in HIV prevention.
- A CAB may be able to incite debate among community leaders concerning what should become the community's preconditions for contribution by a vaccine clinical trial to community HIV health development.
- CABs can help REBs, researchers, and cohort staff by functioning as a kind of chamber of "sober second thought," providing advice on a wide variety of matters, including informed consent procedures and community relations. It can function as a forum for dress rehearsals of communication strategies, press releases, and scientific conferences aimed at informing diverse elements in the community.
- A CAB can help to facilitate informal meetings between public health, community leaders, and researchers in a neutral and unofficial environment. It can also facilitate meetings between representatives of diverse communities likely to be targeted for future vaccine research.

6. A Summary of the Weaknesses (or Potential Obstacles) of the CAB Model

- If the CAB is volunteer-based, this will necessarily impose limits on the volume of work that its members can realistically be expected to contribute.
- A CAB will only be as effective as the underlying working relationships with the cohort staff, researchers, principal investigator, and sponsor. The board is largely dependent upon the cohort for much of the information required to undertake its work. Without an open and trusting working relationship in which a certain willingness to accept criticism and to share power and responsibilities is manifest, the CAB risks becoming a mere "rubber stamp."
- As an advisory group, the CAB's role is defined by the amount of leverage the leadership team assigns to the group. This leverage will in turn impact the attractiveness of the CAB to potential and current members.[281]
- A CAB is comprised of a very small number of individuals. In and of itself, the CAB does not and cannot amount to "community involvement" or to "community mobilization." Community involvement in research requires activities designed to inform the community, incite informed debate, and facilitate responses to community requirements. To be effective at this task, CABs require resources and partnerships. Collaboration and respect from community leaders is essential. The cohort must therefore dedicate the resources needed to support the CAB technically and logistically. It also means providing board members with proper training and information so that deliberations can be informed and accurate. The cohort must allocate additional resources to permit the CAB, acting in collaboration with other community stakeholders, to educate the target community – reaching large numbers of people and the greatest possible diversity within the targeted population.
- Partnerships with local prevention and health services resources are essential in this endeavour. Key players in the field of HIV prevention (community ASOs, public health, epidemiological cohorts, HIV testing counsellors, etc) must also be willing to make an effort to respond to issues of concern raised by the CAB. Without such partnerships, the board will be hamstrung.
- If the clinical trial recruits people from more than one target community, it may be difficult to construct a functional CAB if these communities have widely divergent cultures and development priorities. If the defined target community is characterized by a high degree of heterogeneity, or if the community's infrastructure development is embryonic, it may be difficult to strike a functional and representative CAB.
- If a CAB is to concern itself not merely with the interests of trial participants but also with the larger HIV prevention and health promotion interests of the target community as a whole, the legitimacy of its representation may be called into question. A CAB is not an elected body held accountable to a large democratic constituency. As Juengst notes: "To seek out the perspectives of the population group in non-representative ways is no better than simply recruiting stray individuals."[282] The board must be cognizant of this limitation, understanding the difference between its representative role and its inherent inability to democratically represent the community. It can attempt to palliate the limitation by engaging in strategies of community consultation and partnerships.[283]

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281 S Kirkendale. Supra, note 244.

282 ET Juengst. Supra, note 261, at 53.

283 Note: It is possible to partially compensate for this limitation by recruiting a diverse and representative sample of participants and community members to the CAB. The CAB should maintain close working relationships with local community based not-for-profit organisations which, in theory, are legally accountable to electorates comprised of members drawn from the target community. Through its work, the CAB can engage the community in a process of reflection and ultimately of community consensus. Multiple community information forums,

- Because CABs are comprised of a small number of people operating on a relatively modest scale, the expertise they develop may not survive prolonged gaps between clinical trials. Even if the CAB shares information extensively with local HIV prevention agencies, the human resources turnover in the community sector is relatively high and the knowledge may be lost before the next clinical trial comes along.
- In the context of a multi-centre trial, a CAB has comparatively weak power when requesting that changes, designed to reflect local conditions, be made to the consent forms and procedures. When the clinical trial originates in the United States, CAB requests for adjustments are negotiated (via the local site office) with an American legal expert, who will not necessarily have a good understanding of Canadian provincial health law.[284] Moreover, substantive changes to protocols and procedures granted at any one site but not at others might raise fears that elements of scientific uncertainty and social inequality will be introduced into the multi-centre trial. Finally, any changes to the scientific protocol would have to be approved by the US regulatory authorities. In Canada, such approval would also have to be obtained from Health Canada as well as the institutional REB.
- CABs are but one of several strategies that a sponsor and researchers may employ in striving for community involvement and "rapprochement." The researchers may choose to convene their own public forums and will undoubtedly engage in media interviews promoting the trial. Other strategies include the recruiting community-based researchers to the research team and, by implication, including a component of community-based psychosocial research in the clinical trial. The cohort may also hire local leaders from the community to manage cohort offices. It can contract with local consultants to promote recruitment of research subjects and to manage public relations within the community.
- But when a research cohort draws extensively upon human resources from within the community sector they are typically able to offer higher wages than the not-for-profit sector is capable of paying. This drains qualified staff away from the latter. In addition, it places former allies in potentially adversarial positions. This in turn gives rise to complex emotional and political difficulties as the CAB members now find themselves advocating community interests in negotiations with counterparts who are former colleagues but who are now mandated to defend the interests of the corporate sponsor.

7. Conclusion Respecting Community Advisory Boards

Community involvement in all phases of a vaccine trial is imperative. But CABs are only one element of an overall program of community engagement and mobilization in HIV vaccine research. They can function as a reflective body, initiating questions and providing critique, commentary, information, and advice to researchers. But if left to function in a vacuum and without the necessary resources and partnerships, the CAB will not be able to surpass the limited role of a key informant. If it is to facilitate engagement of the community in working toward a broad-based mobilization in support of vaccine research and a substantive community involvement in vaccine cohorts, then the CAB will require resources. The most important among these resources will be an informal web of interconnected partnerships. Only through meaningful dialogue and working collaboration with all parties – the corporate sponsor, the principal

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consultations and psycho-social research evaluating the target community's knowledge of vaccine research, etc, can also help.

[284] Note: The comparatively lower quantum of damages awarded in liability suits in Canada may mean that requests from Canada for legal and procedural amendments may receive comparatively short shrift.

investigator, the cohort researchers, local HIV community-based prevention agencies, public health, health-care service providers, people with HIV, and representatives of potential target populations for future clinical research – will a CAB be able to stimulate sustained community interest and collective consent to clinical trials of experimental HIV vaccines.

C. Recommendations for Community Involvement in Vaccine Research

This report makes the following recommendations with respect to community involvement in vaccine research:

1. Given the potential importance of vaccination in future HIV prevention, and the potential need for a synergistic interaction involving behavioural prevention, harm reduction, and vaccination, public health authorities and provincial and regional (governmental) AIDS coordination agencies need to join with industry and communities in a concerted effort to generate public support, education, and information for the ethical testing of experimental HIV vaccines on Canadian subjects.

2. Community leaders require information before they can begin to envisage and plan the scope of community involvement in HIV vaccine research. Vaccine researchers, community-based researchers, funders, and community HIV prevention agencies should establish a forum whereby they can regularly inform each other of their respective priorities, capacities, and timelines.

3. Both governments and existing community-based AIDS prevention agencies should encourage and support the development of diverse forms of community-based leadership within populations likely to be targeted for HIV vaccine clinical research.

4. A place must be reserved for people with HIV in the community's response to and involvement with vaccine research and development.

5. Governments should fund, in a sustained manner, qualitative psychosocial research capable of investigating the potential impact of "vaccine and vaccine trial–induced optimism" on collective and individual risk assessment, assumption, harm reduction and management. This research must not be limited to a single assessment but must be verified periodically.

6. Researchers, funders, and corporate sponsors should make a firm commitment to include targeted communities at all levels of vaccine research. There must be a clear and public recognition of the positive contribution that community representation can make to providing a needs assessment for locally based educational plans,[285] setting research priorities, and monitoring the protection of participants' rights and any adverse effects upon the community.

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[285] S Kirkendale. Supra, note 244.

7. If a sustained program of vaccine research is foreseen, then governments, industry, and community alike should invest in community skills building designed to facilitate public comprehension of vaccine research and delivery. This skills building will also elicit interest in participating in clinical trials, and communicate an awareness of ethical and legal standards in clinical vaccine research. It should reinforce the continued need for prevention and harm-reducing behaviours among target populations.

8. Community skills building should include elaboration of suggested procedures by which community advisory boards working in collaboration with other stakeholders can catalyze debate, leading to a kind of deductive collective consensus. Such consensus would be in addition to (and not a replacement for) individual, informed, voluntary, and comprehending consent. In addition, didactic materials should be prepared for distribution to CABs. These materials can help to inform the people volunteering for CABs about best-practice standards for ethical vaccine research, as well as suggested strategies for communications, site monitoring, and checklists for informed consent.[286] Providing such didactic support will help CABs meet the short start-up time frames associated with vaccine clinical trials.

9. Directories, including electronic mail addresses of the members of CABs in various cities involved in multi-centre trials, should be prepared and distributed. CAB members should be encouraged to correspond and exchange ideas with people working on community advisory boards in other cities.[287]

10. Resources should be provided to allow leaders of targeted and potential target populations to engage in discussions concerning political standards for contribution to community development from vaccine trials. A number of political and scientific players, including the Canadian Clinical Trials Network and the Canadian AIDS Society, should assume leadership in this process, which could for example produce a checklist of essential elements for research protocols and for informed consent.

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[286] ID.

[287] ID.

II Recruitment

In this section we will examine many legal and ethical issues that arise when human subjects are recruited to participate in clinical trials of an HIV prophylactic vaccine. The section will examine some of the preparatory work that can help make recruitment an easier process, all the while respecting ethical standards that should protect human subjects. We will also briefly examine some issues specific to Phase I clinical trials.

We will try to determine whether researchers have scientific as well as specific legal and ethical obligations to recruit people from a diversity of HIV-affected communities. In so doing, we will consider the case of five specific study populations, namely (i) street-involved youth, (ii) injection drug users, (iii) women, (iv) prisoners and (v) Aboriginal people.

A. Phase I Clinical Trials: A Particular Subset of Recruitment

1. Key Features

Phase I trials are the first clinical trials conducted on humans and they usually recruit fewer than 100 subjects. Requests for regulatory authorization to conduct Phase I trials are submitted to the Therapeutic Products Program (TPP) of Health Canada. The requests are supported by submissions detailing results of prior pre-clinical research conducted in vitro and in animal models. The TPP reviews the data in order to determine if it indicates probable "relative" safety and a potential path to vaccine efficacy meriting experimentation in humans. It also reviews all scientific aspects of the protocol for the proposed clinical trial.

The primary objective of a Phase I trial is to determine the short-term safety of an experimental vaccine. Scientists also evaluate its bio-availability and its toxicity at different dosages in humans. Because this is the first time the experimental vaccine is tested on humans, the risks must be considered relatively high. Dosages will be cautiously administered in stepped quantities to stratified subgroups within the small cohort. Thus, even if the test vaccine were to be effective, most participants would receive dosages insufficient to confer protective or disease-attenuating immunity. Determining efficacy is not an objective at this stage of research. Rather, participants are tested extensively for possible adverse events and the duration of the trial is kept relatively short – typically lasting approximately six months.

To a lesser extent, Phase I clinical trials also provide a preliminary opportunity to study the short-term immune response to various dosages, over varying schedules, administered by different means. This in turn should provide scientists with information needed to choose hypotheses that may, upon further clinical investigation, prove to optimize cost efficiency, bio-

delivery, and stimulation of the immune response while presenting participants with tolerable levels of inconvenience and risks.

Phase I trials seek young, adult volunteers at low personal risk of contracting HIV. A deliberate attempt is made to recruit volunteers who are healthy. This is done so that the initial immune response and safety data are not muddled by immune-compromising health factors more frequently encountered in populations vulnerable to HIV infection.[288] This is particularly important in HIV vaccine research, since so little is known about the correlates of immunity.

Phase I trials will thus involve people who have little direct personal interest in HIV. And yet these are the clinical trials that will involve the highest degree of risk of adverse health events. If adverse events are detected, the vaccine schedule used in this short trial can be stopped, or dosages immediately adjusted, and the observed injuries should be immediately treated. In view of the relative risks involved, the volunteers recruited tend to be single people with no dependent families. However, given their age and exceptionally "healthy" status, they comprise a cohort of people that could potentially incur relatively high losses (eg, in terms of damage to health, loss of enjoyment of life, and loss of income-earning potential) should the experimental vaccine induce illness. Logically, this would be a strata of volunteers in need of legal, ethical and perhaps financial protection.

2. Legal Protection and Ethical Review

Phase I clinical trials of prophylactic vaccines in human subjects are not currently subject to a legal requirement of prior ethical review by the TPP. Under new regulations to the *Food and Drugs Act* [289] the TPP does not assume this responsibility. Instead, the regulations extend a legal power for ethical review to REBs. Paradoxically, they provide no concrete standards for REB accreditation. Other than a brief reference to the Tri-Council Policy Statement[290] and vaguely defined "best clinical standards,"[291] the proposed regulations do not provide a clear mandate or a clear definition of standards for ethical review. This laissez-faire approach to ethical review is due to some extent to the division of powers between different levels of government, and is particularly worrisome with respect to Phase I clinical trials, since they involve the least benefit and the highest risk to participants.

It is also due to the fact that clinical research today is mobile. Clinical trials are taking place with increasing frequency in developing nations. Sometimes clinical research is exclusively directed by the sponsor itself, by one of its subsidiaries, or by a contractor hired by the sponsor for that purpose _ in other words, without the help of public universities, hospitals, or other research institutions. In certain developed nations, phase I clinical trials are relatively deregulated, with the negotiation of informed consent serving as the principal bulwark against potential subject abuse. In the competitive drive to attract pharmaceutical research and development, Canadian researchers and research institutions are competing against comparatively deregulated economies.

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288 JS James. 2000 Outlook. *AIDS Treatment News* 7 January 2000(334).

289 Regulatory Impact Analysis Statement. Supra, note 89, at 1150.

290 Medical Research Council of Canada. Supra, note 76.

291 Regulations Amending the Food and Drug Regulations. Supra, note 101, at Arts. C.05.001, C.05.010: 1123-24.

In Canada, the TPP must approve the scientific protocol for a Phase I clinical trial. In addition, ideally, an open process of scientific peer review will also help to exercise restraint upon attempts to proceed to trial in humans with unscientific haste. Vaccine trials, like all clinical research, should proceed in a spirit of "rational empiricism."[292] Although few would argue with the concept of rational empiricism, many would debate how it should be interpreted and applied. Every clinical scientist faces relative uncertainty at the inevitable moment when the experimental product is first tested in humans. Consequently, Phase I trials have tended to emphasize direct financial compensation for volunteers and recourse to contractual recognition and acceptance by the subject of the risks inherent in the research. Moreover, in Canada, information concerning adverse events observed in clinical trials is legally deemed to be the intellectual property of sponsors and not subject to public scrutiny.

As demonstrated earlier in this paper, in the section on experimental live-attenuated vaccines, certain types of experimental vaccines will carry higher levels of risk than others. When the potential for adverse events associated with administering a candidate HIV vaccine in humans is relatively unknown, researchers have considered recruiting terminal cancer patients who are not immunocompromised for Phase I research.[293] Terminal patients may see this as an attempt to assert dignity and autonomy near the end of life by making an altruistic contribution to science and their community. However, some, but by no means all, terminal patients may demonstrate accentuated vulnerability, leading to increased risk of a coercive compromise of the voluntary nature of informed consent. Such recruitment obviously would require penetrating ethical scrutiny. This proposal would a priori seem to conflict with the currently accepted principles of research with dying patients.[294]

3. Compensation for Volunteers

At times, pharmaceutical research companies issue contracts to life sciences companies who specialize in the organization and execution of Phase I research. The contractors often undertake recruitment and house subjects in their facilities for the short duration of the study period(s). The contractors collect tissue and serum and conduct some of the tests required by the protocol. Advertisements recruiting volunteers are placed in the classified sections of large-circulation daily newspapers as well as in weekly arts and "alternative" papers distributed free of charge. Advertisements are also placed on billboards in urban public transit systems.

Financial compensation for participation in these clinical trials ranges from a few hundred to a few thousand dollars.[295] The money is designed to compensate participants for the inconvenience of the trial, notably the time, tests, and the controlled living circumstances. It also

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[292] M Liu. An AIDS Vaccine by 2007, myth or reality? Oral presentation to a plenary session on HIV Vaccine Challenges at the XIIIth International AIDS Conference. Durban, South Africa. 13 July 2000. Abstract no ThOr86.

[293] D Gold. Supra, note 80. See also T Beardsly. Supra, note 94.

[294] DJ Roy, N MacDonald. Ethical Issues in Palliative Care. In: D Doyle et al (eds). *Oxford Textbook of Palliative Medicine*. 2nd ed. New York: Oxford University Press, 1998, at 97-138.

[295] Note: One such study (not related to vaccine research) was advertised in an August 2000 edition of *La Presse* and offered six hundred dollars for two forty-eight hour periods of live-in study (over weekends), one thousand dollars if each weekend were followed by a return "follow-up" visit; and fifteen hundred dollars for three forty-eight hour live-in study periods each with a follow-up visit.

reflects the reality of relatively higher risks inherent in Phase I research. In this kind of research, participants are made to sign consent forms acknowledging that they fully understand the nature of the risks inherent in the research and that the company will not be liable for damages should the risks in fact materialise. Strictly speaking litigous rights cannot be waived in Canada; however, if the consent process includes an airtight sponsor disclaimer and participant acceptance of responsibility for injuries and damages arising from comprehensively disclosed risks, then in point of fact, it almost amounts to the same thing.

Can compensation for participation that is paid to all participants actually deform the free nature of their informed consent? Typically, the advertisements recruiting participants are listed in local papers under the heading "odd jobs" alongside advertisements for low-wage, low-skills employment. There are significant numbers of Canadians living in poverty. Montréal, where much of Canada's research-based patent pharmaceutical industry is located, has a substantial population living in urban poverty.[296] Despite the fact that the advertisements are placed in the want ads section of local papers, compensation for participation in a Phase I trial is not officially considered employment income. Income tax declarations are not issued and this makes the compensation a powerful incentive for people on low fixed incomes or social assistance. Moreover, some volunteers who repeatedly participate in Phase I trials of different products admit to using this participation as an income supplement. The point is made here in order to emphasize the potentially persuasive power inherent in offers of even modest sums of money to economically deprived participants.

Finally, questions can also be raised concerning: (i) the participant's right to compensation for vaccine-induced injury, and (ii) the determination of the quantum of such compensation in comparison to the level of risks. Author Stephen Guest has argued that

> [a] subject's informed consent to participate should not limit his access to due compensation [for vaccine-induced injury], as it is not appropriate to balance his right not to be harmed – particularly as a volunteer subject – against the benefits to society of the research of which he is a part.[297]

Given the relatively small numbers of persons recruited to Phase I trials, it should be possible to hold industry to the highest attainable standards of care for vaccine-induced injuries sustained in this level of clinical investigation. However, it is far from certain that industry will consistently and voluntarily adopt this standard on a worldwide scale.

4. Trials in Developed and Developing Countries

The timeline from research to delivery of an HIV vaccine is very long. In its blueprint for vaccine development, the International AIDS Vaccine Initiative, recommends that Phase I

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[296] KK Lee. *Urban Poverty in Canada*. Ottawa: Canadian Council on Social Development, 2000. Note: Poverty levels in the report were calculated using a wide variety of 1996 Statistics Canada census data and Statistics Canada's Low Income Cut-offs. Montréal had the highest poverty rate among Canadian cities in 1995 with a rate of 41.1 percent in the city and 27 percent in the Census Metropolitan Area.

[297] S Guest. Compensation for subjects of medical research: The moral rights of patients and the power of research ethics committees. *Journal of Medical Ethics* 1997; 23(3): 181-85. This article was also published in *Monash Bioethics Review* 1998; 17(1): 4-10.

clinical trials be conducted in the countries where the subsequent efficacy trials will also take place. This favours an acceleration of research by permitting (i) early education of local populations about vaccine research, and (ii) capacity building among local researchers well in advance of large-scale efficacy trials. But there will be a need to alleviate fears that subjects in developing nations are being treated like guinea pigs for the development of expensive vaccines to be distributed in the wealthy nations of the developed North. Researchers must also work to preemptively address the attendant latent issues of apprehended racism. As Dr MW Makgoba, President of the Medial Research Council of South Africa has noted, traditionally, in his country, the people doing the research are white, and those volunteering are black.

One possible strategy is to conduct parallel arms of Phase I clinical trials in both the sponsor's country and the host country. Because Phase I trials do not require people who are at high personal risk for contracting HIV, and because they do not require large numbers of people, they are *relatively* easy to conduct in both developed and developing nations. Conducting a Phase I trial in a developed "sponsor" nation will add credibility to the research effort in the eyes of communities in developing countries where people are likely to be recruited for subsequent efficacy trials. For example, a Phase I clinical trial of an experimental HIV vaccine is currently underway simultaneously in Kenya and in England.[298] By demonstrably endorsing similar standards for the protection of research subjects while meeting the specific scientific criteria for recruitment to Phase I clinical research, these partnerships prescribing the simultaneous recruitment of subjects in developed and developing nations will function as a political gesture expressing good will and transparency.[299]

Indeed, this principle of parallel arms could apply with equal force to clinical research forecast to take place in marginalized communities in Canada. We could not expect any less of a contrast between researchers and subjects along ethnic lines in a clinical trial conducted in an Aboriginal community in northern Canada. Recruiting a parallel cohort of people from mainstream populations in southern Canada could meet both scientific requirements as well as the political objectives outlined above. Such a strategy could be employed whenever marginalized or vulnerable subgroups of society are expected to be targeted for subsequent efficacy trials.

B. Large Scale Efficacy Trials: Preliminary Questions Concerning Recruitment

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[298] B Levings. Phase I DNA Vaccine trial begins in Nairobi. *IAVI Report* 2000-2001; 5(5): 3. See also D Gold. IAVI Launches Two Vaccine Trials in Oxford. *IAVI Report* 2000; 5(4), and A England. AIDS Vaccine Goes on Trial in Africa. *Associated Press* 6 March 2001, and J Grossman. New AIDS vaccine to begin Kenya trials. *United Press International* 2 February 2001, and C Collins. Africa-Based Vaccine Research Advances. Africa American AIDS Policy and Training Institute. Available at www.blackaids.org/durban/news/Africa_vaccine_research.htm, and AIDS Vaccine Trial. *Journal of the American Medical Association* 1999; 281(11): 978.

[299] Note: For an exposé of some of the conflicting ethical and cultural values between sponsor countries and host countries, see also E Bass. Rakai: Twelve Years of Work, Hopes and Uncertainties. *IAVI Report* 2000-2001; 5(5): 13-16.

1. The Necessary Preconditions: Has the Advance Work Been Done?

Ethical decisions concerning whom to recruit to large-scale (Phase II and III) vaccine clinical trials must be grounded on more than mere vulnerability to HIV infection. An ideal target population for recruitment to clinical research will have been identified and "prepared" well in advance according to a number of scientific and social criteria facilitating research, recruitment, and informed consent. Decisions to recruit research subjects from a given community will be made not only as a function of the accessibility of potential subjects and their willingness to participate, but also as a function of the ultimate utility of a vaccine within the targeted community. The "utility" of vaccine research and delivery will have to be evaluated against the backdrop of projected changes in epidemiology. In short, the trial must be designed to yield data that can be generalized to the populations likely to be vaccinated. Ideally, these populations should include the people targeted for recruitment to the efficacy trials. Finally, prior to commencing recruitment, a number of key questions need to be answered concerning the suitability of a proposed target community's infrastructure, its popular support for vaccine research and the political engagement of leaders in favour of vaccine research and delivery.

Advance preparation of target communities will enable recruitment to proceed in a manner respecting the ethical, legal, and human rights of research subjects while promoting equitable and inclusive patterns of recruitment. The challenge is to accomplish this work without unduly delaying or slowing research.

2. What Conditions Will Make a Community More Likely to Support a Vaccine Trial?

(i) AIDS Awareness before Research

An ethical recruitment of volunteers to trials will be constructed upon a foundation of prior success in promoting education and awareness concerning HIV and AIDS. HIV vaccine trials require regular testing for exposure to a serious and ultimately fatal infection. A positive test result will potentially have a severe impact upon a trial participant's sense of well-being and lifestyle.[300] The severity and nature of these impacts will be a function not merely of the individual's own reactions and health but also a reflection of the laws, ethical values, popular beliefs, and resources existing in the community. Vaccine clinical trials will more easily find volunteers in societies in which work has already been undertaken to:

•reduce barriers to HIV testing;
•reduce ignorance, fear, prejudice, and stigmatization consequent upon HIV infection;
•promote the legal and human rights of people with HIV and AIDS;
•provide information, resources, and support to empower people to exercise prevention; and

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[300] Note: An HIV diagnosis will potentially affect the participant's emotional well being, financial situation (access to life insurance), life plans, choice of physicians, social interaction with others, participation in community benefits, travel, as well as sexual and reproductive health. Treatment standards have recently been revised in favour of commencing therapies at a much later stage in HIV infection (i.e.- when CD4 counts decline to levels near 500 or in the event of an earlier serious opportunistic infection). In view of this, persons committed to practising safer sex, and who apprehend the threat of serious discrimination in their community or milieu should their serostatus become known, may be inclined to wait before being tested.

•provide functional access to care, treatment, and support for people with HIV.

This work has not yet been consistently achieved in a manner proportionate to the needs arising in subsets of the Canadian population significantly affected by HIV. Work remains to be done among street-involved youth, injection drug users, prisoners, sex trade workers of both sexes, transgendered persons, certain Aboriginal communities, young gay men, and in certain ethnocultural communities in Canada.

(ii) Anticipating and Minimizing Harms

When planning for clinical trials, researchers need to anticipate harm (direct and indirect) to individuals that may be consequent upon the research. For example, researchers can anticipate and assess potential harms arising as a result of an HIV diagnosis. To minimize these harms, they can ensure that persons in the cohort who seroconvert can promptly access care, treatment, and support as well as support for partner notification when needed. The proactive establishment of links to services should reassure participants and help to facilitate recruitment.

As previously discussed, the arrival of vaccine clinical trials as a new field of research might generate undue optimism and unrealistic expectations in the targeted community. These in turn might lead to a subtle but nefarious decline in the relative importance and value that the collective places upon prevention.[301] Vaccine researchers and community stakeholders must therefore anticipate this harm, taking steps to attenuate its impact by educating the community and monitoring changes over time.

They must also establish a program of effective preventive counseling for individual participants. This plan should be subject to periodic evaluation and monitoring. Resources should be budgeted in order to react if the counseling proves either to be extremely effective, thereby generating a need for supplemental recruiting, or to be largely ineffective, leaving researchers witness to unconscionably high levels of seroincidence.

(iii) Stigma and Discrimination

It would be difficult to ask people to consent to regular HIV testing over the two to three year period of a Phase III vaccine (efficacy) trial if the common reaction in the community is to stigmatize people with HIV. Stigmatization may take many forms including: the forced disclosure of a person's infection, shunning, ostracizing, ridiculing, or moral judgment. Vaccine research should not proceed in a social and cultural environment in which the quasi-totality of the population is ill-informed and uncomfortable or fearful when interacting with people with HIV. Moreover, if it is likely that people with HIV will be illegally denied access to social and economic benefits, - and if the community is unable to offer access to care and treatment, then the immediate short-term disadvantages of testing positive may substantially outweigh the short-term benefits of knowing one's serostatus. It would be unethical and impractical to proceed with vaccine research in such a hostile environment.

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[301] N McLean et al. Description of interest in the AIDSVAX vaccine trial among sexually active gay and bisexual men in Vancouver, British Columbia. Presentation at the Xth Annual Canadian Conference on HIV/AIDS Research. Toronto, 31 May-3 June 2001. Abstract no 339P. Published in the *Canadian Journal of Infectious Diseases* 2001; 12 (Suppl B): 65B.

Similarly, recruitment should not proceed in communities where people vulnerable to infection are overwhelmed with a sense of fatalism and will lack the self-esteem or resources necessary to engage in HIV prevention and personal health promotion.

Preparatory work in the fields of education, sensitization, prevention, promotion of human rights, and development of health services must be undertaken prior to recruitment or, at the very least, as the clinical trial unfolds.

3. Will the Community Benefit from an HIV Vaccine Trial? Will the Community Benefit from an HIV Vaccine?

These are among the most important questions to be asked before deciding to target a given community and recruit people from within it.

> [S]cientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects.[302]

Implicit in the first question above are considerations of whether the vulnerabilities (financial, health, and social) of the proposed target population would render the process of "informed consent" too precarious to proceed. In particular, researchers will have to consider whether uncertainties and inconsistencies in the procurement of the basic necessities of life preclude the ability to ethically request that volunteers make a contribution to science. This question assumes enhanced importance in this relatively early era of HIV vaccine research, given that clinical trials cannot offer any degree of vaccine efficacy as an existing platform standard of care in either the placebo control or trial arms of the study.

However, the corollary of this is that groups and individuals vulnerable to HIV infection should not be refused enrolment in a vaccine trial simply because they are deemed inconvenient or socially undesirable:

> [G]roups or individuals should not be excluded from the opportunity to participate in research without a good scientific reason or susceptibility to risk that justifies their exclusion. It is important that the results of research be generalizable to the populations that will use the intervention. Efficiency cannot override fairness in recruiting subjects.[303]

Answering the question of whether the community will benefit from an HIV vaccine requires an ability to study evolving epidemiology and to predict future levels of seroprevalence and seroincidence. Given the long timelines associated with vaccine research, development, and delivery, it may be wiser for communities that are currently experiencing very high levels of seroincidence (which rapidly lead to high levels of seroprevalence), to make an immediate

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302 EJ Emanuel et al. What Makes Clinical Research Ethical? *Journal of the American Medical Association* 2000; 283(20): 2701-11.

303 Ibid at 2704.

investment in prevention. Longer-term health priorities in such a setting would focus upon therapeutic vaccine research and development of care, treatment, and support for people with HIV/AIDS. Prevention efforts, including attention to prophylactic vaccine research, may have to be focused primarily on new members of the community.

Still other communities may exhibit background rates of seroincidence too low to enable recruitment of an efficient cohort. And if background seroincidence and seroprevalence remain low, delivery of a licensed vaccine with a low level efficacy will not be recommended. In such an environment it would be difficult to stimulate community interest in vaccine research. But even if background seroincidence and seroprevalence rates in the broader community do not indicate a fertile ground for recruitment, there may be subsets of people who nevertheless experience much greater vulnerability to infection over a sustained period. There, researchers may find potential volunteers interested in sharing the burdens and benefits of vaccine clinical research.

4. Is There Broad Political Support for Vaccine Research and Delivery for this Community?

It will also be necessary to evaluate whether a society can muster the political will to promote research and protect those who volunteer as participants. In order to facilitate recruitment to vaccine clinical trials in Canada, steps must be taken to address participants' concerns about risks. Volunteers are likely to be worried about issues such as (i) vaccine-induced injury, (ii) a "false" interpretation of positive test results for vaccine antibodies, and (iii) discrimination. Resolution of these problems lies, at least partly, within the traditional realm of government responsibility for health and social services. Governments in Canada, the pharmaceutical industry, researchers, and HIV- affected communities need to devise a clear strategy engaging responsibility for taking steps to attenuate these and other possible harms.

A further question is whether a given society will be able to muster the political will to deliver a vaccine to those needing it most. Ideally, potential target communities should manifest broad-based political support for HIV prevention generally and vaccine research specifically. A multiplicity of factors will determine whether this support can be found or nurtured. They include:

- HIV seroincidence and seroprevalence rates;
- Whether, within the context of the community's culture, HIV prevention is understood to be both a political and a health priority and accepted as such;
- Whether there are community representatives and health promotion organizations capable of comprehending the methodology of vaccine research and applying that knowledge in order to: support recruitment to trials, explain clinical data to the public, provide counsel to the parties charged with monitoring respect for ethical research standards and the protection of enrolled subjects' human rights, as well as advocate for effective delivery when vaccines become available;
- Whether there exists an accessible public health expertise to evaluate the projected efficiency of vaccinating various communities having different levels of seroincidence and seroprevalence with vaccines that have different levels of efficacy; and

- Whether local research ethics boards, scientists, and community representatives can be rapidly mobilized to meet the requirements of an ethically conducted Phase II or III clinical trial within the short timeframes for recruitment that are typically imposed by sponsors.[304]

The Netherlands has a national strategy for HIV vaccine research that includes funding in excess of US$ 22 million for the International AIDS Vaccine Initiative. A commission headed by the Prince of the Netherlands led this initiative through a review by all political parties and the strategy was adopted by a free-vote resolution in the nation's parliament.[305] Similarly, the undertaking of Phase I clinical trials of vaccines in Uganda has required engaging support at the highest political levels.[306]

Historically, national and provincial AIDS strategies in Canada developed in reaction to an emerging public health problem. Initial work therefore played a "catch-up strategy" by focusing first upon implementing services for the care, treatment, and support of people with HIV/AIDS. Governments also funded community-based organizations engaged in primary prevention initiatives targeting the first-affected communities. In the face of such pressing needs, research into preventive technologies such as vaccines and microbicides and the implementation of innovative prevention strategies (eg, secondary prevention targeting HIV-positive people) was sporadic and largely relegated to a list of future priorities.

Without enduring political support for HIV prevention sciences and vaccine delivery, there is a risk that research in this country will proceed slowly, influenced by economic policies and push pull mechanisms implemented elsewhere without input from Canada. There is also a risk that the burdens and benefits of HIV vaccine research will be inequitably distributed. Governments can help overcome this problem by establishing clear AIDS strategies that reserve a significant place for vaccine research, development, and delivery. Indeed, given the long timelines for vaccine development and the inherent limitations of prevention based upon behaviour modifications, it will be necessary for governments to dedicate consistent funding and incentives, over several years, to pre-clinical and clinical vaccine science as part of their long-term response to HIV/AIDS.

C. Preparing Communities for Recruitment

1. Prior Investment in Community

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304 *Ethical, Legal, and Social Aspects of Vaccine Research and Vaccination Policies*. Report of Final Conference, Community's Role in Ethical Review of Vaccine Clinical Trials. Rome: European Commission Research Report, November 2000. Available at: euroelsav.net/community1.htm. See also: Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Points 3, 5, 6, and 7.

305 D. Gold. Netherlands second government contributor to IAVI: AIDS Fonds becomes partner of IAVI, organizes community vaccine meeting at European conference. *IAVI Report* 2000; 5(1): 9.

306 E Bass. Supra, note 299.

With adequate lead time, and the political will, it is possible to identify and fill some of the gaps in the infrastructure necessary to support ethical vaccine research. As we have seen above, many of these measures make good public health sense and can also be developed in the interests of HIV prevention and overall health promotion.

Local health authorities can help communities to prepare for recruitment to vaccine cohorts by supporting the development of local expertise in health promotion, harm reduction, HIV prevention, voluntary testing and counseling, voluntary partner notification, and vaccine research. It may take several years to develop such expertise (community, professional and non-governmental). This expertise should be accessible, credible in both community and policy-making circles, populist, and sustained. Such an investment will pay dividends in the form of a critical mass of representative spokespersons capable of: (i) functioning as community researchers working as part of a team of vaccine investigators; (ii) advising research ethics boards; and (iii) forming community advisory boards when trials begin. Informed and trusted peers, when supported by researchers, can serve a key role in diffusing information and facilitating recruitment, particularly in unstructured, resource-poor communities where "word of mouth" is an important medium of communication.

2. Vaccine Preparedness Studies

Other measures, such as the instigation of vaccine preparedness studies (VPS) are unique to vaccine clinical research. However investing resources in the conduct of these studies will only make sense if there is a reasonable expectation of a substantial and sustained stream of clinical vaccine research in the given location.[307]

A VPS can be launched to recruit individuals even before any specific clinical trial is confirmed. HIV preventive counseling and testing take place at regular intervals in these studies in order to prepare cohorts and generate the data scientists need to determine the design parameters of the scientific research protocol. Participants are educated about vaccine clinical research and kept up to date about recent scientific developments. The importance of maintaining HIV preventive behaviors is also stressed.

One advantage to proceeding in this manner is a longer lead time in which to develop quality informed consent processes matched to the specific needs of target populations. Indeed experience with these studies generally demonstrates that the proportion of initial volunteers recruited who actually consent to participate when a clinical trial comes along, declines slightly with VPS participation. This is likely the result of careful communication and successful comprehension of trial related information. VPS participants have the opportunity to better understand the complexities and risks associated with the research and thus may be more likely to thoughtfully re-evaluate their initial enthusiasm. This should be regarded as a sign of VPS success rather than failure.

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[307] Note: The increasing use of a multi-centred phase III trial format may mean that individual smaller and medium-sized cities may not be able to count upon a consistent or even periodic stream of vaccine clinical research studies. In these conditions, it will be difficult to develop sustained community awareness, "savoir-faire", and support for vaccine research.

3. Recruiting from Preexisting Cohorts

People participating in pre-existing longitudinal seroincidence studies (eg, the VanGuard,[308] Polaris,[309] and Oméga[310] cohorts) can also be asked if they wish to enroll in vaccine preparedness studies or in vaccine clinical trials. However, when a research participant in a sero-incidence cohort is asked to join a VPS and subsequently to join a vaccine clinical trial, care must be taken to ensure that consent to each successive study is independent of its predecessors. Participants' loyalty to a pre-existing cohort should not inadvertently become a factor pressuring them to volunteer for a subsequent clinical trial.

4. Recruiting Where Little Preparation Has Taken Place

Finally, in communities where vaccine preparedness studies and longitudinal seroincidence / prevalence cohorts have not been present, the "stakeholders" in vaccine research (eg, the pharmaceutical sponsors, public health authorities, researchers, and community resources) would have to respond rapidly to a proposal to conduct a vaccine clinical trial, with dissemination of accurate and comprehensible information to the target community and potential volunteers. This ability to respond rapidly and adequately will be of key importance since timelines for start-up are typically short.

In such a situation, the local HIV prevention agencies will need to conduct a rapid review of the publicity to be used in the recruitment campaign and of the consent procedures. These agencies and other interested stakeholders will have to unleash a concerted and intensive program of community information and development centred around vaccine research and the need for continuous HIV preventive behaviour. During the period of advertising for recruitment, all stakeholders must be prepared to divert significant resources to this education effort.

The need for such efforts will vary with the degree of pre-existing vaccine knowledge in the community (or lack thereof) and its past experience with vaccination and clinical research. It will

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308 Note: The Vanguard Project is an ongoing study of HIV rates and risk factors in young gay and bisexual men in the Greater Vancouver area of British Columbia. The study is coordinated by the BC Centre for Excellence in HIV/AIDS, which is a joint project of St. Paul's Hospital and the University of British Columbia and is funded by Health Canada's National Health Research and Development Program. For more information, please consult the cohort's website at: cfeweb.hivnet.ubc.ca/vanguard/home.html.

309 Note: The Polaris HIV Seroconversion Study is a longitudinal (eg, six year) seroincidence study conducted by the HIV Social, Behavioural & Epidemiological Studies Unit, Faculty of Medicine, University of Toronto. To help ensure that the Study is appropriate and sensitive to participants, three representatives of community-based AIDS organizations are members of the research team. Funding is provided by: (i) the National Health Research Development Program (NHRDP) of Health Canada; (ii) the HIV Prevention and Community Action Program, Health Canada; and (iii) the AIDS Bureau, Ontario Ministry of Health.

310 Note: The Oméga Cohorte is a longitudinal (eg, eight year) psycho-social and epidemiological (seroincidence) research study of approximately 1400 men who have sexual and affective relations with men. Data generated should allow people working in the fields of (i) HIV prevention ,and (ii) support for persons living with HIV, to improve their targeted programmes and services , leading to more effective health promotion and HIV prevention among this subset of the population. The study is funded by the National Health Research Development Program (NHRDP) of Health Canada and also by the Centre Québécois de coordination sur le Sida (CQCS) through the Réseau sida et Maladies Infectieuses du Fonds de la Recherche en Santé du Québec (FRSQ). For further information, consult the cohort's web site at: omega.gre.ulaval.ca.

also be proportionate to the quantity of publicity that the recruitment process itself generates. For many Canadians, the word vaccination is associated with sterilizing immunity or nearly complete suppression of disease. This is because public health programs for licensed vaccines of *low* efficacy have primarily been restricted to precisely defined communities or subsets of the population where endemic infectious disease is present within the adult population.[311] There, the vaccines have been offered with varying degrees of accessibility (variable supply, costs, and eligibility). The result has sometimes been uneven and suboptimal levels of coverage, including less than ideal completion of the schedule of vaccinations.[312] Thus, some individuals and health-care workers alike will recall "adult" vaccination as a costly intervention yielding less than perfect results.

Still others, remembering their childhood vaccinations in school, may presume that HIV vaccines would require a stigmatizing or potentially embarrassing disclosure of risk behaviours to public health-care providers and fellow citizens in a quasi-public setting.

For large portions of the Canadian population, vaccination may only be associated with childhood vaccination, pregnancy, and travel. People, especially adult men, may thus erroneously presume that they will not be eligible for HIV vaccination and may manifest no inherent interest in participating in research or delivery. Others will erroneously presume that they are not sufficiently at risk to warrant vaccination. Community and public health stakeholders will use press briefings, press conferences, meetings with not-for-profit community-based groups, community forums, media interviews, and health practitioners in order to disseminate detailed information to overcome such misconceptions.

They will also target information to those who see the advertisements for recruitment but choose not to volunteer. In this case, they will strive to (i) encourage grass-roots support for vaccine research and general community involvement in vaccine clinical trials, and (ii) ensure that such support is informed and comprehending.

In the absence of advance preparation, the decision to rapidly mount a recruitment campaign will entail risks, including possible failings in the informed consent process, inequities and a lack of representativeness in recruitment, and inaccurate or distorted media coverage. Researchers and community stakeholders must be vigilant and prepared to allocate the resources required to apply corrective measures.

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311 Note: The BCG (TB) vaccine and the influenza vaccine have typically only been administered to people at relatively high risk. Hepatitis A and B vaccines have also been offerred to "at risk" individuals in vulnerable communities. However, recent decisions to expand the programmes of publicly funded influenza vaccination in Alberta, Ontario and Québec to cover a broader segment of the population (in order to alleviate emergency room crowding at hospitals in winter) may have the salutary effect of re-educating Canadians to be more conscious of the possibilities for use of vaccines with varying levels of efficacy.

312 Health Canada. Canadian National Report on Immunization, 1996: Ch. 8, Vaccine Coverage. *Canada Communicable Disease Report;* Supple. 23S4, May 1997. See also M Blackburn et al. Promotion de la vaccination contre l'influenza auprès du personnel des CH et des CHSLD de la Montérégie. Presentation at Prévention 2000: La santé publique en éclosion, 8e colloque provincial en maladies infectieuses. Hull Québec, le 12 mai 2000. Conference programme: 19.

D. Factors Common to Recruitment in All Vaccine Clinical Trials

1. Appeals to Community Solidarity

Very precise targeting of communities or social groups will not only facilitate recruiting, but will also engender commensurate obligations to respect that target population's dignity, culture, priorities, and needs. These obligations will be particularly acute in large scale phase III clinical trials.

In Montréal, the initial development of the public relations recruitment strategy for the AIDSVAX B/B Gp 120 Phase III clinical trial was piloted by the Oméga Cohort, a prospective, longitudinal, HIV seroincidence cohort of 1500 men who have sexual and affective relations with men. This cohort was already well established, with a high profile in the city's gay community. The publicity recruiting volunteers to the vaccine efficacy trials was mailed directly to the participants in the Oméga Cohort.

In addition, 25,000 promotional postcards were distributed door to door in the city's gay neighbourhood, in businesses frequented by gay and bisexual men, and at kiosks at gay community events. Three thousand pamphlets were distributed and 200 posters were placed in bars, restaurants, bathhouses, and cafés serving the gay male population. Numerous advertisements were placed in diverse publications catering to that population as well as in the official program of the city's annual gay pride events. Physicians with a large number of homosexual and bisexual men among their patients also received promotional materials at their offices.

The publicity materials featured photographs of two good-looking male models holding each other in an affectionate embrace and the slogan used as a headline to the text states: "We need your help to find a vaccine against HIV." The university teaching hospital where the research cohort offices are situated is located in close proximity to the city's principal gay neighbourhood. The name of the hospital was featured prominently in the advertisements.

An introductory information forum for not-for-profit community organizations was held at the city's gay and lesbian community centre. Journalists from the local media catering to the community were invited to press conferences and information forums. Articles and interviews were published in this specialized press and broadcast on radio and television programs targeting the gay market.

Cumulatively, these activities constituted a clear appeal to volunteers on the basis of community belonging and solidarity. Frequently, surveys of the participants enrolled in HIV vaccine clinical trials demonstrate that an altruistic desire to help the community is consistently among the most important factors motivating participation.[313] But framing recruitment in these terms also

[313] Studying the volunteers who make HIV vaccine trials possible: An interview with Susan Buchbinder. Supra, note 67, at 9. See also K MacQueen. Willingness to participate in an HIV vaccine efficacy trial among injecting drug users (IDUs) in Bangkok, Thailand. Presented at XIIth International AIDS Conference. Geneva, 28 June-3 July 1998, and M Langan, C Colins. Supra, note 144 at 18, and BA Koblin et al. Readiness of high-risk populations in the HIV Network for prevention trials to participate in HIV vaccine efficacy trials in the United States. Supra, note 165, and SM Kegeles et al. How should large-scale HIV vaccine efficacy trials be conducted? Recommendations from US community members likely to be targeted. Oral presentation to XIIth International AIDS Conference.

implies corresponding obligations. It raises expectations that the best interests of the target population and of the research cohort will be substantially coincident or at least not at odds with each other. While scientific truth must be protected and thus cohort results cannot be censored, researchers can work with community leaders and government funders to ensure that the information generated will be properly understood by both the target population and the general public. If such care is in fact taken, then the research results should be assimilated by the community in a manner consistent with the objectives of public and individual health promotion. A vaccine research cohort must therefore be complimented by mechanisms designed to transfer the information generated by the cohort to the community. This will facilitate delivery of a vaccine where epidemiology and efficacy data indicate it is warranted.

Participants and the gay community will expect researchers to take into consideration their local culture and not act in ways that might unnecessarily or inadvertently hurt the community. For example, the initial version of the consent form to the AIDSVAX B/B Gp 120 phase III study in Montréal provided for the collection of non-nominative DNA samples for the purpose of establishing a tissue bank for future genetic research. Members of the community advisory board voiced concern that this unrestricted use of tissue did not accord with the emphasis placed upon the community and its fight against HIV in the initial recruitment campaign.[314] The consent form was thus amended to provide that future research uses for this tissue (and derived lines of stem cells) would be restricted to HIV-related research – the principal matter of prime concern to this particular target community.

2. Mobility and Personal Information

Populations in which a high percentage of people are frequently mobile over vast geographic distances pose special challenges for volunteer recruitment and retention in vaccine cohorts.[315] A multi-centre trial with agreements permitting the transfer of a participant's file from one site to another or the gathering of data at multiple sites and centralization at one of them, may be the solution. Theoretical legal problems will, however, arise with respect to determining which legal rules govern the protection of nominative data collected at different sites. This subject is further examined in the section of this paper detailing the legal and ethical issues arising with respect to informed consent.

Geneva, 28 June-3 July 1998. Abstract no 43547, and *Project LinCS: Linking Communities and Scientists: The Lessons Learned*. Durham NC: Centers for Disease Control and Prevention, 1999, at 7. Available at www.cdc.gov/hiv/vaccine/lincs.htm, however cf. K MacQueen et al. The decision to enroll in HIV vaccine efficacy trials: Concerns elicited from Bay men at increased risk for HIV infection. *AIDS Research and Human Retroviruses* 1994; 10(Suppl. 2): S262, and RA Jenkins. Incentives and disincentives to participate in prophylactic HIV vaccine research. *Journal of Acquired Immune Deficiency Syndrome* 1995; 9(1): 36-42.

[314] Note: For example, concerns were voiced that the genetic materials collected in this HIV vaccine trial should not be used in future to investigate such unrelated matters as a hypothetical genetic role in potential multi-factorial determinants of homosexuality. It was felt that certain types of research could be politically dissentious in the community.

[315] Note: This would be the case of someone who travels from one city to another for extended periods of time for reasons of employment. It would also apply to certain Aboriginal communities on relatively remote reserves where people are required to travel long distances to larger cities in order access a variety of health and other services.

3. The Search for Personal Protection

When a community shares information via common media, potential volunteers for an HIV vaccine clinical trail may have acquired some prior knowledge about the clinical trial.[316] In the age of electronic media, information circulates beyond the geographic boundaries of the locality in which a site is located.

Recruiting volunteers to an HIV vaccine efficacy trial usually includes a concerted media campaign targeting a specific community or communities. But such a campaign cannot offer full information due to time, space, and budgetary constraints present in most media.[317] Media campaigns are primarily designed to recruit, not inform. Care must be taken to distinguish initial recruitment from the subsequent processes of individual and collective informed consent. The vast majority of volunteers responding will have a lay knowledge of vaccines and HIV research. Canadian volunteers may bring with them a memory of childhood vaccinations with high efficacy vaccines and thus erroneously associate participation in a Phase III clinical trial with an expectation of personal protection.

In the late 1990s, the Laboratory Center of Epidemiology of the New York Blood Center undertook a cross-sectional study of the willingness of individuals to participate in HIV vaccine efficacy trials.[318] More than 4800 people were interviewed in eight US cities where HIVNET (VPS) sites had been established. Subjects were selected from populations where people are relatively vulnerable to HIV-1 infection (homosexual men, male and female injection drug users, and non-injecting women at heterosexual risk). The results, published in the journal *AIDS*, revealed that "altruism" and a "*desire for protection*" from the candidate vaccine were important factors motivating participation. Among the significant predictors of a willingness to participate were: (i) reported high-risk behaviors; (ii) lower levels of education; (iii) not having private insurance for health services or only being covered by public health services, and (iv) not having participated in a previous vaccine preparedness study.

In Canada, a cross-sectional study of 505 young gay and bisexual men enrolled in the Vanguard Project demonstrated that those willing to participate in an HIV vaccine trial ("WTP") "were more likely to be younger, unemployed, live in unstable housing, and to have injected drugs in the past year or in their lifetimes" than those who were unwilling to participate. WTP participants were "[…] more likely to believe they had been infected with HIV in the past year" [….and] they were also more likely to be depressed and marginally more likely to have lower self esteem. In multivariate analysis, unstable housing and belief of likely being infected during the past year were the independent predictors of willingness to participate in vaccine research. The researchers conclude (inter alia) that:

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316 Note: There are a number of popular commercial English language magazines of a cultural and quasi-political nature which appeal to the North American gay and lesbian communities. Articles concerning the AIDSVAX B/B clinical trial were published in this largely American press long before recruitment began at the three Canadian sites. Information concerning recruitment and vaccine trials can also filter into Canada from French language magazines published in France and sold in Canada.

In Kenya, the press became an ally in disseminating information concerning a phase I vaccine clinical trial. Information was disseminated to the community via religious magazines such as *The Catholic Register*, and other similar publications with wide readership published by the National Council of Churches.

317 Note: Press briefings and press conferences resulting in a series of articles or "documentary" television and radio presentations have the potential to communicate more comprehensive information.

318 BA Koblin et al. Readiness of high-risk populations in the HIV Network for Prevention Trials to Participate in HIV Vaccine Efficacy Trials in the United States. Supra, note 165.

> […] emotional need may be a major factor affecting WTP for some young MSM.
>
> Since higher-risk and emotionally or socially unstable individuals in [the…] cohort are more likely to be WTP, HIV vaccine trial design must include measures that safeguard the psychological and physical health of potential participants.[319]

These correlations should give future vaccine researchers cause for concern. They seem to indicate that the most willing participants who respond to a recruitment campaign may very well be among the most marginal members of the target population and potentially some of the most vulnerable to HIV infection. This in turn suggests that they may be coming forward to volunteer because of an ill-informed desire to seek personal protection.

But even once the randomized, placebo-controlled nature of the clinical trial is thoroughly explained, some volunteers may nevertheless persist in hoping for some level of personal protection – in effect attempting to place the best possible odds on their side.[320] When recruiting for efficacy trials, volunteers should be carefully informed that their best hope for preventing HIV is avoiding risk behaviours or adopting harm-reducing behaviours. Obstacles preventing the adoption of harm-reducing behaviours should be carefully analyzed and, where appropriate, referrals made to support services with follow-up. Factors motivating volunteers should be carefully evaluated and, except in cases of unavoidable personal risk, those consistently seeking personal protection through trial participation should be excluded.

The notion that a vaccine trial can not be ethically looked to as a means of statistically augmenting one's chances of personal protection assumes even greater importance in this early era of clinical research involving human subjects. Moreover, in the event that a clinical trial is a hybrid Phase I-II or Phase II-III trial designed to accelerate research, then the relative uncertainty of the proffered hypothesis will likely increase.

In summary, recruits and the public in general must be made to realize that vaccine research is frequently a long, incremental, but ultimately useful process worthy of support, even if it does not offer participants direct vaccine therapeutic value.

> Sustaining public support for vaccine research while communicating the complexity of the research task will require a delicate balance of honesty and optimism....
>
> Researchers must redefine for the public the meaning of "success" in HIV vaccine research so that a human trial is not considered a failure if it contributes to knowledge which can eventually lead to an effective vaccine. Such a redefinition

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[319] JM O'Connell et al. Unstable housing and belief of infection predict willingness to participate in a vaccine trial among young gay and bisexual men in Vancouver. Poster presentation at the 10th Annual Conference on HIV/AIDS Research. Toronto, June 2001. Abstract no 338P. See also SA Strathdee et al. Feasibility of HIV vaccine trials among high-risk cohorts in Vancouver. Presentation at the XIIth International AIDS Conference. Geneva, 28 June-3 July 1998.

[320] Studying the volunteers who make HIV vaccine trials possible: An interview with Susan Buchbinder. Supra, note 67, at 8. See also R Strauss et al. Supra, note 10. Reported in D Gold, P Kahn. Higher Profile for AIDS Vaccines at Retrovirus Conference. *IAVI Report* 2000; 5(1): 1 at 15.

> will require the public and potential trial volunteers to re-orient their expectations to gradual progress and to participation in trials which may not immediately produce a licensable product. The new understanding may make trial recruitment more challenging, but it will also likely make it more sustainable.[321]

4. Treating All Potential Volunteers with Dignity and Respect

For the foreseeable future, vaccine efficacy trials will be distinguished as a "new" and high-profile activity in AIDS research. The trials will generate excitement and hope in target communities. Many different people can be expected to respond to recruitment campaigns.

Subjects will be recruited from communities where epidemiology and socioeconomic conditions suggest that people are vulnerable to infection. Recruitment campaigns will deliberately target volunteers within these communities whose behaviour suggests higher personal risk of infection. Clinical trials will best succeed in detecting and calculating vaccine efficacy when they recruit large numbers of subjects at high personal risk of contracting HIV and who participate with high retention rates over a relatively long study period (eg, two to four years). Volunteers will be people who are either motivated by an altruistic desire to help their community or who feel personally worried because they perceive themselves to be at risk (or a combination of both). Volunteers responding to recruitment campaigns may include people who, despite personal awareness of HIV and its means of transmission, have nevertheless been unable to sustain harm-reducing behaviours. Another possible subset to be targeted are people who, despite risk behaviours, do not realize that information in existing prevention campaigns also applies to them.

(i) Dignity and Respect in the Pre-Consent Process

Recruits should meet individually with a recruiting staff member in an initial interview without being immediately obliged to make a decision. Cohort staff can provide the recruits with the consent form together with more detailed information in a participant's guide, explanatory video, etc. Recruits should be permitted to take information materials (including the consent form) home for study and in order to be able to consult with their families and friends. A sensible period of time (eg, two weeks) should be provided between the initial meeting and a subsequent meeting at which consent is finally given. This cautious process gives recruits time to reflect – to carefully consider the benefits, risks, and inconveniences and, if they so desire, to ask further questions or to withdraw their application. Once consent has been accorded, participants should be provided with their own copy of the consent form and all supporting documentation to keep for future reference.

All information gathered about potential participants should be kept private and confidential.[322] From an ethical point of view, if one is to respect the dignity, autonomy and integrity of the

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321 Vactup. *Sustain.* Chapter 1 at 7. Available at: www.vactup.org/social/sustain1.html#Chapter1.

322 EJ Emanuel et al. Supra, note 302 at 2707. Note: The *Canadian Charter of Rights and Freedoms* (section 7), the Québec *Charter of Human Rights and Freedoms* and the *Civil Code of Québec* all recognize a right to be free from interference with one's physical, as well as psychological, integrity. "It has followed from this principle that [this] includes the right to be free of the psychological stress resulting from unauthorized disclosure of one's personal

volunteers, then neither the research subjects nor the people refused enrolment or who do not agree to participate in the clinical trial should have their information subsequently used for other research purposes (even if stored in non-nominative form) without their specific informed consent. Wherever possible and relevant, researchers should also seek a collective consensus supporting such new research from the targeted community.

(ii) Dignity and Respect for Ineligible Volunteers

Simply responding to an advertisement for participants does not signal automatic acceptance into a Phase III clinical trial. For instance, some volunteers will test HIV-positive in the initial screening blood test and will not be eligible for a trial of a preventive vaccine. Those in monogamous relationships or those who have abstained from sexual or needle-sharing behaviours for significant periods of time will not be of interest to vaccine researchers. Others may not be able to sufficiently comprehend the information provided in order to give valid consent. Still others may be desperately searching for personal protection from infection. Perhaps some individuals will expect to be paid for their participation in an efficacy trial. Thus, a variety of those responding to the recruitment campaign will not meet enrolment criteria. Even those that do meet the criteria should be given the opportunity to ask questions and receive considerate informative answers.

Initial interviews are information-focused and relatively short. However, among the people who do not meet enrolment criteria and those who decide to not to enroll, several may voice personal needs and concerns related to HIV prevention. While it is not the role of the clinical trial to practise social work, it must nevertheless respond to all people (accepted, refused, or refusing participation in the clinical trial) who express serious need. This can best be done by providing referrals to health and social services – including: suicide prevention, post exposure prohylaxis, voluntary partner notification and referrals to other services promoting HIV prevention and harm-reducing behaviours. By ensuring that the clinical trial forms a seamless network with health and social services, the researchers recognize the dignity of volunteers and their communities and the importance of their contributions.

> Ethical requirements for clinical research do not end when individuals either sign the consent form and are enrolled or refuse enrolment. Individuals must continue to be treated with respect from the time they are approached – even if they refuse enrolment – throughout their participation and even after their participation ends.[323]

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health information." *A Compendium of Canadian Legislation Respecting the Protection of Personal Information in Health Research*. Ottawa: Canadian Institutes of Health Research, April 2000.

The Canadian Charter however applies to governmental activities and private sector research would certainly fall outside the purview of its protection. Further legal protection from non-authorized collection, use and disclosure of personal information can be found in diverse provincial health, right to privacy, and freedom of information legislation as well as in the common law tort. For an overview of legislation affecting: the right to privacy; the statutory tort of invasion of privacy; the collection of personal information in the public and private sectors; the use and disclosure of personal information in the public and private sectors; access to clinical records and registries for research purposes; consent and substitute decision making; safeguarding, retention, and destruction of personal health information and electronic records; and the linking of data via electronic networks; please consult: *A Compendium of Canadian Legislation Respecting the Protection of Personal Information in Health Research*. Ottawa: Canadian Institutes of Health Research, April 2000.

[323] EJ Emanuel et al. Supra, note 302, at 2707.

It is also imperative that the decision not to participate or to withdraw be respected, both by the researchers and cohort staff and by persons in the community. Individuals must not be subject to coercive pressure.

5. Impact of Counseling on the Number of People to Be Recruited

Evaluating the effect of preventive counseling upon volunteers' risk assessment and assumption is difficult and controversial. Frequently, cohorts have employed HIV counseling and testing techniques that have failed or that, in and of themselves, have been insufficient to effect a significant reduction of HIV risk behaviours among research subjects.[324]

However, when preventive counseling is effective, it can sometimes result in dramatic reductions in risk assumption by clinical trial participants. This in turn will impact upon the design parameters of the vaccine efficacy trial, resulting in an increase in the number of participants needed to generate statistically significant results.

Data was presented at the XIII International AIDS Conference from an HIV vaccine preparedness study that formed an "open" cohort of female sex trade workers in Mombasa, Kenya. This was an open cohort such that individuals were continuously enrolled in the cohort and then censored after three years follow-up (having remained seronegative) or at HIV-1 seroconversion.[325] Results demonstrated that the risk of HIV-1 infection declined ten-fold during the three years of follow-up. The incidence of gonorrhea, chlamydia, and genital ulcer disease each fell by half, and significant reductions in high-risk sexual behaviour were observed. Over the four years of the study, which began in 1993, HIV seroincidence rates of 17.1, 11.5, 13.8 and 9.1 cases per one hundred person-years were observed respectively. During the same period, no corresponding decrease was observed in the targeted communities at large. It is interesting to note that this seroincidence cohort involved intensive personal contact with research participants. *Monthly* follow-up included STD screening, HIV serology, and risk-reduction counselling. Analysis reveals that there was not a disproportionately high drop-out rate on the part of volunteers who were at particularly high personal risk of contracting HIV. Instead, researchers believe that the counselling was a significant factor motivating behaviour modification.

Thus, preventive counselling potentially exercises a confounding influence upon the ability to accurately interpret the data generated by an efficacy trial of a candidate vaccine. This possibility will be amplified if the trial is testing a vaccine that is not designed to induce immunity immediately, but rather to increase immunity over time with repeated administration of "boosters." Researchers will have to anticipate and monitor very closely variations in HIV-1 seroincidence within high-risk populations. They might even require a parallel unblinded study arm designed simply to evaluate the impact of the preventive interventions offered to vaccine trial participants. This would help to avoid a situation in which expensive efficacy trials end up

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[324] LS Weinhardt et al. Effects of HIV Counseling and Testing on Sexual Risk Behavior: A Meta-Analytic Review of Published Research 1985-1997. *American Journal of Public Health* 1999; 89(9): 1397. See also C Harrison et al. Belief Clusters Among HIV-Sero-converting Drug Users: Implications for Counseling. A presentation of the New York Medical Center at the XIth International Conference on AIDS. Vancouver, July 1996. Abstract no Mo.D.1756.

[325] J Baeten et al. Supra, note 159.

with insufficient numbers of seroconversions to demonstrate protection from HIV-infection by efficacious vaccines.[326] Recruiting additional people is usually a more cost-effective solution to declining rates of risk behaviour than is extension of the duration of the trial. It is also preferable for statistical certainty (eg, in order to minimize the confounding influences of multiple variables such as changes in epidemiology, changing public awareness, and changing community prevention techniques over time).

The nature and content of preventive counselling is a subject discussed in Section III of this part of the paper, which deals with informed consent.

6. The Blurred Line between Compensation and Incentives

Typically, vaccine efficacy cohorts offer volunteers some "compensation" for the inconvenience they incur as a result of participating in the trial. Researchers can resort to a number of different compensatory and inconvenience-minimizing strategies. Examples include:

- the provision of bus tickets (and, exceptionally, taxi vouchers) to enable participants to travel to cohort appointments without incurring personal costs;
- a regular supply of condoms and clean needles;
- a token sum of money (eg, $20) per appointment at cohort offices;
- on-site child care or payment for short-term child care during appointments;
- food can be offered when appointments take place close to meal times;
- voice-mail boxes and a 1-800 message system can be provided to individual participants during the length of the trial;
- active listening at appointments as well as competent and supportive preventive HIV counselling with associated referrals;
- diagnosis of STDs and referrals for prompt treatment with follow-up to ensure that treatment takes place;
- diagnosis and treatment (or referrals for treatment) of parasitic infections/infestations;[327]
- hepatitis vaccination and other licensed vaccines could be offered far enough in advance of the first administration of the experimental HIV vaccine (or possibly placebo) so as not to confound the studies of immunogenicity (Phase II) and efficacy (Phase III). Alternatively, researchers could offer participants free vaccination at the end of the trial; and
- referral to health and social services where necessary.

One issue that immediately arises is whether it would be advisable to offer different subsets of the cohort different compensation as a function of their respective cultures, needs, and propensity to drop out.

According to one line of reasoning, individuals at higher risk of contracting HIV will be found in the subsets of the cohort characterized by socio-economic disadvantage. It is in such subgroups where people may lack the finances to procure condoms, and may be more likely to engage in

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[326] ID.

[327] Z Bentwich et al. Helminthic infections have a major impact on pathogenesis of AIDS and development of HIV protective vaccine in Africa and the developing world. Oral presentation to Late Breaker Session on Vaccines, Immunotherapy and Immunopathogenesis, at the XIIIth International AIDS Conference. Durban, South Africa, 13 July 2000. Abstract no LbOr29.

street prostitution in order to earn extra income. There may be a significant correlation between poverty and (i) higher levels of pre-existing morbidities, as well as (ii) personal disorganization and (iii) stress related to homelessness. Trial coordinators may want to offer the individuals determined to be the most vulnerable to HIV infection a more generous compensation in order to encourage them to continue volunteering for the full duration of the cohort. This would encourage individuals at high personal risk for HIV to remain in the trial and thus prevent an attenuation in cohort risk levels due to drop-out.[328] It would hopefully eliminate or reduce the need to increase the size of the cohort as the trial progresses. But if such a policy were adopted it might seed potential discord among participants and lead to overall dissatisfaction with the trial. Moreover, in so acting, the researchers would surely be crossing the line between compensation and incentive.

Even small financial compensations can become a significant incentive to people living in dire poverty. Researchers must be conscious of this possibility and ensure that the predominant criteria for recruitment to clinical trials remains scientific validity, the equitable distribution of harms and benefits, and the ultimate ability to generalize research results to the populations likely to be vaccinated.

> [F]air subject selection requires that the scientific goals of the study, not vulnerability, privilege [or poverty], or other factors unrelated to the purposes of the research be the primary factor for determining the groups and individuals that will be recruited and enrolled.[329]

As evidenced from the list above, vaccine clinical trials can offer participants preventive health services and treatment of pre-existing morbidity. Occasionally, adjunctive care is mentioned in posters and advertisements designed to recruit people to vaccine clinical trials. When a site is situated in a locality where comprehensive systems of health care exist that are trusted and used by the target population, then the vaccine trial will primarily diagnose and offer referrals. The treatment of pre-existing or new infections (other than HIV) not only benefits the health of individual participants but it is also useful to researchers, since some infections might potentially compromise the immune response to an experimental vaccine. Thus, eliminating or reducing morbidity will help to maximize the clinical trial's potential to detect efficacy and determine immune correlates.

There is, however, a potential for such attendant care to transgress the line between "reasonable compensation" and "consent-deforming incentive." In places and communities where health services are non-existent, suboptimal, or difficult for people to access, the provision of ancillary health care – even for the duration of the trial – might act as powerful motivation to participate. A persuasive influence resulting from an offer of attendant care may be felt on both a community level and by the individual recruits. The Council of Ethical and Judicial Affairs of the American Medical Association notes that research ethics boards need to be cautious when faced with such offers in resource-poor environments:

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[328] SA Strathdee et al. Supra, note 319.

[329] EJ Emanuel et al. Supra, note 302, at 2707. See also the following sources which are listed as references by Emanuel et al: TL Beauchamp, J Childress. *The Principles of Bio-medical Ethics.* New York: Oxford UP, 1996, chapter 3, and RJ Levine. *Ethics and Regulation of Clinical Research*. 2nd edition. New Haven, Conn: Yale UP, 1998, and National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Supra, note 9.

> Whole populations of people lacking *regular* access to health care services may be vulnerable to the offer of medical or related care ... if they collaborate in studies that, if they decline collaboration, will be undertaken elsewhere.[330]
>
> For individuals ... this may create enormous coercive pressures to agree to participate in a research study.[331]
>
> [I]t seems plain that individuals should not be required to enroll in high risk research protocols to obtain *minimum* health care services.
>
> [A] system that uses research participation to remedy inequities in the delivery of basic health care is unacceptable. Only when universal access is established can the argument be made that additional benefits over and above the minimum, gained by participation in research may fairly be considered by a subject in weighing the risks and benefits of enrolment in a protocol.[332] [emphases added]

The possibility that an offer of supplementary health-care services might unduly incite people to volunteer for a vaccine clinical trial looms large in the world's most underdeveloped nations. But even in those developed countries where health care is provided along lines of private insurance and collective employment-related insurance, an offer by a research cohort to provide ancillary medical services might result in the burdens of research falling disproportionately upon socio-economically disadvantaged populations.

But what of Canada? In principle, Canada has a "universal" system of medical care and services as established by provincial health acts and by the *Canada Health Act*. Does this mean that the offer of services such as the diagnosis and treatment of STDs or vaccination against other illnesses will be of little interest to volunteers recruited for clinical trials? Would the Canadian platform of preventive and therapeutic health services permit researchers to offer higher than basic quality care as "compensation" to trial participants?

Unfortunately, there are subsets of the Canadian population where people do not readily access even basic health care and preventive medicine. Worse still, several of these subsets are also the communities where people are most vulnerable to HIV infection and therefore most likely to be recruited for vaccine trials.

Evidence of poor access to preventive health care shows up in suboptimal hepatitis B vaccine coverage among gay and bisexual men. Ironically, the subsets of this population that are most vulnerable to hepatitis B have the lowest levels of vaccination.[333]

Poor access to health-care services and inadequate health care is also a problem in some Aboriginal communities in Canada. The need for better health interventions is evidenced in higher than average rates of teenage pregnancy, sexual and physical violence, suicide, and low

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330 BM Dickens. Vulnerable Persons in Biomedical Research: 50 Years After The Nuremberg Code. *International Journal of Bioethics* 1999; 10(1&2): 13-23 at 14.

331 American Medical Association, Council on Ethical and Judicial Affairs. Subject Selection for Clinical Trials. *IRB – A Review of human subjects research*; March-June 1998: 12-15 at 13.

332 ID.

333 R Noêl. Profil descriptif des participants de la Cohorte Oméga à la première entrevue. *Inf'Oméga* 1998; 2(2): 5.

self-esteem among youth.[334] Poor public health conditions are suggested by statistics and records, which despite their often partial and incomplete character, nevertheless tell a "shocking story of shortened life expectancy, and a disproportionate share of the burden of physical disease and mental illness."[335] Frequently, these problems are compounded by a lack of access to health information and facilities for dealing with an emerging public health problem caused by HIV/AIDS.[336] Many commentators stress the need for a holistic approach to Aboriginal health care in order to avoid competition among medical interests for scarce resources.[337]

Hence, in resource-poor environments and communities where people do not easily access medicine, the offer to provide or to develop better access to health care may reasonably be expected to encourage people to volunteer for clinical trials. This is an issue that also overlaps the domain of informed consent:

> […] extraneous benefits, such as payment, or adjunctive medical services ... cannot be considered in delineating the benefits compared with the risks, otherwise simply increasing payment or adding more unrelated services could make the benefits outweigh even the riskiest research. Furthermore, while participants in clinical research may receive some health services and benefits, the purpose of clinical research [including that of vaccine research], is not the provision of health services.[338]

The offer of attendant health care should therefore not be used as a means to purchase individual and community participation. To avoid corrupting the process of free and informed consent, the adjunctive services should respond to priorities set by the community. Modest, incremental contributions to the development of in situ health care operating independently, or at arm's length, from the clinical trial might be one solution to the problem of undue influence outlined above. Referrals to services (albeit with attendant support and follow-up) may be preferable to offering the supplementary medical care out of the offices of the vaccine trial itself. In the final analysis, it will boil down to a question of balanced judgment exercised by communities and researchers. This judgment should be subject to careful informed review by research ethics boards.

Compensation is also to be offered as a symbolic recognition of the contribution that volunteers make to science and hence to their community. Sometimes, vaccine coordinators will stage a "media event" featuring an individual participant receiving a dose of the experimental vaccine (or placebo) before cameras. Media campaigns sometimes describe the recruits as "heroes" or "pioneers" in the war against HIV/AIDS. While recognition is certainly merited, care must be taken to avoid overemphasizing the so-called "heroic" efforts of volunteers. For rendering clinical trial participation "glamorous" or a source of praise may also deform the free nature of consent, particularly in tightly knit communities.

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334 S Matiation. *Discrimination, HIV/AIDS and Aboriginal People: A Discussion Paper*. 2nd ed. Montréal & Ottawa: Canadian Aboriginal AIDS Network and the Canadian HIV/AIDS Legal Network, 1999 at 12.

335 Ibid, at 8. See also JD O'Neill. Report from the Round Table Rapporteur. In *The Path to Healing: Royal Commission on Aboriginal Peoples*. Ottawa: Minister of Supply and Services Canada, 1993.

336 S Matiation. Supra, note 334, at 12.

337 Ibid at 33.

338 EJ Emanuel et al. Supra, note 302, at 2704.

Finally, when designing strategies for compensating volunteers, recognizing their contribution and encouraging them to remain in the clinical trial until the end, researchers need to be culturally sensitive to the specific values and concerns of targeted communities. For example, in the AIDSVAX B/B Gp 120 Phase III clinical trial, the sponsor company provided principal investigators with a suggested list of retention strategies. Local sites were free to choose the options most likely to be effective with their volunteers. They could also adopt their own activities to encourage volunteer retention. The sponsor-provided list of incentives included the possibility of giving participants token symbols of appreciation in the form of baseball caps, T-shirts, muscle shirts, etc. However, in Montréal, this idea of providing clothing emblazoned with the study name and logo was deemed to be culturally "too public." Fears were expressed that such clothing might be interpreted as a "certificate of seronegativity," thus rendering the wearer more sexually seductive. This is but one small example of how interaction with participants will reveal cultural attitudes that vary from one site to another in multi-centre trials.

The persuasive effect of "compensatory benefits," particularly money, is explored in detail below with reference to recruitment in one specific social group, namely: a cohort of street-involved youth in Montréal.

7. Compensation for Injury

Given our uncertainty in scientific knowledge concerning the probable or possible correlates of immunity, and given the novelty of some of the technologies now being applied to vaccine development, some experimental vaccines will inevitably pose greater risks to research subjects than others. Live-attenuated vaccines, naked DNA vaccines, and delivery of HIV-antigen genes by genetically modified attenuated vectors, are but a few examples of categories of candidate vaccines that will initially present higher uncertainty regarding possible adverse events than the comparatively simple recombinant Gp 120 proteins currently undergoing Phase III testing.

Given that participants in vaccine trials are healthy (eg, not infected with HIV), the level of potential damages that would result from an adverse injury is relatively high. Thus, the issue of compensation needs to be addressed, not merely for pregnant women, but for all volunteers participating in the research. There is a legal regime for compensation of victims of vaccine-induced injury in Québec, but it only applies to licensed vaccines and not to experimental vaccines under clinical research.[339] Similarly, in the United States, the National Childhood Vaccine Injury Act[340] establishes a no-fault compensation process for persons possibly injured by the standard schedule of licensed childhood vaccines.

Compensation funds for injuries sustained in vaccine clinical research are a much rarer phenomenon. The State of California has legislation designed to encourage HIV vaccine research and development by small biotech companies operating within that state.[341] The statute sets out

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339 *Loi sur la Protection de la Santé Publique*, LR Q, c. P-35.

340 *The National Childhood Vaccine Injury Act* 1986, section 2125 of the *Public Health Service Act*, 42USC 300aa- (Suppl. 1987). See also Advisory Committee on Immunization Practices. Update: Vaccine side effects, adverse reactions, contraindications and precautions. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* 1996; 45(RR-12); 1-35.

341 *California Health and Safety Code*, Sections 121250-121280.

a comprehensive programme including; grants for research and development, subsidies for clinical trials, a guaranteed purchase fund, and an AIDS vaccine research and development steering agency. The law also establishes an "AIDS Vaccine Victims Compensation Fund" designed to be self financing with contributions from industry and government. This fund is open to persons injured during participation in a clinical trial. A standing task force has been named to monitor and review the fund's finances and operation.

The fund offers set limits for indemnities in exchange for a waiver of legal recourses. In view of the risks inherent in clinical research, and given the presumably high quality of informed consent, the indemnities provided by such a fund can be smaller than those provided in funds that indemnify the victims of injuries caused by already licensed vaccines.

A wide adoption of such measures in Canada, could reassure volunteers by providing a dependable, easy to access, and inexpensive recourse offering a foreseeable indemnity. Sponsors would see their risks of potential legal liability diminished and would be better able to quantify and manage their legal risks.

> The conditions under which compensation for alleged vaccine-induced injury will be provided should be delineated, including what criteria will be followed for determining if it is vaccine-induced, what kind of compensation will be available ... and how the amount will be determined.[342]

Support for the provision of both care and damages resulting from vaccine-related injury is unequivocally set out in the UNAIDS Guidance Document. It states:

> Guidance Point 9: Potential Harms
> The nature, magnitude, and probability of all potential harms resulting from participation in an HIV preventive vaccine trial should be specified in the research protocol as fully as can be reasonably done, as well as the modalities by which to address these, including provision for the highest level of care to participants who experience adverse reactions to the vaccine, compensation for injury related to the research, and referral to psychosocial and legal support as necessary.[343]

For obvious reasons, the issue of compensating for damages that directly result from participation in a preventive vaccine trial will also be relevant to the question of informed consent. But it is a matter of such fundamental concern and importance that it could easily impact upon rates of recruitment. Simply put, people are more likely to respond if assurances can be provided that investigative science has made a reasonable attempt to protect the financial and personal interests of participants.

Small biotechnology companies can be incorporated solely for the purpose of conducting clinical research (especially Phase III efficacy trials). Once the trials are finished, the companies may be wound up or may declare bankruptcy. Without an assurance fund, practical problems would arise in ensuring payment of long-term compensation and treatment. Alternatively, REBs and representatives from targeted communities could require the parent company legally to guaranty the subsidiary's promises to compensate victims of injury.

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342 C Grady. Supra, note 84, at 137.

343 Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Point 9.

E. A Special Case: The Continuously Open, "High Risk" Cohort

An open cohort design is one that allows for turnover of participants by continuously recruiting volunteers who are highly vulnerable to HIV infection while removing from the cohort those who succeed in reducing personal risk assumption. The Mombasa Kenya vaccine preparedness cohort described above is an example of an open cohort. Participation in the cohort was time limited to three years or by HIV seroconversion. The expulsion of participants who remain seronegative for three years is based upon the assumption that those managing to live three years without contracting HIV are statistically more likely to have succeeded in practising harm avoidance or harm-reducing behaviour. They are therefore deemed to represent a "lower risk" cohort than those freshly recruited from the community at large, where incidence rates remained high. In the Mombasa trial, "[f]ifty-seven per cent of HIV-1 sero-conversions occurred within six months of enrolment and seventy-three per cent occurred within one year."[344] Despite substantial reductions in seroincidence rates observed over the four-year duration of the open-ended cohort, it nevertheless demonstrated an average seroincidence of 13.1 per one hundred person-years. Indeed, the lowest seroincidence was 9.1 per one hundred person-years observed in year four of the study. In Canada, these levels would be considered shockingly high.

There are a number of ethical problems with this open cohort concept, designed to ensure a sample demonstrating consistent high seroincidence rates.

First, if the duration of maximum participation in an efficacy trial were to be shortened to anything less than three years, then this kind of cohort would best be suited to the testing of candidate vaccines expected to rapidly induce immunity instead of ones requiring repeated booster administration to achieve full immunity.

Second, unless managed very carefully, such a cohort might be interpreted as "punishing" people for successfully practising long-term risk-reducing behaviours.

Third, the trial design might be based upon a questionable assumption that once a participant successfully induces harm reduction, the behaviour modification is self-sustaining, long-term, or permanent. In other words, do the researchers assume that the participants expelled from the clinical trial will continue to be able to maintain safer behaviours as well as they could from within? Obviously, this will not be the case if condoms, clean needles, and empathetic support from professionals and peers are in short supply outside the trial. Much will depend upon the extent to which the community and the cohort have put into place equivalent material and human resources required to support prevention on a community-wide basis.

Finally, if the length of participation in a cohort is very short, it will prevent participants from building a sense of communal interest and community. It will also force repeated turnover in the trial participants who sit on a community advisory board.

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[344] J Baeten et al. Supra, note 159.

F. Vaccine Design for HIV Clades and the Ethics of Recruitment

There is considerable scientific controversy as to whether or not it will be necessary to design HIV vaccines that elicit a specific cellular or humoral immune response to specific "clades" or genetically diverse subtypes of HIV.[345] An affirmative response to this question would impact directly upon the kinds of persons and communities to be targeted for recruitment to clinical trials. This controversy adds an element of uncertainty to the design and testing of candidate experimental vaccines that will find echo within the communities where recruitment occurs. Witness the following statement from a prominent HIV vaccine researcher:

> Our preference is to match vaccines to local strains.... Such a strategy not only increases the chances of efficacy, but also increases the level of trust and the local sense of ownership of the project – both important factors in overcoming the political hurdles necessary to get studies started.[346]

On the other hand, there may be very practical economic and resource limitations upon our ability to design, redesign, test, and deliver multiple clade-specific versions of an HIV vaccine.

At this early stage of HIV vaccine clinical research, the clades chosen for candidate vaccines have directly affected recruitment to the world's only existing Phase III (efficacy) trials. Selection of research subjects for the AIDSVAX studies has been limited to cohorts of individuals engaging only in certain specific risk behaviours. The behaviours are matched to a candidate vaccine containing multivalent antigens (in this case glycoproteins) of a clade of HIV predominant in the test environment, which clade is hypothesized to have selected an evolutionary bias for transmission via said behaviour(s). Such a homogeneous selection of subjects to the trial increases the index of confidence in the resulting analysis of efficacy. However, this practice of selective and restrictive recruitment requires ethical analysis and reflection.

It must be remembered that subject selection can bias research results. For example, we know that severe substance use and the poor living conditions as well as other comorbidities sometimes coincident with compulsive consumption can be immunocompromising – possibly weakening

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345 J Gouldsmith. Supra, note 31. For information concerning HIV clades see DL Robertson et al. *HIV sequence database: HIV-1 Nomenclature proposal a reference guide to HIV-1 classification*. Los Alamos, Ca: Los Alamos National Laboratory. Available at hiv-web.lanl.gov/immunology/articles/nomenclature/Nomen.html, and DJ Hu et al. Predominance of HIV-1 Subtype A and D Infections in Uganda. *Emerging Infectious Diseases Journal* 2000; 6(6): 609-15.

346 W Boggs. International initiative spurs AIDS vaccine development efforts. *Reuters Health Wire Service* 3 December 1999. Summary of IAVI presentation to the 48th Annual Meeting of the American Society of Topical Medicine and Hygiene, Washington DC. Available on the Journal of the American Medical Association's HIV/AIDS website.

the response to an experimental HIV vaccine. For example, one German study has demonstrated lower response rates to the hepatitis B vaccine in hepatitis C infected subjects when compared with healthy subjects (69 versus 93 percent).[347] Preliminary, unpublished results from research currently underway with injection drug users living with chronic hepatitis C in Montreal seems to also support significantly reduced levels of immunogenicity of the hepatitis B vaccine among this cohort in comparison to "healthy" research subjects.[348]

For the above-mentioned reasons, exclusion of injection drug users from initial clinical trials of a clade B vaccine may be an ethically, scientifically, and legally justified form of discrimination in the very *early* period of vaccine research in North America. It may help scientists maximize the probability of detecting the slightest evidence of a neutralizing immune response in the vaccinated cohort, identifying desired correlates and their precise surrogate markers. Once identified, researchers may then be able to use this information to learn how to develop a subsequent generation of experimental vaccines capable of better stimulating and amplifying this response. It may be appropriate to refrain from recruiting injection drug users until this later generation of experimental vaccines is ready for testing.

However, if this exclusion is perpetuated in future clinical trials without further question, such restrictive recruitment implies a number of practical disadvantages. Such exclusions will rapidly become "unacceptable on grounds of […] generalizability and [potentially] the requirement for equitable distribution of both burdens and benefits [of the research]".[349] Both HIV clades B and E (and indeed all clades of HIV) can be contracted through unprotected sexual relations *and* the sharing of contaminated syringes. Fortunately, the AIDSVAX phase III trials currently underway include a clade B/E vaccine undergoing phase III testing on injection drug users in Thailand. This should in theory generate information that can be adapted to the situation of injection drug users in North America. However, as a general rule, any trend towards the consistent exclusion of injection drug users from future North American efficacy trials of clade B vaccines would be inconsistent with the fact that the vast majority of injection drug users contracting HIV in North America do in fact contract a clade B strain. This is simply due to the fact that it is the most common clade on the continent. Moreover, at the present time in Canada, injection drug users are among the social groups of people most vulnerable to infection. To date, clinical research involving injection drug users is almost non-existent in Canada and this pattern seems unlikely to change without a concerted lobbying effort on the part of government funders, scientists, and communities.

The choice of clades to be used in experimental vaccine research in Canada and the corresponding choice of populations, communities, and social groups targeted for recruitment to efficacy trials therefore has the potential to compromise distribution of the benefits of research in this country. If the vaccines are engineered primarily to prevent sexual transmission, the data generated may not be easily applicable to injection drug users. Ultimately, this may result in an uneven delivery, delayed delivery or the delivery of suboptimal vaccines to specific vulnerable communities.

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[347] M Weidman et al. Decreased immunogenicity of recombinant hepatitis B vaccine in chronic hepatitis C. *Hepatology* 2000; 31(1): 230-34.

[348] Interview with Dr. Susanne Brisette. Research, Clinique de désintoxication, Hôpital St-Luc, Centre hôspitalier de l'Université de Montréal, November 2000.

[349] C Levine et al. Supra, note 53, at 7.

The use of primarily occidental clades to develop experimental vaccines to be tested in non-occidental settings also raises serious questions about the distributive justice of the burdens and benefits of research. Whenever it is present, such discordance raises obvious questions about the sponsor's intention to actually distribute a vaccine in the host country. An experimental vaccine derived from clade B HIV that proves to be efficacious in a Phase III clinical trial in Africa would reasonably be expected to prove even more efficacious in the West. But if an experimental vaccine derived from clade B HIV was efficacious in the West but not in Africa (or if it is less efficacious in Africa than in the West), will scientists go back to their laboratories and engineer a vaccine designed specifically for maximum efficacy against the African clades? What level of difference in efficacy would justify such investment?

Imagine that a clade B vaccine proves to be safe at various dosages studied in Phase I and II trials conducted in a developing nation. Now let us imagine that Phase III efficacy trials are conducted with arms in both developed and developing nations and that the data generated show efficacy only in the developed nation, presumably due to a lack of cross-clade reactivity. The results would mean that the developing nation will have borne the burdens of research but ultimately reaped few benefits because of a design flaw biased in favour of the developed world from the very outset. "It would be a tragic mistake if we finally generated an AIDS vaccine and found that it protects against subtype B but not other subtypes or recombinants."[350] The developing nation would face a costly and tragic delay while scientists return to their laboratories to conceive of a clade-specific vaccine for that nation and then submit this second version to clinical testing.

Do clades really matter in the design of vaccine antigens and resulting efficacy?[351] Do antibodies and cyto-toxic lymphocytes exhibit different levels of cross clade reactivity? Unfortunately, at the time of the writing of this paper, science had yet to provide clear and convincing answers to these questions. This state of affairs leads to a number of other practical dilemmas that require scientific, ethical and possibly political scrutiny. Should sponsor companies be obliged from the outset to include in their efficacy trials specific arms for people who correspond to the future epidemiological needs for an HIV vaccine in the target community? Should they be obliged to include antigens in candidate vaccines that are designed to correspond to the predominant circulating strains of HIV? Clade-discordant clinical vaccine research currently underway in Uganda may provide some answers.[352] Furthermore, should sponsor companies be obliged to agree to produce clade-specific vaccines for developing nations where clinical trials take place if science determines that the clades really do play a significant role in determining vaccine efficacy?

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350 J Gouldsmith. Supra, note 31.

351 J Gouldsmith. Supra, note 31.

352 H Cao et al. Cellular immunity to HIV-1 clades: relevance to HIV-1 vaccine trials in Uganda. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Abstract no 590. See also P Berman et al. Rational design of multivalent gp120 HIV-1 vaccines for use in phase III clinical trials. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Abstract no 823, and BK Gaschen et al. HIV databases and analysis projects at Los Alamos: An overview. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Abstract no 164, and Re: recombination and mutation of HIV see: M Cornelissen et al. Spread of distinct human immunodeficiency virus type 1 AG recombinant lineages in Africa. *Journal of General Virology* 2000; 81: 515-23.

Some people have suggested that to answer these questions, "[t]rials with three arms should be set up. One with matched antigen, one with non-matched antigen and one with placebo".[353] However, the possibility of testing one arm with a candidate vaccine which researchers suspect may be inferior to the candidate used in another arm may give rise to some concerns. For the time being, Canadian researchers who partner with researchers conducting clinical trials in developing nations will inevitably face these questions and should prepare to engage host countries and communities in a detailed dialogue concerning this matter.

Finally, it should be noted that clades are showing evidence of migrating around the world, keeping step with human mobility.[354] Recombination of clades is also occurring and may be exerting an important influence upon the geographic progression of the epidemic.[355] Moreover, there is now some scientific evidence to indicate that super-infection (eg, by more than one circulating strain of HIV) is likely possible.[356] In the longer run, these observations should encourage vaccine researchers to envisage something other than a "one clade/one community" approach to their methodology.[357]

Should clinical trials in Canada be made to include a branch for injection drug users? Should they include an array of cohort arms – each corresponding to one of the multiple communities and social groups affected by the HIV pandemic in this country? If so, how would these objectives of inclusion best be achieved? These issues are examined from a human rights perspective below, see section I.

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353 C Williamson, R Musonda. Debate concerning Vaccines for testing in developing countries (Db3) at the XIIIth International AIDS Conference. Durban, South Africa. 10 July 2000.

354 J Böni et al. High Frequency of non-B subtypes in newly diagnosed HIV-1 infections in Switzerland. *Journal of Acquired Immune Deficiency Syndromes* 1999; 22(4): 174-9. See also M Cornelissen et al. Supra, note 352, and AK Iversen et al. Presence of multiple HIV subtypes and a high frequency of subtype chimeric viruses in heterosexually infected women. *Journal of Acquired Immune Deficiency Syndromes* 1999; 22(4): 325-32, and SK Brodine et al. Drug resistance patterns, genetic subtypes, clinical features, and risk factors in military personnel with HIV seroconversion. *Annals of Internal Medicine* 1999; 131(7): 502-6, and cf. Xiao-Fang Yu. Emerging HIV infections with distinct subtypes of HIV-1 infection among injection drug users from geographically separate locations in Guangxi Province, China. *Journal of Acquired Immune Deficiency Syndromes*; 22(4): 180.

355 K Motomura et al. Emergence of new forms of human immunodeficiency virus type 1 intersubtype recombinants in central Myanmar. *AIDS Research and Human Retroviruses* 2000; 16(17): 1831-43.

356 J Angel et al. Documentation of HIV-1 superinfection and acceleration of disease progression. Program and abstracts of the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Abstract no LB2. See also WD Hardy. HIV Super-Infection: Has it finally occurred? Summary of information presented at the 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Available at hiv.medscape.com/Medscape/CNO/2000/retro/Story.cfm?story_id=1048 and JI Mullens. Vaccine research ramps up. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Available at: hiv.medscape.com/Medscape/CNO/2000/retro/Story.cfm?story_id=1036.

357 Note: This might be accomplished by the development of multi-valent candidate vaccines. It might also be accomplished by developing vaccines that generate an immune response to invariable elements (i.e. epitopes) exposed during HIV fusion with host cells Experimental vaccines targeting a complex of human CD4 and chemokine receptors might be an approach applicable to multiple clades (although there is evidence for the existence of genetic polymorphisms of chemokine receptors in humans). MP Carolos. Five-component synthetic HIV vaccine binds to wide range of HIV variants. *Journal of Acquired Immune Deficiency Syndromes* 1999; 22: 317-23, and CV Hanson et al. Synthetic AIDS Vaccine by Targeting HIV Receptor. 7th Conference on Retroviruses and Opportunistic Infections. San Francisco, 30 January-2 February 2000. Abstract no 423A.

G. Recruiting Subjects: Confidence, Convenience, and Stereotypes

As has been mentioned, we are in the early stages of HIV vaccine research, where even Phase III trials are designed as much to identify potentially neutralizing immune responses and offer a proof of the basic concept for the vaccine construct, as to detect efficacy.[358]

In Canada, gay men, in absolute numbers, still constitute one of the largest segments of the population vulnerable to HIV infection.[359] There is an established network of community organizations fighting HIV in this country, many of which include substantial proportions of gay men in their targeted populations (for prevention and health promotion), clientele, staff, and administrators. Vaccine researchers looking to recruit subjects to a clinical trial can thus link up with a pre-existing network of non-governmental organizations with well-established roots in the gay community. Ironically, as sero-incidence rates appear to be on the rise again among gay men in parts of Canada, these communities will be increasingly interesting to corporate sponsors of vaccine clinical research. However, in Canada as elsewhere in North America, the epidemiology of HIV and AIDS is dynamic and changing. The practical effect of limiting recruitment primarily to gay men would be to exclude segments of the population that, although less numerous, experience even higher rates of seroincidence.[360]

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[358] Note: The search is for: i) any signs of neutralizing antibodies; ii) measurements of a CTL response; iii) an evaluation of the relative importance of CTL versus humoral responses; and iv) identification of the rare elements of immune response that might generate cross-clade neutralization, etc.

[359] Note: From 1996 through 1999, estimated HIV incidence in Canada remained unchanged, the number of new infections among heterosexuals increased by 26% over this same time period, while among men who have sex with men it increased by nearly 30% (from 1240 to 1610), and there was a 27% decline in the number of new infections among injection drug users.

"Prior to 1999, the proportion of new infections attributed to IDUs had steadily increased from 2% during 1981-1983 to 24% between 1987-1990 to 47% in 1996. However, 1999 incidence estimates indicate that the proportion has now dropped to 34%. Conversely, the proportion of new infections attributed to MSM demonstrated a steady decline from over 80% in 1981-1983 to 30% in 1996. Recently however, there has been a sharp increase in the proportion of new infections attributed to MSM to 38% in 1999. The proportion of new infections attributed to the heterosexual exposure category has increased steadily in the last two decades reaching 21% of new infections by 1999." Source: Health Canada. *HIV/AIDS Epi Update: National HIV prevalence and incidence estimates for 1999: No evidence of a decline in overall incidence.* Ottawa, May 2001, at 3. See also Health Canada. *HIV/AIDS Epi Update: HIV Infections increasing among MSM in Canada*. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, May 2001.

[360] See also L Noël et al. Surveillance du VIH chez les utilisateurs de drogues injectables. Abstract of presentation to Prévention 2000: La santé publique en éclosion, 8e colloque provincial en maladies infectieuses. Hull Québec, le 12 mai 2000. Note: This presentation reported on a cohort of 5,087 injection drug users in the period 1995-1999. Among 1112 repeated users of injection drugs who were initially HIV seronegative, the seroincidence rate for all of Québec was 5,4 per 100 person years. In the regions of Montreal and Ottawa, the respective seroincidence rates were reported at 7.7 (40/519.4 PA; 95% CI = 4.2 - 6.5) and 7.6 (15/197.9 PA; 95% CI = 3.7 - 11.4).

This SurvIDU study has been ongoing since 1995 and consists of seven centres providing needle exchange services to IDUs in the province of Québec plus Ottawa. "HIV incidence among repeat service attendees in the *overall* network [including Ottawa, Montréal and Québec City] has not decreased, being 4.7 per 100 person-years in 1997, 4.7 in 1998, 4.2 in 1999 and 5.3 in 2000. Source: Health Canada. *HIV/AIDS Epi Update: HIV/AIDS Among*

Including just one community (eg, gay men) in vaccine research will leave important questions unanswered about the generalizability of research results to other segments of the population engaging in different risk activities. Should the vaccine prove efficacious, gay men may end up in a relatively privileged position in comparison to women or to injection drug users.

Targeting the gay population for recruitment to vaccine research may however reflect more than a mere scientific concern to match modes of transmission and the clades of HIV proteins used in candidate vaccines.

Scientists will seek to recruit people who (i) can easily be made to comprehend relatively complex concepts, (ii) consistently return for follow-up throughout the length of the trial, and (iii) present with a minimum of secondary immunosupressive characteristics (alcoholism, malnutrition, heavy substance use, etc). Researchers may share a presumption that gay men more consistently meet these criteria than other potential target populations.

Moreover, if socioeconomic factors such as education, stable housing, etc, are allowed to weigh heavily in the balance, a kind of systemic discrimination incompatible with the standards of Canadian human rights legislation may result. There is a danger that the most vulnerable and marginal populations will be excluded from research and, by extension, from access to the resulting benefits. Gay men may be perceived as representing the most numerous, organized, stable, educated, and affluent segment of the North America communities vulnerable to an HIV epidemic. Researchers may equate these presumed characteristics with ease of recruitment to vaccine research and ease of retention.

If allowed to develop and flourish unchallenged, stereotypes involving apprehended comparative difficulties in working with certain populations vulnerable to HIV (notably the homeless, substance users, street-involved youth, Aboriginal populations) may condition researchers to permanently avoid recruiting subjects from these populations. Systemic prejudice, racism, ignorance, and a fear of added costs may contribute to this reluctance.

Researchers might further avoid recruiting individuals doubly stigmatized by a personal risk of HIV infection and some other underlying socioeconomic, health, or political condition because they fear that such participants will present more often with ethically difficult dilemmas that require time-consuming referrals and supportive interventions. Examples of such feared difficult situations might include: informed consent when volunteers are unable to read; risks of HIV transmission when a person testing positive is unable to adopt preventive behaviours; and situations requiring emergency supportive interventions (eg, a serious apprehension of suicide or situations of health-threatening substance use).[361]

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injection drug users in Canada. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, May 2001, at 3.

361 JD Bamberger et al. Helping the urban poor stay with antiretroviral HIV drug therapy. *American Journal of Public Health* 2000; 90(5): 699-701, and K Harrison et al. Supra, note 56, and RF Lago et al. Willingness of Participants in an HIV Seroincidence Study in Rio de Janeiro, Brazil, to Participate in Future Vaccine Trials. XIth International Conference on AIDS. Vancouver, 7-12 July 1996. Abstract no Pub. C. 1119, and BN Trubatch et al. Vaccination strategies for targeted and difficult-to-access groups. *American Journal of Public Health* 2000; 90(3): 447.

But social science research in both Canada and the US demonstrates that such perceptions of socio-economic stability in HIV-negative gay men relative to other communities where people are vulnerable to HIV infection may be more stereotypical than real.[362] There are also a number of vaccine preparedness studies that refute such stereotypes. There is a growing body of clinical research experience demonstrating that with reasonable accommodation, protocols can be adapted to include compensations, structures, and referrals to services that respond to the health needs and priorities of participants drawn from diverse targeted communities, all the while facilitating research. [363] In short, when difficulties are encountered, in many cases they can be overcome.

With assistance from public health authorities and other stakeholders, clinical trials can also become an additional mechanism for the delivery and development of basic community health services (eg, hepatitis vaccines, STD testing, follow-up and harm-reduction counseling re hepatitis C infection, referrals to detoxification and drug maintenance programs, and referrals to general care). The use of the structure of a vaccine trial to augment delivery and development of services to people in need is one way of maximizing benefits to participants and their communities. Key to this process is a willingness on the part of both researchers and community to acquire a measure of cultural and operational understanding and respect for each other. The development of meaningful links that respect autonomy while facilitating communication is essential. Through this process, the scope of recruitment can be potentially widened.

As we have seen above, the scientific search for accuracy and the desire at this as yet early stage of research to uncover even minimal evidence of protective efficacy has so far favoured the recruitment of homogeneous cohorts of people with a common primary risk behaviour for HIV transmission. Such a cohort is less susceptible to unforeseen and difficult-to-measure variations in risk behaviour reflecting variable external factors such as culture, economics, access to health care, etc. This practice however will have to be balanced against the following factors:

1. The objective of generating results that can be applied to a diverse population;

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362 Note: Epidemiology in the United States suggests that black heterosexual Americans will soon overtake gay men numerically as the largest population group affected by HIV. Seroincidence among black and minority men who have sex with men is very high in the US. In Canada, information from the Oméga Cohorte in Montréal, shows that although participants in that cohort (gay and bi-sexual men) have higher levels of post-secondary studies than the average heterosexual male in Québec, their income is significantly lower. It also demonstrates very high rates of attempted suicide and episodes of suicidal intentions relative to rates reported for the population at large. But even assuming that industry is aware of these factors, gay white men may still be the target of preferential recruitment to vaccine trials to the exclusion of other social groups and communities. This might occur due to stereotypical perceptions that injection drug users, «at-risk» women, homeless persons, may be too disorganized, too unstable or have needs that are too complex to make good subjects for longitudinal research. There is however a considerable emerging body of clinical research which suggests that such stereotypes can be challenged and the research can be successfully conducted with injection drug users as research subjects. See R Sherer. Adherence and Antiretroviral therapy in injection drug users. *Journal of the American Medical Association* 1998; 280: 567-68, , and Bamberger et al. Supra, note 361, and K Harrison et al. Supra, note 56, and RF Lago et al. Supra, note 361, and BN Trubatch et al. Supra, note 361.

363 B Snow. Supra, note 170. See also HIV Prevention Trial Unit. What is HPTU and What do we do? Available at depts.washington.edu/hptuDescrp.htm, and L Weldon et al. Supra, note 362, and GR Seage III et al. Feasibility of conducting HIV-1 vaccine trials in the United States: recruitment, retention and HIV-sero-incidence from the HIV Network for Prevention Trials (HIVNET) Vaccine preparedness study (VPS). XIIth International AIDS Conference. Geneva, 28 June-3 July. Abstract no 43543, and GR Seage III et al. Are US populations appropriate for trials of human immunodeficiency virus vaccine? The HIVNET Vaccine preparedness study. *American Journal of Epidemiology* 2001; 153(7): 619-27.

2. An urgent public health need to develop preventive vaccination for a wide diversity of populations, communities, and social groups where seroincidence levels are high; and
3. An array of legal and ethical arguments and guidelines, rooted in a human rights approach to health, favouring an inclusive and distributive approach to research and thus diversity in the recruitment process. These arguments are detailed in the next sub-section.

H. Is Participation in a Vaccine Clinical Trial a Right or a Privilege?

We first consider this question in the light of the law.

In Canada today, the short answer to the question is that participation begins as a privilege but, under the weight of numerous systematic exclusions, it may also become an actionable right. Generally, there is no proactive right to access research in Canada. "A research program is not part of the purview of regular services offered by a hospital within the framework of its institutional mission. [….] Participants are chosen according to the researcher's initiative."[364] Research is not generally classified as a professional service or as a contract, and absent a legal obligation founded in human rights legislation, individuals cannot use the courts to demand access to a clinical trial.

Provincial human rights legislation governs relationships between citizens. This includes relationships between the person volunteering to take part in a clinical trial and a principal investigator exercising an illegal discrimination in the selection of subjects. If the discrimination is a direct expression of purely personal prejudice held by the principal investigator, it is doubtful a sponsor, if uninformed of the situation, could be held liable. The required link of subordination between the discriminating investigator and the pharmaceutical company would be missing. If, however, the discriminatory exclusion of people is apparent on the face of the recruitment statistics, it might be possible to argue that the sponsor, which holds a contractual power to discipline the principal investigator, has been engaging in wilful blindness. In this latter situation, the vicarious liability of the sponsor will be engaged.

A sponsor company whose research protocol prescribes unscientific discriminatory selection criteria on the basis of a legally interdicted ground of discrimination:(eg, race, ethnicity, handicap, physical disability, sex, sexual orientation,) or whose recruitment procedures systematically result in the exclusion of such subsets of the population would also be open to legal challenge under provincial human rights legislation. Once the complainant establishes a de facto pattern of discrimination, the burden of proof shifts to the sponsor and/or principal investigator to establish sound scientific or economic criteria justifying the exclusion(s).

The legal provisions of provincial medical professional codes of ethics also serve as guidelines for the principal investigator, prohibiting discrimination in the selection of patients on illegal and

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364 *Gomez et Labrie* c *Michaud et al*, CS 200-05-011466-997. [Unofficial translation]

non-scientific grounds. With respect to the clinical trials of HIV vaccines, the distinction between research and clinical care is relatively clear. However, HIV testing and the pre- and post test counselling which accompany it, fall squarely within the realm of therapeutic professional practise. Hence, within the trial, legally prescribed codes of ethics will prescribe a non-discriminatory equitable application of good clinical practice on an as-required basis. Clinical trials should not proceed in environments in which good clinical practice for HIV testing does not otherwise exist or cannot be developed. If, however, such a situation were to arise, even temporarily, then the legal protection offered by professional codes of ethics could be extended to the actual process of recruitment itself in order to prevent an otherwise arbitrary and discriminatory bar to a quality medical service.

We now consider this question from the perspective of research ethics.

International documents developed in the decades following World War II, focused upon the protection of vulnerable human subjects. Notable examples include the Nuremberg Code,[365] the Declaration of Helsinki,[366] the Belmont Report, and the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects.[367] However, ethical guidelines governing clinical research increasingly reflect a duality in which the need to protect subjects is necessarily complimented by an equitable and inclusive approach to recruitment.

Where is the relationship between human rights, ethics, and recruitment to HIV vaccine trials today? The demand for inclusiveness finds different but parallel voices in developing and developed countries. In sub-Saharan Africa, the epidemiology reveals an epidemic that is already so prevalent that it corresponds to broad segments of the general population in which people are sexually active. There, the primary requests are for basic access to treatments and supportive infrastructures, clinical trials and primary access to prevention (materials, resources). In North America, by contrast, the epidemic is more confined to numerous marginalized communities varying widely in their cultural, economic, health, and political realities. In some of these communities, access to health care can also be very difficult. On this continent, the fight against HIV and AIDS is a fight against multiple epidemics.

However, despite their differences, calls are increasingly being heard and indeed encouraged in both environments ("developing" and "developed") for access to HIV vaccine clinical research. This fight is not dissociable from human rights, including a basic "human right" to health, and ethical principles of distributive justice. Thus, more than a decade after AIDS activists lobbied for greater access to clinical investigative medicine and more rapid approval of licensed drugs, the same civil rights discourse (albeit as a fainter echo) can be expected to resonate in community demands for inclusive access to clinical trials of experimental prophylactic HIV vaccines.

The seeds for the discourse of primary inclusion exist in many ethical and legal instruments that can be looked to for guidance in the conduct of clinical HIV vaccine research. Notable examples

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365 *The Nuremberg Code*. Supra, note 9, at 181-2.

366 World Medical Association. Supra, note 101, at Recommendations guiding physicians in biomedical research involving human subjects.

367 *The Belmont Report*, supra, note 9; Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS/WHO, 1993.

include the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (1999)[368] and the UNAIDS guidance document entitled Ethical Considerations in HIV Preventive Vaccine Research (2000).[369]

The principle of distributive justice was incorporated into the US *Belmont Report* (1979), which established guidelines for research involving human subjects. In that Report, supra, the principle is used to ground guidelines for the "equitable distribution of research participation, fairness and *inclusion in subject selection* and policies to protect the exploitation of the vulnerable."[370] [emphasis added]

> It is essential that data be developed to serve the well being of all groups affected by the research. In the case of HIV infection, this includes men, women (including those have the biological capacity to become pregnant), children, intravenous drug users, prisoners, racial and ethnic minorities, persons with mental incapacities and others….[371]

Similarly, notes to the Tri-Council Policy include the following statement clearly reiterating the close relationship between justice and inclusiveness:

> [D]istributive justice means that no segment of the population should be unfairly burdened with the harms of research. It thus imposes particular obligations toward individuals who are vulnerable and unable to protect their own interests in order to ensure that they are not exploited for the advancement of knowledge.... On the other hand, distributive justice also imposes duties neither to neglect nor discriminate against individual and groups who may benefit from advances in research.[372]

These notes set out an ethics framework that includes the principle of inclusiveness in recruitment and that anchors research from a subject/participant-centred perspective. Research ethics boards are urged to respect the spirit of the *Canadian Charter of Rights and Freedoms*, particularly the sections dealing with life, liberty and security of the person as well as those involving equality and discrimination.[373]

The equality provisions of the Charter will already apply to research conducted by a federal or provincial government agency, but the Charter's jurisdiction extends to decisions that are founded upon the exercise of statutory governmental authority. Most medical research in Canada

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368 Medical Research Council of Canada. Supra, note 76, at Context of an Ethics Framework, C. Guiding Ethical Principles: Respect for Justice and inclusiveness, and Section 5: Inclusion in Research.

369 Joint United Nations Programme on HIV/AIDS. Supra, note 10, Context notes at 7, Guidance Point 2 and accompanying notes at 13-14, Guidance Point 4 and accompanying notes at 17-18, and Guidance Point 7 and accompanying notes at 22-23.

370 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Supra, note 9, at Part B: Basic Ethical principles (3) Justice. See also C Weijer. Supra, note 217.

371 C Levine et al. Supra, note 53, at 8.

372 Medical Research Council of Canada. Supra, note 76, at Context of an Ethics Framework, C. Guiding Ethical Principles: Respect for Justice and Inclusiveness.

373 Medical Research Council of Canada. Supra, note 76, at Context of an Ethics Framework, D. A Subject-Centred Perspective.

is either privately funded or conducted through entities sufficiently distinct from government that it can not be made legally subject to these constitutional provisions. Nevertheless, the reference to the constitutional measure of equality and non-discrimination in the Tri-Council Policy Statement sets a high instrumental standard for Canadian researchers.

Article 5.1 of the Tri-Council Policy Statement also "imposes a duty on researchers not to discriminate against disadvantaged groups…." "[T]he intention is to obtain a more just distribution of the benefits of research across all groups."[374] However, "[t]his does not necessarily mean that each and every protocol must be open to all affected groups."[375] A careful balance must therefore be struck between (i) the need to satisfy the recruitment parameters required to meet the specific objectives of research, which in the case of HIV vaccines may, for scientific reasons, be legitimately concerned with precise subsets of the vulnerable population, and (ii) society's "overarching reprobation of unjust discrimination". [376] The Tri-Council Policy Statement also notes the need to balance the protection of potentially vulnerable research subjects from undue exploitation with the need to ensure that these very individuals also access needed benefits of research.[377]

Article 7 of the UNAIDS Guidance Document calls upon researchers to acknowledge in the protocol "the social contexts of a proposed research population … that create conditions for possible exploitation or increased vulnerability among potential research participants, as well as [set out] the steps that will be taken to overcome these and protect the dignity, safety, and welfare of the participants."[378]

Thus, the approach adopted by international and national guidelines for ethical research involving human subjects is one in which:

- The potential vulnerabilities of participants and the target communities are recognised;
- Appropriate and reasonable steps are taken to protect research subjects from undue coercion or exploitation, and
- To the extent that such reasonable protection can be achieved, volunteers are selected on scientific grounds, free of discriminatory or arbitrary exclusion criteria and practises, such that
- Clinical trials are guided by a recognition of the need to be able to generalise results and to ensure an equitable distribution of the burdens and benefits of the research.

The Canadian Tri-Council Policy specifically mentions inclusion of women, children, and Aboriginal populations in research.[379] For its part, the UNAIDS guidelines for ethical considerations in HIV vaccine clinical research call for the recruitment of both women and

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374 Ibid, at Notes to Article 5.1.

375 C Levine et al. Supra, note 53, at 8.

376 L Gostin, Z Lazzarini. Childhood Immunization Registries: A National Review of Public Health Information Systems and the Protection of Privacy. *Journal of the American Medical Association* 1995; 274(22): 1793-99.

377 Medical Research Council of Canada. Supra, note 76, at Section 5: Inclusion in research. A. Introduction.

378 Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Point 7 and accompanying notes at 22-23.

379 Medical Research Council of Canada. Supra, note 76, at Sections 5 and 6.

children to trials.[380] Both documents, however, fail to provide special mention for possible involvement of injection drug users in clinical research.

In section J, a brief analysis is provided of some of the issues specific to the recruitment of people from important subsets of the population to HIV vaccine clinical trials.

I. Recruitment Via the Internet

In the United States, research companies are increasingly developing "ways to inform, and recruit participants, and manage trials data through Web-based tools".[381] In fact, some sponsors are out-sourcing their recruitment functions by contracting with a third party electronic internet based company mandated to use the internet and links from websites in order to locate pools of potential volunteers, promote the clinical trial, and contact and link up with participants.[382] These third party e-businesses are sometimes referred to as "contract research organizations" (CROs). CROs can also be incorporated subsidiaries of pharmaceutical firms sponoring clinical research. "These companies operate on the assumption that clinical trials are as paper-choked and bureaucratic as most other areas of the health care industry and overdue for [streamlining and] improvement".[383]

Using the internet to reach potential volunteers probably works best for clinical trials of therapeutic treatments since there a number of websites designed to provide information directly to people suffering from a particular common malady (eg, breast cancer, diabetes, HIV). With HIV preventive vaccine trials however, participants are not yet infected and therefore the potential pool of prospective volunteers is more dispersed across the internet. Advertisements and links could be placed on web sites catering to some of the specific communities likely to be targeted for vaccine research (eg, gay men, and First Nations peoples).

In the text which follows we will examine some of the potential strengths, challenges and disadvantages of using this kind of medium for recruitment.

(i) Potential Advantages

Recruiting via the internet could transmit promotional materials: information about admission criteria, consent forms, and the return of accepted consent forms. The internet could also be used

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[380] Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Points 17 and 18.

[381] S Lutz, SJ Henkind. Recruiting for clinical trials on the web. *Healthplan* 2000; 41(5): 36-43.

[382] Shering-Plough. Shering-Plough reports 2000 second quarter earnings per share, reviews pharmaceutical research and business progress. Press Release of 12 July 2000. See also DA Slayton Shiffler. Austin is national hub for clinical drug trials. *Austin Business Journal* 14 April 2000.

[383] S Lutz, SJ Henkind. Supra, note 381.

to administer comprehension tests to potential participants in order to ensure the individual participant understands the risks and benefits.

Recruiting via the internet may allow sponsors to rapidly reach large numbers of people, many of whom might not otherwise become aware of the vaccine trial through more traditional methods of publicity. The internet is undeniably popular with the younger generations in the Canadian population – where some of the prime target populations for HIV vaccine trials are found.

The internet can become a key element in a highly organized patient recruitment model designed to accelerate recruitment and hence compress the timeline for clinical investigation. The model can include "such elements as a centralized call centre, patient screening, scheduling and transportation to sites, and online patient tracking and reporting."[384] The internet can also serve to facilitate the establishment of links between research subjects and physicians, between site investigators and the corporate sponsor, and between community advisory boards at different sites. It also serves as an efficient means to collect the vast amounts of data necessary for regulatory filing.[385]

There is a further means by which to use the internet to find and recruit volunteers to clinical trials. "Using databases to search for potential patients [volunteers] is more likely to be effective than recruiting them [directly] through the internet".[386] This involves the use of existing websites who ask visitors via a generalized consent form, for permission to transfer their co-ordinates (e-mail) and other data to companies conducting clinical research. This kind of consent could also be solicited in a multitude of different fora - wherever databases containing health and social information are kept (eg, insurance companies, health management organizations (US), community based organizations).

The intermediary website / database can be contractually charged with the responsibility to advertise and promote the clinical trial, and compile a list of potential volunteers interested in vaccine research. They use software to match individual profiles to recruitment criteria, effecting a triage in order to select the most qualified candidates and then provide this triaged list to the investigator's offices.

(ii) Questions Concerning Recruitment Over the Internet

Use of this new media raises a number of interesting questions some of which are set out below:

- To what extent should communication via machine be allowed to supplant communication with a trained intervenant during the recruitment process?
- Can you really evaluate comprehension in such a long-distance relationship, in which a machine is interposed between the people communicating?
- Who will supervise the quality of information and recruitment publicity disseminated on the internet?

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384 DA Slayton Shiffler. Supra, note 382.

385 Shering-Plough. Supra, note 382, and B Richards et al. Conducting Clinical Trials via the Internet. Presentation to the International Conference Addressing Information Technology in Community Health. University of Victoria, British Columbia, 23-27 August 2000.

386 S Lutz, SJ Henkind. Supra, note 381.

- Where will the potential volunteer turn for an impartial, critical and comparative evaluation of the relative merits, benefits and risks of concurrent and competing clinical trials? Large research centres sponsoring many concurrent trials will occasionally provide access to a physician via a 1-800-telephone number. The doctor counsels patients to make their best choice between competing clinical trials.[387] This process effectively bypasses the family physician with his knowledge of the patient's medical and social history.

[387] ID.

(iii) Challenges and Diasadvantages Associated With Recruitment Via the Internet

Use of this relatively new technology raises concerns about: the protection of privacy and confidentiality.

> E-mail, […] can be misdirected, printed, intercepted, rerouted and read by unintended recipients. Most importantly, just as voice mail may be maintained by a computer platform, e-mail mail be stored indefinitely, even after its user deletes a message. Encryption software can act as a type of envelope, scrambling the message contents until the message is received by the intended addressee [….]. Although additional technological safeguards can render e-mail relatively secure, technology alone cannot ensure its legal and ethical use in medical practise. [388]

In the United States:

> […] employers own their e-mail systems and any messages sent or received over them. They have the right to review any e-mail messages and may be subject to disclosing their contents in legal proceedings. Likewise, providers of online services [servers] may also access messages of their subscribers without specific warnings. With these "reasonably anticipated" potential third-party intruders, it is difficult to argue that a one-on-one, private communication takes place over e-mail - particularly if the message must travel over the Internet, whose gateways are numerous and often unpredictable prior to transmitting a message.[389]

A prominent internet site providing information to HIV positive individuals includes a database contract which declines responsibility for "unauthorized interception or infiltration" of the data an individual is required to submit in order to be part of a list of potential prospects for clinical research. The contract also limits liability for misappropriation of the data "by third parties or by employees of technology providers."[390] Thus, connecting with a vaccine study via the internet, may force the volunteer to surrender some of the legal protection normally afforded confidential information when it is communicated directly to the sponsor. It also makes legal enforcement and the practical ability to recover damages for violation of privacy rights much more difficult.

This is not the only problem associated with use of the internet. For example, the intermediary may have the sole discretion to send the potential volunteer's profile to the pharmaceutical sponsor/P.I.. The individual may be certain that he is well suited for a vaccine trial, but in fact has no confirmation and no assurance that his profile will ever get to the study's offices.[391]

Relying upon the internet as the primary tool for contacting and recruiting volunteers, may bias the research in terms of reaching only those who are sufficiently wealthy to have regular access to a computer and the internet. This could further marginalise poor and socially disadvantaged

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[388] AR Apielberg. On Call and Online: Sociohistorical, legal and ethical implications of Email for the patient-physician relationship. *Journal of the American Medical Association* 1998; 280(15): 1353-59.

[389] ID.

[390] Volunteer for Research! Participation Agreement. *The Body* 10 September 1999. Available at www.thebody.com/surveys/health_survey1.html.

[391] ID.

communities where sero-incidence is high and where eventual vaccination could be extremely beneficial.[392]

Further possible problems with respect to online recruitment include:

- the difficulty of assuring that the person operating the computer (at the moment when consent to access e-mail and other data is given out) is in fact the person to whom that information belongs[393];
- the potential erosion of the specific quality of informed consent in favour of a more generalized waiver of privacy;
- practical difficulties in retracting this kind of consent to access data;
- undesired or aggressive solicitation;[394]
- financial conflicts of interest (eg, the website, the third party e-commerce, the research centre)[395]; and
- difficulty in applying provincial privacy legislation over an internet stretching around the world.

A website advertising vaccine research and recruiting volunteers will need to be continually updated and watched closely. Sometimes, other webmasters promoting causes not directly concerned with vaccine research will link to the vaccine trial's site. For example, some years ago at least one internet site promoting unsafe sexual relations for gay men, proposed a meeting of men participating in the AIDSVAX B/B clinical trial. The site also provided a link directly to a webpage promoting the clinical trial.

(iv) Further Uses for the Internet

Some studies in the U.S. have shown that people are more likely to respond honestly to questions concerning their sexual or needle sharing behaviour when answering by machine rather than by filling out questionnaires in the presence of a trial.[396] Using the internet, participants could report sexual behaviour from the privacy of their own homes and at more frequent intervals.[397] This should increase the accuracy and the comprehensiveness of the reported data.

(v) Conclusion

When recruitment takes place via the internet, or if trial participants regularly report sexual behaviour via e-mail, then the trial participant will have a right to know what measures have been put into place to ensure the privacy of the transmitted information, what are the limits of these security measures, who will have access to the data, and whether the data will be forwarded to others via email.

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[392] AR Apielberg. Supra, note 388.

[393] Note: On a somewhat related matter see MJ Steiner et al. Bogus Participation in Clinical Trials: Research Letter. *Journal of the American Medical Association* 2001; 285(3).

[394] S Lutz, SJ Henkind. Supra, note 381.

[395] ID.

[396] Studying the volunteers who make HIV vaccine trials possible: An interview with Susan Buchbinder. Supra, note 67, at 9.

[397] S Lutz, SJ Henkind. Supra, note 381.

J. Issues for Specific Populations

Any review of recruitment processes needs to take into consideration the errors of the past. The Nuremberg Code (1947),[398] the Helsinki Declaration (1964) and [399] the Belmont Report (1979)[400] seek to establish an ethical framework for research to prevent multiple abuses resulting from the recruiting and coercing of vulnerable subjects without protecting their dignity, autonomy, and human rights.

When considering the issue of inclusiveness and equity in recruiting volunteers to vaccine clinical trials in Canada, one begins by recognizing the vulnerabilities of communities and social groups in this country that are affected by HIV epidemics.

1. Street-Involved Youth

It is far from obvious that one can give an unqualified affirmative answer to the question of whether street-involved youth should be recruited to participate in HIV vaccine efficacy trials in Canada today.

In Montreal, "Jeunesse dans la Rue," - a public health sponsored cohort of approximately 700 street-involved youth, aged 14 to 25, offers one concrete reference point for any consideration of this question. This cohort has existed for five years, has a relatively high retention rate, and illustrates that an extremely marginalized and highly mobile sub-population can in fact be reached and be involved in the research process.

Consequently, a systematic refusal to conduct clinical vaccine research in this population, based upon stereotypical projections of poor retention, would be ill-founded in fact, unethical, and probably constitute illegal systemic discrimination under certain provincial human-rights acts.[401]

However, overall data concerning HIV seroconversion do not suggest that the street-involved youth would have a strong interest in participating in HIV vaccine research. This factor alone might amount to a valid scientific criterion justifying exclusion of this group from recruitment to

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398 *The Nuremberg Code*. Supra, note 9, at 181-2.

399 World Medical Association. Supra, note 101, at Recommendations guiding physicians in biomedical research involving human subjects.

400 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Supra, note 9, at Part B: Basic Ethical principles (3) Justice.

401 Quebec *Charter of Human Rights and Freedoms*, LRQ, c C-12, art. 10. See also *Canadian Charter of Rights and Freedoms*. *Constitution Act*, (1982), Part I art. 15.

a vaccine efficacy trial. Nevertheless, one should note that within the cohort there are identifiable subpopulations who are at higher risk of contracting HIV and where priorities, interests, and health imperatives may be propitious to recruitment for a vaccine trial. This underlines the importance of working closely with local health researchers and community in order to first acquire a prerequisite sophisticated understanding of potential target communities and subsets thereof before proceeding to recruit.

If street-involved youth are recruited into vaccine efficacy trials, the issue of compensation will have to be considered carefully.

Street-involved youth who participate in the Jeunesse dans la Rue cohort are offered incentives such as $20 for each two-hour interview, movie passes, concert passes, gift coupons, and food during community forums. These encourage recruitment as well as retention of subjects until the cohort reaches completion.

"Whether or not such financial compensation should be given in a vaccine trial" and; if so, "in what amounts?" are questions relevant to both recruitment and to informed consent. In principle, clinical trials of experimental medicines or vaccines in which there is a potential risk to health do not employ incentives but rather merely offer compensation for inconvenience. But whether offered as an incentive in a seroincidence cohort such as Jeunesse dans la Rue, where risks are minimal, or as compensation in a vaccine clinical trial where there may be potential risks to health, such figures are routinely displayed in publicity recruiting people to cohorts. They are usually offered from the initial screening interview. Thus, the issue of an ethical limit to the quantum of compensation is analyzed in this section of this paper.

The "free" character of informed consent is an essential element reflecting the autonomy and dignity of the research subject. In Canada, it is a legally and ethically imposed imperative that consent to clinical treatment and to participation in clinical research be informed, comprehending, and voluntary.[402] Given the relative novelty and uncertainty associated with experimental vaccines, and given the potential impact of these clinical trials upon participants' commitment to preventive behaviours, there is an accentuated onus upon the researchers to ensure that processes of recruitment and consent respect these standards. Furthermore, researchers must be sensitive to the potential imbalance of knowledge, power, and resources that exists between the researcher and participants at the moment of initial recruitment. This imbalance can be particularly accentuated in the field of HIV vaccine research targeting people from marginalized communities who may be particularly sensitive to economic inducements.

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402 For jurisprudence re consent to medical procedures, see: *Koehler et al* v *Cook* (1976), 65 DLR (3d) 766 (BCSC); *Reibl* v Hughes [1980] 2 SCR 880; Hopp v Lepp (1980) 112 DLR (3d) 67 (SCC); Weiss c Solomon [1989] RJQ 731-745 (CS). For jurisprudence re consent to experimentation (research), see Halushka v University of Saskatchewan (1965), 53 DLR, (2d) 436 (Sask. CA); Cryderman v Ringrose [1977] 3 WWR 109; aff'd [1978] 3 WWR 481 (Alta. CA); Weiss v Solomon [1989] RJQ 731-745 (CS). For doctrine concerning consent to experimentation see DJ Roy et al. Supra, note 77, at 329; G Sharpe. The Law & Medicine in Canada. 2nd ed. Toronto: Butterworths, 1998, at 79. For ethical guidelines concerning consent to clinical trials see Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Point 12; Medical Research Council of Canada. Supra, note 76, at Context of An Ethics Framework, Part C; Guiding Ethical Principles: Respect for Free and Informed Consent; Section 2: Free and Informed Consent; Part A: Requirement for Free and Informed Consent, Article 2.1 a; Section 2: Free and Informed Consent, Part B: Voluntariness, Article 2.2; The Nuremberg Code. Supra, note 9, at 181-2; Federal Centre for AIDS Working Group on Anonymous Unlinked HIV Seroprevalence. Guidelines on Ethical and Legal Considerations in Anonymous Unlinked HIV Seroprevalence Research. Canadian Medical Association Journal 1990; 143(7): 625-27.

> In everyday life … completely free consent is more a myth than a reality, since many factors are likely to have a deciding influence on the will. It must therefore be admitted that, practically speaking, there are various degrees of freedom of consent. The law should intervene only when the degree of constraint on that freedom is unacceptable in comparison with what is at stake; and in medical matters what is at stake is bodily integrity, a value far outweighing mere economic interests. Accordingly, absolute freedom of consent should be considered an ideal to be achieved, a goal to be approximated as closely as possible.[403]

Vaccine researchers will therefore have to be extremely conservative in the use of incentives to recruit and retain participants to trials, especially those from economically disadvantaged populations. At first glance, it may seem reasonable to proffer symbolic tokens of appreciation for the volunteer's altruism, time, effort, and inconvenience. On the other hand, $20 might represent more revenue than could be raised in two hours of soliciting coins on a cold street corner in November. To evaluate the persuasive effect of such incentives, vaccine researchers must understand their target population. They will have to identify the levels at which financial compensation ceases to be symbolic and starts to become a significant incentive capable of deforming the "free" (eg, non-coercive) character of consent.

The research team at Montréal's street-involved youth HIV/Hepatitis C cohort discussed the question of whether they would favour recruiting people from this cohort to a clinical trial of an HIV vaccine, and reported to author of this paper that:

> In principle, everyone who qualifies on the basis of vulnerability to risk of HIV infection should have access to vaccine clinical trials. But given that street-involved youth are generally vulnerable on a multiplicity of levels, we believe that offering an incentive to participate in an experiment that carries potential risk is ethically questionable. To offer them money might encourage them to submit to an experiment with potentially serious long-term consequences, simply because they desperately need the money. Incentives, especially in the form of money, will be the principal motivation behind their decision.
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> Given the above, this vulnerability, and the imbalance between the magnitude of the expected benefits and potential risks, we would not be inclined to widely promote recruitment to vaccine clinical trials among street-involved youth.[404] [translation]

2. Injection Drug Users

[403] Law Reform Commission of Canada. Protection of Life: Biomedical experimentation involving human subjects: Working Paper 61. Ottawa: LRC, 1989.

[404] Email from Dr. Élise Roy, Researcher (Régie régionale de la santé et des services sociaux de Montréal-Centre, Unité de maladies infectieuses), to David Thompson. 1 June 2000. Note: Dr. Roy is principal investigator for the Montréal Street Youth Cohort Study. This cohort presented information concerning high rates of mortality and extreme psychosocial vulnerability of street involved youth in Montréal to Tracking the HIV/AIDS/STD epidemics in Canada, Outline for HIV/AIDS/STD Joint National Meeting. Calgary, 19 November 1999.

> When a homogeneous response cannot be assumed for specific subgroups of the population, it is essential that enough members of the relevant subgroups be included so that a differential response can be detected and measured.[405]

The record of clinical research into antiretroviral medications demonstrates that those working in the field of HIV/AIDS have rarely been able to broadly include users of illegal substances in their clinical investigations. Yet as the complexity of therapeutic choices has increased, so has the number of potential interactions between medications and other prescription drugs, illegal substances, and alternative therapies.[406]

Unfortunately, the vast majority of clinical trials of HIV medications did not contain stratified arms analyzing safety, dosages, and efficacy of experimental medications when used in combination with illegal and alternative substances. Today there is a plethora of anecdotal reports in the gay press of deaths related to excessive consumption of "club drugs."[407] Cross-reactions between club drugs and prescription medications, including antiretroviral medications, are strongly suspected. A few have been documented through post-marketing surveillance.[408] But most such interactions cannot be precisely evaluated for want of serious clinical examination.[409]

Presumed non-compliance and difficulties with facilitating informed consent have often been advanced as reasons justifying the exclusion of users of illegal substances from the clinical research agenda. In the case of vaccine trials, however, the compliance obligations are relatively modest and do not differ substantially from several seroincidence/seroprevalence studies that have successfully recruited and retained injection drug users in Canada for many years. Indeed, vaccine preparedness studies indicate that under accommodating conditions, injection drug users are willing and able to participate in vaccine trials.[410]

Will it therefore be possible to avoid ill-founded exclusionary pitfalls when designing protocols for clinical trials of HIV vaccines? Could trials contain arms to evaluate possible cross-reactions

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405 JC Bennett. Inclusion of women in clinical trials: policies for populations subgroups. *New England Journal of Medicine* 1993; 329(4): 288-92.

406 Note: This unknown potential concerned more than the traditional street drugs (heroine, cocaine, crack-cocaine) and recreational drugs (marijuana, hash, amyl-nitrates [poppers]), but also new pharmaceutical prescription drugs (Viagra). New chemicals or recycled chemicals such as MDMA (Ecstasy), Ketamine (Special K), GHB, Methamphetamine, (Crystal Meth), are used as recreational drugs in the all-night dances of gay circuit parties and youth hip-hop dances and "raves". This latter grouping of drugs are sometimes referred to as "club drugs".

407 Note: Uncompensated dehydration related to use of Ecstasy (R) is one example. Both Viagra and amyl nitrates (poppers) lower blood pressure and the cumulative effect is known to be dangerous. Community based organizations serving the gay population now routinely issue warnings not to consume both simultaneously. See Bad Boy Club Montréal. *Please, party & play safely!* Montréal: Bad Boy Club, September 1999. See also The too-hard drugs: Club drugs, cannabis and clinical research. *The HIV Herald* 2000; 9(4).

408 JA Henry, IR Hill. Fatal Interaction Between Ritonavir and MDMA. *The Lancet* 1998; 352(9142): 1751-2. See also World Health Organization. Ritonavir and Ecstasy: a fatal combination. *WHO Drug Information* 1998; 12(4): 238.

409 A cross-reaction has been documented between the protease inhibitor Ritonavir and MDMA (Ecstasy) and the maker of Ritonavir, Abbott Laboratories, has issued a warning to prescribing physicians of this possible adverse event as well as potential interactions with heroin, methadone, and amphetamine. See also Danger: Possible fatal interactions between ritonavir and ecstasy, some other psychoactive drugs. *AIDS Treatment News* 1997; 265.

410 K Harrison et al. Supra, note 56.

between the experimental vaccine on one hand and any one or combination of: illegal substances (including "club drugs") and prescription medications on the other?

In the case of clinical trials of therapeutic HIV vaccines, it would be essential to study interactions between the candidate vaccines and the variety of antiretroviral medications used as the current standard of care.

With respect to trials of prophylactic vaccines, it would seem equally prudent to study and monitor interactions with illegal substances. In some large Canadian cities, seroincidence rates are highest among older populations of injection drug users. The most recent figures published by the St-Luc Cohort from downtown Montréal shows some of the highest HIV seroincidence rates in North America (7.7 per one hundred person-years).[411] Such extraordinarily high rates would in theory justify the delivery at high levels of coverage of even relatively low-efficacy vaccines. But compulsive consumption of large quantities of certain illegal drugs can compromise the ability of the immune system to respond to infection. Vaccines are designed to prime the immune system. What levels of injection drug use might cause levels of immunosuppression capable of preventing the system from responding to vaccination? Would adjustments of dosage and of the frequency of "booster" vaccinations overcome these difficulties?

Injection drug users are the segment of the Canadian population where HIV seroincidence rates suggest the greatest potential for a decrease in HIV transmission resulting from the widest range of vaccine efficacy. The efficacy figure used in calculating a vaccine's public health benefit should be determined so that it takes into account significant medical factors specific to the target population. Otherwise, "[b]ias can skew research toward results or conclusions that differ systematically from the truth."[412] It would be unethical to vaccinate a human population in which the prevalence of significant immunocompromise renders inapplicable the data generated in clinical trials using healthier populations.

The question of whether injection drug users in Canada constitute a potential target population for HIV vaccine trials is further complicated by the fact that if current seroincidence rates continue unabated, then in some cities the HIV seroprevalence among longer-term users may quickly attain saturation levels. This may influence decisions about whether to recruit among the population of "older" injection drug users. This is a subset of the population for whom priorities may ultimately be better directed toward care, treatment, support, and health promotion for people with HIV and AIDS.

Epidemiological studies of injection drug users in North American cities demonstrate marked variations in seroincidence and seroprevalence levels from one city to another. Often these variations exist between cities located only a few hundred kilometres apart. This heterogeneity is

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411 J Bruneau et al. High rates of HIV infection among injection drug users participating in needle exchange programs in Montréal: Results of a cohort study. *American Journal of Epidemiology* 1997; 146(12): 994-1002. See also P Lurie. Invited commentary: Le Mystère de Montréal. *American Journal of Epidemiology* 1997; 146(12): 1003-5, and C Hankins et al. *Inventory of HIV Incidence / Prevalence Studies in Canada*. Ottawa: Health Canada, April 1998.

412 DJ Roy. Injection Drug use and HIV/AIDS Research: An Ethical Analysis of Priority Issues. In: *Injection Drug Use and HIV/AIDS: Legal and Ethical Issues*. Background Papers. Montréal: Canadian HIV/AIDS Legal Network, 1999, at 66.

present among Canadian as well as US cities.[413] Geographic variation in the supply and demand (preference) for different types of substances, each consumed with relatively different frequencies of injection, may partly explain these observations. Various study methodologies and differing cohort profiles will potentially bias surveillance data. Local law enforcement practices resulting in varying rates of imprisonment will play a role in determining the vulnerability of injection drug users to HIV infection. Other influential factors include the availability of needle exchanges, harm-reduction and detoxification services, and the existence of methadone and heroin maintenance programs. Access to (and support for compliance with) antiretroviral therapies will also affect the dynamic evolution of the epidemic. If these criteria do in fact create substantive variations in epidemiology from one city to another, then this will make the design of a multi-centre vaccine efficacy trial with injection drug users among the research subjects and the interpretation of the data it generates a difficult task.

For legal, ethical, cultural, political, and practical reasons, it is more difficult for industry to engage in controlled experiments in which precise dosages of both anti-HIV experimental vaccines and of illegal drugs could be varied and studied in various combinations of dosages.

> The Minister of Health has the power under the *Controlled Drugs and Substances Act* (s. 56) to exempt any person or class of persons from the law. The Act also allows for regulations by Cabinet that could have the same effect (s. 55). Thus, current law anticipates [the possibility of] exempting certain individuals and groups from criminal penalties.[414]

Hence, clinical trials of experimental HIV vaccines involving controlled arms in which illicit drugs are provided in combination with either an experimental vaccine or a vaccine placebo might be legally and bureaucratically possible.

But there are a number of practical difficulties particular to this kind of study. Indeed, numerous challenges must be anticipated in designing a clinical trial that takes into account the use of illicit drugs (either through prescribing same or though self-reported behaviours):

- There has been very little work in Canada designing the methodology of research with substance users.[415] This work would require a prior collaborative consultation among vaccine researchers and those working in the fields of addiction research, epidemiology, community-based HIV/AIDS research, as well as injection drug users themselves.
- Researchers will not easily be able to control the quantity of substances consumed by participants outside the trial. There will thus be a higher index of variability and hence uncertainty in studies stratified according to injection drug use.
- It would be extremely difficult, probably impossible to blind such studies.[416]

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413 Note: More recent research (Health Canada, HIV/AIDS Epi Update, May 2001) indicates approximate sero-incidence rates of 2.0 in Vancouver, 5.3 in Québec, 3.5 in Montréal and 2.0 in New York City. These rates are the number of cohort sero-conversions per one-hundred person years.

414 *Controlled Drugs and Substances Act*, SI/97-47, *Canada Gazette Part II* 14 May 1997

415 DJ Roy. Supra, note 412.

416 J Singer et al. Design issues in trials of cannabis for patients with HIV. Poster presentation at the Xth Annual Canadian Conference on HIV/AIDS Research. Toronto, 31 May-3 June 2001. Abstract no 297P. See *Canadian Journal of Infectious Diseases* 2001; 12(Suppl. B): 53B.

- Industry is likely to be adverse to the perceived higher liabilities associated with following active drug users over the length of an efficacy trial.[417]
- Researchers and cohort staff may encounter personal ethical and moral dilemmas if the protocol requires distribution of normally illegal substances to participants.
- Researchers and staff must ensure that participants have access to clean needles and understand the importance of using only sterile syringes. Researchers must have the wisdom and ability to avoid proselytizing messages about detoxification that would scare prospective participants away. They must also be able to respect the participants' present-day capabilities and limits, all the while facilitating references to resources that can empower injection drug users to embark upon detoxification services when desired.
- If, over the course of the clinical trial, the health of the participant deteriorates as a result of additional substance use, clinical researchers will face a difficult dilemma. Cases of compulsive and extensive consumption may ultimately require withdrawal from the trial for both ethical and scientific reasons.
- The public's reaction to such clinical trials may pose a serious obstacle to research. People working within the field of HIV/AIDS are familiar with the theoretical construct of harm reduction. Although the average citizen in Canada practises a variety of different forms of harm reduction in day-to-day living, they are not necessarily familiar with the theory behind the practice. Thus, the prevailing political climate may not permit the Minister or Cabinet to issue the necessary legal exemptions permitting such clinical trials.

On the other hand, if the protocol prescribes that all injection drug use automatically requires expulsion from the clinical trial, participants may tend to exercise self-assessment concerning what levels and what kinds of drug use warrant disclosure and which do not. Other participants may simply decide to lie.

Another approach is to encourage participants to voluntarily report incidents of consumption of illegal substances. Some of the above discussed difficulties might be avoided if researchers avoid moralizing judgments of participants' drug consumption and do not impose the sanction of automatic removal from the cohort. They could instead encourage a frank and open disclosure of patterns of consumption at the moment of recruitment, stratify the trial accordingly, and keep parallel records of drug use.

> In the design of clinical trials, it must be recognized that some (indeed many) members of affected groups routinely use a variety of drugs (licit as well as illicit) and will continue to do so during the conduct of the clinical trial.[418]

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417 ID.

418 C Levine et al. Supra, note 53, at 8.

(i) Recruitment of Injection Drug Users and the Confidentiality of File Contents

If the vaccine trial includes a qualitative study of illegal substance use and its interaction with vaccination, extensive information concerning illegal activities must be gathered and stored. A larger cohort would then be required in order to generate statistically significant data. However, research files may not be impervious to search and seizure when a subpoena is issued by a court of law. The extent to which the limited legal privilege of confidentiality accorded to medical therapeutic files can be extended to research is not entirely settled.[419] As a general rule, rights to privacy encompass territorial, personal and informational privacy, the latter applying to the "intimate details of the lifestyle and personal choices of the individual and it is these details that are most in need of protection in research".[420] However, rights to privacy set out in sections 7 and 8 of the *Canadian Charter of Rights and Freedoms* are balanced against Charter rights to due process, the latter requiring as a general rule "that all citizens involved in court action should have a right of full answer and defense for any actions, criminal or civil [….]"[421]. These rights are balanced against the "lawful interests of others involved in the process",[422] (including those of the researchers who are called upon to testify).

Hence it is theoretically possible that the courts may from time to time order a restricted opening of the confidential lid covering research data. Persons recruited to clinical trials who engage in illegal substance use will be reluctant to volunteer such information if its non-nominative storage and shelter from the criminal justice system cannot be substantially guaranteed.

Authors Palys and Lowman, maintain that researchers can design their protocols and procedures in a manner that will help to shelter their files from crown prosecutors and others who might be tempted to regard the data as a fishing pond for evidence.[423] Researchers directing a clinical efficacy trial of an experimental HIV vaccine that takes extensive records of drug use, will want to take into consideration the authors' suggested criteria in anticipation of the possibility of having to testify in criminal court and invoke a common law defense of privilege known as the "Wigmore Defence".

The Wigmore criteria require that:

1. The communications must originate in a confidence that they will not be disclosed;
2. This element of confidentiality must be essential to the full and satisfactory maintenance of the relation between the parties;
3. The relations must be one which in the opinion of the *community* ought to be sedulously fostered; and

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419 T Palys, J Lowman. Ethical and legal strategies for protecting confidential research information. Penultimate draft of an article published in *Canadian Journal of law and Society* 2000; 15(1): 39-80. See also *Russel Ogden* v *Simon Fraser University*, Provincial Court of British Columbia (Small Claims Court). Burnaby Registry no 26780. 10 June 1998, and *R* v *O'Conner* [1995] 4 SCR 411.

420 T Palys, J Lowman. Supra, note 419, at 8, citing *R.* v *Plant*, [1993] 3 SCR 281 at 293.

421 Ibid, at 8.

422 *R* v *O'Conner*. Supra, note 419. (Mme Justice McLauchlin) -- minority decision.

423 T Palys, J Lowman. Supra, note 419, at 12-13.

4. The injury that would inure to the relation by the disclosure of the communication must be greater than the benefit thereby gained for the correct disposal of litigation.[424]

It should be noted that drug use will not be the only foreseeable information relating to criminal activity gathered during recruitment of subjects and subsequent clinical vaccine research. Information may also be reported to researchers concerning unsafe sexual relations without disclosure of sero-status during the follow-up period in clinical research when people suffering breakthrough infections are tested for viral load. The legal and ethical problems arising with respect to confidentiality of research data should therefore be carefully considered regardless of the particular population subset targeted for recruitment.

(ii) Failure to Recruit Injection Drug Users May Give Rise to Legal Liability

With respect to systemic and repeated patterns of recruitment that exclude injection drug users from clinical trials, it may be possible to use the equality provisions of federal and provincial human rights legislation that prohibit discrimination on the basis of handicap or physical deficiency to argue that systematic exclusion (without credible scientific motives) of dependent injection drug users from the vaccine research agenda constitutes illegal discrimination. Canadian jurisprudence has classified drug dependence as falling within the legal definitions of handicap or physical deficiency that are included in the equality rights provisions of such legislation. Unfortunately, this will not cover the occasional, non-dependent drug user and, moreover, dependency is a level of substance use at which immunocompromise (and hence scientific motives in favour of exclusion) may begin to arise.

Applying the *Canadian Charter of Rights and Freedoms* (including the equality provisions set out in section 15) requires that the subject matter be: i) governmental (federal or provincial), or ii) a matter within the direct exercise of authority by Parliament or the territories, or iii) within the authority of a provincial legislature. It is unlikely that research, even if sponsored by government agencies, would legally be deemed to be sufficiently proximate to the exercise of governmental power to meet these criteria.

Applying the equality provisions prohibiting discrimination in provincial legislation is dependent upon the ability to classify research as a juridical act that either creates or extinguishes legal rights. The use of consent forms that routinely create certain obligations on the part of the principal investigator, the sponsoring pharmaceutical company and the participants certainly seems to meet this criterion. But these matters remain largely untested in Canadian courts.[425]

The failure to include injection drug users in HIV vaccine research may ultimately increase legal liability for provincial public health authorities. These agencies are representatives of their respective governments and derive their authority from public health protection legislation. They

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[424] Ibid at 12-13, referring to JH Wigmore. *A treatise on the system of evidence in trials at common law, including the statutes and judicial decisions of all jurisdictions of the United States, England, and Canada* Boston: Little Brown and Co, 1905. Note: T Palys and J Lowman provide a clear and precise discussion of the procedures researchers can adopt in order to design research in anticipation of invoking the Wigmore criteria. The discussion can be found on pp. 32-3 of their paper (penultimate draft). Researchers should also consult the decision in: *R.* v *O'Conner*. Supra, note 419.

[425] E Oscapella, R Elliott. Supra, note 56, at 66.

are therefore subject to the provisions of section 7 of the *Canadian Charter of Rights and Freedoms*, which states:

> Everyone has the right to life, liberty and security of the person and the right not to be deprived thereof except in accordance with the principles of fundamental justice.[426]

A decision to administer a vaccine to injection drug users might come under legal scrutiny pursuant to section 7 if the decision is not based on sound clinical data applicable to that targeted population. If the results of the vaccination campaign were to be a lower-than-expected efficacy combined with a substantial reduction in preventive harm reducing behaviours, then the epidemic among this subset of the population might actually worsen. Moreover, if clinical testing failed to take into account potential interactions with illegal drugs, vaccination might cause unanticipated adverse events. In either of these aforementioned situations, vaccinated individuals could argue that their rights not to be deprived of "security of the person except in accordance with the principles of fundamental justice" had been breached.[427]

(iii) Conclusions and Recommendations

The consumption of illegal substances by injection drug users

> should not constitute grounds for exclusion unless there is evidence to support specific exclusions – e.g., a known drug interaction that would threaten the subject's safety.… [Researchers] should encourage [… participants] to be candid about their drug use and refrain from penalizing their candor. They should also monitor the effects of concomitant medications, and, when appropriate and feasible, introduce stratification into the randomization assuring that equal numbers of users of a particular drug are stratified into each arm of the randomized clinical trial."[428]

The following recommendations are advanced:

1. Wherever a demonstrated need grounded in accurate epidemiology exists, public health, pharmaceutical companies, the Canadian research councils, clinical and community researchers, addiction research specialists; and injection drug users should develop a comprehensive research agenda that identifies priorities for vaccine research and, in particular, methodologies for the recruitment, consent, and retention of injection drug users. Proactive strategies for delivery of eventual vaccines in this population must be an integral part of research strategies.[429]
2. As a general principle, clinical researchers and professional associations should take measures to ensure removal of barriers to participation of drug users in … (vaccine) trials.[430]

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426 *Canadian Charter of Rights and Freedoms*. *Constitution Act*, (1982), Part I art.7.

427 E Oscapella, R Elliott. Supra, note 56, at 65.

428 C Levine et al. Supra, note 53, at 8.

429 E Oscapella, R Elliott. Supra, note 56, at 71-2.

430 Ibid, at 72.

3. Clinical researchers, regulatory authorities, research ethics boards, and community stakeholders should hold the pharmaceutical industry to a high burden and standard of proof concerning exclusions from clinical trials. Community representatives and researchers should refuse to support those trials that fail to adopt an inclusive approach to recruitment while simultaneously failing to demonstrate persuasive scientific reasons for excluding social groups and communities in which people are vulnerable to HIV infection.
4. Federal and provincial officials, including law enforcers, should be prohibited by policy (and possibly by law) from having access to identifying information respecting participants in research files. Researchers should educate themselves concerning how to structure their protocols, the information they provide to research ethics boards, their communications with community, the informed consent and procedures to favour application of the Wigmore defense to subpoenas seeking access to nominative research data.

3. Women

The development of an HIV preventive vaccine is a health priority for many women. Women account for approximately one-half of the global total of people with HIV. They constitute the majority of new HIV infections.[431]

In the US, approximately 20 percent of adults with HIV between the ages of 15 and 49 are women and more than one-third of all new HIV infections occur in women. In 2000, more than 80 percent of new HIV infections in women in the US occurred as a direct or indirect result of the sharing of non-sterile injection paraphernalia.[432]

In Canada, somewhat similar patterns are emerging:

> Women account for a growing proportion of positive HIV test reports with known age and gender among adults in Canada. Before 1995, 9.9% of all positive HIV test reports were among women. Between 1995 and 2000, this proportion increased from 18.8% to 23.9%. [….] In 2000, women accounted for 51.5% and 40.8% of positive HIV test reports among those aged 15 to 19 years and 20 to 24 years, respectively.[433]

The Centre for Infectious Disease Prevention and Control at Health Canada concludes: "Women in Canada are increasingly becoming infected with HIV, especially injection drug users and women with high risk sexual partners."[434] In the mid 1990s, injection drug use outranked heterosexual exposure in this country as the primary exposure category among adult females with HIV-positive test results. This pattern has now reversed. Approximately 56 percent of

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431 Joint United Nations Programme on HIV/AIDS. *Report on the global HIV/AIDS epidemic*. Supra, note 12.

432 Health Canada. Supra, note 18.

433 Health Canada. *HIV/AIDS EPI Update: HIV and AIDS Among Women In Canada*. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, May 2001, at 2-3.

434 Ibid at 4.

positive HIV tests among adult females in Canada in the year 2000 were due to heterosexual contact while an estimated 39 percent contracted HIV as a result of injection drug use.[435]

But in a country the size of Canada important regional variations in the epidemiology of HIV seroincidence among women are inevitable. In Montréal for example, there is recent evidence to of a sharp increase of seroincidence among women. The data from that city suggests that injection drug use accounts for only a small part of the recently observed increase and that the increase is occurring primarily among women born in Canada and other non high HIV endemic countries. This in turn suggests that heterosexual transmission is on the rise.[436] There is also evidence of sharply increasing HIV prevalence among pregnant women undergoing HIV testing in Ontario.[437]

In Vancouver research suggests that women who inject drugs in that city are more vulnerable to HIV infection than male IDUs.[438] The use of illegal substances will inevitably be present in a wide variety of populations, communities, and social groups that can be targeted for clinical trials of HIV vaccines. Canadian women are no exception. Researchers intending to actively recruit a large number of women to an efficacy trial in Canada must be prepared to encounter a number of volunteers who use illegal substances to varying degrees. To ensure the generalizability of cohort data, the sponsor should be prepared to accommodate this reality – particularly in efficacy trials which must result in data applicable to women, including women who injection drugs and use a variety of other illicit substances. This in turn will impact upon trial design, stratification of arms, data collection, and on the content of referrals, counseling, and support services offered to volunteers.

In Canada "women have historically been excluded from participating in some research."[439] There have been fears that experimental medication (or vaccines) might damage either a foetus or the woman's reproductive capacity or that newborns might be harmed through breastfeeding. These concerns have given rise to a fear of legal liability that has been one of the primary factors making researchers reluctant to include women in clinical research.[440] This has been particularly true for Phase I trials designed to investigate safety and tolerance as well as for Phase II trials that study immunogenicity and conduct an expanded evaluation of safety.[441] Unfortunately, there is some evidence to suggest that the pathogenic effect of HIV may have evolved since the

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435 Ibid at 2-3.

436 RS Remis et al. Supra, note 158.

437 RS Remis et al. Uptake of HIV testing among pregnant women in Ontario: Results from the HIV seroprevalence study to September 2000. Presentation at the Xth Annual Canadian Conference on HIV/AIDS Research. Toronto, 31 May-3 June 2001. Abstract no 317.

438 PM Spittal et al. Risk Factors for HIV among female and male injection drug users: Does sexual transmission explain why female IDUS are being disproportionately affected by HIV in Vancouver? Presentation to the Xth Annual Canadian Conference on HIV/AIDS Research. Toronto, 31 May-3 June 2001. Abstract no 301.

439 Medical Research Council of Canada. Supra, note 76, at Section 5: Inclusion in Research, Part B: Research Involving Women; Notes to Articles 5.1 and 5.2.

440 ID.

441 ID. See Also B Snow. Consenting Adults: The Challenge of Informed Consent. *The Bay Area Reporter* June 1998. Reprinted in B Snow (ed). Supra, note 58, at 43.

mid 1980s and that it differs along lines of gender and route of HIV infection. This in turn may result in differing vaccine and drug efficacies.[442]

> Because sexual intercourse is the route of transmission in more than 80 percent of HIV infections worldwide, many experts believe the best chance to prevent the spread of HIV infection is by building up an immunological barrier at the port of entry – the mucosal surface of the genitals or rectum.[443]

Scientists are now developing candidate vaccines that are designed to specifically protect against vaginal transmission.[444] Obviously, inclusion of women in clinical efficacy trials of such vaccines will be absolutely essential.

It should be noted however that the uneven inclusion of women in vaccine clinical research frequently plays out differently in developed nations than in developing nations. At the XIII International AIDS Conference, MW Makgoba, President of the Medical Research Council of South Africa, drew attention to the *overrepresentation* of women among recruits to clinical research in South Africa. He pointed out that until very recently, the history of research design and leadership in South Africa has been dominated by a white and androgenic perspective.[445] In a society in which women have little economic and political power, participation in vaccine trials might be one way by which they will seek to exert some control over their lives. If vaccine research is to specifically target women who are at personal risk of contracting HIV, then the preventive interventions that should accompany the clinical trial should include the distribution of female and male condoms and the distribution of sterile injection paraphernalia upon demand.[446] In a resource-poor environment, these modest preventive efforts may, in and of themselves, constitute a significant incentive for women anxious to obtain some protection from a burgeoning epidemic.

In some cultures, this overrepresentation by women might also reflect their inherent vulnerability in terms of higher rates of illiteracy, higher susceptibility to HIV infection because of sexual and domestic violence, and unjust perceptions of women as "vectors of the disease."

In sub-Saharan Africa the record of vaccination has often been one of incomplete coverage and delivery of vaccines mainly to women and to young children. Consequently, men may tend to believe that vaccination is not for them. Dr Makgoba underlined the relative lack of research on how men and boys define their role in the fight against AIDS, how they make decisions concerning health management, their attitudes toward women, sexuality, and children. In a

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442 P Vanhems et al. Association between the rate of CD4+ T cell decrease and the year of human immunodeficiency virus (HIV) Type 1 seroconversion among person enrolled in the Swiss HIV cohort study. *The Journal of Infectious Diseases* 1999; 180: 1803-8.

443 S Crotty et al. Protection against simian immunodeficiency virus vaginal challenge by using sabin poliovirus vectors. *Journal of Virology* 2001; 75(16): 7435-52. Reported by University of California, and available at www.eurekalert.org/pub releases/20001-07/yoc-fvt071801.php.

444 ID.

445 MW Makgoba. Ethics of AIDS research in developing countries. Plenary Session: HIV Vaccine Challenges. XIIIth International AIDS Conference. Durban, South Africa, 13 July 2000.

446 D Patterson. *Resolving legal, ethical and human rights challenges in HIV vaccine research: A discussion paper.* Montréal: Canadian HIV/AIDS Legal Network & AIDS Law Project South Africa, November 2000, at 16.

society that is patriarchal and polygamous, leaving men out of the equation makes no sense at all.[447]

As mentioned previously, it is useful to run parallel arms of a clinical trial in the sponsor's home country and in developing countries in terms of developing partnerships and building trust with target communities. But if Canadian researchers are to organize clinical trials of experimental vaccines partly in Canada and partly in developing nations, these inconsistencies will have to be addressed and reconciled.

(i) Women, Pregnancy, and Vaccine Trials

Author Christine Grady has suggested that "based on the risk/benefit analysis for neonates, it might be better to postpone Phase I trials of therapeutic HIV vaccines in infected pregnant women or neonates until there is some evidence of efficacy in animals or other adults".[448]

But pregnant women are often excluded from all phases of research and safety information must be inferred from data generated from animal studies and clinical trials involving men. Typically, the prescribing information that is provided to physicians for many medications includes a message similar to the following: There is no clinical evidence to support the use of this medication in pregnant women. Therefore this medication should not be administered during pregnancy except in life-threatening situations.

There are at least four contrasting lines of analysis that can be applied to the role of pregnant women in HIV vaccine trials.

- The first recognizes that women are more than mere vessels for bearing children. Researchers should respect the dignity and autonomy of women volunteers and acknowledge their capacity to make their own decisions on matters concerning their health and the health of their foetus. Many women will wish to participate in clinical research and will decide not to get pregnant during the process.
- The second recognizes that vaccine efficacy cohorts involve many thousands of people and that statistically it is inevitable that some women in such cohorts will become pregnant. After all, HIV is a sexually transmitted infectious disease. Accordingly, researchers should simply accept, anticipate, and plan for this situation. Informed consent needs to be explicit and detailed concerning potential harmful effects to the foetus and to the pregnant mother. Again, through voluntary, comprehensive, and comprehending consent, women of childbearing age will be able to decide whether to enter vaccine clinical trials, and whether they wish to continue to participate if they become pregnant.
- The third returns to the issue of generalizability and reliability of research data. The epidemiology of HIV both in Canada and throughout the world indicates that women, including many pregnant women, have a strong interest in development of both prophylactic and therapeutic vaccines. Pregnancy does not automatically reduce a woman's risk of contracting HIV. Couples continue to have sexual relations during the woman's pregnancy. Female volunteers who are pregnant will thus remain at risk of contracting HIV through

447 MW Makgoba. SAAVI (South African AIDS Vaccine Initiative). Round table discussion: AIDS Vaccine Development for Africa. XIIIth International AIDS Conference. Durban, South Africa. 11 July 2000, and MW Makgoba. Supra, note 445.

448 C Grady. Supra, note 84, at 127.

sexual exposure and women in general will have a strong interest in development of a preventive vaccine that can be administered in spite of pregnancy. Hence, women and pregnant women should be involved in clinical trials. The decision to proceed to recruit women and pregnant women must be founded upon an evaluation of pertinent pre-clinical research and the risk/benefit ratio calculated for these specific subsets of the cohort.

- The fourth is a purely legal line of reasoning. Ever since the Supreme Court of Canada's decision in *Tremblay* v *Daigle*,[449] as followed in *Winnipeg Child and Family Services (Northwest Area)* v *DFG*,[450] it is clear that in Canadian law a foetus is not a legal person. Until the child is born alive and viable, its rights and interests are virtual and incomplete. In *Winnipeg Child and Family Services*, the majority decision of the Supreme Court affirms that this is a general principle applicable in all fields of law. This latter case involved an attempt by the state agency to require detoxification and confinement of a pregnant mother who had a severe dependency upon the inhalation of toxic fumes from glue. But in refusing the application of the *parens patriae* jurisdiction, the Court recognized that from the point of view of civil responsibility or delict, the foetus has no standing and no cause of action. Hence, it is highly unlikely that fetal interests could be advanced at Canadian law to justify preventing a pregnant woman from taking part in a clinical trial that has been scientifically and ethically approved for research on women. Note however that providing the pregnant mother with detailed information in the clearest possible manner concerning any potential adverse effects for herself and the foetus will respect the aforementioned legal values, allow her to make a comprehending decision, and therefore shelter the sponsor and principal investigator from liability.

(ii) Ethical Standards for the Inclusion of Women and Pregnant Women in Clinical Research

Without exception, subject to valid scientific concerns, the principal ethical guidelines for clinical research involving human subjects presumptively favour the recruitment of women to trials. Citing the underlying principle of distributive justice of the burdens and benefits of research across all possible groups, in articles 5.1 and 5.2 the Tri-Council Policy Statement plainly sets out the case for including women.[451]

The Policy underlines the undesirable consequences of an unscientific exclusion:

> the exclusion of women as research subjects raises serious concerns regarding the generalizability and reliability of some research data; and research data on ... dosages, the effects of devices, treatments, cultural norms, moral development and social behaviour obtained from male-oriented studies likely will not be generalizable to women."[452]

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449 *Daigle* v *Tremblay*, [1989] 2 SCR, at 530.

450 *Winnipeg Child and Family Services (North-west Region)* v *G (DF)*; [1997] 3 SCR, p 925. See also *Richard B and Beena B*; [1995] 3 SCR, p 925.

451 Medical Research Council of Canada. Supra, note 76, at Section 5: Inclusion in Research, Part B: Research Involving Women; Articles 5.1 and 5.2.

452 ID.

Information to facilitate vaccine delivery among women needs to be gathered and the vaccine efficacy cohorts provide an opportunity to do this. Factors such as awareness of risk, culture, and access and attitudes to medicine will play a key role in the population's willingness to be vaccinated. Psychosocial research conducted during clinical trials can shed light on these factors while simultaneously providing information that helps intervenors and public health workers to refine prevention.

As we have seen from the discussion above, the role of *pregnant* women in clinical vaccine research is potentially more controversial. The fact that the law will not consider the interests of the unborn does not necessarily preclude ethics from doing so. Ethics is a reasoned debate, weighting values and applying them to the analysis of complex dilemmas, including evaluation of the risks and benefits of research participation. Prominent among the applied values will be the criteria of legal pragmatism and scientific validity. Oviously, it would not be scientifically valid to administer a vaccine to pregnant women if pre-clinical teratogenic investigation clearly indicated a risk of fetal deformation.

For the pregnant woman who is considering volunteering for a clinical trial of an experimental vaccine, ethics can provide guidelines that will shape the information, powers, and protections offered to participants, thereby helping her to make an informed choice. These guidelines will also help researchers and research ethics boards to prudently exercise their respective mandates. Ethical considerations do not support research when the potential harms outweigh the benefits, when pre-clinical research indicates significant dangers to health, or when subjects are used as a means to benefit others.

Article 5.2 of the Tri-Council Policy Statement reads: "Women shall not automatically be excluded from research solely on the basis of sex or reproductive capacity."

The notes to this Article state:

> If, in the past, many women have been automatically excluded from research on such grounds, Article 5.2 rejects such an approach as discriminating and unethical use of inclusion or exclusion criteria. Rather, in considering research on *pregnant* women, researchers and REBs must take into account potential harms and benefits for the pregnant woman and her embryo, foetus or infant. The ethical duty to assess the harms and benefits of research thus extends to the special case of research involving pregnant or breast-feeding women. [453]

It is important to realize that the above ethical obligation is only to evaluate and not necessarily to permit recruitment of pregnant women to research cohorts. There is however an initial presumptive bias in favour of inclusion. Exclusion, if imposed, must be the result of considered analysis and not merely of an automatic and blind rule of practise.

Informed, voluntary, prenatal screening of pregnant women for HIV has become the clinical standard of care in Canada.[454] In the event of a positive test result, combination antiretroviral therapies for pregnant women and neonates together with a recommended avoidance of

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[453] Ibid, at Section 5: Inclusion in Research, Part B: Research Involving Women; Notes to Article 5.2.

[454] Health Canada. *HIV/AIDS Epi Update: Perinatal Transmission of HIV*. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, April 2000.

breastfeeding is the current standard of care.[455] This reduces the risks of vertical and perinatal transmission to extremely low levels. Since the adoption of this clinical standard, the neonate's personal need for a preventive vaccine in Canada is not nearly so compelling.

Of course, the newborn does have a vicarious interest in the development of an efficacious HIV vaccine. After all, if the mother is considering volunteering for a vaccine efficacy trial, she will likely be part of a target population in which people are highly vulnerable to HIV infection. But the real problem is how to help the mother achieve and maintain effective personal prevention. A history of high personal risks does not signify automatic inclusion in HIV vaccine research. Given that participation in vaccine clinical research can not be looked to as a source of increased personal protection, once again the mother's interest and especially the child's interest in vaccine research remains somewhat distant. Eventually the child may, if warranted, be personally interested in receiving a successfully developed and licensed vaccine at puberty or when commencing the use of injection drugs. This is a general interest in vaccine development shared by many members of Canadian society.

In the absence of contraindications, "breast-feeding is associated with a reduction in infant mortality" and "morbidity from infectious diseases," while it decreases the "subsequent risk of immunologically mediated disorders.[456] Not surprisingly, therefore, many cultures attach great importance to the act of breastfeeding. Now, unfortunately, breastfeeding has been identified as a means of HIV transmission from mother to child. But in some cultural environments (including communities in Canada) a refusal to breastfeed might amount to a public declaration of HIV infection. In addition, mixing formula feeding with breastfeeding has been shown to correlate with higher rates of transmission than breastfeeding alone.[457]

In theory, a prophylactic vaccine could also be administered to neonates in order to prevent vertical transmission of HIV via breastfeeding. Vaccinating newborns is potentially a relatively inexpensive intervention, since the required dosages would be small. Moreover, even a vaccine that stimulates immunity for only a short time might be successful in newborns, if immunity is maintained during the period of breastfeeding.

(iii) Women and the Case for Inclusion in Clinical Trials of Therapeutic Vaccines

If the vaccine developed is a therapeutic rather than a prophylactic one, it might lower viral loads in blood, lymphatic tissue, and other bodily tissues and fluids, possibly including breast milk. HIV-infected mothers could be vaccinated with a therapeutic vaccine in order to improve their

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[455] A Rachlis, D Zarowny. Guidelines for anti-retroviral therapy for HIV infection. *Canadian Medical Association Journal* 1998; 158: 496-505. See also EM Connor et al. Reduction of maternal-infant transmission of human immmunodeficiency virus type 1 with zidovudine treatment. Paediatric AIDS Clinical Trials Group Protocol 076 Study Group. *New England Journal of Medicine* 1994; 331: 1173-80. See also HP Katner et al. Nelfinavir based highly active anti-retroviral therapy (HAART) use in Pregnancy. XIIIth International Conference on AIDS. Durban, South Africa, 11 July 2000. Abstract no TuPeB3252, and M Lallemant et al. Perinatal HIV prevention trial (PHPT), Thailand: Simplified and shortened zidovudine prophylaxis regimen as efficacious as PACTG076. XIIIth International Conference on AIDS. Durban, South Africa, 9-14 July 2000. Abstract no LbOr3.

[456] S Ito. Drug Therapy For Breast-Feeding Women. *The New England Journal of Medicine* 2000; 343(2): 118-25.

[457] A Coutsoudis. Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: Prospective cohort study from Durban. XIIIth International AIDS Conference. Durban, South Africa, 9-14 July 2000. Abstract no LbOr6.

health and longevity, as well as to reduce risks of perinatal transmission and of vertical transmission via breastfeeding.

In Canada, an extensive program of prenatal, perinatal, and postnatal antiretroviral therapies reduces transmission by more than 70 percent, such that seroincidence is approximately one per one hundred person-years. Given this demonstrated efficacy, a preventive vaccine for neonates and a therapeutic vaccine for HIV-positive mothers could only be evaluated in a clinical trial that adds the candidate vaccine to the existing standard of care. Mothers and infants in both arms of the study (vaccine and control) would have to receive the antiretroviral therapies. This means that very large numbers of cohort participants will be necessary for a clinical trial seeking to evaluate vaccine efficacy for prevention of vertical transmission. Canada alone will not be able to produce this number of volunteers.

Clinical research in the developing world has already definitively shown that a very short course of nevirapine administered in monotherapy to the mother prior to birth and to the child following birth can reduce rates of perinatal vertical transmission by almost 50 percent.[458] The cost of this treatment is only $US4.[459] This cost is less than the likely price of an anti-HIV vaccine (therapeutic or preventive). In the case of a clinical trial of a therapeutic vaccine, it would not seem ethical to conduct an efficacy study without at least offering nevirapine as perinatal HIV prevention to people enrolled in both the vaccinated and the control arms. Given that industry, government budgets, distribution systems, and aid programs are presently unable or unwilling to offer people with HIV in developing countries longer-term antiretroviral therapies at an affordable price, placebo control outside the short period surrounding birth might be permissible. This is, however, a matter of considerable controversy that requires an in-depth ethical analysis exceeding the scope of this paper.

To merit delivery, therapeutic vaccines would have to present levels of efficacy that are higher than the efficacy presented by current best available antiretroviral therapies in both improving the mother's health and in reducing vertical transmission. Alternatively, the vaccine would have to be less costly or present fewer adverse events for the same level of efficacy. Finally, if the vaccine were to demonstrate weak but incremental efficacy when added to an antiretroviral regime, then funding would be required to add the vaccine to the protocol for prevention of vertical transmission.

Thus, the testing and development of therapeutic vaccines for mothers (and prophylactic vaccines for neonates) might be particularly difficult in Canada. Yet, if successful, these vaccines would be ultimately useful here. They would be even more so in developing countries where alternatives to breastfeeding are not always available, safe, or affordable and where important obstacles stand in the way of delivery of antiretroviral therapies – even over the relatively short duration of pre- and postnatal care.

Finally:

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[458] M Gysels et al. Attitudes to voluntary counselling and testing for HIV among pregnant women and maternity staff in rural south west Uganda. XIIIth International AIDS Conference. Durban, South Africa, 9-14 July 2000. Abstract no TuPpB1159.

[459] M Owor et al. The one year safety and efficacy data of the HIVNET 012 trial. XIIIth International AIDS Conference. Durban, South Africa, 9-14 July 2000. Abstract no LbOr1. See also D Moodley. The SAINT Trial: Nevirapine (NVP) versus zidovudine (ZVD) + lamivudine (3TC) in prevention of peri-partum HIV transmission. XIIIth International AIDS Conference. Durban, South Africa, 9-14 July 2000. Abstract no LbOr2.

> The analysis of the risk of an infant's exposure to a drug [or a vaccine] excreted in breast milk needs to take into account the answers to two key questions: How much of the drug [or vaccine] is excreted in milk, and at this level of excretion, what is the risk of adverse effects?[460]

(iv) A Summary of Ethical Guidelines Regarding Vaccine Testing in Pregnant Women

The testing of preventive and therapeutic vaccines for pregnant women in Canada will raise difficult questions. Concerns about safety, indemnity, and the role to be accorded to our existing standards of therapeutic care, may work together to discourage women from volunteering and reduce the size and number of possible vaccine cohorts.

Before vaccines can be tested on pregnant women, ethics will require that the scientific protocol be based upon careful pre-clinical research into possible teratogenic effects in animal models (fetal malformation and toxicity).

> A decision to enroll pregnant or lactating women ... must be individualized and based on a careful risk/benefit assessment taking into consideration ... the availability and results of pre-clinical animal data, ... the stage of pregnancy and the potential for harm to the foetus or infant, [and the fact that trials of preventive vaccines offer no immediate therapeutic benefit].[461]

Voluntary, comprehending, and informed consent will help women arrive at the best possible decisions.

Most ethical guidelines developed for clinical research involving human subjects adopt an *a priori* principle favouring the recruitment of women, including pregnant women, to clinical trials. The international ethical guidelines for HIV preventive vaccine research as proposed by UNAIDS strongly make the presumptive case. Guidance Point 17 of the UNAIDS Guidance Document states:

> As women, including those who are potentially pregnant, pregnant, or breast-feeding, should be recipients of future HIV preventive vaccines, women should be included in clinical trials in order to verify safety, immunogenicity, and efficacy from their standpoint. During such research, women should receive adequate information to make informed choices about risks to themselves, as well as to their foetus or breast-fed infant, where applicable.[462]

Use of the words "safety, immunogenicity and efficacy" in Guidance Point 17 indicate that women are to be included in all phases of vaccine research.

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460 S Ito. Supra, note 456.

461 Health Canada. *Inclusion of Women in Clinical Trials: Therapeutic Products Programme Guidelines*. Ottawa: Therapeutic Products Directorate, 17 April 1997 at 2.

462 Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Point 17.

At the present time, however, Health Canada's policies propose a more cautious approach. The Guideline for Inclusion of Women in Clinical Trials used by the Therapeutic Products Programme is a partial-inclusion standard. It states:

> The guideline proposes the inclusion of women in clinical trials from the earliest stages of drug development….
>
> In accordance with good medical practice, clinical protocols should include measures that will minimize the possibility of foetal exposure to the investigational drug. These would ordinarily include providing for the use of a reliable method of contraception (or abstinence) for the duration of drug exposure (which may exceed the length of the study), and the use of pregnancy testing prior to initiation of study treatment and at predetermined intervals during treatment, depending on the length of the study.
>
> Further, it is expected that appropriate precautions against becoming pregnant and exposing a foetus to a potentially toxic agent during the course of the study will be taken by women participating in clinical trials.[463]

Hence, the TPP policy can be summed up as: "women yes – pregnant women no." But these policies were primarily designed for the testing of therapeutic drugs and not of preventive vaccines. Such a cautious policy may work best in countries such as Canada, where antiretroviral therapies are readily available. But they nevertheless conflict with the obvious need to ultimately develop a vaccine that can be offered to those Canadian women of childbearing age who are vulnerable to HIV infection. Here once again, researchers are confronted with the reality that HIV is sexually transmitted, and that in large scale efficacy trials it is virtually certain that some women will become pregnant.

In commenting upon the ethics of HIV testing of pregnant women and their newborns, Barry Hoffmaster and Ted Schrecker have adopted an inclusive and comprehensive vision that suggests an analogy for the testing of HIV vaccines upon pregnant women and new mothers. The authors note:

> A morally enlightened approach to testing would not pit vulnerability against vulnerability. A morally inspired and sympathetic approach would, instead, presume that the interests of women and the interests of their children are congruent and would strive to promote all those interests.[464]

This is consistent with the majority decision of the Supreme Court in *Winnipeg Child and Family Services*, in which the pregnant woman and the unborn child form one and the same person.

A study of the legal and ethical issues associated with recruiting women, pregnant women, and children to vaccine clinical trials highlights the difficulties implicit in seeking to apply universal ethical standards to relatively different epidemics in different societies with widely diverse cultural, economic, and technological characteristics.

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463 Health Canada. Supra, 461 2.

464 B Hoffmaster, T Schrecker. Pregnancy and HIV/AIDS: An Ethical Analysis of HIV Testing of Pregnant Women and Their Newborns. *Canadian HIV/AIDS Policy & Law Newsletter* 1999; 4(4): 5-11 at 10.

While grand inclusionary principles may appear interesting on paper, the reality is that industry is concerned about liability – especially in North America. If an experimental vaccine administered during a Phase I or II vaccine trial induces severe adverse effects in either the mothers or the newborns (or both), who will compensate the injured parties? What if the mother's health is significantly injured and her ability to care for her child is compromised? Are industry and governments in Canada willing to finance an insurance program, to provide financial damages and "state of the art" health care to trial participants who suffer injuries induced by an experimental HIV vaccine? If not, it may be difficult – if not impossible – to recruit pregnant women to Phase I and II clinical trials without very strong (and practically difficult to obtain) pre-clinical indications that the experimental vaccine is completely safe.

The experimental AIDSVAX B/B Gp 120 vaccine was the subject of teratogenic pre-clinical research using female rats, pregnant rats, and newborn rats. This research demonstrated no indications of fetal malformation, birth defects, poor coordination, or slow development of neonates. In addition, recombinant Gp 120 vaccines are generally acknowledged to be one of the safest of all possible candidate HIV vaccines. But despite this, women were not recruited to the three sites in Canada. Only a few women (approximately 300) were recruited in the United States. Pregnant women were refused entry to the Phase III clinical trial. If any of the female participants become pregnant, they are asked to withdraw from the study. Male participants are made to agree to practise contraception with their female sexual partners during the three years of the trial and for a three-month period following its end.

Unless governments and regulatory agencies are willing to exercise their powers by providing appropriate incentives and by pressuring sponsors to modify scientific protocols to provide more pre-clinical teratogenic research and recruit pregnant women to trial arms when the risk/benefit ratio is sufficiently balanced, it is unlikely that this impasse will be resolved in the near future.

4. Prisoners

Rates of HIV seroprevalence in Canadian prisons have increased markedly over the past several years. The prison environment is characterized by high rates of illicit substance and injection drug use via shared needles. The market for illegal injection drugs inside Canadian prisons is controlled by organized crime notorious for its resort to extreme levels of violence. HIV prevention and promotion of safe harm-reduction measures are often lacking (eg, needle exchange programs) or inadequate (insufficient methadone maintenance, inadequate counselling, substandard health care) to prevent the spread of HIV inside Canadian prisons.

> [M]easures that have been successfully undertaken outside prison with government funding and support, such as making sterile injection equipment and methadone maintenance available to injection drug users, are not being undertaken in Canadian prisons, although other prison systems have shown that they can be introduced successfully, and receive support from prisoners, staff, prison administrations, politicians and the public.[465]

[465] R Jürgens. *HIV/AIDS in Prisons: Final Report*. Montréal: Canadian HIV/AIDS Legal Network & Canadian AIDS Society, 1996.

Inasmuch as they do not perceive any immediate threat to their own health, many Canadians simply do not care about the health of injection drug users and even fewer express concern about the health of prisoners. Yet prisoners have the same rights to health as other Canadians. Moreover, the captive nature of the prisoner's existence places a fiduciary duty upon corrections authorities to ensure that prisoners have adequate access to health care and prevention. This fiduciary duty extends to the offering of clinical therapeutic research to prisoners, particularly those for whom options of licensed treatments are no longer clinically effective.

The non-therapeutic nature of HIV vaccine clinical research and the fact that healthy uninfected volunteers must be recruited at time zero make it more difficult to argue persuasively that corrections authorities have a fiduciary duty to facilitate prisoners' access to clinical trials of candidate vaccines. In this inherently coercive environment, issues such as verification of informed consent, the balancing of risks and benefits, and the protection of vulnerable human subjects require particular attention and care when seeking informed consent to clinical trials. Sponsors may look to prisoners, particularly those serving long terms, as a "captive, low cost, low drop-out" cohort.[466]

Often sponsors pay principal investigators a fixed amount per subject recruited to a clinical trial.[467] In the prison environment, the potential conflict of interest that could arise should this fee be paid either to Corrections Canada or to medical personnel in the employ of corrections authorities is obvious. Further work needs to be done to determine which organizations should be responsible for conducting research inside Canadian prisons and which organizations should be responsible for the ethical review and monitoring of that research.

A code of conduct and an organizational protocol needs to be devised for vaccine trials in prisons so that:

•fully voluntary consent can be guaranteed;
•potential conflicts of interest are minimized;
•confidentiality is protected;
•prisoners can continue to participate despite inter-prison transfers; and
•prisoners' human rights and health are protected in the research process.

Recommendations proposed by researchers at the University of Connecticut and at Yale University for the organization of clinical trials in American prisons include:

•Improved oversight of research, including site-specific evaluation of prison conditions both before and during research;
•Provision of HIV therapy and management for all HIV-infected prisoners that conforms to current national standards of best clinical care;
•Elimination of financial incentives that may unduly influence prison authorities or investigators to encourage prisoner participation; and

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466 Z Lazzarini, FL Altice. Legal and ethical issues in the conduct of HIV-related research in prisons. Oral Session on Ethics of Research at XIIIth International AIDS Conference. Durban, South Africa, 12 July 2000. Abstract no WeOrA601.

467 R. Whitaker. Forum to discuss protecting prison inmates as drug test subjects. *The Boston Globe* 11 October 1999: A03.

•Clarification by regulatory authorities of regulations governing prisoner research.[468]

5. Aboriginal People

Before recruiting Aboriginal people to HIV vaccine trials, numerous issues specific to some of these communities will have to be addressed. Aboriginal peoples in Canada display most of the characteristics of strong communities. People share a common culture and traditions, representatives and leaders, legitimate political authority, common geographic localizations, and a common sense of identity and community.[469] In several communities, native languages remain an integral part of the culture. In such distinct and culturally rich communities, one of the principal driving forces behind the ethical protection not only of individuals but also of communities is that the latter also have interests that are entitled to respect and protection.[470] Vaccine researchers who propose to test an experimental vaccine in a native community, will have to ensure that their research protocol and procedures are sufficiently flexible to permit local communities to have a meaningful voice in determining how the research will proceed, and most importantly, how it will benefit the community.

Local communities are the logical parties to determine how best to use a clinical trial to contribute to the development of knowledge, skills and services centered around HIV prevention as well as care, treatment, and support for people with HIV. Development of community research expertise and infrastructure is frequently a priority. Indeed, "[c]apacity building at the community level which results in the development of broad research skills [has] become fundamental to any proposed health research" in Aboriginal / First Nations populations.[471] Only through such collaborative efforts will scientists be able to ensure the collective's support for conducting vaccine clinical trials.

Efficacy trials of HIV vaccines will generate data concerning seroprevalence and seroincidence among volunteers. The research protocols will have to offer a variety of testing venues where counseling is culturally sensitive to persons of Aboriginal descent. "As a general rule, HIV testing in this environment should be undertaken only with quality pre- and post-test counselling."[472] Aboriginal peoples will likely want this counselling to be offered by Aboriginal health care workers / intervenants. Fear of discrimination and issues of confidentiality, and community health, will be of utmost concern and will require close attention.

People in these numerous communities will have concerns about the potentially stigmatizing effects that may result from the release of information suggesting that a given community or subgroups within that community are experiencing high levels of seroincidence and

468 Z Lazzarini, FL Altice. Supra, note 466.

469 C Weijer, EJ Emanuel. Supra, note 10.

470 Ibid, at 1144.

471 Health Canada. *Research on HIV/AIDS in Aboriginal People: A Background Paper*. Ottawa: Northern Health Research Unit, University of Manitoba, Minister of Public Works and Government Services Canada, September 1998, at Section 4.2.

472 S Matiation. *HIV Testing and Confidentiality: Issues for the Aboriginal Community: A discussion paper.* 2nd ed. Montréal: The Canadian Aboriginal AIDS Network and The Canadian HIV/AIDS Legal Network, 1999, at Section E: How should voluntary testing be done? and Conclusions, at 26.

seroprevalence, or risk behaviours. Communities will want to avoid stigmatization, discrimination, and nefarious economic impacts, that might result if the publicity and reporting of research results is sensationalist and insensitive to Native cultures. The research must anticipate these difficulties and prescribe protective measures designed to provide for accurate data interpretation and communication, and encourage a relevant response thereto.

> Studies underway or under consideration should identify that Aboriginal people have participated so that conclusions can be drawn that reflect the experience of Aboriginal people.[473]

> Aboriginal communities, tired of decades of externally controlled research agendas which appear to do little to benefit communities, are insisting that all forms of research, regardless of the methodology, must be developed in full partnership with Aboriginal organizations and communities. Indeed, many organizations insist that the research agenda be developed under the control of the Aboriginal community, and require strict protocols governing access to data and publication.[474]

When such communities are targeted for recruitment, they will most likely want to exercise a management role in vaccine research, either as principal investigator or by exercising the power to retain the investigator on contract. The principle of Aboriginal control over and ownership of research and data will be of prime importance in this process.[475] This principle must however find ways to co-exist with the need to generalize trial data to many other communities (Aboriginal and non-Aboriginal) that may also contribute to large-scale efficacy trials and which are also currently vulnerable to HIV.

One example is an agreement reached concerning a study of juvenile diabetes in the Kahnawake community:

> Researchers and the Kahnawake community have negotiated a mechanism in which consensus between the researcher and the community on data interpretation is sought.[476] If consensus cannot be attained within a reasonable amount of time, the competing interpretations of the study will both be published.[477]

Native councils have also established research management infrastructures to serve as the gateway to collaborative clinical research. “The development of collaborative relationships involving research communities and scientists has become [the] accepted practise” among Native

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473 Health Canada. Supra, note 471, at Section 4.2

474 Ibid, at Section 5.0: Research Methods and Ethics.

475 K Barlow et al. Involving Aboriginal communities in HIV/AIDS surveillance and research. Notes from a Presentation to the 7th Annual Canadian Conference on HIV/AIDS Research. Québec, Qc, 1998. Abstract no 150P.

476 AC Macaulay et al. *Canadian Journal of Public Health* 1998; 89: 105. Cited in C Weijer, EJ Emanuel. Supra, note 10.

477 Health Canada. Supra, note 471, at Section 5.0: Research Methods and Ethics. See also *Protocol for review of environmental and scientific research proposals*. Akwesasne - Hogansburg, New York: Indigenous Peoples Council on biocolonialism, Akwesasne Task Force on the Environment, Research Advisory Committee, 1996, and C Weijer, EJ Emanuel. Supra, note 10.

communities in Canada today.[478] Thus, several other codes similar to the one developed at Kahnawake already exist elsewhere in Canada. They govern the conduct of ethical and culturally sensitive clinical research in specific Aboriginal communities and include "strict protocols governing access to data and publication".[479] These codes are the result of careful negotiations and deliberations and should not be taken lightly. Vaccine researchers who ignore this developing record of native management risk facing accusations of "biocolonialism". They must therefore acquire knowledge of their target community, and of the pertinent political and ethical standards / instruments that the community has developed (or wishes to develop). Sponsors should recognize that this is a long term investment that will strengthen recruitment and the overall quality of their research.

The above mentioned issues are primarily centered around securing the collective's support as a necessary precondition to recruitment. But recruiting subjects in these communities will also require that researchers address individual concerns. These will include the need for culturally adapted informed consent and the preservation of the confidentiality of trial participation and of serostatus. Many people believe that confidentiality is not possible in a small community.[480] This may constitute a serious obstacle to recruitment in small Aboriginal communities or from urban Aboriginal populations in which people frequently return to small "hometown" communities. Even an *urban* Aboriginal population can be a "small town" within a metropolis. Research cohorts can offer participants a variety of testing venues with clear assurances that access to any stored nominative data will be strictly controlled.

Cohorts should also work with the general population, community leaders and intervenants to facilitate a general understanding of HIV and of vaccine research in target communities. This will help to reduce the stigma and discrimination associated with both HIV and AIDS and with participation in a clinical trial of an experimental anti-HIV vaccine.

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478 Health Canada. Supra, note 471, at Section 5.0: Research Methods and Ethics.

479 ID.

480 S Matiation. Supra, note 472, at 33-9.

K. Summary Observations Regarding Recruitment in Canada

Canada is in a strong position to develop a capacity to equitably include multiple target communities in HIV vaccine efficacy trials. To do so, we must cultivate a degree of vaccine preparedness in these communities and build a capacity to rapidly respond to multiple announcements of clinical research. This will best work if vaccine research is firmly situated within national and provincial HIV/AIDS strategies. In particular, recruitment to clinical trials of HIV vaccines must be anchored within overall strategies of prevention and community capacity building.

Potential target communities should strike a forum by which they can establish principles and guidelines aimed at developing minimum community requirements for collaboration and consent in the research. Key among these requirements must be the ability to have input into the ethical review process. The adoption of universal ethical policies for the protection and empowerment of research subjects who will be drawn from vulnerable communities is to be recommended. The influence of such universal standards should extend regionally, nationally, and internationally. Universal standards must be carefully designed, however, so that they do not stifle cultural sensitivity and the ability to take into account local concerns with respect to recruitment campaigns and ethical review.

Within provincial jurisdictions in Canada, human rights law applies beyond the sphere of relations between the state and the citizen. It encompasses many juridical relationships between private interests. A creative use of human rights law can support codes of ethics in promoting inclusiveness in research participation as well as equity in the distribution of its burdens and benefits. A human rights approach to research can be used to hold government funders, public health, sponsors, and researchers to platform standards of care and hopefully prevent a situation in which the most destitute and vulnerable are either overrepresented or underrepresented in vaccine clinical trials.

> International and national human rights law imposes obligations on states to safeguard and promote health not only of their own citizens and people within their borders but of all people.[481]

States therefore have a moral and perhaps legal obligation to ensure that HIV vaccine research proceeds as a necessary means to promote the health of their own citizens but also to help developing countries address the HIV epidemic. If private industry finds itself faced with economic conditions which place HIV vaccine research at a net disadvantage to other forms of research, then it can legitimately look to the governments of industrialized nations to redress this disadvantage.

But implicit in both a human rights and an ethical discourse, is the need to ensure that the benefits of vaccine research ultimately inure to those in need of a vaccine without regard to factors such as wealth and social status, race, gender, sexual orientation, geography, religion and culture. Preparing for a just and equitable distribution of an HIV vaccine begins years, perhaps decades earlier, when cohorts are designed and people are recruited into efficacy trials. Framing

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[481] D Patterson. Supra, note 446, at 34.

recruitment in the context of human rights means that people can approach vaccine research with notions of entitlement to both participation and protection throughout the research process.

In addition, collective human rights recourses can be used by a knowledgeable populace to hold public health officials and industry accountable for any negligent applications of clinical trial data to culturally and epidemiologically distinct communities unjustly omitted from primary research.

By working to include non-traditional populations in vaccine cohorts, while protecting participants and recognizing their capacity for directive contributions, Canada can set a high standard for the ethical recruitment of human research subjects to HIV vaccine efficacy trials.

III Informed Consent

In this part of the paper we will undertake a detailed analysis of informed consent in the context of clinical trials of HIV preventive vaccines. As elsewhere in this paper, the primary focus will be upon consent to phase III efficacy trials. This part of the paper can be broadly divided into three sub-sections.

- In sections A through C, we examine and describe the nature and quality of informed consent.
- In sections D through F, we study the specific legal and ethical qualities and requirements of informed consent with particular attention paid to the resulting obligations and recourses.
- In sections G through J, we turn our attention to the specific content to be included in informed consent providing some an in-depth focus on certain key issues.

A. Introduction

Providing the volunteers who answer recruitment campaigns with an opportunity to exercise an enlightened acceptance or refusal to participate in the HIV vaccine clinical trial is a direct means of protecting them from exploitation, disappointment and harm. In order for this protection to be effective, their consent must be informed, comprehending, and voluntary.[482] Moreover, informed consent is much more than a single decision made at the point of entry to the trial. Rather, it is a continuous process involving consent to each significant element of the research in the trial at its beginning and as it unfolds. Vaccine efficacy trials take a relatively long time to gather raw data (two to four years).[483] During this period, once-clear concepts learned through the initial process of informed consent can become confused as memory dims, and as the participant discovers new sources of potentially confusing information. Consequently, the understanding and the consent of participants in clinical trials of HIV vaccines will require periodic re-evaluation, corrective information when indicated, and frequent opportunities for renewal throughout the trial.

> The crucial question is not whether the written consent form contains all the information a reasonably prudent patient would need to know - although that is certainly a good beginning. Rather, the question is whether the participant through the consent process, can actually access and understand such information so that he can appreciate the nature,

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[482] DJ Roy et al. Supra, note 77, at 116-22.

[483] Note: It takes at least another year to analyze data and even more time to thoroughly disseminate the results of the trial. If the clinical trial has demonstrated efficacy and safety warranting marketing, it can take up to two more years to secure regulatory review of the clinical science and approval for licensing. Production facilities must then be constructed and are subject to regulatory approval. Marketing then follows. The provinces must also decide whether to include the new vaccine in the list of vaccines covered by public medical insurance. All of these steps typically add a further year or two to the process.

> risks and benefits of the experiment to which he is submitting.[484] To be ethical and effective, informed consent must also be comprehending.

Because informed consent is positioned at the beginning of the trial and continues throughout its duration, the impact of a well structured, efficient process of consent will be of immediate, direct and continuing benefit to the participants.[485] By virtue of its interactive involvement with every single volunteer, the process of informed consent is probably the single most influential mechanism of protection, for all concerned – safeguarding the interests of participants as well as those of researchers.[486] The process serves to protect vulnerable recruits and target populations that might otherwise easily be susceptible to exploitation.

Ironically, despite its protective role, the informed consent process offers the volunteer very limited options, - essentially reduced to a power to either accept or refuse participation. This is not a process of bargaining between parties of equal status and power over contractual terms and conditions. While it is true that researchers will be dependent upon a steady supply of volunteers in order to conduct the multiple clinical trials required to discover a safe, efficacious and efficient preventive vaccine, the power to dictate the content of informed consent nevertheless lies with the sponsor. There is a considerable imbalance of power between participants on the one hand and researchers and sponsors on the other. This imbalance of power is relevant to consent even within the context of ordinary medical treatments offering prescription medications.

> Dependence and inequality characterize these relationships, colouring the legal principles and affecting their impact. The patient is dependent both on the company and on the doctor to provide sufficient information for an informed decision to be made [....].[487]

This disparity will be even more accentuated with respect to informed consent to participation in a clinical trial of an experimental HIV vaccine. The relative novelty of this type of research will mean that the number of sources of available and impartial scientific information will be somewhat limited. The disparity between researcher and participant will show up with respect to matters such as: (i) technical knowledge; (ii) the perception of authority; (iii) the resources to protect volunteers from potential discrimination; (iv) the ability to indemnify or compensate for vaccine-induced injury; and (v) the persuasive power of even minimal benefits in marginalised and disadvantaged communities. The imbalance in clinical trials thus clearly favours the researcher / corporate sponsor.

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484 *Hopp* v *Lepp*, [1980] 2 SCR 192 4 WWR 645 112 DLR (3d) 67. See also *Couglin* v *Kuntz*, 42 BCLR (2d) p 108. (CA) Note, however, that this case involved an experimental therapeutic surgery and thus cannot be compared directly to a clinical trial of a non-therapeutic (eg, preventive) vaccine.

485 AJ Rosoff. Truce on the battlefield: A proposal for a different approach to medical informed consent. Commentary. *The Journal of Law Medicine & Ethics* 1994; 22(4): 314-17.

486 Note: A diligent and detailed approach to informed consent can also help researchers by protecting their good reputation in the targeted communities; encouraging people in the targeted communities to trust the research process, thereby improving prospects for recruitment to large scale vaccine efficacy trials as well as prospects for high levels of coverage with an eventual vaccine; and offering researchers improved protection from liability.

487 P Peppin. Drug / Vaccine Risks: Patient Decision-Making and Harm Reduction in the Pharmaceutical Company Duty to Warn Action. *The Canadian Bar Review* 1991; 70: 473-516 at 474.

Therefore, while informed consent has the potential to provide considerable protection to volunteers, participants, researchers and to the scientific process itself, much advance work is necessary in order to ensure that the process reflects the highest practicable levels of substantive content. Improvements can not be contractually negotiated at the level of individual consent. Moreover, unless new information of urgent importance becomes available, protocols and consent procedures should not, for obvious reasons, undergo extensive revision after recruitment, and especially after vaccination, has already begun. Thus, the informed consent procedure must be reviewed, evaluated, corrected and fortified before the clinical trial commences.

B. Preparation to Ensure that Informed Consent has Substantive Meaning

Even the most carefully conducted informed consent procedures will be unable to acceptably protect research subjects if other levels of scientific and ethical regulation, review and monitoring are absent or carelessly and negligently undertaken. Expecting informed consent to fulfil the entire role of protecting participants would be like asking the traveller who carefully shops for the best price / quality in an airline ticket to use the shopping process to verify whether the jet engines are properly maintained. To achieve its noble goals, informed consent must be but one small part of an integrated and well prepared strategy of legal and ethical protections, including: regulatory review, a local capacity to conduct ethical review, and effective local HIV prevention. Without these essential links, informed consent risks becoming a mere hollow, diminished, and procedural shell.

The consent process needs to be carefully prepared. This preparation will at least involve:

- consultation of international and Canadian ethical guidelines for research, of which there are many;[488]
- review and revision of consent documents by Research Ethics Boards; [489] and

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488 Joint United Nations Programme on HIV/AIDS. Supra, note 10, Guidance Points 6, 7, 12, 13, 15, 17, and 18. See also: World Medical Association. Supra, note 101, and Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization. Supra, note 367, and *The Nuremberg Code*. Supra, note 9, at 181-2, and *The International Covenant on Civil and Political Rights* 1996: Article 7, and Medical Research Council of Canada. Supra, note 76, and Medical Research Council of Canada. Unpublished document by the Best Practices Working Group: Informed Consent sub-committee. Informed Consent in Clinical Trials: Competent Adult Participants, General and Specific Guidelines 2000 (in progress), and *Model Informed Consent Form*. Vancouver: Canadian HIV Trials Network, 1999.

489 For legal sources of REB authority, please see Regulations Amending the Food and Drug Regulations. Supra, note 197, at Arts. C.05.001, C.05.006(1)(c), C.05.010: 1116, 1120, 1123. See also Regulatory Impact Analysis Statement. Supra, note 89, at 1131, 1134, 1137, 1141, 1142, 1143, 1146-47, and 1150, and Article 21, al. 3; CCQ, for the case of consent to clinical research involving a group of minors or incompetent adults in Québec. At a policy level please see Medical Research Council of Canada. Supra, note 76, at Section 1: Research Requiring Ethics Review, and Section 4: Conflicts of Interest Involving Researchers, and *Éthique de la Recherche et en Intégrité Scientifique.* Québec: Ministère de la Santé et des Services sociaux: Direction générale de la plannification et de l'évaluation, June 1998, and Canadian Medical Association. *Code of Ethics*: Article 25, and *Local Research Ethics*

•community input into the review and revision of informed consent documents and procedures.

Ethical review and community input into that review process might face particular difficulties in the context of multi-centre trials. At the present time, it is not clear just how far local research ethics boards and community input can effect changes to informed consent procedures used in such trials. Several of the communities targeted for HIV vaccine research will likely be characterised by high levels of diversity, marginalisation, vulnerability, and economic disadvantage. Given these characteristics, some mechanism for local input into the design and evaluation of the informed consent processes seems logically desirable. But community development in such settings is sometimes uncertain and incomplete and input into the informed consent process of clinical vaccine research will be practically difficult to realise at each and every site.

In addition, even as policy and legal regulations increasingly recognise the necessity of ethical review in Canada, arguments are being advanced to minimise local input. Critics of local review cite problems such as: (i) time delays and (ii) the potential for local variations to introduce a relative bias into the process of subject selection and consent thereby creating politically difficult inequalities and threatening the ability to compare the data generated at different sites. "National" REBs are proposed as one potential solution, although regulations in some provinces will require a local "institution-specific" REB review.[490]

Multi-centred clinical trials sometimes use a "competitive recruiting" strategy. According to this format, the sponsor invites potential principal investigators at numerous sites to recruit a set number of participants at each site. However, the sponsor also fixes the total number of trial participants for the overall clinical trial at a figure substantially lower than the number that would result if all the invited sites were to respond. The sponsor then awards research contracts on a "first come - first served" basis to the sites skilled enough to be the quickest to complete scientific and ethical review and recruitment. Two different hospitals in the same city can be competing for the privilege of obtaining the same contract to conduct the same research. When the REBs are institutionalized, there is a possibility that members of the board, even if they are independent from the research contract, will feel considerable sympathy for the research colleague from the same institution who is caught up in the race to qualify. Institutional research ethics boards at these hospitals will be under significant pressure to rapidly approve the protocol and the proposed consent process. They will need to do this by limiting their requests for amendments, hence keeping delays to a minimum. They may also require added resources to accomplish their mandate more rapidly. Once again, national or provincial REBs with a developed expertise in HIV/AIDS related research might be a solution, but at the cost of minimizing local input [491].

Rigorous, independent, and prior ethical review of the informed consent process is required to ensure that the process has substantive content. HIV clinical trials will target diverse and marginalised communities. If the opportunities for local review are stunted, the accessible and comprehensible qualities of this substantive content may be compromised. Without the

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Committees. England: National Health Service Management Executive, 1991, HSG(91) 5, and JK Mason, RA McCall Smith. *Law and Medical Ethics*, 4th ed. London: Butterworths, 1994, at 353.

490 G Beauregard. L'injonction paradoxale découlant de l'obligation faite aux Comités d'éthique de la recherche d'examiner les protocoles multicentriques. In JF Malherbe. *Compromis, dilemmes et paradoxes en éthique clinique*. Montréal: Artel-Fides, 1999, 80, at 89-92.

491 JK Mason, Supra, note 489, at 353.

guarantees offered through prior review and revision, the process in and of itself may be of little or diminished utility to the participant.

> There is a growing fear that informed consent is increasingly being regarded as a technical matter, removed from wider ethical considerations, of it merely consisting of a written signature on a consent form serving to pre-empt any litigious action should research or treatment give rise to damage. In the field of vaccine research, recently developed technologies and rapidly evolving basic scientific knowledge are posing important challenges to the traditional doctrine of informed consent.[492]

Carefully drafted consent forms containing detailed and complex information concerning all foreseeable risks can, if they are signed in a routine and cursory manner, effectively betray the ethical objectives of informed and especially comprehending consent. Perfunctory treatment of consent does no justice to the protection of participants' autonomy and dignity or of their corporeal integrity. Communities need to become aware of the potential for the informed consent processes used in large-scale vaccine efficacy trials to help secure protection for participants, target communities and researchers alike. They also need to be aware of the potential for abuse, especially if written forms are used to witness a consent that is more illusory than real. Community leaders and members of REBs need to promote the protective role of informed consent by working closely with researchers to ensure that all parties understand that voluntary, informed and comprehending consent is in everyone's best interests.

C. Describing Informed Consent

One can draw from a number of sources to shape the concept of "informed consent" to participation in a clinical trial of an HIV vaccine. These include: (i) the ethical values and objectives which the process of informed consent promotes and protects, (ii) the various laws prescribing informed consent, (iii) the description of informed consent contained in ethical guidelines for research on human subjects; (iv) the composite elements routinely included in consent forms; (v) the diversity of procedures that can be used to secure the consent; and (vi) the requirements for informed consent that are specific to an HIV vaccine trial. This sub-section emphasizes the basic nature and qualities of informed consent that are particularly important in an HIV vaccine trial. Attention is centred on the foundations, the objectives, the scope, and the limits of informed consent.

1. Foundations

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[492] For information concerning REBs and ethical review of informed consent, see: RL Penslar. *Institutional Review Board Guidebook.* 2nd Ed. Rockville MD: 1993, and J Katz. Reflections on Informed Consent: 40 years after its birth. 1997 Ethics and philosophy lecture, American College of Surgeons, Regents Committee on Ethics. Available at www.facs.org/about/committees/ethics/katzlect.html.

The doctrine of informed consent is rooted in the human condition - the notion that humanity and accompanying volunteerism for clinical research will only exist if research subjects and investigators are held to be fundamentally equal in matters of dignity, spirit, and intrinsic self worth. This philosophy presumes that all human beings equally feel pain, and have an equal right to take measures to avoid it. Informed consent necessarily implies that people should not be used in experiments designed to develop knowledge and products (eg, vaccines) that will only be of benefit to others. Informed consent recognises that each person has a fundamental, *prima fasciae*, human right to control what is done with their own body. Informed consent empowers individuals to take decisions promoting their own health and contributing to public health within their communities. It thus facilitates subject participation and collaboration in clinical research.

The concept is also designed to help prevent repetition of a tragic history of incidents of abuse and of exploitation of vulnerable or incompetent research subjects [493]. These incidents add further impetus to the need to ensure that verifiable informed consent plays a protective role for those altruistically volunteering to take part in medical and pharmaceutical research.[494]

The doctrine of informed consent can also be seen as rooted in western concepts of "respect for the person" and of "human dignity" as expressed through the particular values of individualism, autonomy, and inviolability of the person.

> To provide informed consent, individuals must be accurately informed of the purpose, methods, risks [and] benefits [to the participant and to the target community / society[495]], of participating in the vaccine trial, and of the alternatives to the research. The participant must understand this information and its bearing on their own clinical situation, and make a voluntary and uncoërced decision whether to participate. Each of these elements is necessary to ensure that individuals make rational and free determinations of whether the research trial is consonant with their interests.[496]
>
> Four elements must be present for a valid consent to medical treatment to exist, regardless of who is to give it:
>
> - there must exist the mental capacity to give the consent;
> - it must be voluntarily given;
> - it must be an informed consent; and

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493 HK Beecher. Supra, note 9. See also *Advisory Committee on Human Radiation Experiments (ACHRE) Final Report*. Washington DC: USGPO, 1995, and SM Reverby. Supra, note 9, and *The Nuremberg Code*. Supra, note 9, at 181-2, and National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Supra, note 9. Note: Canada has not been immune to controversy surrounding use of vulnerable populations in medical experimentation and treatment without their informed consent. Questions have arisen concerning allegations of: forced sterilisation of Native women, experiments conducted for the CIA at the Montréal Neurological Hospital without divulging the sponsorship and without informed consent; alledged use of prisoners in prisons for the criminally insane and in a women's penitentiary for psychiatric experiments and / or treatment without informed consent.

494 *The Nuremberg Code*. Supra, note 9, at 181-2. See also *United Nations International Covenant on Civil and Political Rights*. UN General Assembly, 1974, Article 7, which reads as follows: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation."

495 JK Mason, RA McCall Smith. Supra, note 489, at 360.

496 EJ Emanuel et al. Supra, note 302, at 2706.

•it must be directed toward or related to a specific act or set of acts.[497]

Wherever clinical research involves significant risk, or variance from standard procedures, the need for informed consent is intensified.[498] At the present time, there is not yet scientific proof of an efficacious vaccine against HIV. In view of: (i) the absence of any vaccine; (ii) the relative lack of scientific knowledge concerning the probable correlates of HIV immunity; and (iii) the frequent resort to new genetic technologies in the design of candidate vaccines, adjuvants and vectors; HIV vaccine clinical trials meet the criteria of "significant risk" and "variance from standard procedures" head on. This imposes a particularly onerous legal and ethical burden upon the researcher to facilitate informed consent.

2. Objectives

The first, and perhaps most important, objective of the informed consent process is to protect the rights, interests and well being of research subjects. The revised World Medical Association's Declaration of Helsinki emphasized that "considerations related to the well-being of the human subject should take precedence over the interests of science and society."[499].

Moreover, an adequately conducted informed consent process empowers research subjects to make enlightened autonomous decisions related to their health. The objective is "to ensure that individuals control whether or not they enrol in clinical research and participate only when the research is consistent with their values, interests and preferences"[500].

The informed consent process can also promote "self-reflection in the biomedical research community" as well as "self-scrutiny and rational decision-making among investigators"[501]. The probability of this objective being achieved increases with the degree to which research subjects and their communities can ask questions and interact with researchers in critical discussion.

The exchange of information and knowledge that is inherent in a properly conducted process of informed consent will also help to screen out individuals who are unsuited for vaccine clinical research.

> Finally, research subjects and their communities should know if the researchers who are recruiting subjects and conducting trials are involved in conflicts of interest. Lobbyists, universities, private corporations, international development agencies and international finance and trade organizations, all have a vital role to play in facilitating pre-clinical science, vaccine clinical trials, and ultimately vaccine delivery around the world. These parties increasingly engage in close partnerships with industry with the inevitable result that "apparent" conflicts of interest will abound.

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497 G Sharpe. Supra, note 402, at 30.

498 JK Mason, RA McCall Smith. Supra, note 489, at 310.

499 World Medical Association. Supra, note 101, at Recommendations guiding physicians in biomedical research involving human subjects.

500 EJ Emanuel et al. Supra, note 302, at 2706.

501 TA Kearns. Supra, note 50, at 153.

Declaring these interests in a transparent manner and publicly demonstrating that steps have been taken to disarm their potential influence, will help participants, scientists, regulators and consumers to exercise some degree of scrutiny over HIV vaccine research.[502] This scrutiny should serve the goals of: (i) promoting the integrity of scientific inquiry; (ii) helping to ensure that the best candidate vaccines are selected to move through the successive phases of clinical research; (iii) helping to ensure that the data generated by these trials is not manipulated; and (iv) generally keeping HIV vaccine research on track [503].

Otherwise, if conflicts of interest in clinical trials are undeclared only to subsequently leak into the public realm, they can serve as ammunition to certain fringe elements of society in which some people generally oppose all vaccination and treat even tested and licensed vaccines with unscientific suspicion.

3. Scope

Informed consent must be comprehending: "Informed" does not automatically mean nor even imply "comprehending".[504] The investigator must take reasonable steps to ensure that the subject actually can understand and has understood the information that is given to him concerning the clinical trial. "Ethics Review Committees will probably require that researchers have designed a clear method of assessing understanding and have explained the manner in which they will administer it"[505]. This means that researchers need to be aware of the participants' cultural perspectives on medicine, sexuality and research. They must also be prepared to take reasonable measures to accommodate the individual's requirements for help in assessing and understanding their proposed role in the clinical research.

Consent forms can be pre-tested on the target population and carefully edited to improve their ability to render information accessible to that population. They can be written using a simple level of language in order to be as comprehensible as is practically possible to the broadest spectrum of potential volunteers.[506] Participants can be given a consent form to take home for one or two weeks in order to facilitate a careful reading before a subsequent signature. This was done at the AIDSVAX phase III clinical trial site in Montréal.

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[502] EA Boyd, LA Bero. Assessing Faculty Financial Relationships With Industry: A Case Study. *Journal of the American Medical Association* 2000; 284(17): 2209-14.

[503] D Korn. Conflicts of interest in biomedical research. Commentary. *Journal of the American Medical Association* 2000; 284(17): 2237-38. See also C DeAngelis. Conflict of interest and the public trust. Editorial. *Journal of the American Medical Association* 2000; 284(17): 2237-38; F Davidoff et al (eds). Sponsorship, authorship, and accountability. *The New England Journal of Medicine* 2001; 345(11): 825 – 827; World Medical Association, supra, note 101, at Recommendations guiding physicians in biomedical research involving human subjects. Also see Proposed Revision of the *Declaration of Helsinki,* Article 22 -- Text of the Working Document prepared for a working group of the WMA Medical Ethics Committee in preparation for the 52d WMA General Assembly, Edinburgh, Scotland, 3 October 2000.

[504] TA Kerns. Supra, note 50, at 156-60.

[505] Ibid at 158.

[506] Medical Research Council of Canada. Supra, note 488, at 2. *Model Informed Consent Form.* Supra, note 488. Note: Both of these guidelines suggest that consent forms in Canada should be drafted at an 8th grade English level. This clearly was not the case with the consent forms initially proposed for the AIDSVAX B/B Gp120 clinical trial in Montréal.

One key difficulty however, arises in the tendency to merely reduce informed consent to the contents of a very long consent form. But in the end, even the best consent form cannot guarantee the literacy and understanding of the reader. In point of fact, verbal communication (questions and answers) is probably just as important if not more so than a written form which may only receive a cursory glance by its reader. The written consent form is only one small part of the participant - investigator discussion.[507]

"Comprehending" means that researchers must not only coherently transmit the information that they wish their subjects to understand, but that they must also be prepared to take the time to answer questions from both participants and their communities. Examples of such questions will include:

- Why are we being targeted for testing this experimental vaccine?[508]
- Who else is being targeted for recruitment?[509]
- Are you taking the experimental vaccine?[510]
- Is this candidate vaccine safe?[511]
- What company, institution or government agency is sponsoring the research?[512]
- If this vaccine makes me ill, will you pay for my care and financial losses?[513]
- How will you guarantee this obligation to compensate?
- If far in the future, (long after the end of the clinical trial), my HIV test is incorrectly interpreted as HIV antibody positive, when in fact I am only vaccine antibody positive, who will protect me?
- If I contract HIV during the vaccine trial, what standard of care will be offered to me and by whom? - the very best proven therapy; or merely the best therapy commonly available to people in my community?
- Is this test vaccine designed for the clades and sub-types of HIV circulating in this community? If not, why not?[514]
- What is the probability that this experimental vaccine will work?[515]
- When will an effective vaccine be available?[516]
- If this vaccine (or any other vaccine you should develop) works, will you make it available in my community at a cost that people here can afford?[517]

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507 Medical Research Council of Canada. Supra, note 488, at 2.

508 D Mbori-Ngacha. KAVI: Kenyan AIDS Vaccine Initiative Oral Presentation / Roundtable: AIDS Vaccine Development for Africa. XIIIth International AIDS Conference. Durban, South Africa, 11 July 2000.

509 ID.

510 SM Kegeles et al. Supra, note 313.

511 RB Hays et al. How would gay men decide whether or not to participate in an HIV vaccine efficacy trial? Oral presentation to XIIth International AIDS Conference. Geneva, 28 June-3 July 1998. Abstract no 43546. See also D Mbori-Ngacha. Supra, note 508.

512 TA Kerns. Supra, note 50, at 153.

513 RB Hays et al. Supra, note 511.

514 J Cohen. Africa Boosts AIDS Vaccine R&D. *Science* 2000; 288: 2165-67.

515 RB Hays et al. Supra, note 511.

516 J Cohen. Supra, note 514.

517 D Mbori-Ngacha. Supra, note 508.

A multitude of processes can be used to communicate the required information in a comprehensible fashion. The choice of methods will be shaped by factors such as the culture, language, traditions, levels of education, and the past record of experience with vaccination and of involvement in clinical research within the target population. Examples of means of conveying information include: interviews with cohort staff; explanatory videos; written articles; the opportunity to pose questions to the principal investigator and to the cohort staff; frequent use of analogy to explain difficult or culturally foreign concepts; theatre presentations; computer questionnaires and other forms of examinations to test understanding; and community forums, focus groups and meetings.

A growing body of commentary and doctrine also suggests use of a "participant's bill of rights" as a means of enhancing the informed consent process.[518] The "bill of rights " explicitly states the participant's right to free, voluntary and informed consent. It summarizes the most basic representations made by the corporate sponsor and principal investigator and the various procedures by which participants can raise complaints. Such a document was in fact submitted to participants in the AIDSVAX B/B Gp 120 phase III clinical trial taking place in North America, Puerto Rico and in Amsterdam. The bill was not however formally included in the text of the informed consent form.

4. Limits and Challenges

(i) Informed Consent As Only One Part of an Ethical Framework

People have criticized the model of informed consent as being inflexible and culturally biased in favour of western concepts of individual autonomy. Others point out that in and of itself, informed consent does not guarantee that clinical research is ethical. These commentators criticize what they perceive to be a "near obsession with autonomy in US bioethics".[519] This criticism, brings us back to the self-evident proposition that informed consent is an incomplete protection for the research subject. "Informed consent is a meaningful, ethical concept only if it can be realized and promoted within the boundaries of good medical practice [and of good medical research]."[520] [text in square brackets added]. For example, Emanuel et al propose seven over-arching ethical requirements for good clinical research, of which informed consent is only one. The proposed requirements are as follows:

- The research must have social or scientific value.
- The research protocol must be conducted in a scientifically valid fashion.
- There should be fair subject selection.
- There must be a favourable risk-benefit ratio.
- The research must be subject to independent scientific review.
- Research subjects must give informed consent to participate in the trial.
- The research must be conducted in a manner that respects the autonomy and welfare of potential and enrolled subjects.[521]

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[518] TA Kearns. Supra, note 50 at 152. See also HIVNET National Community Advisory Board. Participant's Bill of Rights. December 1998. In B Snow (ed). Supra, note 58, at 111, 112, 113.

[519] EJ Emanuel et al. Supra, note 302, at 2701.

[520] Ibid.

[521] Ibid at 2701-2.

Viewed from this perspective, informed consent is only one small part of an overall need for "a systematic and coherent framework for evaluating clinical studies that incorporates all relevant ethical considerations."[522]

(ii) Sensitivity to Cultural Diversity

One may argue that the ethical values for research involving humans are in fact universal but that the procedures and policies used to apply these values can be varied to accommodate and respect local traditions and cultures. This argument would imply that adapting the requirements of informed consent

> to the identities, attachments, and cultural traditions embedded in distinct circumstances neither constitutes moral relativism nor undermines their universality; doing so recognizes that while ethical requirements embody universal values, the manner of specifying these values inherently depends on the particular context.[523]

HIV vaccine clinical efficacy trials are most efficient at detecting the broadest range of efficacy when conducted in populations in which seroincidence levels are high and likely to remain so for a number of years. This factor, combined with the uneven geographic distribution of clades, and the severity of the epidemic in developing nations, suggest that vaccine research must inevitably be an international collaborative effort between developed and developing nations.

Canadian researchers will likely conduct various phases of vaccine clinical research not only in this country but also in selected nations in the developing world. But, "[...] problems in the process and documentation of informed consent in international collaborative research appear especially difficult to resolve in cases where the nations involved do not share common cultural values, attitudes, and ethical commitments."[524] Applying the principle of individual informed consent

> may be much more difficult in developing nations, where levels of literacy are much lower than in developed nations, and where beliefs about the nature and causation of disease may be different from those held by the researchers, and where the notion and value of personal identity and individuality may be strikingly different than that held in Western nations.[525]

HIV vaccine trials, wherever they take place, will require that participants undergo repeated and periodic vaccination with an experimental vaccine or placebo as well as testing for HIV infection. In some cultures, there are strong beliefs that language and thought directly influence health with the result that the doctor is routinely expected to minimize the disclosure of risks while resolutely accentuating the advantages of any given medical intervention.[526] This has led

[522] Ibid at 2701.

[523] Ibid at 2708.

[524] *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries (Vol 1).* Report and Recommendations of the National Bioethics Advisory Commission. Bethesda MD, April 2001, at Ch 3.

[525] TA Kearns. Supra, note 50, at 153.

[526] R Macklin. Against Relativism: Cultural Diversity and the Search for Ethical Universals in Medicine. New York: Oxford University Press, 1999, at 122.

some authors to suggest that a lower quantity of information in the consent process may be rendered acceptable by the notion that this is what the patient culturally prefers. Thus, providing less detailed information about risks serves the objectives of respecting the person, his autonomy within the context of his culture, and the principles of beneficence.[527]

A further challenge to "informed consent arises when people do not understand or accept scientific explanations of health and disease" as for example may be the case in remote or traditional societies where the precepts of medicine are not based upon germ theory or virology.[528]

In communities where collective decision making is common, or where family members are routinely included in medical decisions, it will be more difficult to facilitate individual, voluntary and comprehending consent in a manner conforming to Canadian legal notions of privacy and confidentiality. Ruth Macklin comments on this issue by noting:

> The danger of a reliance solely on local assessment is that in societies where there is no tradition whatsoever of individual rights, the local assessment may reject the very concept that individual research subjects have rights, and therefore they may be enrolled simply with the permission of [...a proxy].[529]

At first glance, cultural traditions of "family or spousal authorization for research" seem to conflict with a universal ethical standard calling for an individualized informed consent. However, Macklin deftly reconciles the two in a logical framework of analysis that preserves the universality of individual consent and yet makes a place for spousal consent under either parallel or exceptional circumstances. In support of her analysis, she cites Guidelines on Reproductive Health Research and Partners' Agreement prepared for the World Health Organization.[530] These Guidelines begin by recognizing that spousal consent violates the autonomy of research subjects and their right to confidentiality. She notes:

> The guidelines do not assert that partner agreement should be permitted because in some cultures that is the custom or the norm. Rather, the guidelines justify [...a limited] exception on grounds that a denial of the eventual benefits of the research to the entire society would be so great as to outweigh the usual prohibition against partner agreement for the individual subject.
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> This is quite clearly a utilitarian justification. Its use in this context demonstrates the difference between the universality of ethical principles and the very different idea of "absolute" or "exceptionless" principles. The principle of respect for

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527 Ibid, at 121.

528 P Marshall. The Relevance of Culture for Informed Consent in US Funded International Health Research 2000. Background report prepared for The US National Bioethics Advisory Commission. Published in Ethical and Policy Issues in International Research. Bethesda, MD: 29 September 2000, at 10-11. See also N Bahmarapravati. Asian Perspectives: Vaccine Trials in Thailand. In Z Bankowski, RJ Levine, (eds). Ethics and Research on Human Subjects: International Guidelines. Proceedings of the XXVIth CIOMS Conference, Geneva, 5-7 February 1992. Geneva: CIOMS, 1993, at 181.

529 R Macklin. Supra, note 526, at 194.

530 World Health Organization. Guidelines on Reproductive Health Research and Partners' Agreement (unpublished). Scientific and Ethical Review Group, Special Programme of Research, Development and Research Training in Human Reproduction, WHO.

> persons is universally applicable, which means that laws support it. It is not "absolute" in the sense that exceptions cannot ever be countenanced.[531]

Moreover, this rationale, "certainly does not allow an individual to enroll a spouse in research without the spouse's own informed consent to participate."[532] As such, the universality of the principle of individual informed consent is recognized and upheld even as the door is opened to a parallel pursuit of collective or proxy consent in exceptional circumstances. Notes to UNAIDS Guidance Point 13 also endorse this point of view, recognizing the important role that spousal and proxy consent occupy in some societies while at the same time insisting upon individual consent.[533]

In Canada, there will certainly be communities in which attitudes and values surrounding individual informed consent, individual autonomy, the role of the family in managing disease, death and dying differ substantially from, or run parallel to, the prevailing views in our mainstream medicine. But Canadian medicine and medical research already have considerable experience in functioning in a multi-cultural society. By virtue of the fact that in Canada and in North America, marginalized minorities and certain ethnic populations are disproportionately vulnerable to HIV, vaccine researchers who seek to ensure the highest quality of informed, comprehending and voluntary consent will want to be sensitive to the cultural specificity of these target populations. Understanding and respecting local cultures may give rise to diverse accommodations. These may include:

i) involvement of people from the target community in the design and management of the research;
ii) engaging the help of anthropologists as cultural interpreters in facilitating comprehending consent;
iii) shaping the research to provide some benefit to the community;
iv) seeking the consensus of group leaders as a matter of respect and courtesy in parallel to the pursuit of legally required individual consent;
v) translating consent forms; and
vi) effectively communicating information in a culturally appropriate manner.

Unfortunately, the Canadian *Tri-Council Policy Statement* [534] gives short shrift to the impact of culture on the effective granting of voluntary, informed and comprehending consent. For example, for want of time and a lack of necessary discussions with representatives of First Nations and Aboriginal peoples, the Councils postponed establishing any specific policy for research involving these specific populations. Nevertheless, Canadian researchers wishing to conduct clinical trials of HIV vaccines in Canada's Aboriginal and First Nations communities will have to take into consideration traditional values and decision-making processes regarding risks, health, and ownership of research materials and data.

"A general principle is that the obligation to respect human dignity in research involving Aboriginal groups gives rise to both special considerations and to basic ethical duties regarding

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[531] R Macklin. Supra, note 526, at 199-200.

[532] Ibid at 199.

[533] Joint United Nations Programme on HIV/AIDS. Supra, note 10, at Guidance Point 13.

[534] Medical Research Council of Canada. Supra, note 76, at Section 2: Free and Informed Consent; Section 6: Research Involving Aboriginal Peoples; Section 8: Human Genetic Research.

ethics review, *informed consent*, confidentiality, conflict of interest and inclusion."[535] [emphasis added]. As mentioned in the prior section of this paper concerning recruitment, guidelines have been developed in Canada (and in other nations) for specific research projects conducted in specific Aboriginal communities.[536] These guidelines provide at least some indication of the likely requirements for informed consent in vaccine efficacy trials.

For example, the application of the American common-law concept of personal property to human tissue gathered in an HIV vaccine cohort for future, and possibly unrelated, research is extremely difficult to justify given the current status of Canadian laws. But beyond the legal difficulties, cultural concepts of property in Aboriginal and First Nations communities in Canada may not even include an individualized approach to blood, body tissues, DNA, etc. Indeed in some communities, these may be considered as belonging to the collective's patrimony or the patrimony of the ancestors.[537]

> The central issue for discussion is: When it is legitimate for researchers to interview individuals in their own right as individuals, without regard to the interests of the group as a whole and without seeking permission from any group authority or spokesperson? Or, conversely, when should the approval of the community as whole be required?[538]

A vaccine clinical trial may generate ancillary epidemiological data which, if not presented in an explanatory and culturally contextualised manner, could potentially stigmatize certain Aboriginal communities. There may therefore be a compelling interest to engage in a process of obtaining general community assent according to local values and traditions at the same time as individual consent is sought from each and every volunteer.

Culture is not an insurmountable obstacle to the granting of informed consent. Rather, it is a factor to be weighed and accommodated in order to improve the overall quality of the

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535 Ibid, at Section 6: Research Involving Aboriginal Peoples.

536 Ibid at Section 6: Research Involving Aboriginal Peoples, Subsection A: Introduction, Endnotes 3-6 which cites Inuit Circumpolar Conference. Principles and Elements for a Comprehensive Arctic Policy. Alaska, Greenland, Canada, and National Health and Medical Research Council of Australia. Guidelines of Ethical Matters in Aboriginal and Torres Strait Islander Health Research. Canberra: NHMRC, 1991, and American Anthropological Association. Statement on Ethics: Principles of Professional Responsibility. Adopted by the Council of the American Anthropological Association, May 1971, and American Public Health Association Task Force. National Arctic Health Science Policy. Washington DC: APHA, 1984, and American Indian Law Center. Model Tribal Research Code. Albuquerque: 1994, and US Interagency Arctic Research Policy Committee. Principles for the Conduct of Research in the Arctic. Arctic Research of the United States 1995; 9: 56-7, and Association of Canadian Universities for Northern Studies. Ethical Principles for the Conduct of Research in the North. Ottawa: ACUNS, 1982, reprinted 1988. See also Six Steps Toward Cultural Competence: How to meet the health care needs of immigrants and refugees. Recommendations from the Minnesota Public Health Association's Immigrant Health Task Force, August 1996. Note: The six steps proposed are: 1) Involve immigrants in their own health care; 2) Learn more about culture, starting with our own; 3) Speak the language, or use a trained interpreter; 4) Ask the right questions; 5) Pay attention to financial issues, and 6) Find resources and form partnerships. D Plooij. Cultural Training Manual for Medical Workers in Aboriginal Communities (Australia). Faculty of Social Sciences, Flinders University, South Australia, 1973. Available at www.medicineau.net.au/AbHealth/contents.html, and AC MacCaulay et al. Participatory Research With Native Community of Kahnawake Creates Innovative Code of Research Ethics. Canadian Journal of Public Health 1998; 89(2): 105-8.

537 Medical Research Council of Canada. Supra, note 76, at Section 6: Research Involving Aboriginal Peoples, Subsection A: Introduction.

538 ID.

volunteer's comprehension. Many HIV vaccine efficacy trials will span the international stage and target a multiplicity of populations with distinct cultures, traditions, medical systems and resources. What is proposed is that these trials find culturally attuned "ways to disclose of information that is necessary for adherence to the substantive ethical standard of informed consent, (with particular attention to disclosures relating to diagnosis and risk, placebos and randomization, alternative therapies, and post-trial benefits),"[539] - at the same time as they take specific steps to respect participants and host communities thereby encouraging broad-based informed support.

D. Informed Consent As a Legal Imperative in Vaccine Clinical Research in Canada

In Canada, informed, comprehending and voluntary consent is not merely an ethical prerequisite to good clinical science, it is also a legal requirement. This legal requirement applies where a clinical trial or principal medical intervention exposes the participant / patient to any one or more of the following: (i) physical touching or corporeal interference; (ii) access to personal, medical or private information; and (iii) levels of risk exceeding background levels present in day to day living.

The record of jurisprudence is somewhat clouded in that it does not consistently distinguish between the law as it may apply to informed consent in: (i) standard clinical care; (ii) innovations in care; (iii) the use of experimental, unauthorised and untested therapeutic treatments; and (iv) a structured clinical trial of an experimental drug or vaccine. It is imperative to emphasize that an HIV prophylactic vaccine trial is non-therapeutic and participation in such a trial is quite altruistic in nature. These trials distinguish themselves from other forms of clinical investigation and medical treatment in that they recruit healthy, uninfected subjects. They offer no immediate, direct therapeutic care for the disease that is the "raison d'être" of the research. Nor do vaccine trials fit within any over-arching programme of pre-existing clinical care. Unless a deliberate initiative is made to redress the relative lack of benefits, preventive vaccine trials do not even provide participants with a high level of non-therapeutic benefits.

In addition, experimental HIV vaccines will frequently incorporate relatively new technologies and may therefore, (depending upon the kind of experimental vaccine being tested and the particular phase of clinical research), pose accentuated uncertainty and risk of grave adverse events. The adverse events may be medical or psychosocial in nature.

Thus, the risk / benefit ratio in preventive vaccine research is potentially relatively large. As part of the informed consent process, volunteers need to be made aware of this. There is an evolving tendency in Canadian law to impose higher burdens of disclosure and higher standards of care in ensuring informed consent as the degree of experimentation, uncertainty and the potential gravity

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[539] National Bioethics Advisory Commission. Ethical and Policy Issues in International Research: Draft Report. Bethesda MD, 29 September 2000, at Recommendation 3.2.

of adverse events increase.[540] Applying these criteria, the law will impose some of the highest standards of informed consent upon the clinical testing of preventive HIV vaccines.

> In the area of medical research the standard [of disclosure] is greater particularly when the subject is not in need of treatment and is merely participating in the research experiment.[541]

Thus, as the principal objective of an experiment shifts from therapeutic research to the pure acquisition of scientific knowledge, one can expect the courts to be less sympathetic to the notion of therapeutic privilege.[542] Indeed the courts have expressly rejected the notion that an investigating physician might use professional therapeutic privilege to justify hiding information from research subjects for their own protection.[543]

1. The Need for Multiple Consents

There is also some confusion in Canadian law as to whether simple routine blood tests and other routine medical acts that are conducted within the course of an overall program of medical care or clinical research each require an express and independent act of informed consent. In the case of *Weiss* v *Solomon*, the Québec Superior Court held that a clinical trial is an integrated whole and therefore every testing procedure and medical examination prescribed by the protocol and which poses risk, is part of the risks that must be divulged in the experiment's informed consent.[544] The approval of the content and procedures for informed consent by an ethics committee will not shield the researcher from liability if the consent neglects to communicate a significant element of the risks.[545]

Therefore, the safest way to proceed is to ensure that important medical acts within the protocol require both concise enumeration in the initial consent to the trial and independent consent when the specific intervention arrives as the research unfolds.

(i) Multiple HIV Tests

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[540] Cyderman v Ringrose, 89 DLR (3d) 32 (Alta. Sup. Ct). See also K Cranley Glass. Research Involving Humans. In J Downie, T Caufield (general eds.) Canadian Health Law and Policy. Toronto: Butterworths, 1999, at Ch 12, 385, and Weiss v Solomon, [1989] RJQ 733, and JL Baudouin, P Deslauriers. La Résponsabilité Civile. 5e édition. Cowansville Qc: Yvon Blais, 1998, at 865.

[541] Couglin v Kuntz, (1989) 42 BCLR p 108.

[542] RP Kouri, S Philips-Nootens. L'Experimentation et les "Soins Innovateurs:" L'Article 21 CCQ, et Les Affres de L'Imprécision. Revue de Droit de l'Université de Sherbrooke 1996-97; 27(1&2): 89-137 at 121. See also P Lessage-Jarjoura, J Lessard, S Philips-Nootens. Éléments de responsibilité civile médicale. Cowansville Qc: Yvon Blais, 1995, at 129.

[543] Halushka v University of Saskatchewan (1966) 53 DLR at 436. See also Videto v Kennedy, 107 DLR (3d) 612. Although not concerned with experimentation or research, this case may nevertheless provide an interesting analogy. Grange J, holds that within the context of medical care, a sharp distinction with respect to informed consent can be made between therapy and "unnecessary" treatment." And cf. Ciderman v Ringrose, 89 DLR (3d) 33 at 41 where Stevenson, DCJ in obiter distinguishes between pure research and medical practise involving new research and therefore declines to give much weight to Halushka as a precedent for the latter situation.

[544] Weiss v Soloman [1989] RJQ 731 (CS).

[545] G Sharpe. Supra, note 402, at 84.

The extent to which informed consent is required for an individual HIV test within an overall program of medical care or clinical investigation is in need of clearer juridical definition.[546] However several arguments can be advanced to suggest that HIV testing is not a simple routine test that could escape the need for individual test-specific express consent. Firstly, the consequences of HIV infection and diagnosis are quite severe. Aside from the profound psychological impact upon the individual's life, testing positive for HIV antibodies will interfere with an individual's ability to procure life insurance, insurance guaranteeing some forms of commercial financing as well as certain consumer loans, and financing for the purchase of a home. It will also render the individual ineligible to travel or immigrate to the United States and will give rise to the application of various limitations on travel, immigration, employment and residency that exist in many nations around the world.

It is reasonable to assume that people may wish to exercise some control over the timing of their HIV tests. This is particularly true given that the recent revision of treatment guidelines now recommends the commencement of anti-retroviral therapy only relatively late in the pathological progress the infection (eg, when disease becomes apparent or when CD4 counts decline to approximately 300/ml). In most cases, this threshold level for commencing treatment will only be reached several years after infection.

But an HIV vaccine trial requires frequent HIV testing according to a relatively inflexible and periodic scheduling. Given: i) the fact that testing has important consequences for the participant both within and outside of the cohort; and given ii) the relatively long duration of efficacy trials and the fact that personal life circumstances can change during that time-span; it seems reasonable to suggest that each HIV test included in the vaccine trial be subject to a separate and express informed consent.

Despite the existence of guidelines and standards issued by professional associations,[547] pre and post-test counselling in Canada does not consistently offer people fully detailed information. In many situations the non-medical elements are all but forgotten. For one thing, these matters fall largely outside of the scope of the medical professions. For legal and structural considerations, it is notoriously difficult in Canada to facilitate a de-cloistering and opening of professions to one another. Time constraints and economics also impose pragmatic obstacles to such thoroughly informed consent. However, the case of HIV vaccine trials offers an opportunity to succeed where others have failed. Before the trials begin, proposed consent procedures and forms will be scrutinized by research ethics boards (and in some cases also by community advisory boards). The trials themselves offer a stable long-term framework in which a periodic and structured evaluation and correction of counselling techniques can take place. In this environment, it should be possible to overcome obstacles and ensure that consent procedures offer all pertinent information to participants consenting to successive HIV tests.

(ii) Consent to Medical Treatment

[546] R Elliott, R Jürgens. Rapid HIV Screening at the Point of Care: Legal and Ethical Questions. Montréal: Canadian HIV/AIDS Legal Network, 2000, at 51. See also Canadian AIDS Society v Ontario (1995), 25 OR (3d) 388; aff'd in (1996), 31 OR (3d) 798 (CA).

[547] Canadian Medical Association. Counselling guidelines for HIV testing. Ottawa: Expert working group on HIV testing: counselling guidelines, 1995-1996, at Section 3: Components of pretest counselling, Section 5: Components of post-test counselling. See also MW Tyndall, MT Schechter. HIV testing of patients: Let's waive the waiver. *Canadian Medical Association Journal* 2000; 162(2): 210-11.

HIV antibody testing constitutes but one small part of the overall therapeutic and caring relationship between the professional and the research subject. In addition to pre- and post-test counselling, this relationship may include provision of preventive materials; vaccination with licensed vaccines (eg, hepatitis A and B) before or after the trial; and diagnosis of secondary morbidities that exacerbate vulnerability to HIV infection with a consequent referral to medical and social services. When the practice of medicine is intertwined and integral to the conduct of a vaccine trial, the clinical trial may require multiple consent as this practice unfolds. The challenge will be to determine when a portion of the research or the provision of ancillary therapeutic benefits is either so important or so distinct from the principal purpose of vaccine research that it warrants its own independent informed consent. Specific medical interventions posing significant risk, discomfort or inconvenience and for which there may be alternatives should be subject to their own informed consent. Additional medical and preventive interventions would also require consent.

(iii) Consent to Research on Human Genetic Variation

Phase III efficacy trials of candidate HIV vaccines will involve thousands of uninfected volunteers in specific targeted and vulnerable communities. Opportunities may present themselves for genetic sampling from some relatively homogeneous subsets of the Canadian population that will be targeted for recruitment to such vaccine cohorts (eg, participants recruited to vaccine cohorts from First Nations and Aboriginal communities or from specific ethnicities).

Although the ethical and legal issues relating to consent for the collection, banking and research uses of DNA samples are too numerous and complex to be discussed in this chapter, and, indeed, in this paper, the following basic points should be made regarding requests for DNA samples in the context of HIV vaccine trials.

First, the collection and storage of nominative genetic material for research purposes or for the diagnosis and study of specific genetic disorders should be subject to a distinct individual informed consent.[548]

Second, consent for the collection and storage of DNA samples should not be treated as a blank cheque authorizing researchers to use these samples for any and all kinds of research. If requests for DNA samples are made in the context of an HIV vaccine trial, consent could be sought for use of DNA samples in future research that is limited to the development of therapeutic and preventive HIV/AIDS related treatments. This was the approach taken in the AIDSVAX B/B Gp120 consent form used in Montreal.

Third, volunteers participating in a vaccine trial should be allowed to opt out of DNA or tissue banking without prejudicing their right to participate in the vaccine efficacy trial. However, this was not the case in the AIDSVAX B/B Gp 120 phase III clinical trial where consent to donation of DNA was included within the principal consent form and was repeated in a separate "stand alone" consent form. In this latter trial, volunteers who refused to give blood for purposes of DNA banking for future HIV-related research, were refused entrance to the main vaccine trial.

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[548] GJ Annas. Rules for Research on Human Genetic Variation: Lessons From Iceland; Sounding Board. The New England Journal of Medicine 2000; 342(24): 1830-33 at 1833.

Fourth, individual informed consent can not solve all of the questions related to the collection of DNA samples for research on genetic variation. Blood samples in a multi-centred trial may be shipped for storage to tissue banks in a foreign country. Even if a consent form used in Canada contains promises to restrict utilisation of linked or unlinked DNA, who will monitor the future uses of the genetic material and how could this obligation be enforced?

Fifth, the Canadian public is as yet relatively ill informed concerning the creation of stem cell lines and related genetic research. In an article published in *The Globe and Mail*, Maureen McTeer noted:

> The concerns over stem cell and embryo research are questions that will become more, not less, complex as time goes on. We all need to know the basics of this biology if our opinions are to be helpful. Government has the resources and the responsibility – to provide this information.[549]

The move to legislate / regulate in this field may be pushing the pharmaceutical industry to collect stocks of human genetic material before possibly more restrictive rules come into place. It is likely however that the present day level of comprehension of stem cell research among people living in the populations and communities likely to be targeted for DNA collection through an HIV vaccine clinical trial, is no higher than among average Canadians. Indeed, work in this field is so new that it is virtually impossible to imagine all of the uses to which this research might be applied in even 10 or 15 years. For these reasons, consent to DNA collection in a clinical trial of an HIV vaccine is best limited to use for matters closely related to HIV and ideally HIV vaccine research. In addition, the storage and use of the tissues collected and of derived lines of stem cells should be limited to a relatively short time span.

(iv) Consent to Ancillary, Additional and Subsequent Research Projects

Informed consent would also be required whenever a parallel qualitative psychosocial or epidemiological research is to be conducted which focuses upon questions unrelated to or distant from vaccine efficacy.

Researchers might want to access data generated by an HIV vaccine cohort in the conduct of a new research study. For instance, proposals to collate and study risk behaviours among specific subsets of the vaccine cohort (eg, commercial sex trade workers, injection drug users, and bisexuals) may not have been foreseen at the outset of the vaccine study. Identification of persons repeatedly resorting to high-risk behaviours but who remain uninfected, may give rise to a cohort for the study of inherent immunity. Whenever the subject of proposed research is only distantly related to the principal matter of vaccine efficacy, a separate, new consent should be sought without prejudicing the subject's right to continue to participate in the original vaccine trial.

Seeking independent informed consent for ancillary, additional or subsequent research offers the participant the ability to support those branches of scientific research which are of greatest interest to him. It reinforces his sense of autonomy, community interest and empowerment in clinical research. It permits the participant to opt out of additional research without prejudicing their right to continue in the original HIV vaccine trial. It also avoids resort to overly vague

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549 M McTeer. Stem-cell research: Where to draw the line? In The Globe and Mail 25 July 2001: A13.

language in the vaccine trial's consent form in an attempt to cover possible but as yet unknown future studies – something that would effectively undermine the substantive quality of the informed consent.

2. Understanding the Role of the Principal Investigator

One of the prime elements to be contained in the informed consent is an understanding of the experimental nature of the vaccine and the role of the principal investigator (P.I.) as a researcher. For the participant, it is important to understand that the researcher is not fulfilling the role of a personal physician. Local researchers need to take great care to assure that this point is made abundantly clear. Canadians think first and foremost of doctors as professionals engaged in acts of care tailored to the patient's individual health needs. Volunteers for an HIV clinical trial may therefore have some difficulty understanding that the physician who is the P.I. is acting according to the rules of an inflexible protocol and not for the purposes of personalized therapeutic treatment. Recruitment publicity is often mailed directly to general medical practitioners in the community, who may refer patients to the trial. Indeed in some cities, the local site of a multi-centred trial is a private medical clinic, rather than a hospital or research institution. This may further create initial confusion and incorrect expectations concerning the role of the P.I.

The degree to which the physician investigator can be seen uniquely as a scientist and not as a clinician is the subject of some controversy in medical ethics. J Katz argued forcefully for a strict separation of these roles and advocated that to the greatest extent possible, the PI should be seen only as a scientist:

> A morally valid consent in research settings requires a radically new personal and professional commitment to the patient-subjects and the informed consent process: Physician-investigators must see themselves as scientists only and not as doctors. In conflating clinical trials and therapy, as well as patients and subjects, as if both were one and the same, physician-investigators unwittingly become double agents with conflicting loyalties.[550]

There are however a number of practical problems with this approach. As previously discussed, the HIV testing in a clinical trial has clear therapeutic overtones, especially since the research study is under a strong ethical obligation to counsel participants to practice their highest achievable levels of safer and harm reducing behaviours. Second, frequent and periodic meetings with participants during the course of an efficacy trial present an opportunity for diagnosis of secondary morbidities and referrals to medical treatment. Third, the participants who altruistically volunteer for non-therapeutic research such as a vaccine efficacy trial, will be more likely to maintain interest in the research and continue to collaborate and participate through to the end of the study if they sense that the intervenants are also interested in them as persons and not merely as a somewhat more advanced form of laboratory guinea pig.

Researchers from the University of Virginia and the National Institutes of Health have thus adopted a different view from that stipulated by Katz above. Miller et al note

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[550] J Katz. Human experimentation and human rights. St Louis University Law Journal 1993; 38: 7-54. Cited in FG Miller et al. Professional integrity in clinical research. Journal of the American Medical Association 1998; 280(16): 1449-54.

> The fact that the complexity of clinical research does not permit a clean cut between therapeutic and nontherapeutic studies suggests that alternating between a clinical or scientific orientation will not prove satisfactory. The root meaning of "integrity" is wholeness. The professional integrity of physician investigators depends on a coherent moral identity that is proper to the enterprise of clinical research, which is neither medicine nor laboratory science. We need to cultivate a conception of the moral identity of the physician investigator that integrates the roles of the clinician and the scientist without giving predominance to the one or the other.
>
> The first step, we believe, is to acknowledge forthrightly that the moral problems associated with the conflicts of interest and loyalty between the role of the clinician and the role of the scientist are inherent to clinical research.[551]

Resolving this issue of tension can be achieved though resort to the informed consent process and through the presence of an informed, conscientious, compassionate and responsible investigator.[552] The latter must understand that the duty of nonmaleficence […] carries over from medicine to clinical research. The first place where this conflict must be recognised, explained and resolved is in the informed consent process itself. The resolution of the conflicting roles of researcher as clinician and as scientist should be made clear in the terms and conditions of the consent so that the participant understands exactly what kind of relationship to expect. If the resolution emphasises the predominately research interests of the P.I. then the informed consent should also clearly encourage participants to continue to consult their own doctors (eg, someone other than the PI), throughout the duration of the trial. They must be free to seek medical diagnosis, as well as care and advice on matters of sexual health and HIV prevention at locations other than the offices of the clinical trial. They must have the freedom to access available post exposition prophylaxis promptly in the hours following high-risk behaviours. In the event of a seroconversion, the clinical trial must neither slow nor impede the participant's access to the best standard of clinical care.

Vaccine research does however require that the participant restrict his HIV testing to sites involved in the clinical trial. This in turn means that the latter have a firm obligation to make testing and the accompanying counselling available promptly upon demand. All of this information must be made abundantly clear at the moment of initial consent and should be repeated and reinforced frequently throughout the duration of the research.

3. The Duty to Disclose Pertinent Information

(i) The Scope and Content of Legal Disclosure

Informed consent to participation in medical research in Canada translates into a legal right to information. Both the standard of care in facilitating informed consent and the resulting scope of disclosure are more rigorously applied as:

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551 FG Miller et al. Supra, 550.

552 Ibid.

•the degree of experimentation increases;
•the risk / benefit ratio increases;
•the potential gravity of risks increases; and
•the absolute potential for therapeutic benefit decreases.

The decision of the Saskatchewan Court of Appeal in *Halushka* v *University of Saskatchewan* expressed several of these basic principles which anchor the Canadian law of informed consent. Justice Hall wrote:

> In my opinion the duty imposed upon those engaged in medical research, [...] to those who offer themselves as subject for experimentation, […] is at least as great as, if not greater than, the duty owed by the ordinary physician or surgeon to his patient. There can be no exceptions to the ordinary requirements of disclosure in the case of research as there may well be in ordinary medical practise. The researcher does not have to balance the probable effect of lack of treatment against the risk involved in the treatment itself. The example of risks being properly hidden from a patient when it is important that he should not worry can have no application in the field of research.[553]

This emphasis upon the distinction between therapeutic and non-therapeutic experimentation is important because it shapes the legal obligations imposed upon both parties in "negotiating" an informed consent. Following *Halushka,* we can conclude that since HIV preventive vaccine efficacy trials are vast experiments and since their risk/benefit ratios are comparatively large, the law will impose an obligation of extensive disclosure without permitting recourse to the shield of therapeutic privilege. This obligation of most thorough disclosure can apply to vaccine research whether one views the therapeutic / non-therapeutic distinction as clear cut or as a continuum.

How does one decide precisely which types of information should be included in consent to an HIV vaccine trial? Is there some information that is simply too remote or unimportant to merit communication? Once again, *Halushka* provides some guidance.

> The subject of medical experimentation is entitled to a full and frank disclosure of all the facts, probabilities and opinions which a reasonable man might be expected to consider before giving his consent.[554]

With the passage of time, the Supreme Court of Canada has increasingly endorsed an interpretation of informed consent which applies a "full disclosure test" - even in matters of medical treatment.[555] In the decision of *Hopp* v *Lepp*,[556] the court held that the gravity of a proposed medical intervention and any material risks as well as any special or unusual risks should be the subject of disclosure and discussion.

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553 Halushka v University of Saskatchewan (1966) 53 DLR at 436.
554 Ibid.
555 JL Baudouin, P Deslauriers. Supra, note 540, at 858.
556 Hopp v Lepp, (1980) 2 SCR 192.

> [A] certain risk [may be] a mere possibility which ordinarily need not be disclosed, yet if its occurrence carries serious consequences, as for example, paralysis or even death, it should be regarded as a material risk requiring disclosure.[557]

In matters of clinical experimentation, this means that even extremely rare or remote risks must be disclosed if their potential gravity would be such that a reasonable participant placed in the circumstances of the plaintiff, would be inclined to consider these remote but frightening risks when making his decision.

Thus, the physician's margin of discretion as to which of the risks to leave out of the informed consent is largely restricted to those lying in a "grey" zone situated between the sufficiently probable and the sufficiently serious.[558] And in matters of clinical experimentation, the grey zone is extremely restricted. This principle was further confirmed by the Supreme Court of Canada in the case of *Reibl* v *Hughes*, [1980] 2 S.C.R. 880.

These Supreme Court cases have been heralded as affirming the patient's role as a "partner" in an informed consent process by which information is shared on both sides in a relationship that has become a hallmark of modern medicine.[559] This jurisprudence sets the common-law standard for evaluating and defining the scope of information required to legitimize an informed consent and it applies in all provinces except Québec. According to this standard, the measurement of the scope of disclosure is an "objective" test of the "ordinary reasonable man". But the test goes further, requiring that we consider this objective man as though he were placed in the particular circumstances of the individual who volunteers for the HIV vaccine clinical trial. Thus, the "objective" is tempered by a subjective appreciation of the factual circumstances of each individual patient.[560]

In Québec civil law, the standard for evaluating the scope of disclosure is slightly different. The determination of what needs to be disclosed and what does not, is determined by reference to the objective standards that a competent, reasonably prudent and diligent physician / researcher would apply. This is referred to as the "professional disclosure test".[561] It means that in Canada's civil law jurisdiction, professional codes of conduct and customary standards of clinical care will assume somewhat greater importance as primary sources of the law of informed consent. But this test also has a second stage. The idealized "objective" physician is presumed to take into close consideration the particular circumstances of each individual volunteer. Thus, once again, the objective is tempered by the subjective.[562]

This common secondary deference to the circumstances of each individual case also applies to consent to clinical experimentation. It has practical application in the case of people volunteering for HIV vaccine trials. For example, a relatively low proportion of people receiving Gp 120

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[557] Ibid, cited in Reibl v Hughes (1980) 2 RCS 880 at 884-5; cited in Weiss v Solomon [1989] RJQ 731 at 743.

[558] JL Baudouin, P Deslauriers. Supra, note 540, at 863-5.

[559] P Peppin. Supra, note 487, at 477.

[560] JL Baudouin, P Deslauriers. Supra, note 540, at Section 1433: 859.

[561] ID.

[562] ID. Note: Baudouin cites Dodds c Schierz, [1981] CS 589; [1986] RJQ 2623 (CA); Chouinard c Landry, [1987] RJQ 1954 (CA), (leave to appeal to the Supreme Court denied); Gingues c Asselin, [1980] RRA 630 (CS); Pelletier c Roberge, [1981] RRA 726 (CA); Chabot v Roy, [1997] RRA 920 (CA).

recombinant envelope vaccines have an immune response that gives rise to a sustained possibility of an incorrectly interpreted Elisa test result. A research volunteer who is on the verge of purchasing property requiring a mortgage would certainly want to be informed of this possibility. Similarly, in a clinical trial recruiting pregnant women, volunteers would be entitled to be informed of extremely rare probabilities of any teratogenic adverse events. A volunteer with a family history of cancers may want to be informed if there is a remote possibility that the HIV genes or epitopes selected as antigens in a candidate vaccine might be carcinogenic.

In both common-law and civil-law jurisdictions, the researcher must give the volunteer opportunities to ask questions. He must accept to answer these questions even if the subject matter falls outside of the realm of what the researcher considers pertinent.[563] Some of these questions may stem from the participant's own personal or religious convictions.[564] The law does not go so far as to impose a subjective standard that would require the researcher to anticipate the individual's state of mind. He is not obliged to anticipate any privately held, irrational and unforeseeable beliefs the volunteer may harbour. Mind-reading is a subject probably more suited to speculation and fiction and one that is best left outside the realm of clinical HIV vaccine research. But once the volunteer raises issues that are of material importance to his own decision, both the researcher and participant should explore these questions and decide whether the answers are sufficient to permit the volunteer to feel comfortable with a decision to proceed.

The fact that non-therapeutic experimentation is placed at the high end of the spectrum commanding the broadest scope of informed consent will ideally mean that the objective reasonable physician standard used in Québec should be that of a doctor ordinarily engaged in research. The standard should be defined as a function of the activity (research) and not as a function of the professional qualifications of the particular principal investigator.[565] Similarly, the "objective reasonable participant" standard used elsewhere in Canada should be set with reference to the nature of the clinical trial and its target population. Pertinence of information to be communicated for consent to a clinical trial of an experimental preventive vaccine will be judged by the standard of a reasonable person, in relatively good health, drawn from a specific target community and who is altruistically volunteering for this particular type of research. Once again, the standard is defined at least in part, as a function of the activity (research). Thus, although the two legal analyses define the scope and content of informed consent by different analytical routes, they arrive at substantially similar results.

The operation of these different common law and civil law measuring standards is however also set against the background of the *Haluska* decision and a considerable body of legal doctrine which requires the highest standards of care and sweeping disclosure in cases of non-therapeutic clinical research.[566] These demanding standards were reaffirmed in the case of *Weiss* v *Solomon* which went so far as to incorporate into Canadian law the standards for informed consent that are

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563 RP Kouri, S Philips-Nootens. Supra, note 541, at 121. Note: In support of this principle the authors cite: Hopp v Lepp (1980), 2 SCR 192 at 210.

564 RP Kouri, S Philips-Nootens. Supra, note 541, at 124.

565 RP Kouri. The Law Governing Human Experimentation in Québec. Revue de Droit de l'Université de Sherbrooke 1991; 22: 76.

566 JL Baudouin, P Deslauriers. Supra, note 540, at Section 1433; 865. See also RP Kouri. Ibid, and Weiss v Soloman [1989] RJQ 731 (CS).

set out in the *Declaration of Helsinki*.[567] The Declaration is used by the court to impose legal obligations upon a Canadian researcher to disclose to the participant all hazards associated with the trial, - even those that are only "potential". The court refers the following articles from the *Declaration* in support of this position:

> *Part I (Basic Principles), Article 6: The right of the research subject to safeguard his or her integrity must always be respected.*
>
> *Part I (Basic Principles), Article 9: In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study, ... [emphasis added].*
>
> *Part III (Non-Therapeutic Biomedical Research Involving Human Subjects), Article 4: In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.*

The first draft of the proposed regulations to amend the *Food and Drug Regulations* published in June 2000, contained a specific reference to the *Declaration of Helsinki* as setting comparative standards for good clinical practice in clinical trials in Canada.[568] This reference was however deleted from the final version of the modified regulations adopted by decree in June 2001.[569] The discarding of this reference may reflect concern on the part of the legislator that the *Declaration* in its recently revised form is perhaps too vague and too exacting for Canada's pharmaceutical research and development industry. Whether this will influence the courts however in their propensity to turn to the *Declaration* as a tool to be used in interpreting the adequacy of informed consent in Canada, remains an open question.

The Nuremberg Code gives even greater prominence to individualized informed consent than the Declaration of Helsinki. Incorporated into the judgement of the war crimes tribunal, if forms a jurisprudence that is now firmly anchored in western legal interpretation, including jurisprudence in Canada.[570]

At the present time, the record of jurisprudence uses the most important international ethical codes as interpretative tools. These concord and further reinforce the now generally accepted legal view that the standard and scope of disclosure are set extremely high for clinical research involving non-therapeutic medicines (eg, vaccines). The civil law and the common law accord slightly different indicative value and priority to jurisprudence, international conventions and legal doctrine. However all of these sources cite the need for wide disclosure, such that the overall standards of care for informed consent in medical experimentation are set so high that

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567 World Medical Association. Supra, note 101. Note: The decision in Weiss citing the above Declaration follows the same path laid out in the earlier decision in Halushka which had cited the Nuremberg Code as an inspiration for the interpretation of informed consent in Canadian law.

568 Regulatory Impact Analysis Statement. Supra, note 192, at Art. C.05.001: 247.

569 Regulatory Impact Analysis Statement. Supra, note 89.

570 Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10. (Nuremberg 1946, October - 1949, April): Washington D.C.: U.S.G.P.O., 1949-1953.

the legally required scope of informed consent in both of Canada's legal jurisdictions is substantially similar.[571]

(ii) Problems With the Legal Model of Informed Consent

The legal analysis used to define the standards and scope of disclosure in informed consent has its critics. Some have argued that the approach should be entirely participant-centred and hence subjective if it is to ensure truly informed and comprehending consent. "[B]y allowing the responses of the mythical "reasonable patient" to determine the rights of a particular individual patient, the standard undermines the premise of individual autonomy."[572]

Others attack the standard as too imprecise to provide much concrete direction to the parties involved in very complicated research protocols.

> The standard fails to see that every medical intervention presents a nearly infinite array of ever-more-remote possibilities for harm; that is, the dangers exist on a continuum, rather than with a "bright line" separating the significant from the insignificant. Because the risks exist only in shades of grey, the courts have been unable to state expressly what a "small" risk is - that is, to indicate how small a risk must be before it is considered so minute that it does not require disclosure.[573]

Still others attack the informed consent process as striving for an impossible degree of thoroughness. They argue for a flexible standard noting that in certain circumstances of severe illness requiring therapeutic care, this level of detail in consent is impractical. They generally advocate that the protection of patients and of participants in research cohorts will primarily be achieved by strong enforcement of rigorous professional standards in which the relationship between the physician / researcher and the patient / research subject is one of confidence and trust.[574]

Some authors maintain that the law sets the bar so high that in clinical trials, the doctrine of informed consent requires an unattainable level of mathematical certainty to evaluate the probability of risks and weigh them against anticipated benefits. These critics point out that clinical trials invariably involve elements of uncertainty, whereas the standards of informed consent seem to seek a "degree of certainty and precision that [...] medicine can almost never deliver". "[...T]he hard numbers necessary for quantitative decision making often simply do not exist in the medical literature."[575] Even when the sponsor has estimated the probability of risks occurring in a phase III vaccine efficacy trial, it can only be based upon an extrapolation of data attained from pre-clinical study and from the earlier phase II trial. But since the estimates are

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571 JL Baudouin, P Deslauriers. Supra, note 540, at Section 1433: 859.

572 R Epstein. Medical Malpractise: The Case for Contract. American Bar Foundation Research Journal 1976; 35: 121. Cited in A Piper, Jr. Truce on the Battlefield: A Proposal for a Different Approach to Medical Informed Consent. The Journal of Law, Medicine & Ethics 1994; 22(4): 301.

573 A Piper, Jr. Ibid, 301 at 310.

574 ID. And cf. ST Bogardus Jr. et al. Perils, pitfalls, and possibilities in talking about medical risk. Journal of the American Medical Association 1999; 281(11): 1037-41.

575 A Piper, Jr. Supra, note 572, 301 at 305.

extrapolated from smaller trials, they will necessarily tend to be imprecise and have relatively large intervals of confidence. Moreover, this kind of data is a "statistical analysis - designed for large populations, [which] cannot be applied readily to individual patients."[576]

One obvious difficulty that arises in attempting to implement the very comprehensive scope of disclosure that the law imposes on non-therapeutic experimentation, is the challenge of finding accessible ways to communicate so much information. On one hand, informed consent is supposed to be comprehending. This implies that consent forms should not be overly lengthy. It also implies that the quantity of information communicated through the overall process should not be so voluminous that it dazzles participants, overwhelming them, - leading to disinterest. But clinical trials of preventive vaccines are relatively complex. They involve such diverse matters as: defining the concept and parameters of vaccination; new technologies; communication of scientific information concerning efficacy; HIV testing and possible diagnosis; support for sustained preventive behaviours; community development issues and potential risks of adverse effects. Transmitting this quantity of information in a comprehensible form is a significant challenge. Unfortunately, the law provides no clear solution to this problem.[577]

(iii) Conclusion

Despite the above-described difficulties, Canadian legal standards prescribing disclosure in informed consent provide some concrete assistance to researchers, participants and their advocates.

1. In matters of clinical science, the law clearly favours an extensive disclosure.
2. By articulating the questions to be asked, the law provides a framework for analysis - a procedure through which the parties can arrive at a decision as to whether to include or discard a particular information.
3. Both the common-law and civil law legal measurements are sufficiently contextualized that researchers would be wise to acquire basic background knowledge of their target communities. This effort should be documented.
4. Because the researcher is required to frame consent with secondary reference to the particular circumstances of each individual participant, the process must permit real dialogue. Volunteers and ultimately participants must be given the chance to ask questions and obtain answers. The researcher must take steps to inquire into the basic concerns of each subject and make an effort to ascertain that his consent is in fact comprehending. This means that negotiating and evaluating consent via the Internet may be particularly difficult. Researchers should be wary of incorrectly conflating technological progress in communication with a relaxation of standards in informed consent. The former does not legally nor ethically imply the latter.

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[576] Ibid, 301 at 306.

[577] T Leroux. Réflexions éthiques et juridiques suscitées par la réalisation d'essais cliniques en milieu hospitalier québécois. Développements récents en droit de la santé. Cowansville Qc: Yvon Blais, 1991, 155-70 at 161. See also G Sharpe. Supra, note 402, at 87.

5. When these standards are applied to consent as a continuous process lasting throughout the clinical trial, both the sponsor and the researcher will be legally obliged to release any important new information that may be susceptible of influencing the participant's decision to continue with the trial. This could include matters such as discovery of grave or probable adverse events; extremely good or poor mid-term efficacy data; and especially negative efficacy data at mid-term. Similarly information concerning the development of new potentially efficacious prevention techniques (eg, new anti-HIV microbicides, better post exposition prophylaxis, better condom or barrier protection) cannot be withheld from trial participants.

E. Legal Recourses

In theory, participants in an HIV vaccine efficacy trial would have a number of legal recourses in the event that the consent process was deficient or improperly conducted. In this sub-section, the pathways and possibilities for legal recourse are identified.

1. Human Rights Statutes

If such a trial were to be conducted by an agency of the federal or provincial governments, which is rather unlikely, then the *Canadian Charter of Rights and Freedoms* [578] would provide some degree of constitutional protection for the right of research subjects to give voluntary and informed consent. In view of the record of Canadian jurisprudence, it is hardly conceivable that the courts would allow a public authority to submit prisoners, soldiers or any other employees or wards of the state to an HIV vaccine trial without first duly obtaining informed consent. Unfortunately, there is a historical record of isolated events involving less than perfect informed consent to innovative medical treatments in Canadian penal institutions. Government authorities should expect the courts to exercise a high degree of human rights scrutiny over consent to clinical trials that are state sponsored and run.

There is also the pathway of provincial human rights legislation. Complaints could be filed before human rights commissions alleging that an HIV vaccine trial conducted without voluntary, informed and comprehending consent constitutes an infringement upon basic human rights. The right to corporeal integrity, autonomy of the person, and the right to be free from discrimination on the basis of any one of a number of legally interdicted discriminatory motives - several of which may apply to populations targeted for vaccine clinical trials, are examples of potentially applicable legal rights.

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[578] Canadian Charter of Rights and Freedoms. Constitution Act, (1982), Part I.

2. Criminal and Civil Law

(i) Criminal Law: Assault and Battery

Although the criminal law has virtually never been used in Canada to sanction research conducted without informed consent, charges of criminal assault or criminal negligence could be options for legal recourse were the requisite conditions ever to be fulfilled in an HIV vaccine trial.[579]

(ii) Civil Liability

In common law jurisdictions of Canada, consent obtained under misrepresentation or fraud could give rise to the legal recourse of an action in battery.[580] In Quebec civil law, experimentation on human beings without their informed and voluntary consent would constitute a breach of legal rights to physical integrity and autonomy of the person.[581] Other possible options for legal recourses based upon an alleged inadequate or incomplete consent in an HIV vaccine clinical trial include suing for professional negligence or filing complaints for professional misconduct with professional colleges – corporations / licensing boards.

(iii) Liability of the Research Institute

The overwhelming focus of Canadian liability law has been on the relationship between the principal investigator and the research participant. However, there is precedent in Canadian and American case law for also holding the research institution responsible for the quality of informed consent procedures within research protocols conducted on its premises.[582] Scientific and research ethics review boards report up a hierarchical chain of command that ends at the institution's board of directors. By virtue of this link, the institution can be held liable for serious

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579 JL Baudouin, P. Deslauriers. Supra, note 540, at 858. See also M Sommerville. Medical Interventions and the Criminal Law: Lawful or Excusable Wounding? McGill Law Journal 1980; 26: 82; DT Marshall. The Law of Human Experimentation. Toronto: Butterworths, 2000, at 49. Note: Criminal liability may lie under diverse articles of the Criminal Code including criminal negligence (article 219(1) and (2)); causing bodily harm with intent (article 244); administering a noxious thing (article 245); assault (article 266); unlawfully causing bodily harm (article 269), and criminal negligence causing death (article 220).

580 G Sharpe. Supra, note 402, at 29. See also: Reibl v Hughes, 1977, 16 OR (2d) 306, 78 DLR (3d) 35, and Ardnt v Smith, [1997] 2 SCR 539.

581 Civil code of Québec: Article 10: Every person in inviolable and is entitled to the integrity of his person. Except in cases provided for by law, one may not interfere with his person without his free and enlightened consent.
Article 11 al. 1: No person may be made to undergo care of any nature, whether for examination, specimen taking, removal of tissue, treatment or any other act, except with his consent.
Article 20: A person of full age who is capable of giving his consent may submit to an experiment provided that the risk incurred is not disproportionate to the benefit that can reasonably be anticipated.
Article 24: Consent to care not required by a person's state of health, to the alienation of a part of a person's body, or to an experiment shall be given in writing. It may be withdrawn at any time, even verbally.

582 Weiss v Solomon, et al; (1989) RJQ 731. See also Halushka v University of Saskatchewan et al, (1966) 53 DLR at 436.

errors committed by these review committees.[583] An example of such a serious error would be a research ethics board that approves a manifestly incomplete consent procedure that lacks the information necessary to permit the participant to weigh risks and benefits in an enlightened way.[584]

Similarly, imagine that a research institution fails to ensure that its scientific and ethics review committees have adequate resources and personnel to accomplish their respective mandates. At the very least, this represents a breach of an ethical duty of care owed by the institution to its research subjects. Now imagine that this same lack of resources results in a sub-optimal review, evaluation, and monitoring of informed consent. If the research subjects in a vaccine trial were to suffer damages as a direct consequence of the resulting deficient consent procedures / content, then the institution could probably be held vicariously liable for these damages.

(iv) Liability of the Sponsor

There is relatively little Canadian jurisprudence concerning civil liability incurred by a pharmaceutical sponsor for inadequate disclosure of risks during a clinical trial. The high Canadian legal standards necessitating a careful and comprehensive disclosure of risks, particularly those associated with non-therapeutic research, exercise an instrumental influence upon industry. The pharmaceutical industry, like all commercial ventures, is economically risk adverse. Good corporate risk management will use the thorough dissemination of information to avoid unnecessarily incurring risks of potential liability. Thus the high costs of litigation and damage awards, particularly in the United States, have encouraged industry in both countries to be forthcoming with the information the principal investigators need to communicate to research subjects.

However, it is important to emphasize here that pharmaceutical sponsors of HIV vaccine research are not immune from liability under Canadian law. It is possible to hold the pharmaceutical company that sponsors an HIV vaccine cohort liable for negligently failing to adequately inform physicians functioning as on-site principal investigators, of the risks of adverse events and the inconveniences that trial participants may incur. This duty to disclose is indirectly prescribed by the *Regulations of the Food and Drug Act*, governing clinical trials. These newly amended regulations require that sponsors of each and every proposed clinical trial submit their scientific protocols and informed consent procedures to both scientific and ethical review. The review procedures will check to ensure that the consent provides for an efficient communication and effective comprehension of all information necessary to facilitate informed consent.[585] This corporate obligation to ensure an adequate informed consent is of course also circumscribed by the common law torts of battery and negligence and by the civil law concepts of inviolability of the person and of civil responsibility.

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583 Weiss v Solomon, et al; (1989) RJQ 731. See also T Leroux. Commentaire de l'arrêt Weiss v. Soloman: Le rôle imparti aux comités d'éthique pour la recherche: garants du respect des principes éthiques à l'échelle locale. La Revue Juridique Thémis 1991; 25: 193-200, and M Cotnoir. La Mise en Marché du Médicament en Droit Pharmaceutique Canadien. Les Éditions Thémis, 127-9, and Kus v Sherman Hospital, 644 north Eastern Reporter, 2d series; 644(III): 1214-22. (Appellate Court of Illinois, Second District. (5 Junuary 1995), and Fritter v IOLAB Corporation, 607 A2d 1111 (Pa. Super. 1992).

584 RP Kouri. Supra, note 565, at 78. See also M Cotnoir. Supra, note 583, at 127-9.

585 Regulations Amending the Food and Drug Regulations. Supra, note 197, at Art. C.05.001: 1117.

The initial primary duty of information is owed to the physicians conducting and managing the clinical trial at local sites. This is known as the "learned intermediary" doctrine. It holds that a vaccine manufacturer has a duty to warn administering physicians, but not vaccine recipients, of foreseeable risks in using a vaccine.[586] This doctrine can be extended to cover the risks that are known or ought to be known by the company sponsoring the clinical research of HIV vaccines. It is important to note that the legal obligation placed upon the pharmaceutical company to disclose to the intermediary physician is a continuous one that cannot be fulfilled by a one-time disclosure made at the moment of initial informed consent.[587] As new risks become evident in a vaccine trial, the company must disclose them to the investigator, who in turn will evaluate whether they (investigator and sponsor) should take steps to ensure participants are notified. As is the case with informed consent in the doctor-patient relationship, the law requires that the company sponsoring the vaccine trial disclose even extremely remote risks presenting improbable but potentially serious harm.

Under the new *Food and Drug Act Regulations*, the sponsor is obliged to inform the Minister of Health of any serious unexpected adverse reactions that are fatal or life threatening within seven days of becoming aware of the information.[588] The ministry should take steps to promptly advise researchers, and thus the participants.

But in clearly extreme cases, the sponsor may not be able to rely solely upon competent notification of its contracting clients (eg, government or physicians) and hence the learned intermediary doctrine to shelter from liability. For example, in rare cases of extremely serious and rapidly developing adverse events, the company might determine that communicating this information through site investigators and government would incur delays costing lives and unnecessary injuries. In such circumstances, it must take all reasonable steps to warn its research subjects as quickly as possible. Failure to do so could constitute actionable gross negligence, and in at least one province - a breach of a quasi-constitutional obligation to procure assistance to persons whose lives are in imminent danger. This obligation could extend therefore to convening press conferences, and placing advertisements in the public media warning participants of the dangers and the appropriate actions required to obtain a remedy.

3. Conclusion

There is relatively little jurisprudence in Canada concerning defective consent in clinical trials. Numerous factors, some of which are of positive social value and others negative, may contribute to the infrequency with which Canadians have turned to the courts to settle claims.

This dearth of jurisprudence may reflect a high degree of care on the part of sponsors and researchers when obtaining informed consent to non-therapeutic experimentation in Canada. It may also indicate that companies, anxious to avoid liability, are taking care to fully inform researchers of all known and potential risks that are probable, or possibly grave in nature (or

586 WH Smith III. Vaccinating AIDS Vaccine Manufacturers Against Product Liability: Notes. Case Western Reserve Law Review; 42(147): 207-54 at 215. See also Buchan v Otto Pharmaceutical (Canada) Ltd, (1986) 35 CCLT at 1, and J Lapierre v AG Québec [1985] 1 RCS 241.

587 Buchan v. Otto Pharmaceutical (Canada) Ltd., (1986) 35 CCLT at 1.

588 Regulations Amending the Food and Drug Regulations. Supra, note 197, at Art. C.05.014: 1126. Note: All other adverse events should be reported to the Minister within 15 days.

both). Hence, the "learned intermediary" doctrine may encourage the free flow of maximum quantities of information.

Insurance-driven settlements of disputes out of court may also serve to protect corporate sponsors from the development of a potentially restrictive body of case law.

On the other hand, the relative paucity of jurisprudence may also represent some of the structural and technical difficulties in actually putting the law into practice. Litigation is expensive and lengthy. It submits plaintiffs to the glare of public scrutiny. In matters of clinical investigative medicine there is an extreme disparity of technical knowledge between the pharmaceutical sponsor and the participant. This may lead to evidentiary problems in litigation. There will also be extreme disparities of wealth between participant plaintiffs and corporate defendants. Their relative abilities to financially support lengthy litigation will be unevenly matched. This will be particularly true if HIV vaccine trials target marginalized communities in which people are both vulnerable to HIV infection and socio-economically disadvantaged. We need to critically examine whether there exists within Canada a sufficiently accessible professional litigation capacity and expertise to represent plaintiffs in such cases.

The ability to resort to legal recourses based upon ill-informed consent or to enforce promises made at the time of consent, will be further challenged in HIV vaccine trials by the fact that some adverse health problems may not materialize for many years. They may manifest themselves in the form of multi-factorial disease where the vaccine's specific role in causation will be difficult to determine. Moreover, the sponsor may be long gone by the time the health problems appear.

Thus, while Canadian law provides abundant legal recourses that should serve to reinforce the overall quality of informed consent, it is not clear that its remedies are in fact accessible. As is so often the case in matters related to HIV and AIDS, the law is but one small part of the overall solution. On a more encouraging note, the law can be used to demonstrate instrumental standards for research. When combined with reference to international ethical standards and a developing body of international law, the law can provide a framework for public scrutiny and community empowerment in the process of evaluating clinical research. This instrumental role may prove to be as powerful a deterrent as the threat of litigation in deterring uninformed consent in clinical HIV vaccine research.

F. Informed Consent as an Ethical Obligation

Much has already been written in this paper concerning guidelines and ethical standards for international clinical research. This sub-section discusses the potential assistance that bioethics can offer to sponsors, researchers, participants and targeted communities in seeking to define and facilitate informed consent to HIV vaccine research.

1. An Introduction to Bioethics as it Relates to Informed Consent in HIV Vaccine Research

In the preceding section we examined how the law in Canada sets a framework prescribing certain elements, standards and procedures for informed consent to HIV vaccine clinical research. The law also requires a rigorously comprehensive scope of disclosure while providing for a wide variety of recourses and remedies.

Ethics on the other hand, presents some distinct advantages. Applied ethics and research bioethics allows the interested parties to identify, deliberate and attempt to solve trial-specific problems, many of which are too case specific to have been foreseen by the law. Applied ethics and research bioethics, also strive to be pragmatic, practical and inclusive. This discipline operates by way of conducting "a comparison and a criticism of the practical judgements it has reached in cases of a similar kind".[589] As such, it considers the full complexity of a problem and is inductive and adaptive in nature. It involves a continuous feedback loop drawn from practical experience and contributing to new and carefully tailored ethical judgements.[590]

However ethics allows even greater flexibility in as much as it can accommodate local variations in culture, traditions and community values with respect to how people give their consent to medical experimentation. This capacity for accommodation exists so long as a consensus can be achieved to continue to respect a parallel, underlying and universal ethical value of individualised free and informed consent.

> It is important to distinguish substantive ethical principles and standards from the procedures used to implement them. Although procedures are important, they can often be modified without compromising ethical principles or standards.[591]

2. A Case-study for Bioethical Analysis -- The Standard of Care for Breakthrough Infections

One concrete example of the application of ethics in a consensual problem solving exercise concerns the issue of what standards of medical care should be offered to participants in HIV vaccine trials who suffer "breakthrough" infections. This issue has elicited extreme controversy during the consultations in preparation for the drafting of the UNAIDS guidance document: *Ethical considerations in HIV preventive vaccine research*.[592] It was also the subject of considerable debate as the World Medical Organization recently struggled to revise the

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589 DJ Roy et al. Supra, note 77, at 50.

590 ID.

591 National Bioethics Advisory Commission. Supra, 539, Ch 3: Voluntary, Informed Consent, at 4.

592 Joint United Nations Programme on HIV/AIDS. Supra, note 10.

Declaration of Helsinki,[593] and it continues to elicit much debate in both domestic and international fora.[594]

The issue of standard of care for breakthrough infections involves interests on many levels. For the participants in vaccine clinical trials who are making an altruistic gesture for the benefit of science and the community at large, offering the very best proven quality of care to people who become infected may be seen as one way to recognize their contribution.[595] Thus this is one of the questions that rises to forefront at the moment when someone considers consenting to participation in the trial. On the other hand, treatments for HIV and AIDS are very expensive and lifelong. In the case of a phase III efficacy trial involving thousands of participants recruited from communities with relatively high seroincidence, several hundred people may sero-convert during the course of the trial. Requiring the sponsor to offer evolving, state of the art care and treatment to this number of people may constitute a serious and impractical economic burden, and thus a significant disincentive to investment in vaccine research.

Some have suggested that the treatment of people infected with HIV during the trial should be the responsibility of the national governments in the nations in which the clinical trials take place. In essence, the standard of care would be the "best available" standard rather than the "best proven" standard. This however would seem ineffective and largely meaningless in extremely poor nations where virtually no treatments are available. Moreover, it would seem a clearly unreasonable standard in the unlikely event that vaccination with an experimental vaccine actually renders trial participants more susceptible to HIV infection.[596]

> [However t]hose who would maintain the "best proven therapy" standard for participants infected during a trial need to be able to respond to those who are equally committed to ethical research but are also confronted by the realities of life and research in the developing country context [....][597]

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593 World Medical Association. Supra, note 101.

594 S Coudret. Towards defining a community position on care of persons infected during microbicide trials. Poster presentation to the XIIIth International AIDS Conference. Durban South Africa, 13 July 2000. Abstract no ThPeC5293.

595 Brazil: The ebbs and flows of AIDS vaccine trials: An interview with Dirceu Greco. IAVI Report 1999; 4(4): 10-11. Note: Brazilian clinical researchers have vigorously defended the "best proven" standard of care for people who experience breakthrough infections in HIV vaccine trials.

596 Studying the volunteers who make HIV vaccine trials possible: An interview with Susan Buchbinder. Supra, note 67, at 9. See also N French et al. 23-Valent Pneumococcal Polysaccharide Vaccine in HIV-1-Infected Ugandan Adults: Double-Blind, Randomised and Placebo Controlled Trial. *The Lancet* 2000; 355(9221): 2106. Note: As an analogy see the following reports concerning clinical trials of microbicides which suggest higher rates of infection in the study arms given the exeperimental microbicide than in the placebo control arm: L Van Damme. Advances in topical microbicides. Oral presentation to a plenary session of the XIIIth International AIDS Conference. Durban, South Africa, 12 July 2000. Abstract no WeOr62, and J Kreiss et al. Efficacy of nonoxynyl-9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes. *Journal of the American Medical Association* 1992; 268(4): 477-82. Cited in Health Canada. *HIV/AIDS Epi Update: Nonoxynol-9 and the risk of HIV transmission*. Ottawa: Laboratory Centre for Disease Control, Bureau of HIV/AIDS, STD & TB Update Series, May 2001, and C Retzlaff. A Tapestry of women's experiences. XIIIth International AIDS Conference presents information about women and HIV/AIDS. *International Associations of Physicians in AIDS Care Journal,* October 2000.

597 D Patterson. Supra, note 446, at 27.

Any diminishment in quality of care from the best proven standard of treatment should logically be compensated by a concerted effort to augment the promotion of preventive and harm reducing behaviours among the trial participants and in their communities. If the best available standard of HIV treatment is none at all, the sponsor company would have an even greater responsibility to provide preventive materials to participants and to make sure they comprehend the importance of practicing preventive and harm-reducing behaviour. The sponsor would also have an accentuated responsibility to ensure that participants understand that: (i) the trial is double blinded; (ii) the efficacy of the experimental vaccine is unknown, and (iii) they can not count on any degree of personal protection from their participation in the experiment. If this prevention is effective, it could significantly reduce risk behaviours in the cohort. A larger number of participants would be required to demonstrate efficacy and this in turn would increase the sponsor's costs.

Any downward deviation from the best-proven standards of treatment for breakthrough infections should also be accompanied by an effort to make a lasting contribution to the development of health services infrastructure. Hopefully through such incremental contributions, from a variety of sources (eg, industry, government, charity, international development aid), the host community will see this infrastructure evolve to the point where it will be able to offer the best-proven standards of care.

The issue of standard of care also has a potentially significant impact on the ability to obtain a consent that is free and voluntary.

> There may be circumstances in which some populations can never, because of the degree of their impoverishment, give free and informed consent. This is because any treatment or compensation for participation in a trial would in this context be an undue inducement [....].[598]

In a target population where seroincidence levels are extremely high, the prospect of receiving state-of-the-art anti-retroviral treatment may be a powerful incentive to enroll in a vaccine trial. The economic value of the medications relative to the socio-economic conditions in the target population may be so significant that it will constitute a powerful economic incentive effectively deforming the "free" quality of consent.

In a target community where medications including vaccines are usually unavailable, participation in an HIV vaccine trial would take on an even greater altruistic character since there would be few personal medical benefits to HIV testing. It is highly controversial as to whether or not a vaccine trial should even take place in such a setting. But if one did, the sponsor should commit itself to very firm (eg, legally enforceable) engagements concerning (i) delivery of the vaccine should it prove to be efficacious; and (ii) contributions to the development of the target community's health infrastructure. These engagements should be part of the informed consent process.

How then is this issue addressed in international declarations of ethical guidelines for clinical research involving human subjects?

(i) The Declaration of Helsinki

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[598] Ibid.

The Declaration of Helsinki sets a very high standard for care and treatment of clinical trial participants who require care at the end of the study:

> Article 30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[599]

In recent years, there has been considerable controversy as to whether the Declaration of Helsinki or parts thereof can serve as a guidance document for prophylactic research. The drafting of this article certainly suggests that the Declaration is meant to cover both therapeutic and prophylactic research. Moreover, the provision would clearly apply to clinical trials of experimental treatments designed to prevent vertical transmission of HIV as well as to clinical trials of anti-retroviral therapies. These are frequently conducted using cohort populations drawn from developing countries. Ensuring the provision of life-long therapy to infected new-borns or to participants in cohorts testing anti-retroviral therapies, will not differ significantly from the obligations to provide such therapy to the participants of vaccine cohorts.

Note however, that the Declaration does not require the sponsor to carry these obligations. They could instead be borne by the government in the host nation or shared by any number of collaborating partners. Controversy however, surrounds the use of the words "at the conclusion of the study" in article 30. They seem to shift the focus of the obligation to provide the best-proven standard of care away from an obligation to respond promptly during the clinical trial (and thus probably implicating the sponsor to at least some degree), to a post-trial phenomenon. Fears have been raised that at the end of most trials, corporate sponsors and researchers will pack their bags simply leaving the provision of health care to the host country.[600]

(ii) *UNAIDS Guidance Document: Ethical Considerations in HIV Preventive Vaccine Research*

This guidance document represents a consensus approach to bioethics and vaccine clinical research. For obvious reasons, many of which are discussed above, UNAIDS could not present a simple recommendation capable of fully resolving the controversy surrounding standards of care. However it does provide useful guidance to help researchers and communities arrive at a decision. The *Guidelines* require that the results of this decision be clearly communicated to participants at the moment of informed consent.

Guidance Point 10 states:

> Some of the activities related to the conduct of HIV vaccine trials should benefit those who participate. At a minimum, participants should: [...] have access to a pre-agreed care and treatment package for HIV/AIDS if they become HIV-infected while enrolled in the trial; [....].

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599 World Medical Association. Supra, note 101, at Recommendations guiding physicians in biomedical research involving human subjects.

600 P Lurie. Letter from Deputy Director of Public Citizen's Health Research Group to Dr. Delon Human, World Medical Association. 29 September 2000.

Notes to Guidance Point 12 reiterate the necessity of incorporating information about the provision of care and treatment into the informed consent process:

> All prospective participants of phase I, II or III trials should be informed of the nature and duration of care and treatment that is available, and how it can be accessed, if they become infected with HIV during the course of the trial.

Guidance Point 16 deals expressly with the standard of care and treatment to be applied:

> Care and treatment for HIV/AIDS and its associated complications should be provided to participants in HIV preventive vaccine trials, with the ideal being to provide the best proven therapy, and the minimum to provide the highest level of care attainable in the host country in light of the circumstances listed below. A comprehensive care package should be agreed upon through a host / community / sponsor dialogue which reaches consensus prior to initiation of a trial, taking into consideration the following:
> •level of care and treatment available in the sponsor country;
> •highest level of care available in the host country;
> •highest level of treatment available in the host country, including the availability of anti-retroviral therapy outside the research context in the host country;
> •availability of infrastructure to provide care and treatment in the context of research;
> •potential duration and sustainability of care and treatment for the trial participant.

In summary, while not providing a definitive response, this document functions as a kind of applied ethics providing a detailed framework for an analysis of the problem leading to a solution. Firstly, the Guidelines, supra, and accompanying notes require the sponsor to assume a key role in providing care and treatment to those infected. They do not necessarily require the sponsor to assume full responsibility, but they strongly suggest that participation in an effective solution is part of the pharmaceutical company's responsibility. Second, they set minimum levels below which the standards of treatment should not be permitted to fall, although admittedly this minimum threshold will vary from host country to host country. Third, they require the parties to aim to achieve as closely as possible, the ideal provision of the best proven therapy. Fourth, they require that this information be integrated into the consent process, ensuring that participants are fully informed of exactly what to expect before they enroll. And finally, they prescribe extensive multi-partite consultation in arriving at a consensus resolution of this problem.

For example, the notes to Guidance Point 16 include the following statements:

> A consensus on the standard / level of care and treatment, its duration, and who will bear the costs should be reached prior to a decision to host HIV vaccine development.
>
> This consensus should emerge from an extensive dialogue involving […] competing concerns among sponsors, and representatives from potential host country and communities from which potential trial participants would be drawn e.g. government officials, national scientific and ethical communities, affected populations, relevant NGOs, local religious and community leaders.

Canadians should not believe that this dilemma is irrelevant in their country with its public health care system. For one thing, Canadian researchers are likely to be involved in multi-national vaccine cohorts in all phases of clinical research which include sites in Canada and overseas in developing countries. Some ethical analysis and resolution of the problem of standards of care will be required if researchers are to avoid accusations of exploiting populations in developing countries. Here in Canada, we are already making hard budgetary choices concerning HIV treatment and prevention. For example, the timid support given to the promotion of post exposition prophylaxis for possible sexual exposition to HIV, was initially founded in ethical uncertainty concerning levels of efficacy, difficulties with compliance, and concerns for the potential impact upon the maintenance of preventive and harm-reducing behaviours. In recent years, clinical evidence has developed to somewhat ally these concerns, and the question increasingly boils down to one of money.[601] All of these debates are set against a general fiscal debate in which standards of living for so-called "middle income" Canadians have been falling relative to those in the United States for a number of years.

It is of course quite possible that a new, highly efficacious but very expensive treatment (or vaccine) for HIV might become available to wealthy Americans but be too costly for full subsidy by Canadian medical systems. This is after all, the situation that already prevails for the vast majority of people living with HIV in the world. In such an event, Canada will find itself facing the "standard of care" dilemma head on.

3. The Bioethics Approach to Defining Informed Consent

Consultation and a collective search for a solution is at the heart of a bioethical approach to HIV vaccine research. Unlike litigation, participation in the ethical debate is not limited to a select group of people with legal standing before the courts. Bioethics casts a wider invitation to interested parties to become involved in problem identification, deliberation over competing potential solutions, and resolution of the problems. It thus involves an important component of public ethics which holds that

> The common good, as potentially threatened or enhanced by biomedical developments, is too important to be left in the hands of any one elite group or any collection of elite groups.[602]

> Finding a common ground and achieving consensus and compromise as a basis for policy when people are divided on issues of liberty, rights and values, is the work of public ethics…[603]

This inclusiveness is particularly important in the context of HIV and AIDS where many affected communities in Canada are marginalized and have historically fought for a place at the table where policy decisions are made. In a previous section of this paper we examined how it is useful for vaccine researchers to establish close collaborative links with target communities before commencing field research. But before communities can take their place at the policy

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601 S Low-Beer. A reality check: The cost of making post-exposure prophylaxis available to gay and bisexual men. *AIDS* 2000; 14(3): 325-6.

602 DJ Roy et al. Supra, note 77, at 54.

603 ID.

table for HIV vaccine testing and delivery, they must become familiar with the basic parameters of clinical investigative science and of vaccine science. Community skills building could help to further this goal thereby opening the door to involvement and representation in processes of ethical review, commentary and study of proposed informed consent. Given the very large numbers of people involved in phase III efficacy trials, it makes good sense to find a structured and productive voice for their interests.

Bioethics will therefore seek to ensure that the multiple parties become mutually cognizant of each other's priorities and act consensually to resolve dilemmas as they arise. It will "pit the many and the wise in a mutually corrective interplay" [.... embodying a] "peaceful coexistence and collaboration of free and reasonable people in a pluralistic society."[604]

> The root of ethics is found in the unfolding of rational self-consciousness; the unfolding of the rational self-consciousness of many people, involved in mutually corrective deliberation to reach the best possible judgements for specific cases and situations.[605]

Canada, is a multi-cultural and pluralistic society. But thankfully, there is already a strong body of law and of ethical discourse which represents a convergence of views on the necessity to safeguard and promote informed consent that is individual, free, voluntary, comprehending and continuing.[606] Bioethics can bring together the parties by providing an analytical forum for the review of the content, procedures, implementation, monitoring and evaluation of this consent. When multi-centred clinical trials cut across international and cultural boundaries, this process will become more difficult, but not impossible.

4. Ethics and Law as Mutually Reinforcing the Requirements for Informed Consent

As noted above there are international guidelines such as the UNAIDS *Ethical considerations in HIV preventive vaccine research* that provide an ethical framework for the evaluation and conduct of vaccine research generally.[607] Although they do not have the obligatory force of laws, these instruments of guidance are rapidly extending their influence around the globe. They exert a certain moral authority as a source of minimal ethically imperative standards guiding the evaluation of both private and publicly funded vaccine research.

These international declarations are perhaps the precursors to international legal instruments (covenants, treaties), that might someday bind governments, obliging them to adopt national AIDS strategies, and to enact human rights legislation and regulations governing HIV / AIDS related research.[608] Already UNAIDS and the Office of the United Nations High Commissioner for Human Rights have produced the *International Guidelines on HIV/AIDS and Human*

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604 Ibid, at 58.

605 ID.

606 Medical Research Council of Canada. Supra, note 76, at Section 2.

607 Joint United Nations Programme on HIV/AIDS. Supra, note 10.

608 D. Patterson. Supra, note 446.

Rights[609] recommending that states adopt the guidelines "to ensure an effective and inclusive public health response to HIV / AIDS."[610] The drafting of these International Guidelines suggests a "top down" approach by which human rights legislation results in enforceable ethical codes of research conduct. It may however be closer to the truth to describe the relationship between ethics and human rights as a two-way interaction. Whatever their epistemology, the very close relationship between ethics and human rights legislation is underscored by the drafting used in the International Guidelines:

> **Guideline 5** States should enact or strengthen anti-discrimination and other protective laws that protect vulnerable groups, people living with HIV/AIDS and people with disabilities from discrimination in both the public and private sectors, [and] ensure privacy and confidentiality and ethics in research involving humans subjects, [....]
>
> **Guideline 10** States should ensure that government and the private sector develop codes of conduct regarding HIV/AIDS issues that translate human rights principles into codes of professional responsibility and practice, with accompanying mechanisms to implement and enforce these codes.

Among the promoted human rights, the following are particularly relevant to the issue of informed consent in HIV vaccine clinical trials: (i) the right to privacy; (ii) the right to information; (iii) the right to liberty and security of the person; (iv) the right to the highest attainable standard of physical and mental health; and (v) the right to freedom from cruel, inhuman or degrading treatment or punishment.

Canada and its provinces and territories have already extensively legislated in the field of human rights. Domestic ethical standards also provide strong instrumental guidelines helping Canadians to evaluate proposals for HIV research.[611] But private industry, particularly at the level of Phase I clinical trials, remains relatively unregulated although TPP regulations under the *Food and Drug Act* do require ethical and scientific review of consent forms.[612] There is room for further improvement in this field, particularly with respect to prescribing enforceable legal standards for ethical review of clinical trials. A better legal definition of the role and extent of REB responsibilities (if any) in monitoring respect for the ethical standards of informed consent during a trial would also be welcome.

5. Conclusion

Ethics has the ability to reach beyond the strict limits of the law and function as an applied discipline helping the parties to vaccine research solve difficult dilemmas. At the same time, ethics provides a positive feedback loop directly to legislators and to the courts interpreting human rights legislation, legal regulations of professional practice, and civil liability between the

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609 Office of the United Nations High Commissioner for Human Rights and the Joint United Nations Programme, Supra, note 44.

610 Ibid, par. 48.

611 Medical Research Council of Canada. Supra, note 76.

612 Regulations Amending the Food and Drug Regulations. Supra, note 197.

parties. It would be in the best interests of all the players to familiarize themselves with the language and substantive content of ethical guidelines and of legal standards for informed consent. Communities in particular have much to learn in this regard. Legislators and regulators need to recognize, reorganize and provide substantive content to the legal void in which review ethics boards in this country operate.

G. The Specific Legal and Ethical Content of Informed Consent

Perhaps the first vital component to facilitating informed consent is a clear explanation that participants have this right and that researchers have a correlative obligation to ensure its respect. The right is a right to information, comprehension and to a free exercise of choice. The nature and extent of these rights and obligations must be carefully explained. We should approach the content of informed consent by recalling that the scope of disclosure in this kind of experimentation is extremely large - exceeding that normally exercised in the field of medical treatments.

But this doctrine may appear somewhat threatening to researchers. There is after all, "an essential need for some measure of ignorance in the trial".[613] Vaccine trials are experiments and as such the outcome cannot be predicted in advance. Researchers may fear that a too thorough or too detailed disclosure of facts, risks and benefits may either frighten potential participants away or bias their reports of adverse events.

And yet informed consent by its very legal and ethical nature requires this thorough disclosure. And disclosure requires some prediction and evaluation of risks and benefits. Volunteers must be apprised of the hypothesis, the results from prior research, the "hoped for" results, the end points of the trial and its principal objectives. These can all be precisely described. Admittedly, we cannot know of all of the potential adverse events in advance. Extremely rare but serious side effects may only be revealed in the course of large-scale efficacy trials.[614] Nevertheless, as discussed in the earlier section on the legal scope of informed consent, participants must be provided with full disclosure of all pertinent risks, (known or suspected) at the beginning of the trial and as well as those that become apparent as it unfolds.

The participant should also be apprised of administrative details such as the identities of the sponsor, its parent corporation, and of the principal investigator. He should be made aware of the general nature of any conflicts of interest linking these parties, and especially the sponsor with the principal investigator.

Participants should be given a detailed overview of the advantages and disadvantages of participating in an HIV vaccine trial. In the text that follows, we will attempt to highlight many

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613 JK Mason, RA McCall Smith. Supra, note 489, at 359.

614 *Coughlin* v *Kuntz*, (1989) 42 BCLR at 108.

of the essential advantages and disadvantages that should be included in the information supplied for informed consent. Despite the presentation of these generic advantages and disadvantages in list format below, it is important not to adopt a checklist approach to informed consent. Ethics committees and communities need to make the effort to thoroughly educate themselves on the specifics of each individual proposal for clinical research. Sometimes what is missing from the informed consent is every bit as important as what has been included.

1. Advantages to Participating in an HIV Vaccine Clinical Trial

- You have an opportunity to contribute to science and an opportunity to make an altruistic contribution to your community's fight against HIV/AIDS;
- You can learn about an interesting new field of clinical research;
- With this knowledge and through volunteer participation in a community advisory board, by attendance at periodic information forums, and through other community information activities you may have the opportunity to become more directly involved in the research process;
- You will indirectly contribute to development of your community's health infrastructure and HIV prevention infrastructure if the sponsor has agreed to allow the trial to contribute to same;
- You will have access to HIV prevention materials including male and female condoms, clean needles and other injecting equipment and post exposition prophylaxis;
- You will have access to periodic, HIV testing accompanied by state of the art counselling over a period of several years. This counselling should be empathetic, supportive and also include referrals when necessary. You can access testing between regularly scheduled appointments on demand;
- Early detection of HIV infection, should it occur;
- In the event of vaccine-induced injury or a breakthrough HIV infection, you will receive access to pre-agreed standards of care and treatment;
- Identification and diagnoses (and / or referrals to diagnoses) of health problems with referrals to ancillary health, social and community services;
- Modest compensation for travelling costs and time required for periodic appointments;
- If the vaccine should prove efficacious and you have received a placebo, you will be offered the vaccine free of charge.

2. Disadvantages to Participating in an HIV Vaccine Clinical Trial

- Possible vaccine-induced injury or placebo-induced injury:
- There is a rare possibility that vaccination might actually make the participant more susceptible to infection and enhanced disease progression;
- Possible long-term carcinogenic effects;
- Possible hyper-sensitivity reaction (to vaccine or to placebo);
- Risks of retro-version to virulence of attenuated vectors or attenuated HIV;
- Possible vertical / lateral transmission of live DNA vaccines and live attenuated vaccines;
- Unknown risks associated with genetically altered vaccine vectors;
- Possibility (theoretical and rare) of auto-immune disease stimulated by the vaccine;
- Unknown duration of immunity;

•Danger of reduced vigilance in risk assessment, management and reduction by participants and their communities;
•A positive vaccine test might be incorrectly interpreted as evidence of an HIV infection and this in turn might trigger discrimination;
•Even a correctly interpreted positive vaccine test result might trigger social and economic discrimination.
•A positive vaccine test incorrectly interpreted as evidence of an HIV infection might trigger incorrect mandatory declaration.
•Discrimination may arise simply as a result of participation in the cohort;
•No access to future clinical trials of experimental vaccines;
•Remote possibility of a negative interaction reducing efficacy of a future vaccine;
•In the event of breakthrough infection, no access to clinical trials of anti-retroviral medications;
•Unknown interactions with illicit injection and recreational drugs;
•Inconvenience with no guaranty of any benefit to personal health; and
•Interdiction to conceive children during the course of the trial.

3. Further Key Elements to Be Included in Informed Consent

Participants should also be informed of the choice of research methodologies and why they were selected. For instance they must comprehend the double-blind, randomized, and placebo-controlled methodology of the trial and hence the importance of not unblinding his status. They will want to know the probability of assignment to each arm of the clinical trial. They need to know what phase of clinical research they are participating in and what phases will follow. The different stages of the clinical trial as described in the scientific protocol should be translated into accessible language that the participants can understand.

They must know of the various obligations they will be required to fulfil. Information describing the nature, timing, frequency and duration of foreseeable examinations, tests, diagnostics and controls, and the risks related thereto must therefore be provided. The importance of maintaining safer behaviours (including the possibility to access post-exposition prophylaxis) in order to reduce the risk of contracting HIV must be communicated and understood.

The consent process should give specific emphasis to:

•the fact that the trial will involve multiple and periodic tests for HIV and the potential harms and benefits that may result from an HIV test or an HIV diagnosis;
•the fact that during the period of a vaccine efficacy trial, the participant must use the cohort as their only site for HIV testing to prevent the unblinding their status within the trial; and
•the fact that receiving a placebo can also sometimes cause side effects.[615]

4. Designing the Content of Informed Consent

As previously mentioned, informed consent should take the form of a dialogue between the researcher and the participant in which the latter feels free to ask questions. In anticipation of this, the designers of the entire process should ask themselves what would a "reasonable person",

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[615] Studying the volunteers who make HIV vaccine trials possible: An interview with Susan Buchbinder. Supra, note 67, at 9.

drawn from the target community, want to know and consider before consenting? Needless to say, vaccine preparedness studies can also help to flag important questions that will likely arise in the informed consent process. Some examples of questions participants might ask are:

1. What measures will be taken to preserve the confidentiality of my identity?
2. Will positive HIV test results be subject to mandatory declaration under provincial public health protection legislation?
3. Does the candidate vaccine pose risks to my present or future health?
4. If I become ill as a result of the vaccine, who will care for me? Will I be compensated for loss of income, home health care, the cost of medications, and loss of enjoyment of life?
5. What is the probability that future HIV test results following vaccination with the experimental vaccine might be incorrectly interpreted as proof of HIV infection when in fact they only indicate an immune response to vaccination?
6. If confusing test results are possible, what measures will be taken to help me deal with any resulting discrimination? Who will help to correct any misunderstanding and how will this be done? Will this service be available after the end of the clinical trial?
7. Does the protocol permit me to take post-exposition prophylaxis during the vaccine trial? Where can one access PEP?
8. If the vaccine is of relatively low efficacy (eg,- 35 - 40 percent), will I still be given access to it if I have been receiving the placebo?
9. If the clinical trial reveals that vaccine-induced immunity is of short duration, thus requiring continuous periodic booster shots, will the booster shots be permanently available in future?
10. Will the target community also have access to the vaccine if proven efficacious? What are the plans for its manufacture and delivery?

And finally, researchers have "an ethical obligation throughout the trial to provide participants with any other information that may reasonably be expected to influence their willingness to participate."[616] The researchers themselves have an obligation to evaluate whether, in light of new information, the trial should be halted. Where unforeseen difficulties are encountered that are case-specific (eg,- certain acts of social discrimination), the researchers must also evaluate whether it is in the individual participant's best interests to continue.

This continuing obligation of surveillance, data gathering, and vigilance extends beyond merely providing information to a data safety and monitoring board. "[I]t also could include information that becomes available through the vaccine research of others, HIV research in other realms, such as behavioural research, or relevant changes in public policy, if this information can reasonably be expected to influence participants' willingness to participate" [or to continue to participate].[617]

H. Key Issues to Be Resolved at the Moment of Informed Consent

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[616] NE Kass. Ethical Issues in the Design and Conduct of HIV Vaccine Trials. In *Adverse Reactions to HIV Vaccines: Medical, Ethical, and Legal Issues.* Washington DC: USGPO, September 1995, at 65.
[617] ID.

In this section, we continue to examine the content of informed consent, with a more detailed examination of four critical elements concerning participants' interests, expectations and well-being. Although many of these issues relate to on-going matters that are either continuous or recurrent throughout a clinical trial, they are of such capital importance that the volunteer needs to be apprised of their existence and understand their potential consequences, before agreeing to participate.

1. Informing Participants What the Trial is Most Likely and Least Likely to Prove

One of the key questions that merits attention in an informed consent to enrolment in a vaccine efficacy trial is: Do participants have a right to be informed of the experimental vaccine's "best estimates for probable success / efficacy"?

Volunteers surely have a right to access the results of pre-clinical research, of clinical research in animals, and the results of research in humans in earlier phase clinical trials. But the evidence generated by pre-clinical and pre-efficacy trials does not demonstrate efficacy in humans, but rather merely safety, required dosages and immunogenicity. Phase II trials suggest the potential for efficacy but in no way constitute statistical evidence of probable efficacy outcomes in a subsequent phase III clinical trial.

A purely scientific approach to the question above would probably yield a negative response. A clinical trial is an experiment designed to prove or disprove an hypothesis. Indeed, in the case of a phase III trial, barring levels of efficacy that are so extremely high that they are already self-apparent at mid-point, there will be no statistically significant evidence of efficacy until after the trial has run its full course and the data has been analysed by independent statisticians. How therefore, could a responsible scientist include in an informed consent a meaningful "best guess" for efficacy? The degree of imprecision would be so high as to render such an exercise unscientific and statistically meaningless.

However, if 75 percent of scientists working in the field of HIV vaccine research believe that a given candidate vaccine undergoing a phase III trial is unlikely to demonstrate efficacy or will demonstrate only extremely low levels of efficacy, do the participants in the trial have the right to know this information? Who would provide volunteers with an impartial summary of the controversy?

Perhaps the answer lies in the notion that participants do have a right to be informed of the objectives of the research. Objectives such as: i) developing an expertise in running an efficacy trial, and ii) generating scientific information to better determine the correlates of immunity for a future vaccine, may be as important to the sponsor as the hope that the experimental vaccine undergoing testing today might demonstrate some degree of efficacy. In such a case, the participants have a right to know of the relative order, priority and weight accorded to the multiple objectives in today's clinical trial.

2. Standard of Preventive Care

The informed consent to clinical trials of HIV vaccines must recognize first and foremost that these experiments belong to a particular class of research – namely "non-therapeutic" research offering relatively few personal benefits and posing some important potential risks.

In these vaccine trials, there are unfortunately no alternative pharmaceutical preventive treatments to which potential volunteers can be referred in the place of cohort participation. Simply put, there do not yet exist any alternative vaccines nor microbicides that are efficacious against HIV. Researchers must therefore treat existing prevention techniques as the available and alternative "standard of care". Included in these techniques are: the provision of condoms (male & female); access to post exposition prophylaxis; distribution of sterile injecting equipment; community support; pre-and post-test counselling; referral to HAART for HIV positive sexual partners; referral to community-based workshops for sero-discordant couples or for individuals at high personal risk; diagnosis and referral to treatment of STDs; diagnosis (or referral to diagnosis) and treatment for other morbidities; and access to detoxification and methadone or heroin maintenance programs. All of these diverse measures can help volunteers to reduce their risks of contracting HIV today.

Not only must researchers accept these measures as the alternative / existing standard of care, but the volunteer must be made to understand that these standards will be respected throughout the vaccine trial. Participation in a clinical trial should not unnecessarily harm research subjects. Scientists and investigators have an ethical and professional obligation to minimize potential and actual harms to the subjects. Since counselling, and referrals to social and health services with follow-up should be generally available within the framework of most HIV testing facilities in Canada today, participants in clinical trials for HIV vaccines should expect nothing less. In order to preserve clinical equipoise within the trial, the highest quality of this information and services must be present in both the placebo control arm and in the arm of the study where participants receive the experimental vaccine. Informed consent should contain the sponsor's and investigator's solemn promise to live up to these standards.

3. Preventive Counselling for Participants

In this subsection, we will look specifically at the content of the important obligation of providing preventive counselling, support and referrals to clinical trial participants. This is a subject which fits awkwardly into a chapter on informed consent since the counselling will mostly take place after consent and during the trial. But the potential for vaccine research to influence risk assessment and assumption clearly exists. An incomplete or erroneous comprehension of the experimental nature of the vaccine and of the randomization of one's assignment to vaccine or placebo control arms might lead some participants to reduce their assessment of risk. The consequences of such an ill-informed course of action are so nefarious that this issue needs to be thoroughly discussed in the consent form and throughout the consent process itself.

Vaccine trials often deliberately attempt to recruit sub-sets of people at greater personal risk of contracting HIV. This can even apply within populations that have already been targeted because they are characterized by relatively high seroincidence and socio-economic conditions indicative of vulnerability. For example, the AIDSVAX B/B Gp 120 clinical trial in Canada, limited recruitment to a subset of gay and bisexual men engaging in anal penetrative sexual intercourse

(with or without condoms) with someone other than a regular sexual partner during the six months preceding enrolment. If recruitment parameters in clinical trials are designed to triage volunteers for successively higher levels of vulnerability, then this engenders an accentuated responsibility on the part of researchers and cohort staff to carefully counsel individual participants to continue to reduce risks.

The inherent conflict of interest between the need to have a sufficient number of volunteers who risk infection in order to generate a sufficient number of sero-conversions to demonstrate or disprove vaccine efficacy, and the ethical need to protect research subjects will not escape the attention of potential volunteers. This in turn is further reason for addressing the issue of preventive counselling at the beginning to the clinical trial.

Researchers are "ethically obligated to take all reasonable actions to reduce HIV risk behaviours in the trial participants".[618] Preventive counselling offered to participants is one way to do this. It begins before informed consent, at the moment when volunteers are screened and it continues throughout the duration of the trial. The consent process should inform participants that they will have access to the highest standards of counselling, referrals and support equivalent to or better than what is available elsewhere in their city.

The informed consent should provide clear information stressing: i) the experimental nature of vaccine trials; ii) the double blinded, randomized and placebo-controlled structure of the research; iii) the uncertainty of the candidate vaccine's efficacy; (iv) and the futility of attempting to extrapolate conclusions about vaccine efficacy from one's personal test results following risk behaviours. As a general rule, if the volunteer is unable to understand these key elements of information he should be refused access to the trial.

Of course once informed consent is given, the obligation to promote prevention is a continuing one. All vaccine studies require volunteers to undergo periodic testing for HIV infection. Counselling must take place at pre- and post-test meetings. Successive negative HIV testing might lead volunteers to incorrectly hope or conclude that they have received the experimental vaccine and that it is efficacious. "Counselling for these vaccine trial participants should address the probabilistic nature of HIV transmission so that instances of risk behaviour with a known HIV-sero-positive partner do not generalize into beliefs about invulnerability [via hypothesized vaccine-induced immunity] to HIV infection."[619]

The following considerations outline some of the practical steps that can be taken to support and strengthen preventive interventions in vaccine efficacy trials:

- Researchers should take every reasonable step to protect the confidentiality of nominative information gathered during pre- and post-test counselling interviews. This will encourage free and frank discussions with participants.
- Cohort staff should be able to help volunteers access other health and community services through referrals and follow-up.

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618 DC Des Jarlais et al. Why I Am Not Infected With HIV: Implications for Long-Term HIV Risk Reduction and HIV Vaccine Trials. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1997; 16: 393-99. Note: Des Jarlais et al cite the following sources in support of this ethical obligation: P Lurie et al. Ethical, behavioral, and social aspects of HIV vaccine trials in developing countries. *Journal of the American Medical Association* 1994; 271: 295-301, and J Esparza et al. Supra, note 98.

619 DC Des Jarlais et al. Ibid at 393.

•HIV testing should include free, voluntary, informed, comprehending and specific consent every time a test is performed.
•Comprehension of the clinical research and consent to participation therein should be periodically reviewed throughout the course of the trial. Participants who despite clear information, indicate that their participation is motivated by a desire for personal protection from infection should be asked to leave the cohort.
•At every visit, participants could be surveyed about their sexual and needle sharing behaviours. This information could be compiled and reviewed on a local, regional, national and cohort-wide basis. It could be compared with information generated in seroincidence cohorts conducted in the target population or in similar populations elsewhere.
•The principal investigator and his colleagues on the research team, should not be the persons who conduct preventive counselling for participants.
•Cohort staff responsible for conducting preventive counselling should be trained to understand the local culture of the target population, including attitudes towards sexuality, illness, family, injection drug use, etc. They should also seek the advice of local health care providers and community-based HIV prevention agencies concerning effective techniques for HIV prevention within the target population.
•Cohort staff responsible for counselling should be subject to objective evaluation by an external expert. This could help to identify areas where staff require further training.
•Cohort staff could hold yearly seminars with others in the community engaged in HIV testing and counselling in order to update their techniques.
•Multi-centred trials could elaborate basic standards for preventive counselling to be applied at every site. At the same time, they could permit local sites to adapt counselling techniques, language and frequency to local conditions.
•Counselling sessions should be made available to participants on demand.
•The study could also maintain a small, parallel unblinded arm, merely for the purpose of evaluating the efficacy of the counselling over time.
•Without unblinding the study, mid-term statistical review of results from a phase III efficacy trial could signal any inordinately high levels of seroincidence in placebo control groups to cohort managers, who could then take steps to revise and intensify preventive interventions.

4. Informed Consent in Future: Placebo Control or Clinical Benefit?

Since there are no available HIV vaccines, clinical efficacy trials which administer placebos in control arms are ethically acceptable. However, this may not always be the case. The CDC in the United States has agreed to recommend marketing of the AIDSVAX B/B and B/E Gp 120 vaccines if phase III trials demonstrate safety, immunogenicity and an efficacy level of 30 percent or more in attaining sterilizing immunity. Should that happen, this vaccine will rapidly become the standard of care in high seroincidence populations and, should therefore become the required minimal standard of preventive benefit in the placebo control arm of future clinical trials of subsequent HIV candidate vaccines.

Guidance Point 11 of the UNAIDS *Ethical Considerations in HIV Preventive Vaccine Research* states that, "a*s long as there is no known effective HIV preventive vaccine*, a placebo control arm should be considered ethically acceptable in a phase III HIV preventive vaccine trial."[620]

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620 Joint United Nations Programme on HIV/AIDS. Supra, note 10, at Guidance Point 11.

[emphasis added] Notes to guidance point 11 further state that "participants in the control arm of a future phase III HIV preventive vaccine trial should receive an HIV vaccine known to be safe and effective when such is available, unless there are compelling scientific reasons which justify use of a placebo."[621]

The subsequent notes to this guidance point set out compelling ethical arguments in favour of replacing placebo with a licensed vaccine when it becomes available. But the choice of the words "when such is available", referring to the availability of a future licensed HIV vaccine are sufficiently ambiguous that we can reasonably expect some sponsors of future vaccine research to try to continue trials with placebo control arms in developing countries too poor to purchase the first licensed vaccine. Already there is considerable controversy concerning standards of care for treatment of breakthrough HIV infections and for vaccine-induced injuries in HIV vaccine clinical trials in developing countries. In future, this same debate will likely reoccur concerning the issue of substituting existing vaccine for placebo control.

I. Anticipating, Preventing and Protecting Participants from Economic and Social Discrimination

The central question of this section is whether and to what extent persons participating in HIV vaccine clinical trials can expect to suffer stigma and discrimination. This possibility has to be a central point in the informed consent process.

1. Stigma and Discrimination -- Background

In a discussion paper on *HIV/AIDS and Discrimination* produced by the Canadian HIV/AIDS Legal Network, author Theodore de Bruyn has described HIV as an epidemic of stigma and discrimination.[622]

> When one … look[s] at the experiences of people with HIV/AIDS, two things stand out. The first is the diversity of people with HIV/AIDS. The second is how often and in how many ways people with HIV/AIDS are stigmatized or discriminated against. Sometimes it appears as if the various people with HIV/AIDS have only two things in common: HIV infection and HIV-related stigma and discrimination.[623]

Stigma is generally taken to be the broader field encompassing positive and passive acts of discrimination but also including the more intangible interpersonal attitudes of disdain, shunning and disapproval.

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621 Ibid, at Notes to Guidance Point 11: 31.

622 T de Bruyn. Supra, note 27. Note: Mr de Bruyn cites and reuses this phrase first published by GM Herek, EK Glunt. An Epidemic of Stigma: Public Reactions to AIDS. *American Psychologist* 1988; 43(1): 891-896.

623 T de Bruyn. Supra, note 27, at 11.

De Bruyn cites work by social scientists describing stigma as: "a powerful discrediting and tainting social label that radically changes the way individuals view themselves and are viewed as persons."[624]

In commenting upon a study of HIV-related knowledge and stigma in the United States, published by the Centers for Disease Control in December 2000, the CDC editors describe HIV related stigma as the broader term encompassing discrimination:

> Stigma includes prejudice and active discrimination directed toward persons either perceived to be or actually infected with HIV and the social groups and persons with whom they are associated.[625] [emphasis added]

People who are stigmatized "are usually considered deviant or shameful, and as a result are shunned, discredited, rejected, or penalized."[626]

The Report of the Commission on Equality in Employment (Canada - 1984) provided the following definition of discrimination in an employment related context:

> Discrimination in this context means practices or attitudes that have whether by design or impact, the effect of limiting an individual's or group's right to the opportunities generally available because of attributed rather than actual characteristics. What is impeding the full development of the potential is not the individual's capacity but an external barrier that artificially inhibits growth.[627]

2. The Risk of Stigma and Discrimination in an HIV Vaccine Trial

The following general considerations prepare the way for a clear recommendation that volunteers for an HIV vaccine clinical trial be informed about the risks of suffering stigma and discrimination that they may encounter as a result of participation in the clinical trial.

First, the cohorts for HIV vaccine clinical research will be comprised of people recruited from communities with high levels of seroincidence where seroprevalence is increasing rapidly. But there is a great deal of prejudice and social stigma surrounding the principal means of HIV transmission notably: (i) unprotected penetrative sexual relations, (particularly when such relations occur between men, between adolescents, or in a commercial sex trade context); and (ii) the sharing of non-sterile equipment used for the consumption of illicit drugs. Religious condemnation, cultural stigma, legal sanction and peer presume may lead people to make blanket assumptions about the private lives of those infected with HIV and those vulnerable to infection.

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624 Ibid, at 12. Note: Mr de Bruyn cites and reuses this phrase first published by AA Alonzo, NR Renyolds. Stigma, HIV and AIDS: An exploration and elaboration of a stigma trajectory. *Social Science and Medicine* 1995; 41(3): 303-15 at 304.

625 G Herek. AIDS and stigma. *American Behavioural Scientist* 1999; 42: 1106-16. Cited in Centers for Disease Control. HIV-Related Knowledge and Stigma: United States, 2000. *Morbidity and Mortality Weekly Report* 2000; 49: 1062-64.

626 T de Bruyn. Supra, note 27.

627 *Report of the Commission on Equality in Employment* (Canada,1984) at 2.

Second, the epidemiology of HIV in Canada demonstrates that many parallel epidemics are occurring primarily among communities and sub-populations that are socially, economically, politically and culturally marginalized. Social stigma, bigotry and racial prejudice may already be directed against people in some of these communities. If the research process identifies specific communities (eg,- specific ethnic or racial sub-groups, prisoners or ex-convicts) as being particularly affected by or vulnerable to endemic outbreaks of HIV, then an already disadvantageous situation may be made even worse when pre-existing racial and socio-economic discrimination are further exacerbated. Vaccine research and delivery will be perceived to be synonymous with vulnerable populations where seroincidence is high. Communities most likely to be targeted and affected include homosexual men, injection drug users, incarcerated prisoners, ex-prisoners, sex trade workers and their clients, people with multiple sexual partners, homeless people, First Nations and Aboriginal peoples and certain specific ethnicities. This is fertile ground for stereotyping and outright discrimination.

Third, even if people in the host community do understand the nature of the candidate vaccine and the experimental nature of the clinical trial, they may assume that the participant is someone likely to become infected. This is not an entirely unreasonable supposition, given that efficacy trials generally take place in high seroincidence communities and sometimes use their entrance criteria to further triage for a selection of participants at particularly high risk within those communities. If people living with HIV are routinely subject to discrimination within a target community, then these attitudes, often founded in a lack of knowledge and concomitant fear, will likely be extended to the participants in clinical research for HIV vaccines.

Fourth, in communities where vaccine trials take place people may simply not understand the concept of vaccination. They may incorrectly assume that an experimental vaccine might risk causing HIV, or increase the risk of contracting HIV. In the vast majority of cases this will not be even remotely possible. However, because the mechanisms of immune reaction to HIV primo-infection are not fully understood, the consent form to the AIDSVAX B/B Gp 120 phase III clinical trials does warn volunteers of the extremely unlikely possibility that the vaccine might actually result in enhanced susceptibility to infection.

Social stigma and discrimination resulting from participation in a clinical trial of a preventive HIV vaccine may take many forms. For example, participants may lose their employment or face a difficult challenge of explaining vaccination in a hostile work environment. They may be shunned or discredited within their community. They may be denied insurance. They may be denied the right to travel across international borders and denied the right to immigrate to a number of countries.

To summarize, stigma and discrimination may occur because:

- People associate vaccine trial participation with HIV infection or probable infection and discriminate on this basis;
- People may equate vaccine trial participation with probable infection and cumulatively add these assumptions to pre-existing racial, ethnic and socio-economic discrimination against minorities in Canada.
- People may strongly disapprove of HIV risk activities and condemn trial participants as people likely to engage in such activities;
- People may erroneously interpret the trial participant's HIV test as indicative of infection when in reality it merely indicates the presence of antibodies against the vaccine;

•People may use an HIV test or similar testing technology to identify people who have been vaccinated and then discriminate for the reasons identified in points one through three above.

Before consenting to be a research subject in an HIV vaccine clinical trial, volunteers need to understand that there is some risk of social and economic discrimination and of an increase in pre-existing discrimination resulting from how others perceive their participation. When considering consent, people need to personally evaluate the potential for such discrimination within their own individual lives and what its consequences might be. They need to understand that the risk of discrimination is neither a short term nor a transitory phenomenon. They must be informed of what, if anything, the research cohort is prepared to do in order to help reduce the risks of social discrimination and attenuate its damages. The participant must also understand the limitations to the cohort's capacity to alter conduct by people who are not connected to the research.

Having established that there are reasonable grounds to apprehend the danger of discrimination, it now bears mentioning that human rights legislation in Canada and the provinces will offer some legal protection to clinical trial participants who are victims of such discrimination. A strong and emerging record of jurisprudence in Canada takes an interpretation of handicap as something extending well beyond physical disability:

> It is important to note that a "handicap" may exist even without proof of physical limitations or the presence of an ailment. The handicap may be actual or perceived and, because the emphasis is on the effects of the distinction, exclusion or preference rather than the precise nature of the handicap, the cause and origin of the handicap are immaterial. Further the *Charter* also prohibits discrimination based on the actual or perceived possibility that an individual may develop a handicap in the future.[628]

Subject to jurisdiction, provisions in federal and provincial human rights legislation prohibiting discrimination on the basis of handicap, as well for motives such as race, gender, sexual orientation, and social condition, will offer some legal protection to vaccine trial participants who fall victims to discrimination based upon such qualities, or the perception thereof.

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628 *Québec (Commission des droits de la personne et des droits de la jeunesse)* v *Montréal*; *Québec (Commission des droits de la personne et des droits de la jeunesse)* v *Boisbriand*, [2000] 1 SCR 665. See also: *Granovsky* v *Canada (Minister of Employment and Immigration)* [2000] 1 SCR at 703.

3. The HIV Test Results of Participants in a Vaccine Trial

As mentioned above, the immunogenicity stimulated by the vaccine may also result in a characteristic "vaccine signature" on an HIV test. In other words, the vaccine elicited immune response would be sufficiently distinct from the immune system's response following HIV infection to permit testing to easily distinguish one from the other. In this case, testing could be used to clearly identify those who have been vaccinated. Of course, people may also find out about a person's participation in a vaccine trial if the participant himself discloses this information. Neither the tests nor the personal disclosures per se are inherently dangerous. Rather, it is the discriminatory reaction of those who learn of this information and how they interpret or use it, that is a matter of concern to human rights advocates.

Information provided to participants in the AIDSVAX B/B Gp 120 phase III clinical trial informed consent, indicates that four to six per cent of vaccinated subjects develop a positive reaction to the HIV-1 Elisa test.[629] After one year of the three year trial, there were reports that slightly higher figures have in fact been observed. In most cases, this "false positive" Elisa test result is expected to be transitory and disappear as the immune reaction converts to long term latent memory cells. Moreover, an HIV diagnosis in Canada uses two tests, Elisa for sensitivity, followed by Western Blot for specificity. The Gp 120 experimental vaccine is relatively simple, containing only one elementary surface envelope protein. It is designed to primarily stimulate a humoral response of blood-borne antibodies, and most Elisa tests should show a pattern of antibody response that is distinguishable from true infection. When it cannot, the Western Blot confirmatory test is expected to be able to differentiate vaccination from infection.

Indeed, in most future vaccine clinical trials, the majority of participants receiving an experimental vaccine, are not expected to experience confusing HIV test results. This is due to a widely respected scientific consensus according to which candidate vaccines should delete a particular immunodominant epitope, present in the retrovirus envelope, - the GP 41 AVERY epitope. This epitope is not believed to play a role in stimulating effective immune protection but in the majority of persons infected with HIV, it leaves a clear signature pattern in both Elisa and Western blot testing.[630] Therefore, a careful reading of traditional test results should, in most cases, provide specific information enabling a laboratory to identify a classic vaccine-induced immune signature in which responses to the AVERY epitope are missing.

However, the AVERY epitope exclusion is optional. Moreover, as experimental vaccines generally become more sophisticated, involving a wider variety of genetic components, they will stimulate broader humoral and cellular immune responses than the current generation of Gp envelope candidates. When this occurs, the probability of incorrect interpretations of HIV tests, (with or without the AVERY epitope) will nevertheless increase.

> In light of the complex antigens likely to enter trial, the question of correctly identifying and discriminating those individuals who are immunized against HIV from those who actually acquire an HIV infection becomes critical.

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[629] VaxGen, Inc. Informed consent form. Used at the Montréal site of the AIDSVAX B/B Gp120 phase III clinical trial, at 11.

[630] J Weber. Distinguishing between responses to HIV vaccine and response to HIV: Commentary. *The Lancet* 1997; 350: 230-31.

> Newer constructs with multiple structural epitopes will lead to more complex western-blot bands, which will be practically indistinguishable from true infection.[631]

Informed consent to HIV vaccine clinical trials should indicate the foreseeable and potential types of social discrimination that might occur with a false interpretation of a vaccine-induced test result or simply as a result of how people react to a test indicative of trial vaccination. Volunteers should carefully consider the possible impacts and consequences of such discrimination, and take available steps to palliate potential difficulties before entering the trial.

Pledges of support (eg, explanatory letters, phone calls, more detailed testing) offered by the sponsor, principal investigator and local research establishment should be clearly described and delineated as should the procedures, limitations and duration of this support. Ideally, support should extend beyond the end of the clinical trial for as long as is reasonably necessary.

The possibility for an incorrect interpretation or an abusive use of vaccine-positive test results, reinforces the importance that the trial participant only be tested at the cohort site. If the potential volunteer is not prepared to respect this restriction, they should not agree to participate.

4. Where Discrimination Could Occur

Discrimination will potentially occur in several distinct fora, including (i) the workplace, (ii) the community, (iii) the insurance market (iv) health services, (v) government services (vi) immigration and travel.

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631 ID. See also RB Belshe et al. Interpreting HIV Serodiagnostic test results in the 1990s: Social risks of HIV vaccine studies in uninfected volunteers. *Annals of Internal Medicine* 1994; 121(8): 584-88.

(i) Discrimination in the Workplace

It must be remembered that participants in a clinical trial of a phrophylactic vaccine will submit to periodic testing for HIV infection. Those contemplating enrollment need to reflect on the possibility of a positive test result and evaluate how this information might impact upon their employment. Moreover, even without actual infection, disclosure at work of one's participation in a vaccine trial might nevertheless precipitate discrimination.

Discrimination in the workplace can take many forms. It can include the denial of insurance and other employment benefits, denial of trade union services; breach of confidentiality with respect to personal circumstances and clinical trial participation; segregation from other employees; harassment by fellow employees; refusal to accommodate an employee's handicap; refusal of promotion; more frequent lay-off; and outright termination.

The employee who is participating in a vaccine efficacy trial should be extremely prudent about disclosing this information at work. Disclosure of trial participation generally concerns personal activities that are not relevant to employment. Depending upon the design parameters of the clinical trial, disclosure may amount to a constructive disclosure of sexual orientation, past or continuing injection drug use, multiple sexual partners, or past incarceration. The protection offered by human rights laws is more often remedial in nature than pro-actively preventive. Indeed unless the employer has implemented pertinent HIV/AIDS-in-the-workplace training and anti-discrimination policies that have been well received by the workforce, the employee should very prudently try to gauge the probable impact of disclosing his trial participation in his working environment.

And finally, the employee has no obvious need to divulge this information in the workplace and cannot legally be compelled to do so. The vaccine trial however, must be prepared to offer sufficiently flexible hours of participation so that appointments can be scheduled outside of the volunteer's working hours.

(ii) Discrimination from Within the Community

Potential volunteers weighing the risks and benefits accruing from enrolment in an HIV vaccine trial will frequently attach considerable importance to how people in their community will react to their decision to enroll.[632] Qualitative research on this subject has been conducted in the United States within the context of vaccine preparedness studies. People were interviewed from three diverse groups (injection drug users from Philadelphia, gay men from San Francisco, and African Americans from Durham N.C.). The research demonstrates that potential recruits fear an unfavourable social reaction to their involvement in vaccine clinical research and consider this to be one of the primary risks associated with participation. Although overall interview results found that people from all three groups would voluntarily join a vaccine trial, the researchers concluded that "scientists ought to be better prepared to address [such] risks and fears associated with such testing in order to ensure a successful [research] program."[633]

As is the case with workplace discrimination, disclosure of vaccine trial participation within the community can amount to a de facto disclosure of information that is of an intensely personal nature (eg,- sexual orientation, injection drug use, sexual relations with partners who use injection drugs or with men who have sexual relations with other men, multiple sexual partners, previous incarceration). This kind of disclosure may carry with it challenges specific to the community in which it occurs (eg,- small towns, ethno-cultural communities, First Nations and Aboriginal populations, members of the Deaf community).[634]

Information from the VaxGen trial presented at the 13th International AIDS Conference in Durban demonstrate that:

> The most frequent negative effects so far (reported by 7.5% of the participnts at 6 months) are disturbances in relationships with family or friends, usually stemming from negative comments about participation or misperceptions that the volunteer is infected.[635]

With respect to discrimination within the community, often the law often cannot intervene when the discrimination arises in purely interpersonal relations. This will mean that the need for cohort support will be more acute in this arena. The best defense would lie in the cohort providing education, and a participatory role to the population targeted for recruitment. This preparation should take place before recruitment begins and individuals are asked to consent. The consent process must nevertheless remind potential participants that discrimination is not limited to financial matters and that social discrimination may hurt and stigmatize just as badly.

All of this implies that consent should not be hastily obtained, but rather the participant should be afforded the time required to make a calm evaluation of his social and economic situation and arrive at a carefully deliberated choice. The sponsor and local research centre need to use the informed consent process to clearly define the nature, extent and limitations of the support they

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632 RP Strauss et al. Willingness to Volunteer in Future Preventive HIV Vaccine Trials: Issues and Perspectives From Three US Communities. *Journal of Acquired Immune Deficiency Syndromes* 2001; 26(1): 63.

633 Ibid.

634 T de Bruyn. Supra, note 27, at 21-4.

635 P Kahn. Vaccines at Durban: A Closer look. *IAVI Report* 2000; 5(4): 5-6 at 6.

are prepared to offer participants who suffer from social discrimination within their communities.

(iii) Discrimination Regarding Immigration

In *The Search for an AIDS Vaccine*, author Christine Grady, chronicles the case history of a "visiting professor at a US university with an AIDS Vaccine Evaluation Unit. In 1993, he volunteered as a "low risk healthy volunteer" for a phase I HIV vaccine trial sponsored by the National Institute of Allergy and Infectious Diseases. Sero-conversion occurred […]. This individual was accepted for a faculty position but was denied a visa by the U.S. Immigration and Naturalization Service (the "INS") because of his seropositivity."[636] The INS refused letters of explication from the principal investigators and would only accept a confirmation of a vaccine-induced test response issued from the CDC. Grady uses this story as an example underscoring "how difficult it can be for individuals to convince others that they are seropositive because of a vaccine, even with documentation."[637]

Canada has recently introduced routine testing of all prospective immigrants for HIV infection. For vaccine research, this shift in immigration policy and procedure is a matter of some concern. Within a decade it is quite probable that hundreds of thousands of people, the majority in developing nations, will have participated in HIV vaccine clinical trials. Some of the experimental vaccines may elicit a prolonged and complex immune response. How will the HIV vaccine-induced immune response be accommodated? If the gold standard for differentiating future vaccine-induced immune response from infection remains the expensive PCR test, who will bear these costs? Will Immigration Canada guarantee that it will make use of technology capable of identifying post infection vaccine endpoints indicative of a promising vaccine-controlled or attenuated clinical outcome? It would be a cruel irony if people requesting immigration to Canada in future were turned away because Canadian immigration policy is too blunt to take cognizance of the altruistic act of clinical trial participation and its medical consequences.

(iv) Discrimination Regarding Insurance

A question of key interest is whether HIV vaccine clinical trial participation, might adversely affect one's ability to procure insurance. As is the case in other for a, discrimination might conceivably occur because of the diagnostic test results that occur following vaccination:

- The insurer considers the simple fact of clinical trial participation to be indicative of significant risk. Participation in a clinical trial might be detected via a vaccine-induced signature appearing on an HIV test requested by the insurance company; or
- An erroneous laboratory interpretation of a vaccine-induced immune response might lead the insurer to wrongly conclude the applicant is HIV infected.

Obviously, if vaccine trial participation were to constitute an obstacle to insurance, participants should be advised of this possibility during the informed consent process.

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[636] C Grady. Supra, note 84, at 141.

[637] ID.

There are a number of key questions about possible discrimination re insurance that should be discussed in the informed consent process. For people who have participated in HIV vaccine trials, questions will arise firstly with respect to their ability to access insurance. Trial participants may also legitimately wonder whether their existing insurance coverage will cover health and disability problems and related damages resulting from an injury induced by an experimental vaccine. Moreover, will clinical trial participation threaten existing insurance coverage, or make it more difficult to renew coverage in future?

Erroneous Interpretation of Test results

With respect to the possible impact of an erroneous interpretation of test results, VaxGen Inc, sponsor of the AIDSVAX B/B Gp 120 phase III clinical trial in North America advises its participants:

> You will have access, whenever you wish, to tests that can distinguish HIV-1 infection from sero-conversion due to vaccination to ensure that a diagnosis of HIV-1 infection is correctly made. We strongly recommend that you use this service before applying for insurance [...] if HIV testing will be required to avoid potential discrimination because of a vaccine-induced HIV antibody response. In addition, to avoid or remedy social discrimination experienced by vaccine study participants who have positive HIV antibody tests done outside of the study, we offer specialized confirmatory HIV-1 testing. The results can be provided to insurance companies, [...] if you request it in writing.[638]

The problem with this approach is that nothing legally compels the insurance company to use the testing facilities of the vaccine clinical trial nor to accept its test results. In addition, disclosing his participation in the clinical trial may suggest to the insurer that he presents a statistically elevated risk of contracting HIV – particularly since there will be no indication whether the participant is in the vaccine or placebo control arm of the trial and there is no guaranty that experimental vaccine under study is efficacious. The assessment that trial participation equals significant risk allows the insurer to legally discriminate under exemptions permitted under Canadian human rights law. The result might adversely impact upon his ability to procure insurance, or if he can get insurance, increase the premiums he will have to pay.

Vaccine-Induced Injury

It is difficult to quantify the risks that stem directly from participation in an HIV vaccine clinical trial. These are certainly not the usual risk factors an insurer considers when deciding whether to offer coverage and what premiums to charge. There are few if any *a priori* reasons that would motivate an insurance company to cover an individual's damages that stem from participation in a clinical trial. A clinical trial is after all an experiment. The safety and efficacy of the candidate vaccine have yet to be conclusively proven. Thus, the risks inherent in participation may be material to the evaluation of risk for insurance purposes. In point of fact, most personal, collective and financial insurance, whether life insurance or policies covering income lost and costs incurred due to health and disability, will not cover losses incurred through medical experimentation.

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[638] VaxGen, Inc. Supra, note 629.

Such exclusionary clauses might have serious implications for a participant's ability to access business and partnership financing. A person considering to volunteer for a vaccine clinical trial would be well advised to update his insurance prior to consenting and verify whether his existing insurance would cover personal injury and losses generated as a result of the clinical trial.

Insurers will also tend to refuse to provide insurance and benefits for injuries induced by experimental vaccines because they occur entirely outside of the domains in which most policies are usually issued. This will certainly be true in the context of collective insurance policies offered within the workplace, since research related injuries have nothing to do with most types of employment nor with the normal daily course of an employee's life. Insurers will adopt the attitude that the clinical trial participant has voluntarily assumed the risk of vaccine-induced injury through a careful process of informed and comprehending consent. While the volunteer is free to do so, nothing obliges the insurer to also accept this risk. Indeed, the industry functions on the principle of risk-adverse management.

If the corporate sponsor of an HIV vaccine clinical trial is unwilling to cover long term financial damages (eg,- loss of income) incurred through vaccine-induced injury, there is little reason to expect that an insurer providing insurance in a milieu entirely removed from medical research will be willing to pick up this liability. And finally, if insurance benefits are paid for matters relating to vaccine-induced injuries they could be subject to extremely restrictive maximum caps and conditions designed to protect the insurer from uncertainty.

In summary, vaccine trial participation might be regarded by the insurance industry as: (i) a voluntarily assumed risk falling outside the purview of coverage; (ii) a pre-existing medical condition; or (iii) as an unwarranted and unacceptably high risk thus barring eligibility for insurance or just cause for contractually limiting benefits.

Access to Insurance

Is it likely that participation in an HIV vaccine trial will make it difficult for a volunteer to procure or renew insurance coverage?

At least in the initial era of vaccine research an affirmative response is likely. Most insurance litigation concerning HIV in Canada and in the United States has turned upon the issues of accessibility. In particular, the courts have been called upon to determine whether HIV infection that occurred prior to purchase of a policy constituted a pre-existing medical condition and whether this information was honestly conveyed to the insurer at the time when the policy was contracted. Classifying vaccination with an experimental HIV vaccine as a "pre-existing" medical condition, would have serious consequences for vaccinees faced with the necessity of periodically "renewing" important insurance contracts.

Consider the case of life and disability insurance contracted to guarantee payment of debts that are contracted for purposes of purchasing a house, or securing financing in business. The debt is re-negotiated periodically in order to allow the lender to hedge its risk against future fluctuations in interest rates. Often the renewal of the accompanying life / disability insurance contract is not so much a renewal as a purchase of an entirely new contract of insurance. If the insured has volunteered for a vaccine clinical trial since the purchase of the previous insurance, this may

constitute a pre-existing condition requiring that notification be given to the insurer when the mortgage is renewed and the new insurance purchased. Failure to advise the insurer of a pre-existing condition can nullify the contract, even if a subsequent claim is presented for reasons entirely unrelated to any vaccine-induced condition.

Every participant in an HIV vaccine clinical trial needs to inquire as to how porous the data storage will be. It is important to remember that both the contents of the informed consent in vaccine research and the contents of personal and commercial insurance policies are essentially non-negotiable contracts of adhesion. Typically, an insurance contract requires the insured to give the insurer free and open access to a broad range of personal medical files on a need-to-know basis. The participant should know whether his information and files are stored on a nominative or non-nominative basis.[639]

The principal factor in a vaccine trial that might influence an individual's ability to procure insurance is the selection criteria used to recruit the participants. If these criteria are designed to triage volunteers to successively focus upon a selection of those displaying the highest vulnerability to infection, then participation in the vaccine trial is likely to be a statistically significant predictor of risk. Phase III vaccine efficacy studies where recruits are specifically drawn from among the ranks of the most highly vulnerable participants in large-scale pre-existing seroincidence cohorts or from large-scale vaccine preparedness cohorts, will provide volunteers with exactly these high levels of risk. Discrimination on the basis of significant risk is legally permissible for the insurance industry. In addition, since personal and work-related insurance is unlikely to cover vaccine-related injury, sponsor pharmaceutical companies might have to consider contracting for such coverage.

Hence, on a fundamental level the risk avoidance objectives of the insurance industry, (applied to the volunteers involved in this early era vaccine clinical research), and those of public health which seek to promote HIV vaccine research and development, appear to be at loggerheads. Obviously, once initial data trickles in revealing vaccine efficacy and safety, the situation may radically change. Indeed, if in future an efficacious vaccine is marketed, people in high HIV seroprevalence communities may be unable to obtain insurance at an affordable premium unless they have been vaccinated. But in the meantime, clinical trial volunteers who are also potentially in the market for insurance may have cause for concern and the informed consent process needs to make sure that they can thoroughly consider all of these issues before signing up.

It is difficult for people to predict their future and even the most thoughtful and prudent volunteer who consents to an HIV vaccine clinical trial cannot predict with certainty his or her insurance needs in future. For this reason, it would be discriminatory and foolish to presume that participants, who do not need insurance today, will never need insurance over the course of their lives. A strong public policy statement issued jointly by industry, public health and researchers censuring insurance discrimination on the basis of vaccination and vaccine trial participation may have a positive instrumental effect. Corporate sponsors and governments can also explore possible means of purchasing or constructing insurance in order to compensate trial participants for injuries. And finally, participants should be encouraged to seek objective unbiased medical,

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639 Note: As a general rule, vaccine trial participants should always inform themselves as to whom (researchers, student researchers, government, police, public health epidemiologists, AIDS prevention researchers, genetic researchers, and insurance companies etc.) might be granted access to all or part of the personal information the cohort has collected. He should know whether or not he will have the opportunity to exercise separate informed consent when third parties seek access to data (nominative and non-nominative).

scientific, and legal advice and information to enable them to better determine the inquiries in their particular legal jurisdictions.

J. Consent and Compensation for Vaccine Trial-Induced Injury

This is also a subject that fits somewhat awkwardly into a chapter concerning informed consent. For even if some kind of medical and /or pecuniary compensation is to be provided to participants for injuries they sustain as a result of participation in a vaccine trial, obviously this protection will only come into play long after the individual is enrolled and has consented. Research however demonstrates that the issue of compensation for vaccine related adverse events is one of the most frequently posed questions when volunteers respond to a recruitment campaign. In this section we will briefly examine some of the issues surrounding whether compensation should be offered, who should bear responsibility for this compensation and how compensation should be described in the consent process.

1. Should Compensation Be Offered?

Qualitative research conducted with participants enrolled in American HIV vaccine preparedness studies indicates that research subjects engaged in a vaccine clinical trial will look to the sponsor, the principal investigator and the host research institute to ensure that they be well cared for should the experimental vaccine cause adverse events compromising health.[640] This is one of, if not the most important of their concerns. Essentially, the human subjects will want researchers to treat them, with the same standards of care as the researchers would apply to themselves if they were in a similar predicament.

In practice however, there may be a gap between these expectations and what the sponsor and researchers are willing and able to provide. Recruits would be well advised to carefully read the promises contained within the consent forms, ask clarifying questions when necessary, and reflect upon whether the promises of future care are legally enforceable. Recruits and community leaders may require legal advice as well as advice from independent government and research experts in order to ensure that their consent in this matter is truly comprehending.

As described in early parts of this chapter, failure to disclose risks can give rise to legal responsibility and recourses in the fields of tort law (negligence or battery) and in civil responsibility (Québec). It may even entail criminal responsibility. However, as we have also seen, the evidentiary burden of proving fault, injury and causation falls upon the injured participant. The record of successful jurisprudence is extremely thin. This is due in part to the fact that adverse events are sometimes unknown and unforeseen as phase III efficacy trials proceed. Therefore, although the legal basis for liability is the same, both the likelihood of claims and the probability that any such claims would succeed is far lower with respect to side effects arising from an investigational vaccine than with respect to a vaccine that has already been licensed and marketed.

In view of the dearth and difficulty of legal recourses for recovery of damages caused by adverse events induced by experimental vaccines, (and especially for those adverse events that were

640 SM Kegeles et al. Supra, note 313. See also HIVNET National Community Advisory Board. Supra, note 518, at 111-13.

declared at the moment of initial consent), perhaps other mechanisms should be put into place to provide easier access to compensation.

Are there other "no-fault" programs that could be put into place to compensate victims? If there are, should we make an eligibility distinction between risks which could not have been reasonably foreseen at the beginning of the clinical trial and those which were known or suspected and hence duly disclosed at the moment of initial consent? In the case of risks duly disclosed, it might be argued that the rare victim of such side effects should not have a right to compensation. After all, was he not "fully informed"? And did he not accept to run the risk of his own volition? For obvious reasons, the answers to these questions will be a key point of interest to potential volunteers considering enrolment in a vaccine trial.

If the researchers have "taken every precaution to avoid injury", and every precaution to disclose possible injuries, there will be "no evidence of negligence."[641] In such situations, the sponsor has no legal obligation to compensate for previously unknown and unforeseen injuries. The sponsor may however face an ethical obligation to do so.

Given the non-therapeutic nature of preventive vaccine research, the act of volunteering for an HIV vaccine trial appears less self-motivated and more altruistic than participation in a clinical trial of an experimental therapy. Some would argue that it is precisely because the participant stood to gain so little, that researchers and government are ethically obliged to take care of him when the result is serious harm.

> Quite apart from the problems of expense or uncertainty, he is entitled to believe he will be looked after in the event of something going wrong - and charity is unpredictable and often ungenerous as a remedy.[642]

Others however may use a descriptive discourse in the informed consent by which participants are described as "heroes" and "pioneers" in the fight against AIDS. This can be a disguised means to limit ethical and potentially legal liability:

> Heroes, […] are seen as willing volunteers who assume risks in order to accomplish a goal, ordinarily for someone else's sake. Since heroes are not supposed to seek any reward, there is no [ethical] obligation to compensate them. At the same time, society may wish to reward them voluntarily for their heroic efforts.[643]

Participants should therefore be suspicious of recruitment and consent language which overly emphasizes the heroic quality of their participation. They should interpret this as a double-edged sword and a warning sign to check the consent form for details concerning future compensation.

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641 JK Mason, RA McCall Smith. Supra, note 489, at 365.

642 ID.

643 W Mariner. Liability and Compensation for Adverse Reactions to HIV Vaccines. In *Adverse Reactions to HIV Vaccines: Medical, Ethical, and Legal Issues.* Washington DC: USGPO, September 1995, 79-146 at 82.

2. Who Should Bear Responsibility for Providing Compensation?

Thus, one of the key questions to be asked well in advance of the informed consent process is: Which of the parties to the research are best suited to absorb losses resulting from trial-induced injury? Should the burden be borne by industry, the state, the injured participant, or some combination of these parties?

Obviously, once physical injury becomes manifest, the physician who is the principal investigator is legally obliged to see that the participant receives prompt attention, and access to diagnosis, care and treatment. This obligation stems from his professional code of ethics as a physician. But in order to provide treatment for medical problems caused by an experimental vaccine, the site investigators and the treating physicians will require detailed scientific information from the sponsor. Moreover, harms may occur in a wide variety of fora with effects stretching well beyond the purely medical domain.

Occasionally, sponsors take it upon themselves to offer provision for limited care and treatment of injuries. This is usually stipulated in the terms and conditions of the consent form. For example, the consent form used in the AIDSVAX B/B Gp 120 phase III clinical trial in Montréal contains the following passage:

> **Research related injury:** "If you are injured or have a medical problem as a result of being in this study, treatment will be available, including any necessary emergency treatment and appropriate follow-up care. Any costs to treat medical problems directly resulting from the study vaccinations will be paid by VaxGen Inc. THESE COSTS WILL NOT INCLUDE THE COST OF ANY MEDICATIONS NEEDED TO TREAT HIV-1 IF YOU GET INFECTED DURING OR AFTER THE STUDY.[644]

Numerous questions will spring to mind when the volunteer reads this undertaking. A literal interpretation of the first sentence suggests that care will be provided in all cases where adverse events are related to trial participation. But in the matter of costs incurred, the second sentence appears to narrow the scope of this undertaking to apply only to costs used to treat medical problems caused directly by the experimental vaccine and not for instance, by the placebo.

Financial costs, such as lost income or wages or child care incurred during periods of vaccine induced illness, as well as other non-medical damages are not covered. The drafting of the VaxGen clause suggests that there will be no compensation for damages incurred simply by virtue of one's participation in the trial (eg,- social discrimination). The sponsor will not be responsible for the bigotry of others. This raises troubling questions about whether practical recourses exist elsewhere that could allow a victim of social discrimination to recover damages.

Additional problems can be anticipated if the participant is but one of a handful of people who suffer a very rare adverse event. It may be very difficult to prove a direct link of causation between an infrequent side effect and vaccination with the experimental HIV vaccine. The clause does not indicate who will be the final arbiter in a claim for reimbursement of care and treatment expenditures. Sometimes it requires vaccination of many thousands of people and many years of

644 VaxGen, Inc. Informed Consent form (English translation). Used at the Montréal site of the AIDSVAX B/B Gp 120 phase III clinical trial. Revised 10 December 1999, at 15.

post-marketing surveillance before rare, (but nevertheless serious) adverse events can be traced back to the vaccine. By this time the sponsor may be long ago dissolved.

The clause does not propose to compensate victims for loss of income, nor for loss of enjoyment of life. It is unlikely that the participant's private disability insurance would indemnify him for such damages, since the injury does not arise as a result of an accidental occurrence or work-related hazard, but rather as a result of a voluntary decision to expose oneself to "unnecessary" risks.

As for the exclusion of HIV related care from any proposed compensation, an uncomfortable and potentially unjust situation would arise if ever the experimental vaccine were to exacerbate vulnerability to infection and accelerate its clinical progress. Sometimes such unexpected results may only occur among specific sub-sets of cohort populations which are defined by such diverse factors as genetics, race, and environmental factors. [645]

Moreover, what does the promise contained in the AIDSVAX consent form really mean in the context of a Canadian publicly funded health care system? In the United States, the undertaking would carry considerable economic importance. However in Canada, the sponsor may escape liability because in the end, the public system will provide most of the care and treatment. Research institutions managing the local sites in Canada might insist that the company reimburse the public health care system for any costs incurred in caring and treating victims of vaccine-induced adverse events. However, the legal and organizational separation of the research institutes from public health insurance agencies means they may not always consider this to be a priority. And even if such an agreement were made, it would change little for the injured participant. In Canada, VaxGen would be responsible for supplementary health care costs incurred by the injured participant that are not usually covered under provincial public health insurance (eg,- some forms of home nursing care, medical equipment needed for home care, special prescription and non-prescription medications).

In view of its promise in the consent form, VaxGen would certainly be ethically obliged to share scientific and medical information concerning known adverse events and their possible treatments with local caregivers. A contractual engagement requiring the sponsor to share with on-site researchers information about known, discovered or suspected risks of adverse events should also be stipulated in the scientific protocol concluded between the principal investigator and the sponsor. However, information about adverse events is considered private intellectual property in Canada, and it is not clear that the company has any direct legal contractual obligation to provide detailed information directly to medical care teams operating outside of the network of clinical trial sites. The data safety and monitoring board should in theory fulfil this role.

A legal recourse would also lie through the participant litigating to enforce the promise to provide "care and treatment". An injured participant might attempt to use this clause in support of litigation against the sponsor, however problems of privity of contract may pose significant obstacles to successful litigation.

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[645] For example, see RF Breiman et al. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for vaccine HIV-infected patients..*Archives of Internal Medicine* 2000; 160(17): 2633-38.

Several authors take a dim view of any proposal to use informed consent to relieve sponsors from the need to compensate for trial-induced injury. Their analysis is based upon the basic principle contained in the introduction to the *Declaration of Helsinki*: "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society."[646]

Author Stephen Guest for example argues that research ethics boards should police proposed consent procedures and interdict those which seek to obtain the subject's waiver of a right to compensation.[647]

> [A] subject's informed consent to participate should not limit his access to due compensation, as it is not appropriate to balance his right not to be harmed – particularly as a volunteer subject – against the benefits to society of the research of which he is a part. In a research climate that seeks to protect researchers rather than subjects, Guest prescribes that research ethics committees deny proposals that do not contain legally enforceable compensation mechanisms for healthy volunteer subjects.[648]

3. Ethical Guidelines Support Compensation for Harms from Non-Therapeutic Research

There are strong ethical arguments and many elaborated ethical guidelines supporting compensation for people harmed by their participation in an HIV vaccine trial.

Commenting upon the notion of providing compensation to those who receive an eventual licensed vaccine and unfortunately suffer from vaccine-induced injury, Wendy Mariner of the Boston University School of Medicine and School of Public Health notes:

> Society might feel an ethical obligation to compensate those who take an HIV vaccine in an effort to abate the epidemic. Even if society does not feel an ethical obligation itself, it might conclude that compensation is nonetheless desirable as a means of rewarding those who suffer adverse reactions in an effort to abate the epidemic.[649]

Mariner thus admits that arguments for compensation can be built upon both ethical and more self-interested grounds. The ethical argument is built in part upon recognition of the fact that even with a licensed vaccine, the act of vaccination includes an important public health component that benefits not merely the person vaccinated, but the entire community where people are vulnerable to infection. This quality of acting in the public interest is proportionately

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646 World Medical Association. Supra, note 101, at Arts. 5 and 29. See also NE Kass. Supra, note 616 at 65.

647 S Guest. Compensation for Subjects of Medical Research: The Moral Rights of Patients and the Power of Research Ethics Committees. *Monash Bioethics Review* 1998; 17(1): 4-10.

648 E DeVaro. Annotation of S Guest. Compensation for Subjects of Medical Research: The Moral Rights of Patients and the Power of Research Ethics Committees. *Monash Bioethics Review* 1998; 17(1): 4-10. In *IRB -- A Review of Human Subjects Research;* March-June 1998: 15.

649 W Mariner. Supra, note 644, at 146.

accentuated in clinical trials of experimental preventive vaccines, given that the efficacy of the experimental vaccine and hence its direct benefit to the participant is still unknown.

The self-interested arguments evoke more mercantile notions of "reward." But it is also important to recognize that the sponsor may also derive benefit from providing volunteers with a financial and medical remedy in the event of damages. The company's reputation will be enhanced and this will make it easier for the sponsor to recruit people to successive clinical trials.

The net effect of these ethical and "good will / self-interested" arguments in favour of compensating, is that the parties involved in clinical vaccine research should at least make and effort to explore ways of shifting at least a portion of the burden away from these altruistic volunteers to those with deeper pockets more capable of providing real compensation. For the most part, the international codes of research ethics seem to agree that compensation is desirable particularly when the harm incurred is a direct result of the medicinal intervention that is the subject of the clinical trial.

For example, Guideline 13 of the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* stipulates:

> Research subjects who suffer physical injury as a result of their participation are entitled to such financial or other assistance as would compensate them equitably for any temporary or permanent impairment or disability. In the case of death, their dependants are entitled to material compensation. The right to compensation may not be waived.[650]

Commentary on Guideline point 13 of the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects* classify such compensation as "equitable", rather than merely a policy of mutual self interest for researchers and research subjects. The commentary however makes a distinction between adverse events in non-therapeutic scientific research where it advocates strongly in favour of compensation and foreseeable side effects from investigational therapies for which they make no compensatory provision.

> Compensation is owed to subjects who sustain significant physical injury from procedures performed solely to accomplish the purposes of research. Justice requires that every subject of biomedical research be automatically entitled to fair compensation. [....]
>
> When, as in the early stages of drug testing it is unclear whether a procedure is performed primarily for research or for therapeutic purposes, the ethical review committee should determine in advance the injuries for which subjects will be compensated and those for which they will not: prospective subjects should be informed of the review committee's decisions, as part of the informed consent process. [....]

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650 Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization. Supra, note 367, Guidance Point 13, at 30.

> Subjects should not be required to waive their rights to compensation or to show negligence or lack of a reasonable degree of skill on the part of the investigator in order to claim compensation. The informed consent process or form should contain no words that would absolve an investigator from responsibility in the case of accidental injury, or that would imply that subjects would waive their legal rights, [...].[651]

In a similar vein, Guidance Point 9 of the *Ethical considerations in HIV preventive vaccine research* states:

> Potential harms: The nature, magnitude, and probability of all potential harms resulting from participation in an HIV preventive vaccine trial should be specified in the research protocol as fully as can be reasonably done, as well as the modalities by which to address these, including the provision for the highest level of care to participants who experience adverse reactions to the vaccine, compensation for injury related to research, and referral to psycho-social and legal support as necessary.[652]

The association of the British Pharmaceutical Industry recommends to its members that compensation be paid "when, on the balance of probabilities, the injury was attributable to the administration of a medicinal product under trial *or any clinical intervention or procedure provided for by the protocol that would not have occurred but for the inclusion of the patient in the trial*."[653] [Emphasis added] It is interesting to note that Canada's research-based pharmaceutical industry has not adopted a similar industry-wide guideline.

In the end however, these ethical guidelines are just that - mere guidelines without the binding authority of law. It is true that elements of *The Declaration of Helsinki* and of *The Nuremberg Code* occasionally find their way into the body of Canadian case law dealing with informed consent to biomedical research. But for the most part, the arguments in favour of a no-fault, non-tort compensation are primarily ethical rather than legal.

Elements such as financial losses due to social discrimination are not part of traditional medical practise. Social harms are probably much more difficult to precisely predict and describe than are possible medical adverse events. Warnings contained in the informed consent will necessarily tend to be somewhat vague and general. Here, once again, the case for warning and compensation is largely ethical and partly legal. The literature increasingly identifies a positive duty to warn of the possibility of non-medical "social" harms. This is interpreted as an extended manifestation of the physician's legal responsibility under the doctrine of informed consent as stipulated in various statutes, case law and by professional codes of conduct. At a strict minimum, the volunteer will be entitled to the clearest possible information concerning both potential medical and non-medical adverse events and the extent to which he will be compensated and supported for these.

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651 Ibid, Commentary on Guidance 13, at 30.

652 Joint United Nations Programme on HIV/AIDS. Supra, note 10, at Guidance Point 9.

653 *The Association of the British Pharmaceutical Industry Clinical Trial Compensation Guidelines* (1991).

The above-cited ethical guidelines do not absolutely require the sponsor to bear 100 percent of the burden of compensating people injured by the experimental vaccine. Instead, they bear witness to a strong current of analysis suggesting that the sponsor must, at the very least, occupy a central role in coordinating the provision of compensation for vaccine trial-induced injuries.

The following statement is included in the notes to this guidance point:

> The sponsor, whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, to provide compensation for any physical injury for which subjects are entitled to compensation. Sponsors are advised to obtain adequate insurance against risks to cover compensation, independent of proof of fault.[654]

It is generally conceded that a no-fault compensation scheme should not cover instances in which injury results from the negligence of the sponsor.[655] Examples of such negligence might include the provision of insufficient information to principal investigators concerning foreseeable risks of adverse events, improper design and explanation of protocols and procedures; and deliberate concealment or manipulation of data concerning side effects or efficacy. By leaving the legal liability recourses intact in such matters, the law can be used as an incentive to reinforce quality in investigative research.

4. Is Compensation a Deterrent to Research?

One problem in seeking to hold the corporate sponsor solely responsible for compensating victims for their vaccine trial induced harms, is the possibility that this might deter industry from investing in vaccine research. It is frequently said that profit margins are relatively thin in the field of vaccine research, development and delivery when compared to the profits realized from developing new therapeutic medications. Most preventive vaccines are limited to one or a very few doses. This restricted number of administrations translates into a limited number of sales in which the company can try to recoup its investment and earn reasonable profits. Thus the price of a vaccine is often significantly higher than that of an individual dose of a long-term therapy. But the consumer's ability to pay higher prices for the vaccine is not unlimited. In view of this, the pharmaceutical research and development industry can be expected to react adversely to any proposal such as compensation for vaccine-induced injuries which might augment costs in a branch of pharmaceutical research in which profit margins are already relatively squeezed.

> There will be a need to protect manufacturers from liability if small innovative corporations without much capital are to be involved in the research process. Yet at the same time it is necessary to make sure that they do not take unnecessary risks and that they adhere to scientific standards.[656]

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654 Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization. Supra, note 367, Commentary on Guidance 13, at 30.

655 AJ Arnold. Developing, testing and marketing and AIDS vaccine: Legal concerns for manufacturers. *University of Pennsylvania Law Review* 1991; 139: 1077-1121.

656 RE Stein. *Adverse Reactions to HIV Vaccines: Medical, Ethical, and Legal Issues*. Washington DC: USGPO, September 1995.

Already, there has been some evidence in the record of distribution of licensed childhood vaccines, that industry has been sensitive to the risks of legal liability to vaccine-injured recipients. As early as 1967, manufacturers in the United States began to pull out of the childhood vaccination market. By early 1984, there were alarming shortages of supply in the US. Drug manufacturers chose to leave the vaccine market for a number of reasons. Among the most common reasons cited were: the small market for vaccines; the high cost of entry into the market with a new product; and skyrocketing litigation costs and damage awards for injuries resulting from the use of childhood vaccines.[657] In response to this worrisome situation, the US government adopted the "National Vaccine Injury Compensation Program."[658] In the event of medical adverse events, this fund offers financial compensation up to pre-set limits for: (i) medical and rehabilitative care; (ii) death benefits; (iii) loss of earnings; and (iv) pain and suffering.[659]

A further example of industry sensitivity to the economic threat posed by potential adverse events can be seen in the history of the swine flu vaccine developed in 1976, to combat an anticipated epidemic in North America. A vaccine was developed but the insurance industry refused to insure the vaccine manufacturers, and the manufacturers in turn, refused to dispense the vaccine without insurance coverage.[660]

Insurers were "primarily reacting to a court decision in the case of *Reyes* v. *Wyeth Laboratories*."[661] In that decision, the court held that failure to warn consumers of potential harms by means of a package insert addressed directly to consumers constituted a product defect and could give rise to a manufacturer's strict liability. The swine flu was a new pathogen and there was an unusually high degree of scientific uncertainty concerning both the virus and the projected efficacy of the vaccine. There was also considerable uncertainty concerning the potential for infrequent adverse events (conditions not dissimilar to the distribution of a hypothetical first anti-HIV vaccine). Ultimately, the American government accepted liability for injuries and the vaccine was released. Unfortunately the vaccine caused Guillian-Barré Syndrome in a small but significant proportion of vaccinated individuals resulting in approximately 4,000 claims for indemnification and 1,600 lawsuits.[662] This experience demonstrates that industry can be extremely sensitive to the risks of claims for compensation and litigation. The case also stands for the proposition that any party (sponsor or government) should be wary of accepting unlimited liability when information is incomplete and the risks are not fully known.

Unlike potential liability arising from undetected risks when a licensed and manufactured vaccine is broadly distributed in a public vaccination campaign, the risks inherent in an efficacy trial are significantly higher. But at the same time, the number of potential victims, is much more limited. If the laboratory and early phase clinical research has been carefully conducted, the probability of widespread, serious adverse medical events occurring in a phase III efficacy trial are diminished. Moreover, the number of participants in the trial is strictly controlled and risk-

657 WH Smith III. Supra, note 586 at 224-5, 238-9.

658 42 USC §§ 300aa – 10 to 33.

659 WH Smith III. Supra, note 586 at 226.

660 Ibid at 220.

661 *Reyes* v *Wyeth Laboratories*, 498 F.2d 1264 (5th Cir), cert. denied, 419 US 1096 (1974). Cited in: WH Smith III. Supra, note 586, at 220.

662 WH Smith III. Supra, note 586, at 221-2.

management estimates can therefore be conservatively estimated well in advance. Imagine that an experimental vaccine causes a serious adverse event that becomes evident over the medium term. Let us further imagine that it occurs in two per cent of vaccinated individuals. In an efficacy trial involving 6,000 participants, two-thirds of whom receive the experimental vaccine, the number of people requiring care and treatment will be relatively small (eg,- only 80 individuals). This may represent a manageable risk for the sponsor who could possibly obtain insurance covering compensatory expenditures should they be necessary.

5. Alternatives to Having Sponsors Bear the Burden

The sponsor need not be the sole party to bear the financial burden resulting from a decision to provide compensation to injured participants. But it is the sponsor's ethical responsibility to take a lead in this question and to make sure that the informed consent process clearly explains whatever policy is ultimately adopted. Many participants do not realize that an undertaking limited to provision of "treatment and care" necessarily implies that the burden of any personal financial losses due to loss of income earning potential is assumed solely by the participant. Instead of communicating these limitations by relying upon interpretative principles stemming from creative omission, the consent form should make them explicitly clear.

One alternative might be to provide some sort of no-fault insurance plan offering compensation up to pre-set limits for vaccine trial-induced injuries. Such a plan could be financed partly by industry and partly by government. Thus, all three parties would effectively bear a portion of the risk. The participants contribute by agreeing to limit their rights to claim compensation to the maximum amounts set out in the policy. In this way, if the risk is spread among all parties, it becomes more manageable. Such a plan would offer a certainty of indemnification to participants who are not forced to prove that the sponsor or principal investigator has behaved negligently or with any degree of civil fault. In exchange for this certainty, participants accepting compensation could be asked to waive their litigious rights (except in cases of gross negligence and malevolence). Alternatively, if they do litigate, the fund could be reimbursed from the amounts awarded in court to the limit of the indemnification the fund has already paid to the participant.

Both Québec and California are jurisdictions that offer no-fault indemnification to persons injured by vaccines distributed in wide scale public vaccination campaigns.[663] Indeed, the United States offers its children and youth a national compensation program for injuries occurring from licensed childhood vaccines.[664] California however has gone much further by legislating the details of a no-fault compensation program specifically for persons injured by experimental HIV vaccines used in clinical trials.[665]

The Québec fund is limited to licensed vaccines and was created under the province's *Public Health Protection Act* [666] following the decision in the case of *Lapierre* v. *Attorney General of*

[663] *Loi sur la Protection de la Santé Publique*, LR Q, c. P-35. *The National Childhood Vaccine Injury Act:* 1986, section 2125 of the *Public Health Service Act*, 42USC 300aa-(Suppl. 1987). See also: Update: Vaccine side effects, adverse reactions, contraindications and precautions. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* 1996; 45 (RR-12); 1-35.

[664] *The National Childhood Vaccine Injury Act*. Supra, 664.

[665] *California Health and Safety Code*, Sections 121250-121280.

[666] *Loi sur la Protection de la Santé Publique*, LR Q, c P-35.

Québec.[667] In that case the plaintiff developed encephalitis after receiving a combined vaccine for measles, mumps and rubella. The vaccine was offered in a heavily promoted public school vaccination campaign run by the public health authorities. The manufacturer was found to have provided adequate warning to its client (the provincial government) and the latter was found to have exercised sound professional discretion in choosing not to advise people of an extremely rare adverse event. In light of the subsequent Supreme Court of Canada jurisprudence cited earlier in this paper, and given the seriousness of encephalitis, it is doubtful that the court would come to the same decision today. But at that time, neither defendant was found liable. The plaintiff had tried to argue that the quasi-necessity of childhood vaccination would create a countervailing obligation on the part of the government to compensate for vaccine-induced injury. The court denied this recourse finding that, barring express legislation stipulating strict liability, a general civil liability could not exist in Québec without a finding of fault. The plaintiff was left facing a devastating adverse event, without any financial assistance. In response, the Québec government legislated a compensatory no-fault fund for victims of adverse events arising from their participation in this kind of public vaccination campaign.

In both California and in Québec, the legislators through these funds implicitly recognize that some vaccines will be "unavoidably unsafe" in an extremely small minority of those vaccinated. A small number of people will inevitably suffer adverse events but the overall benefits to public health are deemed to be so overwhelmingly positive that society chooses to proceed with vaccination while compensating the few who are harmed. It seems ironic however, that a person can be indemnified for damages incurred from a product that in theory presents much less risk than one undergoing testing in an efficacy trial. The irony stems from the fact that the people who volunteer for non-therapeutic vaccine research have little to gain and typically much to lose. After all, preventive vaccine clinical trials recruit healthy uninfected volunteers. And it is through the altruism of these volunteers that the public delivery of the vaccines covered by the public indemnification plans is ultimately made possible.[668]

Creating a no-fault, non-tort compensatory fund applicable to HIV vaccine clinical trials would have many advantages. If access is determined by a schedule of side effects and corresponding pre-set levels of compensation, it will be comparatively easy to administer. In addition, it should provide for relatively rapid recovery. For the participants, legal costs will be kept low. For industry, the risks inherent in vaccine development are reduced and more easily evaluated in advance. This should be reflected in lower prices for licensed vaccines. [669] If managed as a trust fund, excess income may be generated which could be invested in further research initiatives.

On the other hand, such a no-fault insurance scheme does have some drawbacks. If the indemnities are awarded according to a schedule of inflexible amounts, and if the severity of the injuries suffered varies, (even with respect to the same kinds of injury), then some people who are relatively uninjured will receive "windfalls" while others who are more severely injured may receive too little.[670] The money for such a no-fault fund could be raised through government contributions and levies on industry in the form of an excise tax on marketed vaccines, or by the posting of financial guarantees by sponsors themselves. But setting aside money today for a

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667 *Lapierre* v *Attorney General of Québec*, [1985] 1 SCR 141; (1985), 16 DLR (4th) 554.

668 W Mariner. Supra, note 644, at 146.

669 Note: For a thorough discussion concerning various potential compensation schemes for vaccine acquired adverse events see W Mariner. Supra, note 644, at 123-25 and more generally at 123-46.

670 WH Smith III. Supra, note 586, at 243.

problem that may not even occur tomorrow has an opportunity cost. To the extent that the research industry is expected to contribute to the fund, this cost will ultimately be factored into the cost of a final vaccine. Moreover, as research gets underway it will be difficult to set a precise premium for the insurance fund "because unknown risks make premium calculations difficult."[671] If unexpected side effects turn up, the size of the contributions necessary to maintain the compensation fund may have to be increased while the amount of indemnities it offers may have to be decreased in order to ensure the fund can meet demand and remain solvent.

In addition, it is doubtful, that there would be much public support for an indemnification fund that limits its beneficiaries to victims sustaining injuries in one specific type of research (eg,- HIV vaccine clinical trials). For reasons of fairness, it would be difficult to justify such expense for this research but not for similar injuries sustained in other types of clinical trials.[672] A distinction could perhaps be drawn along the line of therapeutic experimentation versus non-therapeutic experimentation, but the fund would most likely have to be generally available to all persons injured in the latter type of research and even that proposal might be controversial.

In considering the issue of compensation for injuries sustained from an eventual licensed HIV vaccine, Wendy Mariner notes:

> A compensation program cannot guarantee that important research will be done, that new products will be brought to market, or that any new products will be affordable to those who need them.
>
> This is not to suggest that a compensation system should not be considered. But a compensation program can and should be adopted on its own merits. [….]
>
> It will be especially important to consider why people who have adverse reactions to a vaccine to prevent HIV infection or progression to AIDS should receive special compensation when people who have adverse reactions to drugs like Zidovudine, ddI, and ddC, do not. Special compensation for HIV-negative people may give the appearance of social indifference to the needs of people living with HIV infections. A public debate about the justification for compensating special injuries may offer a valuable opportunity to reconsider the ways in which responsibility for injuries and illnesses of all kinds should be allocated.[673]

Although these words were written envisaging a program of compensation in the context of vaccine delivery, it does not take a great leap of faith to also find them pertinent to any proposals to provide compensation in the research context. Can the therapeutic – non-therapeutic distinction really solve this debate? Or, (more reasonably), is a more general public consultation and compensation scheme for research participants required?

And finally, it must be remembered that the threat of litigation and of judgements awarding large amounts of pecuniary damages acts to deter an exaggerated assumption of risk in clinical research involving human subjects. The law and civil liability act as a protector of public health

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671 Ibid at 241.

672 W Mariner. Supra, note 644, at 127.

673 Ibid, at 146.

and more particularly of the health and safety of research subjects. Removing this control, and encouraging government to assume the lead role in compensation insurance schemes could amount to governments becoming the re-insurer of risks in an industry which would not longer fear liability in court.

> If deterring unsafe products and services continued to be an important social goal, additional mechanisms would be needed, such as regulation of [vaccines and research] services, or requiring providers of [experimental vaccines] to help finance the program in accordance with the proportion of injuries attributed to their products.[674]

[674] Ibid, at 128.

6. Conclusion

The new genetic technologies creating DNA vaccines, genetically modified vectors for antigen delivery as well as slow but continuing research in the field of live attenuated and whole killed HIV vaccines, may very well raise the stakes in vaccine research by increasing associated uncertainty and potentially risks. The decision as to what type of compensation (if any), should indemnify trial participants is not a decision that can be made at the level of individual informed consent. It is a policy decision that needs to be made by regulators with input from community, researchers and industry. But resolving these issues would require collaboration and contribution from both industry and government at a moment in history when both parties are generally disinclined to support new forms of social indemnification. At the present time, Canada is not even close to contemplating this issue.

In the meantime, volunteers responding to recruitment for a vaccine clinical trial should pay close attention to the issue of indemnity in the informed consent. Vague general promises to pay for care and treatment are unlikely to amount to much. They are at best only an extremely partial palliation of a potentially serious problem. Indeed they may amount to nothing more than access to the public medical system to which the volunteer already has access whether or not he consents to participate in the vaccine trial. The volunteer needs to carefully consider the impact of possible adverse events upon his personal situation and quality of life. He should not hesitate to address questions to cohort staff and might even seek legal advice concerning interpretation of any promises of compensation. Hard questions need to be asked of industry, government and community advocates in determining whether or not the proffered safety net is solid or full of holes.

PART 3: VACCINE DELIVERY

Discovery of an HIV vaccine will not necessarily lead to vaccine delivery in Canada. Moreover, even if a vaccine is made available to Canadians, there is no guarantee that it will reach those who are most at risk of contracting HIV. In this final part of the paper, we examine why vaccine delivery might prove to be a significant challenge to public health authorities and communities affected by HIV. To do so, we look at some past examples of incomplete vaccine coverage in both this country and in the United States and we examine these records with regard to the many obstacles that have stood in the path of effective delivery and uptake. We also state the case for elaborating and preparing a strategy for HIV vaccine delivery well in advance of licensing. Finally, we refer to Canada's potential role in a global HIV vaccine delivery strategy.

I Lessons from History: Discovery Does Not Equal Delivery

Examples of incomplete vaccine delivery, briefly described below, illustrate some of the impediments to vaccine delivery. These impediments allow one to contemplate some of the difficulties that will have to be faced when the time comes to deliver an anti-HIV vaccine.

The recent record in North America concerning the delivery of long-standing routine vaccines with generally high levels of efficacy and safety, and the corresponding records concerning the comprehensiveness of vaccine uptake in targeted populations, demonstrate that there is room for considerable improvement.

A. Childhood Vaccinations

Records of infant vaccination (aged 0 to 2 years) with standard vaccines (diphtheria toxioid, tetanus toxoid, pertussis, measles, and Hib) in Canada demonstrate quite high levels of coverage.[675] But they are far from perfect. Indeed infant vaccine coverage for measles, polio, diphtheria, and Hib remain below national target levels. The recent histories of childhood vaccination in both Canada and the United States show that important weaknesses can exist in

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675 Health Canada. Supra, note 312.

both the maintenance of a public health data base capable of accurately determining overall rates of vaccination and in actual vaccine coverage and uptake. Data from the United States is contradictory, but some authors conclude that "[a]pproximately one third of the four million infants born annually in the United States do not receive all of their recommended immunizations by age 2 years"[676]

B. Adult Vaccinations

There are important sub-groups in the North American population which, for a wide variety of reasons, do not readily access vaccines. Overall, roughly 70,000 people die annually in the United States from vaccine-preventable diseases and "[i]mmunization rates [...] differ substantially within different geographic areas and socio-economic groups."[677] Delivering a vaccine and convincing people in targeted communities to get vaccinated appears to become more difficult with increases in the scheduled age for optimal vaccine delivery.

In Canada, vaccination coverage rates decline abruptly from infancy to adolescence to early adulthood. For example, adolescent booster vaccination coverage for diphtheria and tetanos toxoid in a suburban setting near Montréal has been reported to be as low as 50 percent. Highest coverage was obtained when vaccines were made available in a school setting on a class by class basis.[678] "A national survey of vaccine coverage in the Canadian adult population aged 18 years and over showed [...] rates of [only] 6% for tetanus and diphtheria."[679] Although coverage levels vary from province to province reflecting different levels of public health funding and different priorities, the overall trend towards lower rates of coverage with increasing age at delivery remains constant. Some of this may be due to factors such as increased mobility, geographic and economic dispersion, and a culture in which vaccination is traditionally seen as something reserved for children, the elderly, and the chronically ill.

If initial HIV vaccines are only able to offer a temporary immunity which decreases over time, or if they require multiple booster dosages scheduled many years apart, then vaccination of young adults outside of the setting of educational institutions will require a determined effort.

C. Influenza Vaccination in the Health Care Professions

676 L Gostin, Z Lazzarini. Supra, note 376, at 1793. And cf. Health Canada. Supra, note 312.

677 L Gostin, Z Lazzarini. Supra, note 376, at 1793. See also JM Schrof. Miracle Vaccines. *US News & World Report* 1998; 125(20): 57.

678 L Perron. Couverture vaccinale du vaccine d2T5 chez les adolescents de 15ans rèsident en Montèrègie. Prévention 2000: La santé publique en éclosion, 8e colloque provincial en maladies infectieuses. Hull Québec, le 12 mai 2000. Conference program, 149.

679 Health Canada. Supra, note 312.

Even among the medical professions, rates of vaccination can be surprising low. Researchers from the Cambridge Hospital / Harvard Medical School analyzed data collected in 1997 from interviews with 2,204 American healthcare workers as part of the "National Health Interview Study". Despite the fact that most American hospitals offer annual influenza vaccines to health care workers free of charge, the vaccination rate among hospital workers was only 38% while the rate among healthcare workers in other settings was 32.8 percent. Approximately 28 percent of workers in other industries were vaccinated.[680]

In some health-care networks in Canada, the situation is even worse. In the winter of 1998-99, the Regional Health Board administering the Montérégie health care district in Québec instigated a flu vaccine delivery strategy aimed at vaccinating health-care workers in hospitals and long term chronic care facilities. This district includes the Montréal suburbs on the south shore of the St. Lawrence river and with a total population in excess of 1.2 million, it is the most populous of Québec's 17 regional health care districts. Forty institutions (approximately two-thirds of the establishments in this particular region) participated. Health care facilities were offered i) a free supply of vaccine for delivery free of charge to employees; ii) money to finance vaccine promotion; and iii) training for the nurses charged with implementing the delivery strategy in each institution. A variety of both vaccine promotion and delivery strategies were used by participating establishments. These included providing a wide variety of opportunities for employees to make appointments for vaccination; personal reminders and follow-up to incite employees not yet vaccinated to get vaccinated; extended vaccination hours in the offices providing employee health services; "vaccine patrols" designed to reach employees in the workplace by raising awareness of the campaign and encouraging participation. The campaign lasted for eight days but despite these efforts, vaccine coverage reached only 31 percent in participating institutions and 19 percent in non-participating institutions. It should be noted that this was substantial increase over the figures of 10 and 13 percent respectively from the year before. Nevertheless, these levels of coverage are much too low to significantly prevent influenza transmission in hospital and chronic care settings.[681]

Barring an exceptional case such as the Spanish flu epidemic of 1919, influenza in otherwise healthy working aged adults is rarely fatal. Vaccinating employees in health care settings, is primarily designed to maintain an active labour force in the event of a flu epidemic and to protect those patients in whom influenza might become a severe illness or even a cause of death (i.e.- the elderly, the chronically ill and the immune suppressed). The inability to convince high percentages of health care workers to undergo vaccination may in part be due to the fact that they do not consider the flu to be a serious enough illness to warrant the inconvenience of vaccination. It may also mean that North Americans are reluctant to accept personal administration of a pharmaceutical product for the relatively remote benefit of preserving the collective public health.

In 1999, the head provincial epidemiologist for the Ontario Ministry of Health , Dr. Monkika Naus, stated that "her office [was] becoming increasingly concerned about an anti-vaccination

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680 MM Pennell. Many Healthcare Workers Do Not Receive Flu Vaccination. *Reuters Medical News* 15 May 2000.

681 M Blackburn et al. Supra, note 312.

movement within health-care professions, especially in long-term care facilities and hospitals."[682]

> A lot of health-care workers [like others in the public] are under the impression that watching what you eat, exercising properly, sleeping well (and) maybe taking some herbal remedies is at least, if not more, important in fighting infectious diseases as immunization.[683]

These rather disappointing indices point to a greater need for vaccine education among health care professionals in Canada and an increased emphasis upon not merely the individual benefits of vaccination but also upon the individual's responsibility to help maximise public health benefits. Admittedly, such "healthy living without vaccination" attitudes are much less likely to prevail with respect to a vaccine against an infection as virulent and pathological as HIV. Nevertheless, any movement towards increasing disaffection with vaccination, ill founded notions of invulnerability to infectious diseases, or disengagement from notions of collective responsibility in the health care professions should be cause for concern.

Perhaps the more salient question to be asked is: if we are unable to attain high levels of vaccine coverage with a vaccine as mundane as the influenza vaccine within the health care professions then what hope is there of attaining high levels of coverage with an HIV vaccine first in the marginalised populations vulnerable to that infection and subsequently among the public at large?

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682 P Rich. Anti-vaccine trend gaining momentum: Misconceptions of health-care workers, public, thwarting immunization plands. *The Medical Post* 1999; 35(31): 1 at 55.

683 ID.

D. Measles Vaccine

There can be many causes for disaffection even with very long standing vaccines. Large scale public health vaccination campaigns can render a given disease almost invisible and if vaccine efficacy and coverage are sufficiently high, those who are not vaccinated may simply escape infection as the overall prevalence of the disease declines. These "free riders" might subsequently adopt relatively lax attitudes concerning future vaccination for both themselves and their own children. Canadians may thus become complacent and indifferent to the need for vaccination, when an infectious disease is no longer visibly prevalent in our society. However, if the disease is not eradicated rapidly on a global scale, then the threat of a resurgent epidemic will remain whenever a significant proportion of the vulnerable population is not vaccinated and humans travel to and from the regions in which the disease is still endemic.

A recent example of the public health dangers resulting from low levels of vaccine coverage was the case of a measles epidemic which re-emerged among unvaccinated children in the United States in the mid 1980s. That this outbreak occurred at all is striking given that: (i) the US is one of the wealthiest nations on Earth; (ii) the country has clear medical recommendations for childhood measles vaccinations; (iii) the measles vaccine has a proven track record of efficacy and strong relative safety; (iv) the vaccines have been widely available to the public in that country for several decades. Complacency, practical obstacles to accessing vaccine distribution points and some fear of very infrequent but potentially serious adverse events may have combined to contribute to declining rates of childhood vaccination which ultimately permitted the re-emergence of measles. There were some extremely rare cases of infant mortality associated with high titre measles vaccines used in the 1980s and early 1990s.[684] However, the epidemic among unvaccinated American children in the mid 1990s involved 50,000 cases of measles, 11,000 hospitalizations and 130 deaths.[685] The prevalence of these measles cases among unvaccinated children greatly exceeded (both in terms of frequency and morbidity) the potential for vaccine induced adverse events had these individuals been vaccinated. But even after corrective public health measures were taken, rates of pre-school measles vaccination in the United States remained and continue to remain well below target levels.

Without access to comprehensible scientific information about the possibility of resurgent epidemics, individuals will make empirical assessments of public health risks in their surrounding communities. They may erroneously conclude that the probability of contracting a disease such as measles and the attendant risks of morbidity are lower and less important than the risks of vaccine induced adverse events. Ironically, this kind of evaluation is contingent upon high rates of vaccine coverage in the surrounding community. In essence, those who opt out do so because they count upon others around them to be vaccinated - something called "herd immunity."[686] This can be a very dangerous strategy if too many people opt to become such "free riders" and if public health databases of vaccination are too incomplete to sound an alarm when coverage levels become dangerously low.

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684 BJ Ward. Vaccine adverse events in the new millennium: is there reason for concern? Citation from article abstract: *The International Journal of Public Health (Bulletin of the World Health Organization)* 2000; 78(2): 205-14 at 208. Which cites Expanded Programme on Immunization: Safety of high-titre measles vaccines. *Weekly Epidemiological Record* 1992; 67: 357-61.

685 L Gostin, Z Lazzarini. Supra, note 376, at 1793.

686 Editorial. Responsible Canadians should be pro-vaccine. *The Medical Post* 1999; 35(31): 16.

Canada also experienced its share of measles epidemics in the late 1980s notably in the maritime provinces (1985 and 1986), in Ontario (1986), in British Columbia (1986 and 87); in Manitoba (1986); and in Québec in 1989. In the case of Québec alone, more than 10,300 cases were reported with four deaths directly attributable to measles and more than fifty deaths attributable to secondary complications resulting from an initial measles infection. This was the worst outbreak of measles in more than thirty years, and resulted from low levels of vaccine coverage despite the fact that the vaccine with a 90 to 98 per cent preventive efficacy had been available to school children free of charge for many years.[687] Again in 1995, just a few years after Americans and Canadians had experienced the above mentioned outbreaks of measles, insufficient vaccine coverage among young children in specific communities in Canada again permitted endemic outbreaks of the disease in this country.[688] This time, the outbreaks tended principally to occur in certain religious communities which object to vaccination although as a result unvaccinated children in the general population were also at risk.

E. Implications for a Possible HIV Vaccine.

An HIV vaccine in Canada might encounter delivery problems similar to those described above. Unlike the historical record of measles, HIV is not broadly prevalent in all strata of Canadian society. Instead it moves across human networks associated with risk behaviours from one vulnerable community to another. From the outset of a mass vaccination campaign, it may be difficult to convince a large proportion of the public that HIV is sufficiently proximate to warrant vaccination.

Moreover, in some of the Canadian communities where HIV is endemic, anti-retroviral therapies, prophylaxis and treatment of opportunistic infections, hormone therapies and other medical and social services have helped to extend life expectancies and improve the health and quality of life of persons living with HIV. These longer life expectancies have contributed to an overall increase in the number of people living with HIV in Canada. The effect has also been that AIDS is much less visible today than it was in the 1980's when it frequently occurred as a sudden, catastrophic, debilitating, wasting and fatal illness. Perversely, the medical improvements may be making it harder to promote HIV prevention among vulnerable populations who may be less conscious of the severity of HIV than the preceding generation. In this environment, people may count on others to be vaccinated, but be reluctant to accept vaccination themselves.

And yet the global scale of the HIV pandemic, the large number of people infected world-wide, the lack of resources and medical infrastructure in some of the hardest-hit nations, and the mobility of people in the modern world, will mean that even with the best of delivery strategies it

687 *Charbonneau* v *Poupart et al*; [1990] RJQ, 1135-1144 (CS).

688 P Rich. Cdn. doctors must work to preserve good vaccine record. *The Medical Post* 1999; 35(31): 55. Summary of a address given by Dr. Noni MacDonald, Dean of Medicine at Dalhousie University, to the Federation of Medical Women of Canada, 1999.

would take years to globally eradicate HIV with a highly efficacious preventive vaccine. Thus, as is the case with measles vaccines and indeed most other vaccination programs in Canada, HIV vaccination programs will probably have to extend through several generations before the disease is globally eradicated. Generating initial public interest and maintaining high levels of vaccine delivery and uptake over the long run will most certainly prove to be a challenge.

As the record of hepatitis vaccination indicates, it may be difficult to achieve high rates of coverage in marginalized and vulnerable communities where some people do not readily access medical services and falsely assume that they are not at risk or that they have already been exposed.

As for conscientious objectors, when the refusal to be vaccinated is based upon scientific concern, there is room for dialogue leading to informed consent. When the refusal is based upon religious beliefs, it may be much more difficult to use scientific data to convince the objectors that they or their children or members of their community might someday engage in HIV risk behaviours. Instead, the infection risks being perceived as a disease of "others" - something resulting from scorned and disdained behaviours sometimes interpreted as sacrilegious. In such communities, the collective sense of altruism may not extend so far as to accept to participate in a wide-scale public HIV vaccination campaigns.

II Obstacles to Vaccine Coverage

A. An Overview of Potential Obstacles

There are multiple reasons why vaccine coverage levels are sometimes sub-optimal and why certain specific subsets of the population are particularly under-vaccinated. If one can identify some of the obstacles to public vaccination with the vaccines that are currently in use and understand the relative impact of these obstacles in specific communities, then a clearer portrait will emerge of the potential difficulties facing delivery and uptake of an eventual HIV vaccine in Canada. Hopefully, once these obstacles are identified and understood, industry, public health and affected communities will plan a delivery strategy that anticipates problems and attempts to resolve them or at least minimize their harms. Some of the prime culprits which inhibit delivery and uptake are set out in the list below:

Complacency: Sometimes it is complacency in the face of declining rates of disease and concomitant inadequate records of vaccination that result in important numbers of Canadians remaining unvaccinated.

Scarcity of Resources: At other times, vaccine coverage has been deliberately uneven and incomplete reflecting difficult choices in the prioritization of target populations necessitated by a scarcity of public health resources. This in turn can result in sub-populations of unvaccinated children and adolescents who, as they age, remain susceptible to emergent outbreaks of infectious diseases.[689]

Religious and Conscientious Objectors: The Canadian situation is also complicated by the presence of certain religious groups and communities of conscientious objectors to immunization. These special groups comprise small but significant cohorts whose public health interests are effectively protected only if sufficiently high levels of vaccine coverage are maintained in the surrounding general population and if there is no in-migration of vaccine-preventable infectious diseases.[690]

Scepticism: Periodic resurgence of public scepticism concerning vaccines is a matter of on-going concern as is a lack of effective public health communication. Public knowledge concerning the importance of vaccination, its risks, costs and benefits is lacking. Increased hygiene, sanitation, access to clean water and vaccination in the 20th century reduced the number and frequency of epidemics of infectious diseases affecting broad swaths of the Canadian population – to the point where they are fading from memory. This in turn leads

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689 CA Craig, JF Blanchard. Prenatal Rubella-susceptibility in Manitoba with Reference to Descriptive Epidemiology of Two Manitobal Rubella Outbreaks and Vaccination Policy. *Update: Vaccine Preventable Diseases* 1998; 6(3).

690 SM Isaacs et al. Response to an Acute Hepatitis A Outbreak in a High Risk Rural Community. *Update: Vaccine Preventable Diseases* 1998; 6(3).

people to downplay the importance of vaccination and to forget that vaccination is also an altruistic act promoting the collective well being of Canadians.

Lack of Information: Experience with vaccine delivery to the Canadian public demonstrates that people are anxious to receive information about vaccine efficacy and safety before agreeing to vaccination. One of the most commonly expressed fears are that the vaccine might actually give some people the disease it is designed to prevent. This was the case with an extremely small number of people who received the live attenuated Sabin polio vaccine. People also want to be assured that vaccines are efficacious and thus that the risk / benefit ratio clearly weighs in favour of vaccination. Moving public education beyond these basic concepts into the more complex considerations of low efficacy vaccines with post-infection end points will be a much more difficult task.

In the following sections, certain obstacles to vaccine delivery and coverage will be examined in considerable detail.

B. The Importance of Information

A lack of information can breeds faulty risk perceptions, scepticism and distrust.

1. Risk Perception

When an infectious disease that is sudden and catastrophic becomes an emerging epidemic, people urgently look for protection through prevention (including vaccines) and for assurance of therapeutic care should they fall ill. If the disease presents pain, discomfort, incapacitation, and inconvenience severely compromising the quality of life, people will tend to tolerate a higher degree of vaccine-related risk than they would otherwise for a vaccine against an infection whose effects are transitory, less catastrophic or manifest themselves slowly over a period of decades. Whenever the disease that vaccination seeks to prevent is perceived as distant, remote, or unlikely, the willingness to assume risk associated with vaccination will likely decline.

Unlike meningitis or measles, HIV is not contagious and does not spread through casual "every-day" contact with infected individuals. Nor is AIDS a suddenly catastrophic disease. Rather, the immune system is slowly compromised over a period of several years. Given the long relatively asymptomatic period of HIV infection prior to the manifestation of clinical AIDS, and given the existence of treatments which demonstrate efficacy in slowing disease progression, people may over-estimate the immediate risks of vaccination and under-estimate the risks and consequences of HIV infection.

Even in the face of outbreaks of a catastrophic illness such as meningitis, it has sometimes proven quite difficult to convince healthy young adults in Canada that they are at risk and that

they need to be vaccinated.[691] How then will young adults, adolescents, and their parents respond to an offer of HIV vaccination? A consistent problem with HIV prevention and testing has been that sometimes those who are vulnerable do not consider themselves to be at risk. This may be due to factors such as denial, stigma, cultural inhibitions or a genuine lack of information. With respect to vaccination, young healthy adults may interpret their health as a sign of invulnerability. Unless the public is extremely well informed of the progressive epidemiology of HIV in Canada, and understands the probability and nature of vaccine-induced adverse events, coverage may never reach the levels required to end the many parallel epidemics underway in Canada.

2. Scepticism and Distrust

There have been expressions of concern over the growing levels of vaccine ignorance and distrust of vaccination among the Canadian public. Sometimes referred to as the anti-vaccine movement or lobby, popular opposition to vaccines has existed throughout history – both in terms of urgent mass vaccination campaigns undertaken during virulent epidemics and, in less turbulent times, with respect to routine preventative vaccination campaigns.[692]

Concern regarding vaccination's status in society now center upon: a lack of adequate information and misperceptions held by the public and some health care workers[693]; scepticism about vaccines motivated, in part, by a post-modern distrust of science[694]; and the volume of currently circulating misleading information about vaccines.[695]

Issues of popular but unscientific opposition to vaccination may assume a special significance in the context of HIV vaccination. Prior to the discovery of HIV infection, vaccination against diseases such as polio, measles, small pox and tuberculosis sometimes made use of a common syringe to administer vaccines to successive individuals. This approach persisted in developing

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691 B Kermode-Scott. Taking shots off the ice is preventive medicine: Edmonton health-care staff work around the clock for vaccinations. *The Medical Post* 2000; 36(39): 5. Note: This article chronicled vaccination campaigns in the year 2000 against meningococcal meningitis in Edmonton. It provides the following details which clearly illustrate the difficulties in reaching populations of young adults: In December 1999, public health surveillance detected an increase in infections. Beginning in February 2000, a massive public health vaccination campaign of young persons aged 2 to 19 was undertaken in two successive phases. Approximately 210,000 people were vaccinated. Despite this vaccination campaign however, it became clear in August and September of that year that the number of cases was accelerating again - this time among the remaining unvaccinated population. On Cotober 19th, a third phase of vaccination took place in the form of a free six-day program located in post-secondary educational institutions, health centres and community clinics. This third wave of vaccination targeted children not previously vaccinated and young adults aged 20 to 24. Despite important publicity, the uptake rate was approximately 60 per cent of the target population or approximately 60,000 people. The vaccine is 85% to 90% effective and this undoubtedly helped compensate for lower than hoped for vaccination rates. Although the uptake was twenty per cent lower than the stated objective of 80 per cent, the number of people vaccinated was nevertheless high enough to substantially reduce the infection rate.

692 P Rich. Supra, note 683. See also MR Albert et al. The Last Smallpox Epidemic in Boston and the Vaccination Controversy, 1901-1903. *New England Journal of Medicine* 2001; 344(5): 375.

693 P Rich, Supra, note 683.

694 BG Gellin, W Schaffner. The Risk of Vaccination: The Importance of "Negative Studies." Editorial. *New England Journal of Medicine* 2001; 344(5): 372-3 at 372.

695 R Pless. Vaccine Safety Resource Materials for Providers and the Public. *Update: Vaccine-Preventable Disease* 1998; 6(3); 5-13 at 6.

countries long after it was abandoned in industrialized nations. Following the discovery of HIV, it became increasingly clear that this technique was untenable. Many wondered whether immunization programs had inadvertently spread HIV, particularly in sub-Saharan Africa, ultimately allowing HIV infection to emerge more rapidly as a world-wide pandemic.

More recently, various hypotheses have come forward suggesting a link between human vaccination and the conversion of SIV to HIV; suggesting also that there is a link between human vaccination campaigns and the subsequent spread of HIV in sub-Saharan Africa. While the Edward Hooper hypothesis[696] that polio vaccine campaigns in Belgian colonies in Africa between 1957 and the mid-1960s created a bridge from SIV to HIV has been harshly criticized[697,698], another hypothesis that successive campaigns of public vaccination in central Africa may be responsible for the burst of HIV into several subtypes[699] cannot be discarded out of hand.

Whether or not these hypotheses will ever be verified or falsified, the publicity they have generated may have a real impact upon public confidence in future vaccine research and vaccination programs, particularly in populations that do not have access to detailed information and medical services. There are indications that the Hooper hypothesis has already created problems for HIV vaccine researchers in Africa.[700]

3. What Information Is Needed

Vaccine scepticism and distrust can best be countered by the dissemination of clear, comprehensible information garnered through transparent and ethical scientific research, and by maintaining accessible sources of up-to-date information concerning vaccine safety. This however can be a considerable challenge when the information must be disseminated to a wide diversity of target communities in which levels of health and health care, education and literacy, and vaccine knowledge vary widely both from one community to another and within target communities themselves. Vaccine scepticism and distrust can best be countered by the dissemination of clear, comprehensible information garnered through transparent and ethical scientific research, and by maintaining accessible sources of up-to-date information concerning vaccine safety. This however can be a considerable challenge when the information must be disseminated to a wide diversity of target communities in which levels of health and health care, education and literacy, and vaccine knowledge vary widely both from one community to another and within target communities themselves.

Clearly, as diseases such as polio, diphtheria, measles and others fade from memory, the public needs to be reminded that vaccination remains an indispensable public health defense so long as the infectious diseases remain circulating in the wider world. The public needs to have clear and

696 E Hooper. *The River*. Little, Brown & Co: Boston, 1999.

697 Information presented at the Royal Society Conference on the Origins of HIV and AIDS epidemic, September 2000.

698 L Garrett. Laying Blame for HIV: New book charges 1950s polio vaccine spread AIDS in Africa. *Newsday* 14 December 1999.

699 W Carlsen. Did Modern Medicine Spread an Epidemic? *San Francisco Chronicle* 15 January 2001. This article describes the research hypotheses of Dr. Ernest Drucker and Dr. Preson Marx.

700 L Garrett. Supra, note 699.

understandable explanations of the science of vaccination and requires honest explanations of the frequency and severity of vaccine-related adverse events. To complete the decision making process, they also need to understand the probability of resurgent epidemics whenever vaccine coverage dips below threshold levels required to protect herd immunity. And finally, they need to be reminded of the nefarious consequences of epidemic infectious disease.

This in turn means that the presentation of the case for HIV vaccination in a manner which clearly outlines the possible benefits and disadvantages (on both an individual and public health scale) will be essential to achieving the degree of public confidence, trust and support necessary to ensure the highest possible sustained vaccine coverage and thereby maximizing benefits to public health. But to be able to engage such discussions, Canadian physicians and public health authorities must have access to statistically significant scientific data generated from on-going programs of post-marketing surveillance as well as access to information on rates of infection among unvaccinated individuals.[701] In addition, they must have the training and communication skills necessary to impart information to a questioning and sceptical public. Furthermore, health workers who do the vaccination will need to use didactic materials and methods, which in the case of HIV vaccination, must be designed to be accessible and comprehensible to people in widely disparate and marginalized communities.

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[701] P Rich, Supra, note 683, at 55.

4. Assumption that Children Are Low-Risk

The public can be expected to be particularly risk-adverse if an HIV vaccine were ever included into the childhood schedule of vaccination administered either through primary or secondary schools. This is partly because of the proportionately high value our society places upon the young and their health. Moreover, for reasons stemming from stigma and prejudice as well as the natural tendency towards optimism concerning youth, many parents may not be prepared to admit of even a remote possibility that their child might someday be at risk of contracting HIV. If parents are reluctant to contemplate this possibility, then their tolerance for vaccine-related risks will be virtually nil. Thus despite the preventive nature of vaccination, the parental instinct to shelter children from perceived unnecessary risks may translate into a reluctance to support childhood vaccination campaigns against HIV. In addition there may also be a low tolerance for vaccine-related risk in childhood vaccination programs because these are often perceived as quasi-coercive measures. However, as we shall examine in the sections of this paper which follow, Canadian constitutional law forbids the forced vaccination of its citizens except under the most exceptional of circumstances. In matters of contagious infections spread through casual social contact, an unvaccinated child can be barred from school settings during times of epidemic. But the presence of an HIV positive student poses no risk to the health of others involved in day to day school activities. Indeed inoculation of school-aged children would be undertaken with an eye to preventing vulnerability in future (i.e. by vaccinating children before they might begin to experiment will injection drugs or engage in unprotected sexual relations). The extreme public health emergency conditions necessary to even consider coercive penalties for refusing an HIV vaccine are unlikely to ever occur in a Canadian school setting.

C. The Possible Effects of Stigmatization and Emotions on Vaccine Delivery and Coverage

In Canada, where the epidemiology is characterized by multiple parallel epidemics in relatively distinct and marginalized subsets of the population, HIV vaccine delivery might be restricted for perhaps as long as ten years to vulnerable people in vulnerable communities where sero-incidence and prevalence are high. But even within some potential target communities, the stigma associated with a virus transmitted principally by unprotected sexual relations or by the sharing of non-sterile injection equipment, risks placing obstacles in the path of vaccine delivery.

A public groundswell of emotional support for HIV vaccination is unlikely to spontaneously occur outside of HIV-affected communities. Among young people, HIV is most likely to make initial inroads among young injecting drug users and also among seriously marginalized individuals such as young sex trade workers and street-involved youth. Adolescents in these situations will not as easily garner public sympathy as school children that contract meningitis. Secondly, even if HIV sero-incidence were to rise among street involved youth, the actual clinical symptoms of disease will not emerge until most of the infected individuals have reached adulthood.

Because public emotions may fail to rally support for HIV vaccination, it is important that public health officials rely upon their modeling and join forces with concerned communities to strongly advocate for vaccination wherever it is rationally indicated. Without this advocacy, it is unlikely that HIV vaccination will garner the political support necessary to release the budgets required for effective vaccine delivery, particularly among populations such as prisoners, sex trade workers, and injection drug users.

Moreover, the emotions of despair and fatalism may make also it difficult to attract people from target populations to HIV vaccination. In populations of injecting drug users where the prevalence of hepatitis C infection runs higher than 80 percent, how will one convince people that there is any point in being vaccinated against another disease? Research in Vancouver and in Montréal demonstrates significant gender differences among injection drug users with respect to the relative prevalence and importance of psycho-social difficulties associated with or leading to risk activities for HIV infection.[702] Physicians in Vancouver, paint a truly bleak portrait of the vulnerability of female drug users to HIV, in which the underlying and recurring themes are identified as "power imbalance, physical abuse, sexual coercion, commercial sex work, drug use, vulnerability and despair."[703] Vaccination is an act of hope, of self -motivated health promotion and of clear and informed consent. Encouraging vaccination in settings of dire desperation and dispossession may be an extremely difficult task.

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[702] J Bruneau et al. Supra, note 17. See also PM Spittal, MT Schechter. Injection drug use and despair through the lens of gender *Canadian Medical Association Journal* 2001; 164(6): 802-3 at 802.

[703] PM Spittal, MT Schechter. Ibid, at 803.

III Vaccine Delivery in Marginal Communities

One of the most formidable obstacles in the path of achieving high levels of coverage with an HIV vaccine stems from the fact that HIV in Canada occurs primarily as parallel epidemics in multiple and often radically different communities and environments. In some of these communities, living circumstances are complicated, housing is precarious, incomes are relatively low, education levels are low and public and individual health suffers from a number of parallel co-morbidities. To professionals, the cultures in these communities sometimes appear to be impervious to health promotion and preventive health. Moreover, health services are often inconsistently accessed from a variety of uncoordinated points of service.

A. The Diversity of Marginal Communities

The communities and populations in Canada which are vulnerable to HIV epidemic are frequently marginal and confronted with numerous challenges to public health. People who are at particularly high personal risk of contracting HIV in these communities may be very difficult to reach. HIV vaccine delivery will not only have to focus upon target communities, but also upon targets within the targets - the core sub-sets of highly vulnerable individuals and the networks of behaviour which facilitate infection. Examples of the marginal populations and subsets thereof that need to be specifically addressed in a vaccine delivery campaign include:

- Injection drug users (occasional, addicted, heroin, cocaine, inner-city, suburban, young, long-term): female injection drug users; male injection drug users;
- De-institutionalised and homeless psychiatric patients;
- Street-involved youth, squatters;
- Persons involved in commercial sex trade (male and female): street-operating sex trade workers; sex trade workers who work from their home or on an on-call basis; clients of sex trade workers;
- Men who have sex with men: men who have sex with men but who do not self identify as homosexual or “gay”; gay men who although identifying their homosexuality, do not feel the need to belong to a “gay community” or “gay sub-culture”; sexually active older gay men; bisexual men;
- Prisoners;
- Women who have sex with men from some of the populations identified above;
- Certain Aboriginal and First Nations communities: urban Aboriginal populations
- Women and men with different languages, cultures and backgrounds: cultural communities; communities where a significant proportion of the population has immigrated from regions of the world in which HIV is endemic; cultural communities where people may be sceptical of medical techniques such as vaccination; and specific subsets of cultural communities in

which recently arrived immigrants may continue to suffer from extreme vulnerability to HIV infection. (eg widows in certain cultures are particularly vulnerable).

B. Targeting Within the Target Communities

A decision to vaccinate against a sudden emergent infectious and contagious disease such as meningococcus often must be made by interpreting the trajectory of outbreaks and the probability of epidemic from a database involving only a few initial cases. With HIV however, vaccine delivery strategists will have the advantage of much more developed databases drawn from mandatory declaration registries, public health laboratories, and an established network of community based organizations. Targeting within target groups will enable public health to achieve the maximum impact from a vaccination campaign via the judicious application of a scarce resource. This is perhaps best understood by those working in HIV in Canadian cities where longitudinal sero-prevalence and sero-incidence research cohorts include an important component of psycho-social research and strong ties to the communities under study. For instance, in Montréal the Oméga Cohort strives to: (i) document longitudinal HIV sero-incidence among men who have sex with men; (ii) produce significant results providing leads for HIV prevention and action within the community; and (iii) contribute to a greater understanding of gay men's experience in the context of an important social problem, HIV/AIDS.[704] The Vanguard Cohort in Vancouver is another example of such research. With a focus on prevention, this type of research may prove to be an invaluable source of information helping public health and community leaders to prioritise and target vaccine delivery within the broader gay community.

Data from the first three years of the Oméga cohort, gathered at six month intervals, demonstrates that 3.5 percent of participants consistently engage in unprotected anal sex (recurrence) while on average a further 22.5 percent have had periods of protected anal sex followed or preceded by periods of unprotected anal sex during the preceding six months (intermittence).[705] The latter group is not discrete, meaning that it is not necessarily the same men who take intermittent risks during every six month interval. The cohort provides an in-depth study of the economic, social and environmental factors that significantly correlate with risk taking. This will hopefully provide more accurate information indicative of whom to vaccinate within the broader gay and bi-sexual population in the event that vaccination needs to be restricted to subsets of this population because of limited supply, limited resources, limited efficacy, or some combination thereof.

This kind of research produces an enormous quantity of information which generates new hypotheses and possibly opens the door to subdivision of a target community into increasingly more precise subsets that are commensurably at higher risk and also more difficult to reach. The danger is one of overwhelming complexity, in effect losing site of the forest for the trees. In order to maximize the utility of this kind of research to vaccine delivery, provisions must be

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704 J Otis et al. Supra, note 233. Available at omega.gre.ulaval.ca.

705 ID.

made for a formal link in the planning process between the researchers, affected communities, and public health officials.

Of course, not all target populations for HIV vaccination will have the advantage of readily accessing such thorough and up-to-date prevention–related research. This suggests that public health officials need to identify potential target populations for HIV vaccination and encourage qualitative and quantitative longitudinal research studying factors influencing sero-incidence in these communities. In the meantime, strategists should take inventory of the possible sources of information concerning HIV transmission and prevention within specific communities and be prepared to draw upon these resources when planning for delivery. The decisions concerning whom should be vaccinated will be the most precise and the resulting vaccine delivery within targeted communities will be the most complete if this research data base is up to date at the moment when a vaccine finally becomes available.

Achieving high rates of vaccine uptake with a low-efficacy HIV vaccine within sub-groups of populations that are culturally and economically "marginal" and sometimes quite different from one another, will require a sustained, informed and carefully targeted education and promotion effort – notably in domains and environments where vaccinators may initially feel ill-at-ease and where previous vaccine interventions have achieved less than perfect results. For instance, the history of adult vaccination for hepatitis in this country demonstrates that difficulty has been encountered in attempting to achieve high levels of uptake within certain specific target populations. This is particularly worrisome given the epidemiological similarities between HIV and hepatitis infections in many of Canada's most marginalized communities.

C. Vaccination in Difficult to Reach Populations

1. Hepatitis Vaccination in Canada

Many of the populations and communities vulnerable to hepatitis are also vulnerable to HIV. In North America, both hepatitis A and B have been occasionally and recurrently endemic among urban communities of men who have sex with men. In some cities in Canada, hepatitis B and C are endemic, and even at epidemic proportions among injection drug users. The history of hepatitis B vaccination in Canada began with short supplies and thus difficult decisions in prioritisation for vaccine delivery. This period was followed by an extended period of slowly widening access for high-incidence communities. And finally, the hepatitis B vaccine was added to the recommended schedule of vaccinations for school aged children.

While not an exact match, the similarities between the epidemiology of hepatitis and of HIV should make the record of vaccine distribution for hepatitis A and B a relatively good predictive surrogate for eventual delivery of an anti-HIV vaccine in those Canadian communities where both HIV and hepatitis are endemic.

2. Hepatitis Vaccination Among Homosexual Men

Early data from the Oméga cohort demonstrates that 11 percent of 810 participants interviewed between October 1996 and December 1997 reported having already experienced an illness caused by a hepatitis B infection. In addition, 37 percent had already been tested for hepatitis and of these 39 percent recalled having a positive test. Despite these high levels of hepatitis B, the rate of vaccination in the cohort was only 49 percent and of these only 61 percent completed the full series of three inoculations.[706]

In addition, slightly more than four percent of Oméga cohort participants reported that they had already experienced illness due to a hepatitis A infection. More than 38 percent of the participants reported having received the first dosage of the hepatitis A infection but only 28 percent of the men receiving the first dose reported receiving the second dosage which is required to confer long lasting individual immunity.

The Oméga research also shows that hepatitis vaccines have unevenly covered various sub-groups in the cohort population and that there are some sub-groups that are vulnerable to hepatitis infection but where levels of vaccination remain disappointingly low.

After a decade or more of post-marketing surveillance, some Canadian provinces finally added the hepatitis B vaccine to the list of vaccines distributed to adolescents in secondary school. This was the case in the province of Québec where wide-scale public vaccination campaigns began in the late 1990s. Priority was accorded to vaccinating adolescents aged 18 or younger and anyone attending medical clinics specializing in the treatment of youth. The vaccine administered required three doses, the first being a prime with two subsequent boosters administered some

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[706] R Noêl. Supra, note 333, at 5.

months apart. At most, 41 percent of those vaccinated received the complete vaccination schedule of three inoculations.[707]

Shifting the priority target population to adolescents in school represents an attempt on the part of public health authorities to largely eradicate hepatitis B from an entire generation. However, as the above-cited figures indicate, there remains an important cohort of adult gay men (and indeed other adults) who remain unvaccinated or inadequately vaccinated. Hepatitis B remains endemic in some urban communities of gay men in North America as well as in Latin America and in the Caribbean. Adults are much more mobile than children and susceptible of contracting hepatitis either abroad or in Canada. The sad reality is that decades after the vaccine was first developed, endemic outbreaks of hepatitis B remain possible among unvaccinated cohorts of adults (including gay men) in Canada. If the records of hepatitis A and B vaccination are surrogate predictors for delivery of an eventual HIV vaccine, then the record shows that important difficulties will be encountered in trying to achieve high levels of recall participation for successive booster doses and in trying to achieve high levels of uptake in difficult to reach populations.

Disseminating information in a manner that can reach target populations using comprehensible language and terminology in a manner that affords the recipient dignity, respect and an opportunity to participate through questions and answers, will help to overcome some of these obstacles.

3. Hepatitis and Influenza Vaccination Among the Homeless and Injection Drug Users

The statistics on hepatitis vaccination among extremely vulnerable research cohorts of inner city injection drug users and homeless people are at once encouraging and worrisome. In Montréal, completed schedules of hepatitis B vaccination, (three doses several months apart), among a research cohort of inner city injection drug users stand at approximately 60 percent.[708] Unfortunately, outside of research cohorts, the overall rate of hepatitis vaccination among populations of inner city homeless people, street-involved youth, injection drug users, sex trade workers, is difficult to track, but likely much lower. Clinical research has shown high rates of efficacy for hepatitis vaccines, but this may not be the case with initial HIV vaccines. As a general rule, the lower the efficacy the higher the level of uptake required in order to make a significant impact upon sero-incidence. Even levels of 60 percent coverage may not be sufficient to halt the spread of an epidemic if vaccine efficacy levels are low. In such a scenario, it may only be possible to slow the epidemic and lower the levels of sero-prevalence.

Research concerning hepatitis vaccination, among inner city injection drug users demonstrates that the shorter the overall length of the vaccination schedule, the fewer the number of booster dosages, and the shorter the time between booster dosages, the higher the levels of compliance. Six inoculations scheduled two months apart may result in significantly higher levels of uptake than three inoculations at four month intervals. In general, the vaccine's efficacy rates appear to

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[707] E Levac, F Janelle. Prévention 2000: La santé publique en éclosion, 8e colloque provincial en maladies infectieuses. Hull Québec, le 12 mai 2000. Conference program, 143.

[708] Interview with Dr. Susanne Brisette. Supra, note 348.

be lower among injection drug users, than among the non-consuming cohorts that were studied in clinical efficacy trials. It may therefore be necessary to adjust the schedule of boosters and to increase the dosages administered in order to augment vaccine efficacy.

In attempting to extend hepatitis vaccination into marginalized inner-city populations a number of challenges are immediately apparent. Homelessness results in a high degree of intra-urban mobility and an organizational precariousness in one's personal life. This affects the ability to keep medical appointments and access medical services. Substance use and untreated mental health problems can also negatively impact upon one's ability to organize one's life and to access services, on one's ability to consent and to comply. In order to deliver a vaccine it is probably necessary to operate simultaneously from a fixed location and from mobile sites implanted within the urban geographic network of resources and services frequented by such vulnerable populations.[709] Data presented at the American National HIV Prevention Conference in 1999 demonstrates that opportunities to provide people who are vulnerable to HIV, hepatitis and STDs with hepatitis vaccines are frequently missed. In a highly fractured network of medical services, vulnerable populations access different kinds of medical care in widely varied settings including STD clinics, HIV/AIDS clinics, hospital emergency wards, needle exchanges, drop-in centers and communal shelters. Unfortunately, the opportunity to vaccinate in these diverse environments is often ignored because vaccination has not been fully incorporated into the regular practice of preventive medicine [710]. Unless a more concerted and flexible methodology of delivery is put into place, there is no reason to believe that the situation will not repeat itself when an HIV vaccine is introduced into this same population.

In Toronto, the Vaccine Preventable Diseases Unit of Toronto Public Health (VPD) undertakes a yearly influenza vaccination campaign among homeless and street involved people. Toronto's VPD service also provides an on-going hepatitis vaccination service from the two fixed clinics.

The VPD service highlights a significant problem with respect to vaccinating the homeless, namely the high rate of functional illiteracy encountered in this particular target population. Public health officials are required to produce their own "low literacy" posters designed to convey simple direct messages using a heavy reliance on graphics. Posters from vaccine manufacturers are either unavailable or unsuitable for this target population. Of course, illiteracy also poses a problem with consent. Consent forms must be designed that use graphics as much as possible and vaccinating nurses must be trained to review the client's understanding of the questions and their responses. In the VPD program approximately 50 to 60 percent of the participants at shelters, if left to themselves, cannot fully understand the simplified text used in the consent form. Thus the client does not fill out the consent form alone. Instead, it is reviewed with a nurse who verifies comprehension and responses on a question by question basis.

Despite these efforts, only about 1100 homeless persons are vaccinated each year against influenza in Toronto's VPD program. This is just the tip of the iceberg in terms of the overall population of street-involved people in that city. De-institutionalised mentally ill patients are often missed because they simply do not present themselves for vaccination. As is the case in Montréal, the need for further resources in Toronto is self-evident. This does not necessarily

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[709] ID.

[710] Integrating Hepatitis, HIV, and STD services: Increasing high-risk clients' access to STD clinic-based screening, vaccination, partner and follow-up services. National HIV Prevention Conference, 1999. Abstract no 260. Available at www.cdc.gov/hiv/conferences/hiv99/abstracts/260.pdf.

mean immediately increasing the number of distribution points. Rather, an increase in coverage could first be obtained by increasing the number of people who are vaccinated at present participating centers. Achieving this goal requires more outreach work, whereby the nurses would spend more time at community resources, become a familiar face to clients and be better able to gain their trust and integrate the VPD into the local setting. Once this has been accomplished, then partnering with mobile outreach services including ambulance services, needle exchange vans, motor homes that serve the homeless and street-involved youth can allow vaccination to extend into geographic environments where the physical resources normally would not permit vaccination to take place.

Both the hepatitis B vaccine and the influenza vaccine are well suited to distribution in a wide variety of dispersed institutional and community health care settings.[711] To do so however, requires a concerted promotional campaign and an opening of horizons permitting intervention to occur outside of traditional vaccination sites. An extensive network of fieldworkers present in the street and at multiple service points who are capable of establishing links with potential vaccinees in their own environments, and conducting persistent follow-up and recall is essential to achieving higher levels of uptake.

Such an approach to vaccination might require some data sharing between the multiple points of distribution. Otherwise, fragmentation of records between multiple service points (i.e.- other than VPD chosen sites) makes it almost impossible to detect overall coverage rates. The high mobility of the clientele, many of whom receive only infrequent health care in multiple settings, will make screening for vaccine eligibility very difficult. Unlike the case with hepatitis and influenza vaccines, there might be adverse events associated with over-vaccination with a future HIV vaccine. We simply will not know whether or not this will be the case until an HIV vaccine is licensed for delivery. However, over-vaccination could occur for homeless adults (many of whom have no medical "general" practitioner), during a period in which there is a concerted HIV vaccination campaign offered through multiple vaccination sites.

If this were the case, a data sharing network between distribution sites, would protect the vaccinators from liability and improve safety for vaccinees. For example, without access to the patient's medical history it may be impossible to fully verify whether he presents with contra-indications for vaccination such as a history of seizures and prescribed medications for seizures, allergies to eggs (if the vaccine is made with egg proteins) or previous allergic reactions suggesting a potential for a hypersensitive response to vaccination. Without a comprehensive immunization database, it will be difficult to determine if the patient is presenting at the right date for a booster shot or if they are presenting too soon.

The VPD in Toronto maintains its own immune registry database. This is accessible from mobile sites via a cell phone connection with a centralized modem. However, the VPD is not the only distributor of vaccines in that city and some people may receive duplicated vaccination from different health care settings (i.e.- first at a hospital and again at a VPD site). Establishing a larger immunization registry database in which data is shared among all vaccinators and cross-linked to psycho-social information concerning factors such as mental health and the ability to consent, contra-indications, illicit substance use, immuno-compromising medical conditions, allergies, etc., would raise troubling questions concerning informed consent, confidentiality of

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[711] Interview with Dr. Susanne Brisette. Supra, note 348.

medical files and access to legally protected information. Some of these issues are examined in greater detail in the section concerning immunization registries below.

In conclusion, the general record of influenza and hepatitis vaccine distribution in marginal communities in large Canadian cities suggests that HIV vaccination is feasible. There are people who work on the front lines with vulnerable populations and who have garnered experience in a variety of settings using innovative techniques for delivery. HIV vaccine delivery will require bridging research, strategic planning, financial and human resources and ideally access to documentation of the successes and failures of hepatitis, influenza and other types of vaccination so that we can learn from this experience. The questions that remain unanswered however are what levels of coverage can be attained and with what resources? For the hepatitis record also demonstrates that if delivery efforts are constrained by a lack of resources, low priority, and a disparate and poorly coordinated network of health services, then uptake may only be partial, thus conferring individual benefit without much benefit to public health. Indeed, in so far as hepatitis B vaccination in marginal populations is concerned, we may have settled into a period of relative complacency in which those responsible for resource allocation are content to allow demography and morbidity take their respective courses, waiting for the generation of Canadians vaccinated in schools to take the place of older unvaccinated cohorts.

IV How Will Vaccine Efficacy Affect Delivery?

When a preventive vaccine's efficacy is extremely high it may be possible to brake the progress of an epidemic or even reverse it, despite less than comprehensive levels of coverage.[712] [713] This has been the case with hepatitis A and B vaccination and with meningococcus vaccinations in Canada.[714]

The situation with respect to a future HIV vaccine(s) however may be radically different.

A. Four Possible Endpoints of Vaccination

In order to discuss the impact of vaccine efficacy upon rates of uptake within target populations and the resulting impact upon HIV sero-incidence and ultimately sero-prevalence, we first need to review some of the possible endpoints of vaccination. There are at least four possible scenarios for vaccine endpoints ranging from vaccines which facilitate prevention on both an individual and collective level to vaccines that might primarily serve the public benefit but bring only incidental benefit to individual vaccinees.

- When the vaccine-generated immune response repels HIV and prevents infection from establishing itself in the body, or if HIV infection does occur but the vaccine induced immune response rapidly eliminates it, this is called "sterilizing immunity". The elimination of the virus is the endpoint and the percentage of vaccinees achieving this end point will be the vaccine's efficacy for susceptibility.
- If HIV infection occurs despite vaccination but the vaccine generated immune response prevents or dramatically slows viral replication to the point where it prevents morbidity, life expectancy is close to normal and the vaccinee's infectiousness is greatly reduced, then obvious benefits accrue to both the individual and the collective community. Vaccine efficacy will be the percentage of persons vaccinated who attain the surrogate markers indicative of the end points of contained disease progression and of decreased infectiousness.

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712 D Tessier. Vaccine-preventable hepatitis. Gillian Wansbrought (ed). *The Medical Post* 21 September 1999: Q1-7, at Q1.

713 B Kermode-Scott. Supra, note 692.

714 Note: The recommended schedules of the hepatitis A vaccines commonly used in Canada, yield sero-conversion rates in young persons of 97-99 percent in immuno-competent individuals Efficacy rates for the full schedule of hepatitis B vaccines available in Canada range from 90 to 95 per cent. (It is worth noting however that the efficacy rates for hepatitis vaccination in persons aged forty and over, can be substantially lower). Vaccination in young people against certain types of meningococcus disease (i.e. meningitis), yields efficacy on the order of 85 - 90 per cent. All of these three vaccines confer sterilising immunity, although hepaititis A vaccines can also be administered post infection. With such high levels of efficacy, they have succeeded in steming emerging epidemics in Canada despite coverage levels that fall short of targets.

- A more difficult situation would be that of a hypothetical vaccine stimulating an immune response incapable of preventing infection and which only attenuates disease progression. This end point represents a post vaccination infection with higher viral loads than in the vaccine discussed immediately above. Here, the vaccine generated immune response only delays disease, attenuates morbidity, and may somewhat increase life expectancy. Post-infection anti-retroviral and immune sustaining therapies may still be required. In all likelihood subsequent transmission to sexual or needle sharing partners would remain a possibility, albeit at a lower frequency than in unvaccinated cohorts of HIV positive persons. This is because the vaccine reduces viral load in blood, ejaculate, and vaginal secretions, to levels that decrease but do not eliminate infectiousness. In particular, a rapid vaccine-primed post-infection immune response might nevertheless permit rapid and significant reductions in viral loads during the primo-infection period (i.e., the period immediately following infection with HIV). This in turn should generate significant benefits to public health in the form of reduced transmission rates and significant benefits to vaccinated individuals through a better disease prognosis. The proportion of vaccinees who achieve surrogate endpoints of viral load reduction during primo-infection, and partial reduction thereafter and endpoints indicative of some level of disease attenuation will be the vaccine's efficacy for infectiousness.[715]
- In the forth scenario, the endpoint of vaccination is partial reduction in viral load perhaps by as much as one log, but disease attenuation is minimal - perhaps even altogether absent. Therapies are still required and the prognosis of HIV disease remains relatively unaltered. The principal purpose of such a vaccine would be to reduce infectiousness during the key period of primo-infection [716].The vaccine however confers very few direct benefits upon the individual vaccinee. The proportion of vaccinees who achieve the goal of a reduction in viral load will be the vaccine's efficacy for a partial reduction in infectiousness.

Thus, efficacy is the percentage of persons who achieve the stipulated end points. If 100 percent of vaccinees achieve the given endpoint in 50 percent of their exposures to HIV, then vaccine efficacy is 50 percent. If 50 percent of vaccinated individuals achieve the designated endpoint during 100 percent of their exposures to HIV, and the other 50 percent are not protected at all, then vaccine efficacy is also 50 percent.

Both efficacy and end points will have a significant impact upon who has access to an eventual HIV vaccine. At the time of the writing of this paper, many scientists believe that early anti-HIV vaccines will offer only post infection end points capable of attenuating or delaying disease and reducing but not necessarily eliminating transmission - in other words the model discussed under the third bullet above.[717] In abstraction of all other variables, such a vaccine for infectiousness would require higher levels of coverage to produce the same reduction of sero-incidence that could be achieved with much lower levels of coverage by a vaccine conferring sterilizing immunity. Indeed, from the point of view of controlling the spread of HIV through communities in Canada, "[i]f vaccinated individuals can acquire infection [but with the vaccine acting as an immuno-therapeutic agent], the situation is worse unless the infectiousness of such infected vaccinees is negligible, since vaccinated infected persons will continue to contribute to

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[715] Joint United Nations Programme on HIV/AIDS, World Health Organization HIV Vaccine Initiative. Supra, note 170, at 4.

[716] C Burr. Of AIDS and Altruism. *Us News and World Report* 1998; 124(13): 60.

[717] Perspectives on AIDS Vaccine Research: An Interview with J Gouldsmith. *IAVI Report* 2000-2001; 5(5): 7. See also M Schoofs. Merck Starts Human Trials of Its new AIDS Vaccine. *The Wall Street Journal* 22 February 2001.

net transmission success of the virus" [718]. The only way that a post infection vaccine which leaves a reduced but nevertheless significant residual viral load could halt an advancing epidemic would be if i) extremely intensive delivery results in extremely elevated levels of vaccine uptake; ii) people with breakthrough infections are rapidly identified and receive treatment which further reduces viral load; and iii) vaccinees maintain very high levels of preventive and harm reducing behaviours.

B. Two Levels of Vaccination Impact

In light of the preceding, "[v]accination impact can [therefore] be considered at two levels: (a) the effect on the individual; and (b) the manner in which a vaccine is used to reduce transmission within a community [719]. Obviously, the best scenario for vaccine delivery would be one in which the vaccine offers maximum benefits on both levels. Otherwise, the ability to attain high levels of vaccine coverage may be inversely proportional to the level of individual benefit conferred by vaccination. If a vaccine confers proportionately greater benefit to public health than to individual health, then vaccination campaigns will have to appeal to values such as community appurtenance, altruism, the desire to protect future generations, etc. This may make delivery a much more difficult task, particularly among vulnerable populations where people may not access community support and health services. Moreover, given the emphasis North American culture places upon individualistic priorities and concerns, it may even be difficult to market such a vaccine in subsequent wide scale public vaccination campaigns.

In October 2000, the WHO and UNAIDS jointly organized a consultation involving an international group of experts from 10 countries who met to discuss future access to HIV vaccines.[720] The final draft report of that conference, mentions the rather sobering assumptions upon which the discussions were based:

> In the absence of definitive information on the characteristics of the first generation of HIV vaccines, the following assumptions have been made: the vaccine will (i) have only low to moderate efficacy (on the order of 50%); (ii) not be inexpensive (on the order of 10 to 30 US $ per dose); (iii) require multiple doses; and, (iv) at least initially, it [will] be available in limited quantities.[721]

Moreover, if the efficacy of preventive vaccines varies substantially according to circulating clades of HIV, then the ability to eliminate the world's HIV epidemic will depend upon

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[718] RM Anderson, GP Garnett. Supra, note 124, at 1012.

[719] Ibid at 1011.

[720] Note: This meeting "included: representatives from the AIDS Vaccine Advocacy Coalition (AVAC), Eurpoean Community (EC), International AIDS Vaccine Initiative (IAVI), International Vaccine Institute (IVI), US Centres for Disease Control and Prevention (CDC), US Food and Drug Administration (FDA), World Bank (WB), government and academic institutions and the pharmacetuical industry." Joint United Nations Programme on HIV/AIDS, World Health Organization HIV Vaccine Initiative. Supra, note 170, at 3.

[721] Joint United Nations Programme on HIV/AIDS, World Health Organization HIV Vaccine Initiative. Supra, note 170, at 2.

production of multiple vaccines. Otherwise, delivery of just one vaccine designed for the circulating strains of HIV in the more lucrative markets of the industrialized nations, might result in a vaccine that demonstrates much lower efficacy against the multiple circulating strains in developing nations. This may be the case of the AIDSVAX B/B Gp 120 vaccine now undergoing clinical efficacy trial in Canada. If this vaccine demonstrates clade specific immunity, it may not be appropriate for delivery in developing countries. If we were to deliver such a vaccine in this country then Canadians would be left vulnerable to new in-migration of different circulating strains from other regions. In this scenario, HIV would pose a continued concern to public health requiring long term vigilance and expenditure.

Lest people think delivery of a low efficacy vaccine is improbable, it is worth recalling that the AIDSVAX B/B Gp 120 vaccine might theoretically be licensed to proceed to market with efficacy levels as low as 30 percent. With these kinds of vaccines, the practical ability to achieve high levels of coverage in target populations would assume a crucial importance when deciding whether or not to proceed with delivery, and who should receive it.

C. Effect on Delivery

In the text below, we review some basic rules concerning HIV vaccine efficacy and how it influences delivery. Although mathematically sound, the relationship between efficacy and the kind of cohorts selected for delivery gives rise to some rather perverse results that at first glance seem to defy human nature.

As a general rule, the higher the level of vaccine efficacy, the fewer the proportion of persons in a given community that need to be vaccinated in order to obtain significant reductions in sero-incidence. The higher the level of efficacy, the broader the segment of the overall population that would access delivery. Very high levels of efficacy from a low cost vaccine with extremely low levels of adverse effects (as determined by an appropriate period of post marketing surveillance in restricted cohorts) would allow for almost universal vaccination.

Conversely, the lower the level of efficacy, the more a program of vaccine delivery will be restricted to people at high risk in vulnerable populations where rates of sero-incidence are high. In such situations, particularly if the epidemic is in an emergent phase, even modest reductions in sero-incidence can save many lives. By contrast, in communities with low levels of background sero-incidence, vaccination with a low efficacy vaccine might actually exacerbate incidence if vaccination encourages a significant number of vaccinees and others in the community to relax safer sexual and needle sharing practices.[722]

Ironically, the lower the level of vaccine efficacy, the greater the proportion of the targeted high sero-incidence communities that must be vaccinated in order to achieve a significant public health impact. But many of these populations are marginalized and the record of hepatitis vaccination demonstrates that high levels of uptake, may difficult to achieve. In the case of a low efficacy HIV vaccine, it may be particularly difficult to communicate the relatively complex

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[722] RM Anderson, GP Garnett. Supra, note 124 at 1013.

notions of interface between low efficacy and high sero-incidence and the continued necessity of practicing preventive and harm-reducing behaviours. Paradoxically, the vaccinator is in the uncomfortable position of telling the vaccinees that although we are vaccinating, you must continue to act as though you were not!

In deciding what course of action to take with respect to vaccination, the traditional approach is to call upon public health scientists to provide government with a forecast of the likely epidemiological trajectory of an infectious disease if one proceeds with publicly subsidized vaccination and if one does not. Morbidity, mortality costs and risks are evaluated in each scenario. As outlined in the preceding section, the decision then becomes a political decision with procedures and implications that far exceed the realm of science. At this point, legal and human rights to health, value judgements, ethical considerations, public emotion, public finances, resource reallocation, acceptable tolerance thresholds for risks, and issues of leadership are considered. Frequently in this balancing act, not all human lives are considered equal. Once the political decision has been made, the matter returns full circle to public health authorities, who marshal medical and scientific arguments to buttress the political decision for public relations. Finally, public health and health care workers implement the decision.

Under all of these nuances, there is a basic bifurcation in vaccine delivery between publicly subsidized and delivered vaccines, and vaccines delivered on an individual basis typically within the private setting of the doctor's office.

1. Public Vaccination

Interviews conducted with public health workers in Québec suggest that there may be considerable reluctance to proceed with subsidized public vaccination campaigns with a low efficacy vaccine, even within targeted communities. Fears are commonly expressed that achieving high rates of uptake and coverage with a low efficacy vaccine will be almost impossible, and there is concern about the impact of vaccination upon the collective's assessment of risk. Already, three per cent of participants in the Oméga Cohort report that, taking into account the existence of post-exposition prophylaxis, they may have possibly already engaged in higher risk sexual behaviours. Further, ten per cent of participants report that the announcement of the discovery of a relatively efficacious vaccine could incite them to be less vigilant. In as much as human beings tend to favour a state of least expenditure of effort, the announcement of the discovery of a vaccine might have some impact even before it is actually delivered.

Since delivery of a low efficacy vaccine would require high levels of coverage and would frequently take place in marginalized communities and sub-populations in Canada, public health would have to build strong links with community based organizations and with front-line health care workers in order to complete successful vaccine delivery. This need to include people working at the local level in planning for delivery will be crucial since low efficacy vaccines will dovetail with continued prevention aimed at sustaining behaviour modification and harm reduction. There will be a need for co-ordination between federal government officials who license vaccines, provincial public health authorities who will decide whether or not to deliver it, and the communities targeted for delivery. Without this co-ordination and an accompanying clear delimitation of responsibilities and links, vaccination risks being haphazard and incomplete. Indeed, potential opportunities for targeted public vaccination campaigns might be

lost because of an inability to secure the collaboration and budgets required to realize their full potential.

2. Private Vaccination

Traditionally, people outside of populations targeted for subsidized vaccine delivery are allowed to purchase the vaccine for themselves. However, with an HIV vaccine, this might be a dangerous strategy. If the full schedule of vaccination were to cost individuals $150, then only the well-off would be vaccinated, leaving the poor subject to greater personal risk.

But a low-efficacy vaccine is well suited to delivery within the confines of the private physician's office and other similar settings which permit a direct one-on-one exchange of information and questions and answers. This setting allows for appropriate counselling concerning vaccine efficacy and the continued need to maintain safer and harm-reducing behaviours. With the careful adaptation of the preventive counselling techniques initially developed around HIV testing, it should be possible to minimize the impact of vaccination upon the vaccinee's preventive behaviour. Whereas a lack of resources to conduct a community wide education campaign about the continued importance of prevention behaviours might discourage public vaccination, the circumstances of private vaccination should alleviate these concerns. Moreover, one should be wary of casting broad paternalistic and directive generalizations about a vaccinated individual's ability to continue to engage in preventive behaviours. "After all, it does not necessarily follow that the presence of seat-belts encourages all persons to drive faster or more recklessly" [723].

Although there may be little public health benefit derived from a vaccine that is delivered to individual patients upon request, this does not deny that some people may draw significant personal benefit from receiving a low efficacy vaccine. For instance, the sero-negative partner within a sero-discordant couple would probably have a strong interest in receiving such a vaccine. It is therefore entirely possible that private vaccination might be permitted even while public vaccination is deemed to be of too little benefit to warrant the effort.

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[723] Interview with Dr. Gaston De Serres. Santé Publique (Québec), March 2001.

V Designing a Strategy for HIV Vaccine Delivery in Canada

The literature concerning HIV vaccine development almost unanimously includes some mention of the necessity of mapping out a strategy for vaccine delivery. But until recently, there has been relatively few indications of exactly what the substantive content of such a strategy should be. The development of a strategy will delineate pathways, roles and responsibilities enabling Canadian society to obtain carefully reasoned, pragmatic and practicable responses to numerous complex and inter-related questions.

A. Questions to Be Considered

The following is a selection and not a comprehensive list to be considered in developing a strategy for vaccine delivery.

- Who should be vaccinated and under what conditions?
- What bridging studies are required in order to generate the data needed to (i) "address concerns that manufacturing changes might result in a different vaccine no longer clinically equivalent to the previous version used in the efficacy trial; (ii) provide evidence that efficacy data can be extrapolated to different populations; and (iii) support new dosing schedules that are less costly, more user friendly and yet still efficacious? [724]
- How to determine the minimum proportion of target populations that must be vaccinated in order to minimize the impact of HIV on public health?
- How to ensure that there is sufficient manufacturing capacity in order to guarantee supplies?
- How can we credibly guarantee future markets so as to provide an incentive for private investment in the research, development, production scale-up, and delivery of an affordable HIV vaccine?[725]
- What measures can be implemented to lessen manufacturers' liability?
- What measures can be implemented to provide for reasonable amounts of compensation to persons harmed through vaccine-induced adverse events?
- How best to reach vulnerable people in multiple and diverse target communities and what measures are required in order to encourage the highest levels of vaccine uptake and ultimately vaccine coverage?

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[724] K Goldenthal. Regulatory considerations in relation to HIV vaccine trials. In Joint United Nations Programme on HIV/AIDS, World Health Organization HIV Vaccine Initiative. Supra, note 170.

[725] A Batson. Assuring financing for HIV/AIDS vaccines. In Joint United Nations Programme on HIV/AIDS, World Health Organization HIV Vaccine Initiative. Supra, note 170.

•What is the economic cost/benefit ratio for vaccine delivery to the different target populations?
•What are the projected rates of compliance with booster dosages in various target communities and how can follow-up be supported and improved?
•How should vaccine delivery be financed?
•How can distributive justice be ensured through vaccine delivery?
•Who will co-ordinate vaccine delivery strategies and what are the roles and responsibilities of the key players?
•How can we ensure a continual flow of information such that all stakeholders are well informed about vaccination?

B. Key Steps

As the above list of questions indicates, successful vaccine delivery will be predicated upon an ability to manage the complexity of information needed for delivery to multiple and diverse communities. Essentially, the strategy for delivery should enable policy makers to access specificity in its responses to these and other questions. The radical cultural and economic differences between the various population sub-groups vulnerable to HIV in Canada will mean that public health will have to devise not one strategy for vaccine delivery but rather multiple strategies. This will require time and resources for pro-active planning if we are to avoid the pitfalls of vaccine delivery seen in the United States where "immunization rates differ substantially [and sometimes primarily according to] different geographic areas and socio-economic groups."[726] Indeed, one must emphasize that the improvement of immunization rates will require "not only expanding access to vaccines but also creating an efficient system to distribute them."[727]

"There is however, adequate experience in immunization programs to develop appropriate delivery systems for HIV vaccines, even in the most difficult settings."[728] What is required is political and public support. "Advocacy, political support and long term funding will be critical for delivery of future HIV vaccines to those who need it the most. A sustainable delivery system should be based on infrastructure strengthening rather than [on] the development of a parallel delivery system."[729]

In the Canadian context, direct services in health care, disease prevention and health promotion constitutionally fall under provincial jurisdiction. Conversely, the approval of vaccines for licensing and the management of responses to inter-provincial threats to national public health and security are matters in which the federal government can exercise jurisdiction. This means that in order to marshall political support for vaccine delivery, advocacy must take place on many fronts. Moreover, if a delivery strategy is to function effectively, then very specific

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[726] L Gostin, Z Lazzarini. Supra, note 376, at 1793.
[727] ID.
[728] B Nkowane. Operational issues for HIV immunization delivery systems. Joint United Nations Programme on HIV/AIDS, World Health Organization HIV Vaccine Initiative. Supra, note 170, at Section 4.3.
[729] Ibid.

mandates (jurisdictions) and lines of accountability will need to be carefully defined. The strategy must provide for co-ordination and the flow of relevant and necessary information in order to ensure appropriate financial and organizational responses capable of providing vaccine delivery in widely differing circumstances.

Some resistance to this type of planning can be expected, partly on the basis of a political defense of jurisdictional powers, and partly on the basis of uncertainty and institutional bureaucratic inertia. Preparing for HIV vaccine delivery is a little bit like preparing for an earthquake or some other similarly serious but uncertain event. People naturally tend to conserve energy and will respond more emphatically to an imminent danger than to something perceived to be distant and theoretical - even if the scope of latter is larger than that of the problems immediately at hand. And yet when tornadoes, hurricanes or earthquakes do occur, they invariably require efficient and rapid responses that best unfold according to a response plan prepared in advance. Of course, the higher the index of uncertainty associated with vaccine research, the more difficult it will be to incite and maintain interest in strategic planning for delivery.

Governments can be expected to respond to this issue with a grudging reluctance to assume yet another health responsibility at a time when the health care system appears to be over-burdened and under-resourced. HIV vaccine delivery is likely to be a medium to long-term event. Perhaps one way to stimulate interest in planning for delivery is to link vaccine clinical research and ultimate delivery to the dissemination of other tangential health-promotion efforts that are of more immediate and certain benefit to target communities.

No one knows exactly when an efficacious vaccine will be available. There are nevertheless, certain indicators which planners can look to. These include the potential timelines of numerous clinical trials now underway and the forecast dates for announcement of the results from efficacy trials.

One date is looming on the immediate horizon. The efficacy results from the AIDSVAX B/B Gp 120 and B/E Gp120 clinical trials in North American and in Thailand will be available in early 2003. There are two possibilities that might result from this calculation:

- The efficacy results may demonstrate that the vaccine was inefficacious or of insufficient efficacy to be useful in the fight against AIDS. Worse still would be a scenario in which efficacy results reveal a higher rate of seroincidence in the vaccine arm than in the placebo control arm of the study. A review of the qualitative data collected concerning risk behaviours would allow the company to accurately determine whether this vaccination accentuated physical vulnerability to infection. (this latter scenario is extremely unlikely).
- The efficacy results may be superior to the threshold established by the FDA for potential licensing (eg, greater than 30 percent). The company would likely announce these results with considerable media coverage. Given the competing experimental vaccines now working their way through clinical trials, the company could be expected to move quickly to request licensing of the vaccine and begin planning for commercial production. Researchers may also wish to continue to study the vaccinated cohort (or subsets thereof) in order to concretely observe the duration of vaccine acquired immunity, rather than relying on surrogate indicators. And finally, the parent company might take the opportunity to announce its prospects for development of future improved vaccines.

Future results of the kind described in the scenarios above will generate significant interest within target communities, the media and the general public. People will look to the corporation, local AIDS prevention agencies, public health and to governments for answers to multiple questions. The responses need to be planned and coordinated so that to the greatest extent possible the public receives consistent and accurate information.

> If, against most expectations, the vaccine is even partially effective, there will be an urgent need to review the implications for service delivery, including in countries such as Britain [or for that matter Canada], where thousands of people at high risk attend sexually transmitted disease clinics.[730]

Moreover, even after the efficacy results are known there will remain important but unanswered questions posing a significant challenge to people planning for this vaccine's delivery:

1. How long will any protection last if booster injections are discontinued or given at longer intervals than in the trial?
2. How relevant are these trials to regions [of the world] where HIV differs from the strains VaxGen's AIDSVAX products are based on?
3. Will the vaccine be equally efficacious if administered to a cohort of injection drug users?

The fact that these dates (interim analysis and final analysis) are relatively imminent, means that there is little time to waste on jurisdictional squabbles or institutional lethargy. And yet, there is relatively little evidence that planning of a concerted response on a comprehensive scale in Canada is actually underway.

The strategy for delivery of an HIV vaccine should define best practices for resource poor settings. We should look at the record of hepatitis vaccination (and other vaccines delivered to comprable target groups) in this country and determine what went wrong, what worked, and what could be improved.

The strategy should identify what structures can be used for distribution of an HIV vaccine? Would responsibility lie with primary health care providers or with Public Health or some combination of both or a multiplicity of stakeholders. HIV epidemiology suggests the latter response. But as the number of players increases so will difficulties and delays in obtaining operational feasibility and coordination. Once again, communities will have to be actively involved, so that vaccination reaches out into the environments where the targeted populations live.

Practical solutions need to be found to questions concerning financial constraints to vaccination. For example, most employee insurance plans will not cover preventive vaccinations but will cover disability costs resulting from the very disease the vaccine is designed to prevent. Insurers make this decision based upon cost/benefit ratios and public policy makers should attempt to find ways to tip the balance in favour of insured vaccination.

Vaccination will take place in environments in which pre-existing morbidities and socio-economic deprivation are common (i.e.- substance use, sexually transmitted diseases, pregnancy,

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[730] National AIDS Trust (Gt. Bt). *Impact: HIV Vaccine Update* 2001; 1: 2.

malnutrition, hepatitis C). This will mean that vaccine delivery will have to be compatible with these pre-existing conditions which are, in the short and medium term, immutable and unlikely to change. Protocols for bridging research and strategies for delivery must take these real life conditions into consideration.

The vaccine delivery strategy should propose concrete services to help facilitate front-line vaccine delivery. These include matters such as child care, transportation costs, immunization registries, and most importantly integration of vaccination into a wide variety of routine health, educational, and community services. Finally, to succeed at this challenge, the strategy should emphasize the building of solid relationships with the target communities.[731]

The development of a strategy for HIV vaccine delivery in Canada can hardly bypass work already underway on the Canadian Natural Immunization Strategy. Health Canada in collaboration with the provinces is working toward the elaboration of a national strategy for the delivery of vaccines in Canada. There is no express federal legislation pertaining to immunization. Thus, the participation and agreement from every province and territory is necessary in order to design and implement a strategy "to increase the proportion of Canadians that are protected from vaccine preventable diseases". At the present time the primary focus of this work remains childhood vaccinations, but the strategy is being elaborated to be able to subsequently cover adult vaccines as well.

The proposed strategy is a three pronged approach comprised of:

- The establishment of registries pertaining to immunization and the collection of post-marketing information on vaccine related adverse events;
- The procurement of supplies of vaccines for Canadians; and
- The streamlining the guidelines / programs for vaccination.[732]

C. Anticipating Potential Delivery Difficulties

The Canadian strategy for vaccine delivery should include an attempt to anticipate potential delivery difficulties. The following four potential difficulties or problems deserve attention.

1. Multiple Doses

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731 C Collins. Community roles in HIV vaccine delivery and access. Joint United Nations Programme on HIV/AIDS, World Health Organization HIV Vaccine Initiative. Supra, note 170, at Section 4.2.

732 The National Working Group for an Immunization records Network: Health Canada. National Immunization Strategy: Briefing Note, March 2001. Unpublished Document. This document is to be published in an upcoming edition of The Canadian Communicable Diseases Report.

Recent vaccine research conducted on monkeys at Emory University in Atlanta has generated results showing impressive viral suppression with a post-infection end-point. In this research, the monkeys received two doses of a primer using a vaccine that contains DNA and a third dose of vaccine using a booster with a modified smallpox virus vector. The three doses were administered over a six month period.

A similar vaccine has been developed at Harvard university but it uses more HIV proteins and is administered in six inoculations. In the AIDSVAX B/B Gp120 phase III clinical trial currently under way, seven dosages are administered over a 30 month period. In view of this, it seems likely that the initial generation of vaccines licensed for delivery will require multiple successive dates of administration extending over several months and possibly even several years. It might even be necessary to revaccinate many years after the initial series of doses. The delivery of multiple doses containing multiple antigens will require not merely the ability to keep a vaccine registry but also to keep track of vaccinees through the lengthy period of vaccine delivery. It will be necessary to recall people at successive dates of vaccine delivery.

The possibility (probability?) that an initial HIV vaccine might require multiple doses does not bode well for delivery, uptake and coverage. Audits of hepatitis B vaccination show sharp declines in coverage as one proceeds from one to three doses, with the sharpest declines typically occurring between the second and third dose.

Reminder letters can help to increase return rates but clinical experience with target populations comprised of men who have sex with men and of injection drug users "suggests that some doses are given up to two year late, often opportunistically, when patients present for other reasons."

If post marketing surveillance specific to communities and populations targeted for delivery is to occur, then it will be necessary to follow some of the vaccine recipients over a period stretching as long as five to ten years beyond the already extended period of vaccine delivery. This will present a particular challenge given that the initial target populations will be mainly comprised of adults, many of whom are highly mobile, more likely to migrate for economic reasons, and who live in economically precarious circumstances posing a number of serious threats to their health and social well-being.

Accelerating the schedule for the delivery of successive doses so that the dates fall relatively close to one another may help to improve completion rates. A semi-automated system for generating reminder dates and notices might also help public health authorities conduct follow-up. Nevertheless, without an intensive program of user-friendly recall, it will be extremely difficult to attain high rates of completion in a targeted vaccination campaign that delivers a vaccine requiring multiple doses.

2. Alternative Means of Administration

Methods of vaccination which avoid the use of needles (eg,- nasal inhalants, painting on shaved skin, intradermal exposure via compressed air) will be more popular among Canadians. But this takes on an entirely different meaning in developing countries where sterile needles are in short supply. Improper sterilization techniques, reuse and hence sharing of non-sterile injection equipment, improper disposal techniques and improper recycling of syringes is a source of millions of hepatitis B and C infections as well as thousands of HIV infections every year . In some parts of the world, non-sterile injection techniques used in past public health initiatives have come back to haunt health authorities with a vengeance.

> Egypt knows better than most countries the human costs of re-using needles. An astonishingly high proportion of the population - about one in eight people - is infected with hepatitis C virus (HCV) [….] Part of Egypt's problem can be traced back to a mass treatment for schistosomiasis before the 1980s. The treatment required multiple injections and is believed to have spread HCV widely. [….] Today, studies suggest HCV continues to be spread by unsafe injections and other health care practices.

Thus, injection safety, infection control and safe disposal of used syringes remains a high priority in any vaccine delivery campaign.

In order to avoid the problems and costs associated with handling sterile injection equipment, the ideal HIV vaccine would be an oral vaccine. If syringes are an unavoidable necessity then every national vaccine delivery strategy must contain provisions designed to ensure that vaccines are delivered with matching quantities of auto-disable syringes and sharp boxes. The vaccine campaign should include a component informing vaccinators, vaccinees, and their communities of the risks of unsafe injections. Public health authorities and vaccinators must ensure sharps waste management as part of the vaccine delivery system's legal and ethical duty of care .

3. Limited supply

When a limited supply of vaccine is available, its distribution may involve determining the proportion of the various population groups that must be vaccinated in order to make a perceptible dent in HIV transmission rates. The solution to this problem depends on a number of factors including the following: (i) vaccine efficacy; (ii) circulating HIV subtypes; (iii) important "risk groups", including "core" transmitters; (iv) mixing behaviour of "vulnerable target groups"; (v) quantity of vaccine available; (vi) seroincidence and seroprevalence within vulnerable target populations; (vii) vaccine acceptance and possible distribution levels; and (viii) objectives of HIV control. Obviously, a reliable supply of this kind of data must exist before decisions can be made.

Limited vaccine supply may also impose an ethically difficult choice concerning which communities should be prioritized for vaccination. For instance should the vaccine be first delivered in communities where there are relatively few services available for the HIV infected? The Canadian HIV vaccine plan needs to engage in reflection concerning how to objectify these choices.

Vaccination will likely commence by targeting young adults and then progress slowly through a transition towards a more general public vaccination campaign - most likely among young children. The timing of this transition will also pose an interesting dilemma for public health managers. In part, the decision will await post marketing surveillance data indicating high levels of vaccine safety and longevity of vaccine-generated immunity. But in the context of finite health budgets the decision to move from targeted to public vaccination will not merely depend upon vaccine supply but also upon the availability of other potentially scarce resources (eg,- human resources). In this situation, the decision will be a function of the relative benefits to be achieved by each marginal allocation of further resources in highly vulnerable communities, versus equivalent expenditure in a more generalized vaccination campaign. These decisions will require close evaluation based upon objective scientific data concerning, vaccine safety, efficacy and HIV epidemiology.

4. Durability of Immunity and Its Impact Upon Delivery

Another factor that affects the delivery strategy is the unknown durability of the immunity conferred by a vaccine. A good example of this was the vaccine against measles. At the time when the decision was made to vaccinate, public health authorities in Québec believed that one childhood dose was enough. Many years later when these children were adolescents, there was an outbreak of adolescent measles among some of the vaccinees and it was determined that the protocol's schedule for vaccine delivery would have to be adjusted to provide for a further booster dosage.

This issue is one of the reasons why Canadian provincial health authorities must approach HIV vaccine delivery with cautious and conservative prudence. Immunity may diminish with time, age, co-infections and other chronic immune-compromising illness, malnutrition, stress and certain medical treatments. A prolonged but gradual decline in immunity would have serious implications for prevention. This will be particularly true if the vaccine has a post-infection endpoint. If there is no danger accruing from an extra-immunization, it may be preferable to err on the side of caution and provide for a generous and time extended vaccine delivery schedule. This is a particularly important consideration with respect to HIV because human behaviour plays such a key role in transmission. For if a vaccine initially displays very high levels of efficacy but the induced immunity diminishes over time, it might permit breakthrough infections among populations that abandon preventive and risk reducing behaviours subsequent to vaccination.

A similar but more time-limited problem will arise if immunity is only acquired gradually over a long period of vaccination with successive and booster dosages. In this context, a relaxation of preventive vigilance in the period following early vaccine administration might also have a negative impact upon short term rates of transmission.

In either case, (a slow gradual acquisition of immunity or a slow gradual decrease in immunity following vaccination), preventive and harm reducing behaviours must be maintained in order to carry the maximum possible effect against HIV seroincidence.

Limiting delivery of the vaccine to high prevalence and high incidence vulnerable groups for a number of years, and providing for intensive and careful longitudinal monitoring of immunity

and immune suppressing co-factors as well as clinical follow-up of people with breakthrough infections, will eventually generate the data needed to assess the duration and strength of immunogenicity. The relatively small number of vaccinees to be involved in such initial distribution and intensive surveillance will allow care givers to not only take cognizance of declines in immunity, but also to provide the counselling and possible booster dosages required in order to bolster prevention. If surveillance is conducted in a structured manner taking into account co-factors influencing immune health, then it should ultimately enable public health authorities to determine community specific dosing schedules and also assess whether or not an HIV vaccine can ever be included in the schedule of childhood vaccinations.

D. Expanding the Scope of an HIV Vaccine Delivery Plan

Strategic planning for HIV vaccine delivery in Canada could potentially extend well beyond the three components of the proposed Canadian National Immunization Strategy.

For instance, it could include specific research projects undertaken well in advance of the date when the vaccine actually becomes available in order to evaluate how levels of vaccine uptake will vary as a function of vaccine efficacy, safety and perceived risk. If nothing is done to improve the slow time lines of licensing, and establishment of production capacity, then the issue of evaluating potential uptake for different potential vaccines becomes much less important. Public health officials can wait until a vaccine with a determined level of efficacy is discovered and then undertake the market evaluation in order to determine whether or not to vaccinate. Conversely, if the measures proposed by the International AIDS Vaccine Initiative succeed in accelerating vaccine research, licensing and manufacture, then the situation might be radically different. For if ever an efficacious vaccine were to be rapidly approved in the US and then Canada and at least limited quantities offered promptly to Canadian provinces, then a prior and sound understanding of the market in advance becomes an important advantage.

A Canadian plan could map out specific efforts to be undertaken in order to prepare target communities. It could identify and prescribe the development of infrastructure needed in order to conduct effective outreach designed to promote comprehending free and informed consent to vaccination, encourage high levels of coverage and ensure post marketing surveillance. It can also undertake preparatory research in order to determine which methods of follow-up will ensure the best possible uptake of booster dosages. As emphasized throughout this text, there will be considerable variation in the strategies employed and the timing of their deployment within different communities and settings within Canada.

A Canadian plan for vaccine delivery also needs to consider the special context of HIV vaccine development. For industry there is a relatively high level of risk and uncertainty associated with the science. For the potential recipients of the vaccine, even within developed nations, a significant proportion of those affected by HIV live in conditions of relative poverty and may be unable to purchase an expensive vaccine. In addition these population may feature attendant problems of precarious living conditions, diminished health and lower levels of education, all of

which could complicate informed consent, and compliance with booster dosages. In view of these difficulties, it is not surprising that private sector HIV vaccine research and development has lagged behind research for therapeutics.

> A survey released by the Pharmaceutical Research and Manufacturers of America (PhRMA) in November 2000 identified only 13 AIDS vaccines in development, with only nine companies involved in this research.
>
> There are clear reasons for this dearth of private sector research and development on HIV vaccines. A report by Mercer Management commissioned by the world Bank noted, "Industry sees HIV vaccine development as highly expensive activity of very uncertain outcome."
>
> On the delivery side, the prognosis is worse. [….] No government or international aid agency has pledged sufficient funding to immunize the world, […]. And immunization programs, which are generally set up to reach children, may need to be retooled to reach sexually active adolescents and adults.

An HIV specific delivery plan will therefore need to consider a wide variety of economic push and pull mechanisms designed to reduce this risk and uncertainty by augmenting markets for an eventual vaccine.

Efforts to assure rapid, simultaneous delivery of a preventive AIDS vaccine to the multiple communities in Canada affected by and vulnerable to HIV infection will have to address a daunting array of additional obstacles that are specific to HIV / AIDS. These include: (i) the need to formulate policies in the midst of inherent uncertainty of political pressure; (ii) the large numbers of vulnerable individuals (adults) from widely different backgrounds who will need rapid access to vaccination; (iii) the relative weakness of access to medical services in some of the affected communities; and (iv) social and attitudinal barriers to AIDS prevention.

The Canadian HIV vaccine delivery plan should detail a wide variety of methods for maximizing information, comprehension, vaccine uptake and coverage of vulnerable individuals in marginalized communities. "AIDS vaccines […] will require that new delivery systems be developed for groups who need immediate vaccination (including adolescents; sexually active adults; […] sex workers; […prisoners,] migrant workers and injection drug users)." In order to design these strategies, it will be necessary to prepare the terrain in advance, by educating key informants, taking steps to establish a presence in these communities and gain the trust of future vaccinees. As this advance work is accomplished, reliable estimates can be made of the demand for a first generation vaccine in these priority communities.

A Canadian delivery plan must also take into account the global extent of the HIV pandemic. HIV is the world's leading cause of death by an infectious illness. In order to reap the greatest possible public health benefit, a national strategy for domestic delivery will need to be firmly anchored in a global strategy of delivery. In the very best of scenarios, global vaccine delivery will take years to implement. Given the capacity of the retrovirus to mutate, a national strategy for vaccine delivery needs to take steps to ensure that scientific research capacity and a capacity for vaccine production and delivery is preserved for the benefit of subsequent generations.

E. Timing

If one considers some of the important factors that characterize the HIV epidemics in Canadian communities, it may be advisable not to delay establishing a specific plan for delivery of an HIV vaccine in Canada. The plan should draw upon the strengths of existing national immunization strategies and of the Canadian HIV/AIDS Strategy itself.

Brazil introduced a National HIV Vaccine Plan in 1992. The plan focuses upon pre-clinical research, development, testing and delivery. It was recently amended in the year 2000, to bring it up to date with new scientific developments and experience gained from vaccine preparedness studies and clinical vaccine research. The Brazilian strategy takes a trans-disciplinary approach to clinical trials and vaccine development emphasising: i) virological and immunological studies; ii) clinical and epidemiologicial trials; iii) socio-behavioural studies; and iv) work designed to facilitate development and production of supplies of vaccines.

Obviously, national plans cannot be written in stone but must be subject to periodic re-evaluation and amendment as epidemiology and science change. In addition to the impending dates of release of trial end efficacy data from the AIDSVAX GP120 phase III clinical trials, the International AIDS Vaccine Initiative has proposed estimated scenarios for the availability of successive generations of vaccines that will hopefully be increasingly efficacious and simple to deliver. The proposed timeline is set out in the table below. It represents a summary overview of an amalgam of hypothetical projections based upon IAVI proposals for accelerated timelines for research, development, production and delivery. Obviously, if such acceleration fails to occur, the dates proposed for each generation of vaccine will need to be further extended by several years. As is always the case when one attempts to predict the future, these projections carry a high degree of controversy and uncertainty. For instance, some scientists, feel that the proposal is overly optimistic and that only a very small number of experimental vaccines (eg, perhaps only one or two) will have reached the beginning of phase III efficacy trials by 2008.

Hypothetical scenarios of AIDS vaccine availability (1)
Generation 1: Possibly wide availability in 2004-2008: Low (~ 40%) protection against infection with closely related strains (such a vaccine may not have wide clade or geographic coverage) Moderate (e.g., 10 fold) prolonged reduction in viral load Multiple doses, short-lived protection (e.g., 3 doses and six monthly boosters) Parenteral [e.g., not oral] route of administration.
Generation 2: Possibly wide availability in 2008 - 2012 Moderate (~ 70%) protection against infection, most strains Better or substantial (e.g., 100-fold) prolonged reduction in viral load Multiple doses but longer-lived protection (e.g., 3 doses and 3 yearly boosters) Parenteral route of administration; oral booster
Generation 3: Possibly wide availability in 2010-2020 High (~ 90%) protection against infection, most strains Extreme (e.g., 1000-fold) prolonged reduction in viral load Simple dosing (e.g., 2 doses, 10 years booster) Oral route of administration.
Notes: Hypothetical scenarios on vaccine availability become more complex if vaccines must be specific to the locally/ geographically prevalent clades and sub-strains of HIV. **Source**: This table is reproduced (with minor stylistic adaptations) from: *AIDS Vaccines for the World: Preparing Now to Assure Access* New York: International AIDS Vaccine Initiative, 2000, July; p.7.

Despite their inherent uncertainty, this kind of projection may nevertheless be of use to strategists who have the foresight to understand that HIV vaccine delivery is beginning to loom on the horizon. Hopefully, these strategists will also be conscious of the difficulties that public health authorities in North America have experienced when very strong community demand for vaccination has arisen following reports of positive efficacy data from trials of new vaccines.

> [G]iven that an effective vaccine is probably years away, observers might reasonably ask why decision-makers should focus on utilization strategies now. In fact, the reason is clear. If we wait any longer before beginning to build the foundation for a new global vaccine paradigm, we are almost certain to see potentially useful vaccines emerge without the means to get them to those who most need protection against the virus.

F. A National Plan Within a Global Framework.

A national strategy for HIV vaccine development and delivery cannot realistically be prepared within a Canadian microcosm shielded from events and developments in other countries. A global framework is needed, a framework that would include at a minimum deliberation on the following factors:

- the difficulties of delivering a vaccine in war-torn areas (such as some of the countries in sub-Saharan Africa, the region with the highest levels of HIV infection);
- the challenges of delivering a vaccine in countries or regions with poor health infrastructures;
- the moral imperative for Canadians to be involved in worldwide delivery of an HIV vaccine;
- the obligations concerning vaccine delivery imposed by participation in international vaccine research;
- the call in the Canadian Strategy on HIV/AIDS for Canadians to participate actively in international HIV/AIDS activities;
- the globalization of HIV vaccine research;
- the effects of pricing on delivery of an HIV vaccine and the relationship between prices charged in Canada and those charged in developing countries;
- the need to reverse the negative impact of HIV/AIDS on development;
- the potential positive impact on Canada's international trade; and
- the need to build a broad base of support among politicians and the public for the funding necessary to deliver an HIV vaccine to the world.

VI Summary and Conclusion

Canada requires a national HIV strategy that proactively provides and plans for vaccine delivery. This strategy should provide for a seamless connection with provincial strategies which in turn should provide for a seamless connection with local strategies. Within this framework, roles and responsibilities should be carefully defined. The strategy could be anchored in both the existing efforts to elaborate a national immunisation strategy for all vaccines and also in national and provincial AIDS strategies. At the opposite end of the spectrum, a strategy for HIV vaccine delivery must also be integrated into international efforts to ensure that a vaccine is simultaneously deployed in developing nations, countries with emerging economies and developed nations.

There are numerous elements however which render an HIV vaccine rather unique in comparison to most childhood vaccines. These include the need to initially and urgently proceed with vaccination of adult cohorts. In addition, the first wave of vaccines will likely be characterised by relatively low levels of efficacy. This will pose a considerable challenge for regulators and public health officials. With the exception of the influenza vaccines, Canada has little experience with distributing low efficacy vaccines and strong institutional resistance to this concept can be expected. Low efficacy, uncertainty concerning potential post marketing adverse events, and uncertainty concerning the duration of vaccine-induced immunity will limit initial vaccination to highly vulnerable communities of adults. Often these target communities exist in marginal socio-economic conditions and access to preventive medicine is inconsistent at best. Vaccination in these environments will require a specific expertise and may have to take place outside of traditional settings. It will likely be labour intensive.

Against this background of selective delivery, the possibility that vaccine-induced immune responses may be easily detectable using testing technology, suggests that vaccination might unwittingly become an instrument for use in discriminatory practises. This issue spans public and private sectors of the economy and may affect the willingness of some at-risk individuals to be vaccinated. The utility of vaccination as an indication of risk will diminish over time as more and more Canadians are vaccinated. However, the progressive enlargement of the scope of vaccination is a long process involving incremental advances which will face scientific, budgetary, cultural and political obstacles. Clear and forceful public and private policies are needed to ensure that the potential for public health benefits from vaccination is not undermined by discrimination.

Low levels of initial efficacy will necessarily require a parallel effort to promote vaccination as part of a necessary maintenance of preventive and harm-reducing behaviours. The possibilities that initial preventive vaccines may have a post infection end point and the likelihood that preventive vaccination will be accompanied by a simultaneous effort to test and eventually market therapeutic vaccines has the potential to complicate the public's perception of vaccination. It will certainly complicate the task of those working in the field of HIV prevention. Because behaviour plays such a significant role in prevention, a vaccine of low or medium efficacy released into a community with low or moderate levels of sero-incidence could have a

deleterious impact upon public health if education and promotion of harm reduction is neglected or ineffective.

Canada could undertake vaccine preparedness studies to evaluate the willingness of people in vulnerable communities, not only to participate in HIV vaccine clinical research, but also to receive a licensed vaccine.

Vaccine preparedness research should examine how attitudes and vaccine acceptance may vary from one community to another. For even in a developed country like Canada, the lack of access to medical care and the omnipresence of more pressing daily health and socio-economic needs may mean that HIV vaccination will strike some individuals in these communities as practically absurd. For example, sero-prevalence rates of hepatitis C in injection drug users in Vancouver's downtown east side neighbourhood, exceed ninety per cent. In Montréal's St-Luc cohort, more than 80 per cent of participants are infected with HCV. In the longer term, perhaps as many as thirty per cent of infected persons will develop some form of chronic active hepatitis. There are few treatment options for people living with chronic hepatitis C and who are also consuming injection drugs. In some cities, outside of specific epidemiological cohorts, clinical follow-up and access to hepetologists for people using illicit drugs is piecemeal or non-existent.

An HIV vaccine with a post infection endpoint would not prevent infection but merely attenuate viral load and disease morbidity. HIV and hepatitis C exacerbate each another synergistically, and the efficacy of a preventive HIV vaccine with a post infection end point might be significantly reduced in the presence of the co-infection. Given the almost certain lack of clinical vaccine efficacy data for this population, motivating people to get vaccinated in the face of such a bleak prognosis may be extremely difficult.

Preparedness research should also aim to determine what are the best methods of communicating to target populations such diverse concepts as "post infection endpoint vaccines", "medium to low efficacy vaccines", "preventive" versus "therapeutic" vaccines; and the accompanying necessity to continue harm reducing behaviour. It could further identify cultural nuclei of popular resistance to vaccination and where possible match adapted communication and information strategies to this resistance. The objective is not to force informed consent but rather to identify the best ways of facilitating truly informed and comprehending patient deliberation relative to consent.

Others however have stated the case more forcefully. Susan Lucas, spokesperson for The International HIV/AIDS Alliance notes: "[…I]n the presence of an HIV epidemic there are both helpful and unhelpful cultural values, and […] the latter can and should be changed." However the spectre of paternalism hangs heavily over relations between Canada's First Nations and Aboriginal communities and the federal government, just as the spectre of colonialism continues to haunt international development issues today. Latent and systemic racism are also present in Canada's urban centres. In matters of vaccine delivery, cultural changes must be effected through respectful partnership with national and community leaders.

Vaccine preparedness studies in Canada can also conduct research into how willingness to accept a vaccine may change with variations in: costs to the end vaccinee; forecast efficacy, duration of immunity, and safety. Test cohorts could provide important indications as to how to best achieve voluntary, informed and comprehending consent and thus maximum levels of vaccine uptake while respecting current legal and ethical norms.

It is theoretically possible that this research might demonstrate significant differences between probable vaccine uptake in Canada and in the United States. Such differences might be related to differing cultures of the communities most vulnerable to HIV in the respective countries. Even where target populations for vaccine delivery are substantially similar, levels of sero-incidence in communities affected by HIV may vary widely from one nation to the other and indeed from city to city. In addition, the existence of a publicly funded and accessible system of medical care in Canada may affect tolerance for risk and rates of probable vaccine uptake in this country.

Canada needs to continue to develop an expertise in delivery of vaccines to adult populations. Increasing efforts to implement existing vaccines and other public health initiatives and drawing upon existing experience in order to evaluate various techniques of reaching target communities will be essential in order to prepare for the most rapid, efficient and respectful delivery of a future HIV vaccine.

A Canadian strategy for HIV vaccine delivery should be wary of opting for any single solution proposed to provide for vaccine manufacture and delivery. Most proposed incentives have not yet been evaluated. Multiple strategies should be modelled, applied, and then evaluated at rigorously respected periodic intervals so that unproductive methods will be abandoned but we do not overlook promising possibilities.

In this moment of growing international interest in global health and the AIDS pandemic, we should press for a broad range of push and pull incentives for AIDS vaccines. In the end, some incentives will prove more useful than others. All we really know today is that real disincentives exist for private sector investment in, and timely delivery of, AIDS vaccines for developing countries [and perhaps in small marginalised and vulnerable populations / communities within Canada]. Multiple, credible interventions are needed to correct those disincentives.

The public sector will play an unavoidably important role in the delivery of an HIV vaccine to vulnerable communities in Canada as well as to nations where sero-incidence is high. As discussed throughout this chapter, both federal and provincial governments possess a broad range of policy and legislative options which could be used to reduce the risks associated with vaccine research, development and delivery, to increase the certainty of future markets for vaccines and where necessary, directly subsidise vaccine delivery in resource scarce environments.

“It is very likely that a variety of reinforcing initiatives will have the most impact, and that at different times the importance of one initiative or another will change. Political prospects for these initiatives are uncertain” For instance, governments in Canada may be more willing to provide new funding to agencies such as GAVI and the IAVI, “than to rewrite tax law or redesign purchase mechanisms for vaccines.”

Perhaps more than any other health intervention, preventive vaccination has the capacity to greatly benefit a wide variety of public and private interests in Canada. Responsibility for ensuring delivery and participation in programmes designed to facilitate such an important contribution to population health should logically include contributions from multiple players beyond the narrow scope of health ministries and health budgets. There is a need to begin now to elaborate the public / private / community partnerships that will be most effective in achieving these goals.

These partnerships must not only attempt to achieve distributive justice in access to HIV vaccines within the communities which support and participate in clinical research in Canada, but also on a global scale. To protect their patents and profitable markets in the North, private industry has a strong financial interest in assuring that vaccines are made available to developing countries. "[For i]f an HIV vaccine is licensed in Western countries [eg,- of the developed north] but is not made available to developing world populations, industry's control over IP [intellectual property] and pricing will be swiftly and forcefully challenged."

An HIV vaccine will in all likelihood buy time for prevention and intervention in those specific communities within Canada where people are highly vulnerable to HIV. It will not eliminate the need for prevention nor the presence of HIV from these communities. But unless the vaccine is extremely efficacious and completely safe and hence suitable for wide-scale public vaccination, HIV will only be vanquished when the underlying social, economic and cultural causes of vulnerability are addressed. The licensing and delivery of an HIV vaccine will likely have an impact upon the maintenance of preventive behaviours within vulnerable communities. This impact may reveal itself slowly and progressively over time. A public health commitment must be made to periodically review attitudes toward prevention for many years following the initial marketing of a vaccine. Vaccination will be but one of multiple factors influencing risk assessment, management, reduction and assumption. Minimising the negative feedback of vaccination upon prevention will require concerted co-ordination and leadership at every instance, from the regulatory agency to the targeted communities, to the vaccinator's office. The first acute need for this kind of work may arise as early as the fall of 2001 when the interim results of the AIDSVAX B/B Gp 120 phase III clinical trial are released. At the present time, Canada lacks the kind of leadership, comprehensive overview and co-ordinated yet targeted community support that is necessary to ensure that this country will obtain the maximum possible benefit from delivery of an eventual HIV vaccine.

This paper has tended to ask many more questions than it has answered. It underscores the need for better definition of leadership and coordination in defining Canada's role and place in HIV vaccine research, development and delivery. Many of the pieces of our vaccine puzzle have already been put into place, but much work remains to be done. In the end, this is a role that Canada should not ethically, politically nor practically refuse to assume. Making a substantive and significant contribution to HIV vaccine delivery, could be one of this country's greatest scientific achievement.