Vaccinia, vaccination and vaccinology: Jenner, Pasteur and their successors
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Ethical, political and social aspects of vaccination policy in the third world: the HIV/AIDS example

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The scientific, ethical, and political issues raised by international research are not new. In the context of HIV infection or disease, however, these issues are complicated and intricate, due to the nature of the disease itself, its epidemiological and clinical characteristics.

AIDS is not the first pandemic of this century; it is not the only deadly disease affecting young men, women and their infants; it is not the only disease transmitted sexually and/or through blood. It is all of that, on a large scale.

According to the WHO, since 1992, 10 years after the first case of AIDS was officially reported, 1.8 million people have died from AIDS, and it is estimated that by the end of 1995, an additional 3 to 4 million people will have died. About 70% of these AIDS cases are from Sub-Saharan Africa [1]. Since 1990, in developing countries, AIDS has become the first cause of death among young men, the fourth among young women and the 10th among children. The gap between industrialized and developing countries does not stop widening: the epidemic in Asia began only a few years ago. It has already grown dramatically, with more than 2 million people already infected. By the year 2000, between 11 and 45 million people will be infected [2]. These figures are shocking, yet they reflect only partially the full impact of the epidemic. Beyond its medical and demographic consequences, the social, political and economic consequences of AIDS appear unbounded, especially in developing countries. This new pandemic is a challenge for our societies as it is for the medical and scientific fields.

The pressure on scientists to solve the crisis — to find a vaccine or a cure — places a special burden that must be taken into consideration in decisions related to biomedical research. Essential to these decisions are principles inherent in the Universal Declaration of Human Rights: 1) the principle of respect for persons, which includes informed consent and the right to privacy; 2) the principle of maximal benefit (beneficence) versus minimum harm (non-maleficence), which is derived from the right to life; and 3) the principle of justice, which holds that individuals should equally share the risks and benefits of research.

An unprecedented amount of resources have been deployed to try to contain if not curb the epidemic. Information and prevention campaigns have been orchestrated at a world wide level, and in almost every country a national program on AIDS has been put in place with considerable funding (unmatched by any other national public health programs). Yet nowhere

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is the epidemic controlled. Appeals for an even more massive mobilization have been made. People have even suggested a "Manhatthan project" to develop a vaccine against AIDS, comparing the resource mobilization that would be necessary to the huge scientific, technological and industrial effort that was made during the second World War to prepare the atomic bomb. Indeed, in this context, an AIDS vaccine appears to be the ultimate weapon against the epidemic, making people believe that they could resurrect the fearless way of life of the pre-AIDS era.

As soon as the virus was discovered, researchers started to look for a vaccine. So far, the most powerful, if not the only, weapons against viral diseases have been vaccines. According to the newspapers of the time, everybody should be vaccinated by now. Yet after 10 years, we don't know what this vaccine will look like, and field efficacy trials have been put on hold as much for scientific as ethical reasons.

Evaluation of HIV vaccine candidates

Indeed, due to the extraordinary development of molecular biology, biologists have at their disposal a vast array of vaccine components that may directly or indirectly induce a protection against HIV. These vaccine components include: recombinant viral proteins, synthetic peptides, viral or bacterial vectors able to express HIV proteins after having been introduced in the organism, even HIV viral genes introduced in the organism in the form of naked DNA.

The present impasse is that the immune response that may be induced by these components is not well understood. Ideally, they should be able to induce adequate neutralizing antibodies, cytotoxic T lymphocytes (CTL) and a mucosal response. As a matter of fact, the question of the correlates of immunity has been much more difficult to resolve than anticipated, probably because of the very nature of HIV infection in humans. The initial infection usually remains silent. Virus production is intense and the antigen is easily detectable in blood. During the following weeks, the immune system produces the anti-HIV antibody in large quantities — the subject becomes seropositive — and the antigen becomes more difficult to detect. Clearly, the combined action of antibodies and CTL response (which is detectable later) is able to control the infection, for a while. However, the infection is not eradicated: the virus integrated in the host's DNA never ceases to replicate, constantly mutating and therefore escaping the surveillance of the immune system. Inevitably, the balance favors the virus, while the immune system cells — its principle target — are more and more difficult to replace. In vitro experiments or animal models data are necessary, but sooner or later the best vaccine candidates will have to be evaluated in humans. This will not be easy.

Comparing the rate of infection in the vaccinated group versus the control group may not be sufficient to evaluate vaccine efficacy. Indeed, HIV infection having a 10 year clinical latency, it will be difficult to determine the disease evolution in those who will be infected despite being vaccinated. Aside from a preventive immunity, one has to envision some kind of therapeutic activity. Because of the very physiopathology of HIV infection, it is not clear whether the protective and therapeutic effects will go in the same direction. In the favorable scenario, one may see a marked decrease of the incidence in the vaccinated group, with a longer clinical latency and decreased infectivity in those eventually infected despite being vaccinated. One may however imagine paradoxical effects either immediately or years after infection. One could see an initially protective immunity be replaced by an increased susceptibility to infection and/or an adverse clinical evolution, the so-called "enhancing effect" that some people are concerned about.

To assess these various aspects of vaccine efficacy, large populations with high enough incidence will have to be followed for a long period of time [3]. Health care workers would be the

ideal population to test an HIV vaccine since they are the most able to understand the risks, benefits and constraints of a vaccine trial. It is with this group that the initial clinical trials of hepatitis B vaccines — a viral infection considered a professional disease — were done. However, health workers are generally at low risk with regards to HIV. Therefore, it will be necessary to enroll volunteers in higher risk populations such as male homosexuals, drug users, female sex workers, discordant couples or sexually transmitted diseases (STD) clinic clients. The problem is that, contrary to the situation of health workers, these high risk populations are the most vulnerable, the poorest, the most marginalized, and therefore those for whom the implications of a vaccine trial will be the most difficult to understand. They also are the most unstable/mobile, and therefore the most difficult to follow over long periods. Even in these high-incidence populations, the trial size will have to be very large. For example, where HIV incidence is 1%, a population of at least 16,000 individuals would have to be included and followed without any loss, to evaluate a vaccine with a theoretical protective efficacy of 50%.

Justice and universality: the vaccine's message

One major ethical requirement for human experimentation is to minimize the risks and to maximize the benefits for the study subject. Risks have to be identified first. There are accidents, incidents or side-effects common to any drug or vaccine, that will be monitored and dealt with adequately in the context of the clinical trial. Aside from these biological risks, important social and psychological risks exist for the very reason that this vaccine will be directed against HIV/AIDS, and not against another disease. Indeed, there is no disease for which issues of human rights, civil liberties and justice have been raised to the same extent. In that respect, it is not indifferent that the high risk populations that will be approached for efficacy studies are also at high risk for violence, discrimination and neglect.

One obvious problem is that participation of individuals in the study will designate them as being at high-risk. Before enrollment into the study, volunteers will have to undergo HIV testing to ensure that they are not infected prior to being vaccinated. How will ineligible HIV infected volunteers be taken care of? How will the confidentiality of tests results be ensured ? Finally, half of the participants will have an HIV vaccine serologic scar indistinguishable from infection with conventional tests. Specific steps will have to be taken to protect their privacy and rights with regard to their personal life, employment, access to the health care system, access to credit, and international travel. All of this can be dealt with on paper and genuinely attempted. However, it would be naive to believe that it will be easy.

A much more difficult problem to deal with, relates to one of the major characteristics of HIV, namely the fact that the level of exposure of the individual to infection is not a given, something exterior to the individual. It is, by and large, under the control of the individual him/herself. Investigators therefore face a fundamental contradiction: while they must use all possible means to minimize the risk of HIV infection for the subjects, in particular providing them with the most accurate information about transmission and the means to avoid it (condoms, clean syringes, etc), in the case of success of these preventive measures, they will be unable to determine the efficacy of the vaccine. In other words, the success of the trial depends on the failure of prevention. Finally, things may be even more complicated if the volunteers believe that they are somewhat protected by the vaccine, even though they will have been told that its efficacy is not known and that half of them will receive a placebo.

The difficulties cited above can be dealt with in partnership between investigators, volunteers, communities, sponsoring agencies, drug companies, political authorities, and so forth. We must recognize, however, that our proposal of a trial conforming to the ethical imperative

of respect for persons, beneficence and justice, is no less than to succeed where ambitious preventive programs have failed so far (assuming that they were ever attempted). AIDS is about risk behavior. But it is more essentially about poverty, loneliness, exclusion, injustice, underdevelopment and sex trade.

Developing countries and the international dimension of the future AIDS clinical trials

Research carried out in developing countries brings into contact societies with differing cultural, political and economical backgrounds, and interests and values that may not always coincide. As international researchers, we are accountable to both industrialized and developing societies. Questions about the ethics of this kind of research can be raised at three levels: 1) the fundamental principles we refer to in order to make moral judgments; 2) the codes, the set of specific rules or guidelines for research involving human subjects; and 3) the institutions and the research process itself.

The reality of underdevelopment makes these three levels difficult to implement. Underdevelopment does not mean merely cultural, economic, and linguistic differences. It is, by and large, the result of the transgression of the ethical principles mentioned earlier such as the respect for persons and justice. Researchers have raised questions about these principles, particularly their expression in reference to cultural differences. Do our guidelines really have an absolute significance and are they pertinent everywhere in the same way? Conversely, does their literal application promote the fundamental values?

Indeed, the CIOMS (Council for International Organizations of Medical Sciences) guidelines for an international ethical code set forth in 1982 and revised in 1992 [4] attempt to negotiate a satisfying balance between the reaffirmation of the fundamental values defined in the Universal Declaration of Human Rights [5], and the recognition of a cultural pluralism in the expression of these values in reality. They also try to bar the cynical exploitation of differences whether they correspond to a different perception of the risks of the research, a different understanding of some ethical questions or other legal constraints. Although ethical codes are certainly necessary, they are not sufficient.

As early as 1932, for example, well before the Nuremberg Code [6] and the Declaration of Helsinki [7], the German Ministry of Interior had promulgated very clear and advanced guidelines for the protection of human subjects involved in medical research [8]. We know that under the Nazi regime, these guidelines were systematically violated.

The Tuskegee study on the natural history of untreated syphilis is another example [9]. This research of dubious scientific value began in 1932 in a poor black community in Alabama. It was only halted in 1972, 30 years after the discovery of penicillin, 30 years after the Nuremberg trial and the promulgation of the Nuremberg Code. A journalist, not a physician, disclosed the existence of this study. Essential to the evaluation of research involving human subjects is the public debate implied.

In fact, the presence of a third party, external to the medical world, is a key element brought forth by the Helsinki Declaration. Researchers are not alone vis-à-vis their patients and their conscience. Moral points of view other than theirs co-exist. This is the reason why Ethics Committees and a whole set of legal procedures have progressively been set up.

The situation in many developing countries, however, is characterized by a very imprecise perception of the risks involved in research and the extreme fragility of control mechanisms, especially in crisis situations. Independent ethical and scientific committees are still lacking in many countries. The fragility of the control system is increased by the limited role of the local press, the indifference of the international media, and the scientific isolation of national and foreign researchers.

Finally, the most troubling question may be how the principle of justice will be applied, ie, the equitable share of the risks and benefits of the research, not so much during the trial, but afterwards, when a molecule has been proven efficacious.

It is generally agreed that the community that has accepted the risks of the research will benefit first from the results. We mentioned earlier that neither the animal models nor the in vitro studies would tell us what are the most promising vaccine candidates. Testing in humans is the only way to go forward and any statistical advantage of a vaccine candidate over a placebo will be good news.

So when we say that the population will benefit from the study results, which study and which population are we referring to? Clearly, we will have to work from a little efficacious 'first generation' vaccine to a better 'second generation' to a 'third' really protective one. The first volunteers to enroll in a study to test the vaccine candidate developed by a company located in Thailand will have contributed considerably to the success of the 'third generation' vaccine that will be developed by another company and tested in Brazil or Uganda.

Some may say that this is how science works. That is precisely the point. The convenent of Human Rights states that all humans have the right to benefit from the progress of science. How does that translate in reality?

Hepatitis B is a typical example. The first population-based efficacy studies of the hepatitis B vaccine were done in rural Senegal, 20 years ago. This population has not yet benefited much from the results of this trial, despite the activism of the investigators themselves.

The real question is: will the international community shy away from the good news when it finally comes?

The prevention of perinatal transmission of HIV is another example, even though it is not a vaccine: the results of the AIDS Clinical Trials Group Protocol 076 (ACTG 076) last year have demonstrated that the prophylactic use of zidovudine (ZDV) during pregnancy can reduce mother-to-child transmission of HIV by two-thirds [10]. Despite the drug's high cost and the complexity of administering the treatment to mothers and infants, most industrialized countries have developed specific protocols to ensure the availability of ZDV to all HIV-infected pregnant women. Prophylactic use of ZDV is one of the most cost-effective interventions for the prevention of an infant's death one can think of. It ranks at a level comparable to that of EPI (the Expanded Program on Immunization) or the safe motherhood initiative, to remain in the domain of mother and child health. The challenge the scientific community and international public health organizations are confronted with, however, is how to make this treatment available to the 97% of HIV-infected women world-wide who live in developing countries. Already six and a half million women in sub-Saharan Africa and 1.5 million women in southeast Asia are infected with HIV [2]. Developing countries will be confronted with daunting obstacles if they contemplate implementing a ZDV program to prevent perinatal HIV infection. Due to logistic problems, compliance and cost, the lengthy (18–20 weeks) ACTG 076 regimen may not be feasible in many settings.

To improve its use as a public health tool, we need to determine whether the duration of ZDV treatment can be safely reduced without compromising the demonstrated efficacy of the standard 076 ZDV regimen. Placebo-controlled studies of abbreviated ZDV regimens have been proposed in many developing countries, thereby denying for developing countries the validity of the results of the study conducted in the US and in France. It has been argued that in some settings, especially in Africa, breast-feeding makes the results of 076 not applicable. Really, if the situation is such that medically supervised bottle-feeding cannot be safely administered, one may question the rationale of going to the great effort of administering an abbreviated ZDV prophylaxis, and then letting mothers infect their infants through breast-feeding.

When a treatment has been demonstrated to be effective, especially when the outcome for patients is death, it is standard practice to use the effective treatment (if this is feasible) and not a placebo as the reference in subsequent clinical trials, such as those designed to examine new dosing alternatives and to assess newly-proposed therapies. ACTG 076 is one of the rare successes in HIV clinical research that has an immediate application potential. This discovery is most directly and unequivocally relevant to the developing world, where nearly all perinatal transmission of HIV occurs. Once again, however, a life-saving public health tool may prove to be elusive for developing countries, unless heroic measures are taken.

By nature, this was Pasteur's view of it: vaccines speak for universality and human solidarity. The pursuit of a vaccine against HIV, the disease of the century that has most exposed the dysfunction of our societies, will be the opportunity for our societies to fully reaffirm this message.

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