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Editorial

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EDITORIAL

AIDS vaccine trials in India: ethical benchmarks and unanswered questions

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Vaccines have fascinated public health and clinical practitioners since Edward Jenner's experimental inoculation of a young boy, James Philip, using cowpox blisters of the hand of Sarah Nelmes, a dairy worker. Less than 50 years later vaccination became the preferred method of combating smallpox in Britain and its empire, and the race to develop new vaccines against other diseases ensued. The fascination with vaccines gripped the scientific community and also shaped the social imagination with the vision of a world free of disease. This led to scientists experimenting not only on vulnerable subjects like children, prisoners and the poor but also on themselves. Indeed, in the early years of vaccine development, ethical considerations and the human rights of individuals and groups being experimented upon were sometimes given less importance. Enmeshed in this indifference to human rights is the history of colonialism and racism.

Although the Nuremburg Trial and the Code that emerged from its judgment represent a watershed in the development of ethical guidelines and regulations, the abuses and scandals did not cease. Subsequent generations have made attempts to reassess history. They have critiqued violations and strived to apply higher standards of human rights and ethics in medical and vaccine research, to the extent that these concerns take precedence over the potentials of scientific discoveries.

AIDS vaccine research

The fact that HIV compromises the same immune system that is needed for an effective vaccine, the variations in sub-types of the virus, the difficulties and cost of HIV treatment and management and the acute social stigma attached to the condition have posed challenges to basic vaccine science as well as to the standards of care needed during research. These in turn have affected the socio-economic commitment needed to develop and, potentially, to use preventive vaccines against HIV/AIDS. The situation is further complicated by the fact that early estimations and projections of the course of the HIV epidemic in developed countries are now being questioned following evidence that public health interventions without vaccines have slowed down the epidemic considerably. A similar situation is now being projected for India, even though there has been no definitive evidence of this so far.

In India, during the last two years, two preventive Phase I AIDS vaccine trials have been launched, the first at the National AIDS Research Institute (NARI) in Pune and the second in Chennai at the Tuberculosis Research Centre in collaboration with the non-governmental organisation YRG-Care. However, unlike what happened in Uganda or Thailand, both trials have steered clear of significant national and international controversy. They therefore need to be assessed in terms of the gains made in ethical standards as well as some challenges that need further public discussion.

AIDS vaccine trials in India and ethical benchmarks

While one may disagree with the decision by the political establishment and by scientific institutions to provide higher priority to investment in AIDS vaccine trials, one must acknowledge certain achievements in raising standards of ethics in the preparation and conduct of clinical trials. It does not matter if such standards were established due to pressure from activists or the international community.

The preparatory process for the AIDS vaccine trials was regularly reported in the media. Strategic attempts were made to evolve a "political will" by involving some members of parliament, the Prime Minister's office and the President. Efforts were also made to involve persons with various professional expertises in periodic consultations through an advisory body; some of these contributed actively to laying down the informed consent process. And lastly, at both the trial sites, there was an attempt to ensure greater local involvement through community advisory boards.

The informed consent and participant information documents were drafted using the inputs of diverse stakeholders and experts. It was ensured that all known risks were clearly disclosed and the right to withdraw from the trial at any stage was made very explicit. Several other issues were addressed as well. Thus guidelines for recruitment were developed to exclude the possibility of coercion and gender imbalance; a recommendation was made to recruit educated persons through public advertisements; a test of comprehension was to be administered; and, to avoid the possibility of undue financial incentive, a standard nominal

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reimbursement of expenses for each visit was fixed for all participants. Participants who became HIV positive during the trial would receive free access to care, support and treatment, including anti-retroviral therapy, for five years, and an assurance was given that continued access would be advocated for. The sponsor insured all participants for care, treatment and compensation for trial-related injuries. An independent arbitration board was created to redress trial-related complaints, and this included compensation for injuries and the care of participants who become HIV positive. A stipulation was laid down that the ethics committee and the arbitration board's recommendations would be respected.

Although there is no independent assessment available on the extent to which these standards were actually implemented during the trials, the fact that all sponsors agreed to these standards has established a benchmark for all clinical trials taking place in the country.

Some critical issues for discussion

Before conducting any clinical trial, it is essential to consider whether there is a strong justification for exposing participants to the risks of the trial. Some doubts still persist about the justification for the hasty beginning of the first Phase I trial at the NARI of the tgAAC09, a recombinant adeno-associated viral vector-based candidate vaccine.

Phase I trials of the tgAAC09 vaccine had started in December 2003 in Belgium and Germany and their results were awaited in early 2005. Instead of waiting for these results, a trial of the same candidate vaccine, with the same protocol, was started in India on February 7, 2005. On February 22, barely two weeks after the trial was launched in India, Targeted Genetics, the company conducting the trials in collaboration with the International AIDS Vaccine Initiative (IAVI), issued a press statement announcing the preliminary results of the Belgium-Germany trials. It stated: "The Phase I trial is … primarily designed to evaluate safety and tolerability of the vaccine at escalating dose levels. The study is also designed to evaluate immune responses following vaccination. No safety concerns were identified and the vaccine at the doses evaluated was well tolerated. In addition, a single administration of the vaccine at the doses evaluated in this initial study did not elicit significant immune responses." (1)

Since the overseas sponsors of the India trials, IAVI and Targeted Genetics, were also involved in the Belgium-Germany trials, it is inconceivable that they did not know of the latter's preliminary findings two weeks before the extension of that trial in India. Did they share this information with the Indian sponsors – the Indian Council of Medical Research, the ministry of health and family welfare and the National AIDS Control Organisation? Did the Indian sponsors ask to examine the data of the Belgium-Germany trials before commencing the trial of the same vaccine in India? This apparent lack of communication raises questions on the nature of the partnership between the Indian and overseas partners. It may be argued that even if India was to eventually conduct a Phase II trial of the same candidate vaccine with a different dosage, a Phase I would still be necessary. But would a more detailed analysis of the data prior to the Indian trial have resulted in a radically altered Phase I protocol here?

Under the circumstances, the sponsors in India were compelled to make amendments -- including amending the informed consent form to give information on the results of the Belgium-Germany trial to participants -- a few months after the trial started.

A related question pertains to the complete absence of a "political and scientific will" to systematically develop and test therapeutic vaccines. This is perhaps an inadvertent outcome of depending on a single sponsor. The therapeutic vaccine would pose fewer ethical challenges. The scientific challenges may be comparable but it would cost less to vaccinate infected persons alone, rather than an entire population. Why is this option kept out of the policy debate?

The field of vaccine development today is driven not entirely by altruistic motives. It is shaped as much by philanthropy as by competitive market interests, global institutional arrangements of intellectual property rights, patents, scientific capacities (or the lack thereof), and the interests of investors and shareholders. Hence, another critical area that needs public debate is the arrangement between the company holding patents of the candidate vaccines and the government. It is essential that only those candidate vaccines are tried whose technology will be transferred to the host country, with the commodity to be made available at a price that the country can afford. In the absence of specific agreements and mechanisms for accountability even a successful trial may not necessarily benefit the country.

Conflict of Interest: *Amar Jesani is a member of the advisory group of IAVI and Lester Coutinho was formerly a consultant with IAVI.*

Reference

1. Targeted Genetics Corporation [homepage on the internet]. *Targeted Genetics announces preliminary safety data from phase I HIV vaccine trial*. [cited 2007 Jan 8]. Available from: http://ir.targen.com/phoenix.zhtml?c=84981&p=irol-newsArticle&ID=677299&highlight