# HPV vaccine trials and sleeping watchdogs

**SANDHYA SRINIVASAN**

**Independent journalist, 8 Seadoll, 54 Chimbai Road, Bandra (W), Mumbai 400 050 INDIA e-mail: sandhya_srinivasan@vsnl.com**

In April 2010, the government announced an enquiry into the conduct of a study on the Human Papilloma Virus (HPV) vaccine in Andhra Pradesh and Gujarat. More than a year later, the committee's final report is yet to be made public. The committee's preliminary report (1) records a number of ethical violations but does not assign responsibility to any individual or institution. Further, the central information commission has refused to provide any details of the study protocol that might constitute "intellectual property". As the project is described as a feasibility and acceptability study of an approved vaccine, it is not clear what intellectual property is involved here. The CIC's refusal raises concerns that commercial research is being conducted in the garb of providing a public service.

We must ask whether the existing regulatory mechanisms are able to ensure ethically conducted research that is relevant to Indians.

## History of the controversy

The enquiry committee was set up following a public outcry because of evidence of serious ethical violations in the conduct of a research study using the HPV vaccine. This study was described as a demonstration project to evaluate the feasibility and acceptability of using the vaccine in an immunisation programme. It started in July 2009 and involved the administration of the HPV vaccine to some 25,000 girls between the ages of 10 and 14 in Andhra Pradesh and Gujarat. It was conducted by an international non-governmental organisation (Program for Appropriate Technology in Health or PATH) and supported by the state governments of Gujarat and Andhra Pradesh and the Indian Council of Medical Research. The vaccines were supplied by Merck and GlaxoSmithKline, two multinational drug companies that have lobbied aggressively to introduce the HPV vaccine into public immunisation programmes worldwide. The project was funded by the Bill and Melinda Gates Foundation.

Following press reports that some girls had died after being given the HPV vaccine, an investigation led by the Sama Resource Group for Women and Health uncovered a number of ethical violations: the vaccine was used on a particularly vulnerable population – very poor children, mostly unlettered, many unable to speak the local language. Many lived in hostels, which allowed the researchers to bypass the children's parents and obtain consent from hostel wardens. These wardens were unlikely to refuse consent to the government officials who accompanied PATH staffers. There was no infrastructure in the study sites for reporting adverse events and treating them, let alone following them up. Seven girls died following administration of the vaccine (2).

## Larger context of the HPV vaccine

The inquiry committee's findings must be seen in the context of the international agenda to promote the HPV vaccine. Though the vaccine has been questioned on many grounds, including those of efficacy and public health value, drug companies have worked hard to promote it by various means, including bribing professional associations (3).

PATH has led the campaign for the HPV vaccine in India, and it has done so with the government's scientific review, ethics review and logistical support. PATH's research agenda is to look for ways to introduce the vaccine into the national immunisation programme. The question is not "whether" but "when" and "how". For example, one of PATH's decisions was to get the vaccine into a few state immunisation programmes, making it easier to obtain national approval. The AP and Gujarat trials were the second stage of this project. The first stage set out to look at delivery methods, communications and advocacy strategies, using schools and government health centres, training government staff, exploring the use of the private sector, using the media, and getting endorsements from the government, professional associations and other influential individuals and organisations (4).

## The committee's findings

The committee was asked to investigate whether there was any link between the vaccine and the seven deaths, and to examine the ethics of conducting the study on children of a marginalised population, particularly whether appropriate consent was taken. It concluded that there was no apparent link between the vaccine and the deaths, but identified two major concerns. First, the research included vulnerable groups and consent was not taken properly. Second, there was no system for proper identification and investigation of adverse events. It also noted that violations occurred at every level:

- The research was conducted on a particularly vulnerable population. The committee called for a halt to all research on tribals unless it was of specific benefit to them. It also noted that the study should not have been done in areas where parental consent would have been difficult to obtain. It was legally and morally wrong for the government to authorise hostel wardens and headmasters to give consent on behalf of minors, particularly for research, and particularly for an elective vaccine.
- The project used government machinery, including state immunisation officers, blurring the distinction between a government immunisation programme and a research study. Further, there is a conflict of interest created when drug companies which want to introduce a vaccine into the immunisation programme are permitted to supply the vaccine for studies to evaluate the feasibility of such a programme.

- Though the committee concluded that the deaths were "most probably" not related to the vaccine, it noted that there was insufficient information on three of the deaths. It described the lack of monitoring and follow-up of serious adverse events as a "major deficiency". Most important, it called for funders and ethics committees to ensure increased and better monitoring of all vaccines for four years after their approval, and investigation of any adverse events regardless of whether they appear to be related to the vaccine. It also called for the Drugs Controller General of India (DCGI) to review safety mechanisms and approval of post marketing trials of the HPV vaccine.
- The study should have included insurance, especially since it was on healthy volunteers. (In fact, this is a requirement for clinical research, and PATH seems to have got away without providing insurance on the argument that this was not a study but a demonstration project.) The committee noted that PATH had taken insurance cover for itself.
- Each halted HPV study should be reviewed for its ethical and scientific aspects and a decision taken.

It is shocking that the committee negated all these observations by concluding that the deficiencies were "minor" and there was "no major deficiency for which the responsibility could be fixed on any individual or agency". Instead, the report seems to focus on providing lessons towards "enhancing public confidence and avoiding a crisis in a public health programme", emphasising the need to give the public confidence in government programmes rather than to ensure ethical practice.

## Transparency

There are other issues that the committee did not see fit to comment on, and these are generic problems with the ethics review and monitoring process for research in India.

For one, the proposal was cleared by a number of institutional ethics committees (IECs) in India and abroad. How did these IECs clear the proposal without noting the concerns that the inquiry committee identified on the basis of the same documents? It seems that many IEC members do not have the skills or the perspective necessary to identify basic ethical concerns in research. Or perhaps, they are influenced by the pressure to permit certain research.

Second, at least one IEC, from the Public Health Foundation of India, rejected the proposal as it did not address the ethical issues in the project (5). However, guidelines for ethics review in India do not require a proposal's sponsors to inform ethics review committees of decisions made by other committees on the same proposal. This allows ethics committee shopping - a practice that has been noted in the case of other commercial research, and may be very common.

Third, the many ethical violations in the HPV vaccine trials would never have come to light if it were not for civil society organisations and the press. In other words, the existing structure for monitoring research provides no assurance that proposals are reviewed properly to protect participants, that research is monitored correctly, that adverse events are reported and investigated correctly, and that all this information is available in the public domain.

Indeed, the lack of transparency is an underlying theme in the HPV vaccine trials. The government has consistently refused to make public details of the research itself. In June 2009, the DCGI made it mandatory for all clinical trials up to phase 3 to be registered on the Clinical Trials Registry-India. The study which was earlier called a demonstration project is now described as a phase 4, post-marketing trial to evaluate strategies for delivery of the vaccine and its acceptance by the population. Post marketing trials are exempt from registration. However, the committee's preliminary report notes that four of five primary outcome measures were to do with the vaccine's safety. We do not know what these outcome measures were and whether they might be used towards any further approval process.

In any case, why should post-marketing trials be excluded from registration requirements?

Efforts to get details of the study protocol have been stalled. On March 29, 2011, the central information commissioner dismissed an appeal under the Right to Information Act (Sama, personal communication) asking for information such as details of the pre-licensing trials, the basis of approval for import, sale and marketing, and study protocols for the PATH study. The CIC refused on the grounds that an inquiry was underway, and in any case, it would not provide any information that dealt with the "exclusive intellectual property rights" of the drug companies involved. What intellectual property rights can be had by a project with government collaboration purportedly for public benefit to evaluate the acceptability of the vaccine? Or is the study collecting information for commercial benefit?

The story of the HPV vaccine trials illustrates the failure of many systems - the ethics review and monitoring process, regulatory requirements, and even the inquiry process. Existing governance mechanisms are clearly unprepared for the pressures of an industry which sees India both as a site for its research and a place to sell drugs and vaccines.

**References**


1. Interim report of the committee appointed by the government of India vide notification no.V.25011/160/2010-HR dated 15th April, 2010, to enquire into "Alleged irregularities in the conduct of studies using Human Papilloma Virus (HPV) vaccine" by PATH in India November 9th, 2010.
2. Sarojini NB, Srinivasan S, Y Madhavi, Srinivasan S, Shenoi A. The HPV vaccine: science, ethics and regulation. *Econ Polit Wkly*. 2010 Nov 27. 45(48): 27-34.
3. Kang G. HPV vaccines:separating hope from drug company hype. *Indian J Med Ethics.* 2010 Jan-Mar; 7(1): 56-7
4. PATH and NARI. *Shaping a strategy to introduce HPV vaccines in India. Formative research results from the HPV vaccines: evidence for impact project.* [Internet]. Seattle, WA: PATH; 2009 [cited 2011 Mar 15]. Available from: http://www.rho.org/files/PATH_FRTS_India.pdf
5. Dhar A. PHFI rejected HPV vaccine project proposal. *The Hindu* [Internet]. New Delhi; 2011 Feb 18 [cited 2011 Mar 15]. Available from: http://www.hindu.com/2011/02/18/stories/2011021864301300.htm