

# The HPV Vaccine: Science, Ethics and Regulation

SAROJINI N B, SANDHYA SRINIVASAN, MADHAVI Y, SRINIVASAN S, ANJALI SHENOI

A recent civil society-led investigation has highlighted serious ethical violations in a trial of the Human Papilloma Virus vaccine on girls in Khammam district in Andhra Pradesh. The findings are presented along with a review of clinical trials of the HPV vaccine in India and an analysis of the Drugs and Cosmetics Act and Rules. Together they illustrate how the promotional practices of drug companies, pressure from powerful international organisations, and the co-option of, and uncritical endorsement by, India's medical associations are influencing the country's public health priorities.

The authors would like to acknowledge Vrinda Marwah from Sama for her inputs.

Sarojini N B ([sama.womenshealth@gmail.com](mailto:sama.womenshealth@gmail.com)) is the coordinator of Sama-Resource Group for Women and Health. Sandhya Srinivasan ([sandhya\\_srinivasan@vsnl.com](mailto:sandhya_srinivasan@vsnl.com)) is an independent health journalist based in Mumbai. Madhavi Y ([y\\_madhavio1@hotmail.com](mailto:y_madhavio1@hotmail.com)) is a scientist at the National Institute of Science, Technology and Development Studies, New Delhi. Her comments are made in her personal capacity and do not represent the institution. Srinivasan S ([sahajbrc@gmail.com](mailto:sahajbrc@gmail.com)) is Managing Trustee, LOCOST, Vadodara, and a member of the All India Drug Action Network and Medico Friend Circle. Anjali Shenoj ([sama.genderhealth@gmail.com](mailto:sama.genderhealth@gmail.com)) is a research coordinator from Sama-Resource Group for Women and Health, and was part of the investigation described in this article.

On 7 April 2010, the government called a halt to trials of the Human Papilloma Virus (HPV) vaccine in the country. According to a press report, "In the wake of reports of violation of ethical guidelines and exploitation during the 'clinical trials' of HPV (Human Papilloma Virus) vaccine, meant to prevent cervical cancer among women, the Centre on Wednesday advised the state governments to suspend the vaccine programme until the issue is settled" (Dhar 2010a).

On 29 April, V M Katoch, Secretary, Department of Health Research and Director General of the Indian Council of Medical Research (ICMR), admitted to the Parliamentary Standing Committee on Health that the "Drugs Controller General of India's guidelines had not been adhered to in the clinical trial of the Human Papilloma Virus (HPV) vaccine", and a committee was constituted to inquire into the demonstration projects (Thacker 2010).

Both the announcement and the statement came after strong opposition by civil society groups and a Member of Parliament (Parliament Proceedings 2010)<sup>1</sup> to what were described as "demonstration projects" of the HPV vaccine<sup>2</sup> being conducted in the country. Civil society groups in India have been voicing their concerns regarding the safety and efficacy of the two HPV vaccines; the unethical promotion of the vaccines in the private and public sectors; the public health implications of their administration; the need to investigate reported deaths and adverse events post vaccination; and the consequences if the vaccines were introduced into the country's universal immunisation programme (UIP). Two memoranda have been submitted to the union minister of health and family welfare (MOHFW) enumerating these concerns and calling for a halt to the demonstration projects (Dabade et al 2010; Jan Swasthya Abhiyan et al 2010).

In March 2010, a team of women's rights activists<sup>3</sup> visited one of the vaccination sites in Bhadrachalam mandal, Khammam district, Andhra Pradesh (AP), to understand the ground realities of the project. In particular, they sought to look at the nature and procedures of taking consent and providing information to the girls and their parents, and the availability of the health infrastructure required to support cancer screening and prevention. The team visited residential schools, hostels and primary health centres (PHCs) where girls were vaccinated. Interviews were conducted with vaccinated girls, hostel wardens, schoolteachers, PHC staff, local activists from adivasi networks and women's groups. The team also interacted with the parents of one of the girls who died in January 2010, following the third dose of the vaccine.

A look at the findings of this visit, along with the recent admissions by the MOHFW and the ICMR about the nature of the projects and other related concerns, suggests that these projects – which were in fact research – violated existing ethical guidelines on clinical research, as well as child rights. These violations include – but are not limited to – testing on vulnerable and marginalised groups (particularly paediatric populations), who are not likely to benefit from the results of the research, and without taking their proper informed consent or assent.

In addition, a scrutiny of other trials on the HPV vaccine and of ethical and regulatory documents highlights problems in the implementation of Schedule Y of the Drugs and Cosmetics Act (DCA) regarding requirements for clinical trials, and the interpretation of the law by the Drugs Controller General of India (DCGI). Trials conducted for regulatory requirements may be insufficient from a scientific point of view. Further, there is no harmonisation between Schedule Y of the DCA, the ICMR's ethical guidelines on biomedical research on human participants, and the World Medical Association's Declaration of Helsinki. Schedule Y is legally binding on clinical trials in India. While the other two documents are not legally binding, Schedule Y requires that clinical study

reports include a declaration that they conform to the Declaration of Helsinki and that ethics committee notifications follow the Central Drug Standard Control Organisation's (CDSCO) good clinical practice guidelines as well as the ICMR's ethical guidelines (MOHFW 2005: 516). Violations of provisions of the other two documents do not appear to invite any legal action – a situation that trial sponsors and research organisations may wish continues for ever.

This has also drawn attention to the lack of transparency in clinical research. The scientific purpose of certain trials may be kept unclear and sponsors may be able to avoid making information on these trials public, given that the DCGI specifically requires the registration only of certain types of trials on the Clinical Trials Registry-India (CTR-I) (NIMS/ICMR).

Finally, the case of the HPV vaccine illustrates how promotional practices of drug companies, pressure from powerful international organisations, and the co-option of India's medical associations to uncritically endorse a vaccine, are influencing public health priorities. These findings, along with evidence – in the HPV trials and elsewhere – of the poor quality of ethical review and monitoring of clinical trials, add to growing apprehensions about unethical clinical and epidemiological research in India.

This paper outlines the investigation findings before presenting a summary of HPV research in India. It identifies a number of ethical violations and scientific ambiguities in this research, and comments on the public health implications.

## 1 Path and HPV

### The AP 'Demonstration Project'

In mid-2009, the Indian unit of Program for Appropriate Technology in Health (PATH), a US-based healthcare organisation, began a two-year HPV vaccination drive, vaguely described as a "demonstration project", in two states in India. The project was a collaboration between the ICMR and the state governments (*The Hindu* 2009), with support from the Bill and Melinda Gates Foundation (Dhar 2010a). In all, 14,091 girls in Bhadrachalam, Kothagudem and Thirumalayapalem blocks in Khammam

district in AP and 10,686 girls in Dabhoi, Kawant and Shinor blocks in Vadodara district in Gujarat were given the vaccine. The vaccines used were Merck's Gardasil (in AP) and GlaxoSmithKline's Cervarix (in Gujarat) (Parliament Proceedings 2010).<sup>4</sup>

The findings of the investigation (Sarojini et al 2010) and their implications are summarised below:

### A Vulnerable Population

The girls selected to participate in the ICMR/state government/PATH research were in the age group of 10-14 years. The girls from Bhadrachalam, which the team visited, were from four social groups with poor economic backgrounds: scheduled tribes (STs), scheduled castes (SCs), Muslims and other disadvantaged communities. Some girls were from families that have been displaced by the ongoing conflict in the neighbouring state of Chhattisgarh – circumstances that served only to compound their vulnerability. They seem to have been chosen without the use of inclusion and exclusion criteria regarding their health.

Moreover, the existing health infrastructure in the region is woefully inadequate. There are no pap smear facilities and no qualified gynaecologists in the public health set-up at Bhadrachalam. Quality healthcare is not available for malaria, diarrhoea and other preventable and curable health problems common in this region. The community has no access to information, and there is no adverse event reporting mechanism, required in any medical research. All these intensify the vulnerability of this community on which the research was conducted.

Though the ICMR guidelines for biomedical research on human participants require researchers to justify the involvement of those with "reduced autonomy as research participants, since their consent may be under duress or [due to] various other compelling reasons" (ICMR 2006b: 29), no such justification has been made public regarding the HPV vaccine research in AP and Gujarat.

**No Informed Consent:** Many of the vaccinated girls were residents of *ashram paathshalas* (boarding schools for tribal children).

The selection of these girls for the research is striking, given that their parents, living separately, could not have monitored and responded to any adverse developments in their children's health; the researchers could also use this to avoid seeking parental consent. And the "target group", as these girls are described, could not question the motive or the procedure of the project.

Some, but not all the girls received documents in Telugu. These consent forms seem to have been used primarily in the case of non-residential schools. Here, children were asked to get signatures from their parents; the researchers did not approach the parents to obtain their consent.

Researchers seeking informed consent must provide information that includes the risks and discomforts; the policy on compensation; the availability of medical treatment for injuries; and alternative therapies if available (ICMR 2006b: 21). This information was not given.

Though both Schedule Y of the DCA (MOHFW 2005: 510) and the ICMR guidelines (ICMR 2006b: 28) require that trials on children can be undertaken only with the consent of the parent or guardian, and with the assent of the children where appropriate, the interviews suggest that neither was taken.

The girls selected for immunisation were given "HPV Immunisation Cards", which were in English, an unfamiliar language for both the girls and their parents. The logo of the National Rural Health Mission (NRHM) was printed on the card. All those interviewed (wardens, teachers, parents and students) believed the research to be part of the government's immunisation programme. The girls and their parents were unaware that they were part of some kind of research. They were under the impression that the government was providing an expensive and otherwise unaffordable vaccine free of cost, which would prevent "uterine" or "cervical cancer". They did not know that they could have refused the vaccine. Those interviewed indicated that they were told that the vaccine would provide lifelong protection. No side effects or possible long-term problems associated with the vaccine were mentioned. The fact that the vaccine protects against only two

types of HPV, necessitating regular pap screening even after vaccination, was not mentioned at all – neither verbally, nor in the written material given to some girls.

**No Follow-up and Compensation for Adverse Reactions:** In the ICMR/PATH/state government research, four post-vaccination deaths were reported from AP, and two from Gujarat. No formal investigation of these deaths seems to have been carried out, but the deaths have been attributed to suicide, drowning, viral fever, suspected snakebite and severe anaemia with malaria (Parliament Proceedings 2010).<sup>5</sup> Side effects reported to the team that visited Bhadrachalam ranged from severe stomach ache, headache, dizziness and skin allergies to extreme mood swings, irritability, uneasiness, epileptic seizures, heavy bleeding and severe menstrual cramps following the vaccination (Sarojini et al 2010). Standard procedure in clinical trials – as well as in any immunisation programme – requires that all such reports be recorded and investigated. However, these reports are not mentioned in public documents on the website of PATH; nor is there any evidence that the government has recorded them. Though the ICMR guidelines (ICMR 2006b: 5) assert that every research study must provide mechanisms for compensation, treatment and aftercare for any injury or harm, the informed consent forms seen by the team made no mention of this mechanism.

**Explanations from the Government and PATH:** The reports of the fact-finding visit led to a public outcry. Due to the sustained advocacy work in this regard by civil society groups and the pressure on the health minister in the Parliament, on 7 April 2010, the government announced a halt on all trials of the HPV vaccine in India.

On 22 April 2010 – almost a year after the launch of the trials – Ghulam Nabi Azad, Union Minister for Health and Family Welfare, stated for the first time that the “demonstration project” was a “post-licensure (operational research) study”. He also called it a phase 4 (post-market) trial and said that the “demonstration project in a working model to study the

impact of public health and management of a particular illness in this age group is part of the operational research” (Parliament Proceedings 2010).<sup>6</sup>

An update (PATH 2010) on the PATH website stated that what was thus far referred to as “demonstration project” in all their documents was a “‘post-licensure observational study’ involving administration of human papilloma virus (HPV) vaccine in India” with the vaccines being provided free of cost by the two pharmaceutical companies involved. The objective of the study was stated to be:

...to generate critical data and experience on effective strategies for public-sector HPV immunisation programmes, as part of a broader cervical cancer prevention and control strategy. The project seeks to assess HPV vaccine coverage achieved, acceptability in the community, feasibility, and cost of implementing HPV vaccination through different strategies...Project results will help the Ministry of Health and Family Welfare, Government of India, with future programme planning, if and when a decision is made to introduce HPV vaccine and/or to expand screening and treatment programmes.

The government’s response and the press release from PATH contain a number of underlying assumptions that needs to be questioned. First, they take it for granted that the HPV vaccine’s public health value has been established and that India needs the vaccine in its national UIP. This is a matter of debate. Second, measuring “vaccine coverage” is relevant only after the vaccine’s public health value has been established. Third, “acceptability in the community” depends on the community’s confidence in the existing UIP, as well as on the advice given by the researcher/health worker on the risks and benefits of HPV vaccination; the community will tend to believe whatever the health worker tells them. Finally, “acceptability” can be determined only when there is a proper adverse drug reaction system in place. There is no functioning system of reporting of adverse events in the country following vaccination. Despite the presence of pharmacovigilance centres, there is no meaningful follow-up of adverse drug reactions; reporting by medical practitioners is voluntary. Indeed, the investigation showed that adverse events reported following HPV vaccination were not documented.

## 2 Scientific and Regulatory Issues

**Licensing of the HPV Vaccine in the West:** According to a press release from the US Food and Drug Administration (USFDA), one US and three multi-country clinical trials, evaluating the safety and efficacy of Gardasil were conducted on 21,000 girls. These trials were conducted largely on girls in the age group of 16-26 years; two studies were conducted on girls in the age group of 9-15 years to demonstrate the immunogenicity and tolerability of the vaccine in lower age groups. Following these trials, through a fast-track approval process, in 2006 Gardasil was approved by the USFDA for use by girls in the age group of 9-26 years (USFDA 2006).<sup>7</sup>

(Incidentally, fast-track approval is reserved by the USFDA for life-saving drugs with the potential to fulfil an unmet medical need such as new cancer treatment or AIDS drugs, for which approval may be granted within six months of the initial testing. Fast-track approvals may be appropriate for drugs to prevent or treat life-threatening medical emergencies for which there are no other options. This is certainly not the case with the HPV vaccine.)

Cervarix was first approved in September 2007, by the European Union, for use in girls and women in the age group of 10-35 years. Approval was granted based on the “demonstration of efficacy in women 15-25 years of age and demonstration of immunogenicity in girls and women in the 10-25 years of age” (USFDA 2009a: 14). In October 2009, the USFDA approved Cervarix for use in females aged 10-25 years (USFDA 2009b).

**Questions about Licensing in the Indian Context:** There is a lack of clarity on the purpose and regulatory status of the various HPV vaccine trials in India.

According to the DCA, “all vaccines shall be new drugs unless certified otherwise by the Licensing Authority ...” (MOHFW 2005: 134). The Act also states:

For new drugs approved outside India, Phase III studies need to be carried out primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as

recommended in the prescribing information. Prior to the conduct of Phase III studies in Indian subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad (MOHFW 2005: 508).

These non-specific requirements – without, for example, details of a minimum number of trial sites and participants – for a specific phase trial leave much room for interpretation according to convenience.

**Clinical Trials of the HPV Vaccine in India:** Data submitted for marketing approval of Cervarix and Gardasil in India are not available in the public domain.

According to the trials listed in the US government clinical trial registry and in published articles in medical journals, marketing approval for the HPV vaccines in India seems to have been based on two trials conducted on small sample sizes, and on testing and approval by other regulatory agencies including the USFDA. One was a “phase 3b double-blind, randomised, controlled study to evaluate the immunogenicity and safety” of Cervarix on 354 “healthy Indian female subjects aged 18-35 years”. This was reported in the US government registry (USNIH) (NCT00344032) and completed in November 2007. The other was a “phase 3 trial” looking at the “safety, tolerability and immunogenicity” of Gardasil in “healthy females 9 to 15 years of age in India”; conducted on 110 girls aged 9-15 years (NCT00380367), and completed in February 2008. While this is how these trials have been described by the US registry, it is not yet known how they were described in the documents submitted to the DCGI prior to their approval.

Both the DCA and the ICMR guidelines state that drugs should be tested on children after testing on older children or adults (MOHFW 2005: 509; ICMR 2006b: 28). The Gardasil trial seems to have violated both ICMR guidelines and the DCGI’s requirements in this context. At the very least, safety should have been established in older groups before testing on children. However, the DCA leaves room for interpretation: “When clinical development is to include studies in children, it is *usually* appropriate to begin with older

children before extending the trial to younger children and then infants” (emphasis added).

The DCGI licence for sale, marketing and import, granted in 2008, approves Cervarix for use in girls between 10 and 45 years, though trials have been conducted only on women between 18 and 35 years in India and on girls and women between 10 and 25 years in other countries. Gardasil was approved for use in girls in the age group of 9-26 years. It was tested on women in the age group of 9-15 years in India, and on girls and women in the age group of 9-23 years in other countries.

In sum, the vaccines were tested in India on children before they were tested on adults, instead of the other way around, and received approval in India for use in an age group outside the age group on whom they were tested during the trial stage in India. There are a number of clinical trials of the HPV vaccine in India, in addition to the two trials before the vaccines were approved.

The vaccination programmes in AP and Gujarat have variously been described as “a post-licensure operation research study” and a “Phase IV, post-market trial”.<sup>8</sup> According to at least one media report, Katoch stated to the Parliamentary Standing Committee on Health that proper guidelines with respect to protocol on selection of participants were not adhered to (Thacker 2010). Unfortunately, he did not provide further information on this. These trials are not registered in any public registry and information on the trial protocol, ethics review and other details are not available in the public domain. These were preceded by “formative research” that PATH has stated was

“designed to guide development of a vaccine delivery strategy, a communications strategy (for outreach to communities), and an advocacy strategy (for outreach to policymakers)” (PATH undated). Details of this research are not in the public domain.

In September 2009, a “Phase 4” trial was launched comparing a two-dose regimen of Gardasil with the standard three-dose regimen (CTRI/2009/091/000137, NCT00923702). This was to be conducted on 20,000 girls aged 10-18 years. Interestingly, this “India only” trial on dose comparison covers almost as many girls as the total number covered in the pre-approval trials conducted across 33 countries, thus raising concerns about the use of vulnerable populations in resource poor countries like India, which have a history of poor trial regulation. The trial is described as “suspended” on US registry clinicaltrials.gov and “not yet recruiting” on CTR-I.

Further, in October 2009, Merck commenced another “phase 3 trial” of 600 women to study the tolerability and immunogenicity of a three-dose regimen of Gardasil administered to “healthy females” between 16 and 23 years of age in India (16-26 according to the Indian registry). As of 28 April 2010, following the ministry’s statement in Parliament regarding the vaccination “projects”, the CTR-I lists the status of this trial (CTRI/2009/091/000787) as “temporary halt or suspended”, while clinicaltrials.gov (NCT00733122) continues to list it as “currently recruiting participants”.

Yet another trial of HPV vaccine on HIV positive women (CTRI/2009/091/000298, NCT00667563), described as “phase 1” in CTR-I but with no phase mentioned in

**Institute of Applied Manpower Research  
Sector A-7, Institutional Area, Narela, Delhi-40.**

**CORRIGENDUM**

Reference advertisement published in EPW (16 October 2010) for faculty positions. The last date for receipt of applications for all the posts is extended upto 10-12-2010.

(Raj Kumar)  
Administrative Officer

clinicaltrials.gov, is described as currently recruiting on both registries.

The following questions are illustrative of what needs to be asked about a number of clinical trials being conducted in India for regulatory and other purposes:

- Should the DCGI approve a new drug on the basis of a single trial in India just because it has received USFDA or European Medicines Agency (EMA) approval?
- Why did the DCGI approve the HPV vaccines for use in an age group outside the age group on whom they were tested in India?
- On what basis did the DCGI grant approval for the Gardasil trial on children in 2007, before it was done on Indian adults?
- Should not the Phase 3 trial of Gardasil on women aged 16-23 years, starting in 2009, have preceded the Phase 3 trial in 2007 on 110 girls aged 9-15 years? This would be in conformity with both Schedule Y of the DCA and the ICMR ethical guidelines.
- What additional information was the Phase 3 trial of Gardasil, starting in 2009, meant to provide after the licensing of the vaccine? If additional information was needed, should not it have been obtained before licensing?
- If, according to the DCA, a new dose of a drug is considered a new drug, why is a trial comparing the standard dose of Gardasil with a new dose described as a Phase 4, or post-marketing trial?
- Why is Gardasil being tested on 20,000 children? Why are all trial sites in India?
- Should research described as a “demonstration project” be exempt from registration in public registries?
- What are the implications of discrepancies in information given in the Indian and US registries?

### Regulatory Discrepancies

There are problems with the interpretations of clinical trial requirements (given in the DCA) by the DCGI, the licensing authority. The DCA 1945 and the related rules, especially Schedule Y of the rules (especially rules 122A, 122B, 122D, 122DA, 122DAA and 122E) contain several clinical trial waiver clauses.

For instance, according to Clause 1.3 of Schedule Y,

(3) For drugs indicated in life threatening/serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority.

Also, under Rule 122A for “Application for permission to import New Drug”:

(2) The importer of a new drug when applying for permission under sub-rule (1), shall submit data as given in Appendix 1 to Schedule Y including the results of local clinical trials carried out in accordance with the guidelines specified in that Schedule and submit the report of such clinical trials in the format given in Appendix II to the said Schedule:

Provided that the requirement of submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries: Provided further that the submission of requirements relating to Animal toxicology, Reproduction studies, Teratogenic studies, Perinatal studies, Mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries if he is satisfied that there is adequate published evidence regarding the safety of the drug, subject to the other provisions of these rules.

A similar exemption is available under Rule 122B for application for approval to manufacture a new drug other than the drugs classifiable under Schedules C and C(1).

The point is that there seem to be arbitrary powers vested in the DCGI as to when and how he can waive clinical trial requirements. There is not even a formal requirement that the DCGI’s office should consult a more competent group of clinicians and public health experts.

The website of CDSCO (undated) contains, in the left column under the rubric “Drugs Approved for Marketing”, a list of drugs imported from abroad. Most of them cannot qualify under the category of public interest or those urgently required under “threatening/serious diseases or diseases of special relevance to the Indian health scenario”, such as, for example an H1N1 vaccine might qualify. Herein, scope for considerable money changing hands cannot be ruled out, and the law needs to be tightened.

The waiver clauses in the law mentioned above appear to protect the DCGI or the Government of India. The DCGI may have

used these powers to waive clinical trial requirements for the HPV vaccine. It is possible that the DCGI exercises such powers not on the basis of professional judgment, but under compulsion from policymakers higher up in the establishment.

### Unclear Definitions for Trial Phases:

There is also lack of clarity on what a “bridge study” and a “Phase 3b study” are. Though both terms have been used with reference to the HPV vaccine trials, neither is mentioned in the Drugs and Cosmetics Act and Rules.

“Bridging studies” are mentioned twice in the CDSCO’s Guidance to Industry (CDSCO undated), but described only on page 33 and in passing: “This may also include disclosures of the formulation intended to be marketed and/or any bridging studies which may be necessary, planned, initiated and/or already performed if different formulations have been used during clinical development”. The ICMR guidelines state: “Bridging studies in vaccine trials are conducted to support clinical comparability of efficacy, safety and immunogenicity of new formulation when there is change in vaccine composition with regard to adjuvant, preservative, or a change in manufacturing process, site or scale...” (ICMR 2006b: 45).

It is also not clear from the DCA whether drugs such as the HPV vaccine can be made available in the market when such trials are still under way. Can drugs be approved for marketing when trials are going on, whose purpose inter alia is to look into their safety?

The union health minister has indicated that the trials in AP and Gujarat were Phase 4 post-marketing trials. However, they do not fit the description of Phase 4, post-marketing trials, or Periodic Safety Update Reports (PSUR) for Post-Marketing Surveillance as given in Schedule Y of the DCA:

Post-Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug’s safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimising the drug’s use. They may be of any type but

should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), e.g., mortality/morbidity studies, epidemiological studies, etc (emphasis added) (MOHFW 2005: 508).

Nor do they fit the slightly different definition in the ICMR Guidelines on Phase 4 Studies (post-licensure evaluation):

These studies are done in the entire population or a subgroup to detect the rarer or unexpected events that may not be seen in smaller Phase II/III studies. Post-licensure studies of large populations, in a more heterogeneous group of people, over longer periods of time are necessary to provide ongoing assessment of vaccine safety and effectiveness (ICMR 2006b: 44).

So if these trials are not sanctioned by the scope of Schedule Y, then technically they would be illegal. The larger question raised by this survey of trials is one of research methodology: can conclusions be made about a drug's long-term efficacy on the basis of short-term studies? What periods of trials and follow-up are appropriate in such cases?

**Right to Information Denied:** In May 2010, health activists<sup>9</sup> filed applications under the Right to Information Act 2005 seeking facts related to the HPV vaccine trials in India. Among the details sought were: the status and basis of approval that granted permission to Merck, Sharp & Dohme to import, sell and market Gardasil in India; the status, design and intent of the trials of the vaccine by Merck and ICMR, and information on, and copies of, the approved protocols for the "demonstration project".

Some of these applications were directed to the office of the DCGI and received a reply that information on the demonstration project and licensing of the vaccines was a "trade secret and commercial confidence of third party and exempted from disclosure under Section 8 (1) (d) of RTI Act" (Dhar 2010b).

Why is the study design or protocol of a demonstration project that sought to gain experience and build evidence for the future introduction of HPV vaccination into the public health system in India considered a "trade secret"? All information on a public service should be

public knowledge and should be in the public domain.

### 3 The Larger Implications

#### The Pressures of 'Public Private Partnerships'

The "demonstration project" by the MOHFW, ICMR, PATH International and the state governments of AP and Gujarat is a public private partnership, and highlights concerns around such partnerships, which are implemented without the necessary health system reorganisation, or any mechanism to enforce transparency and accountability.

There is a lack of clarity regarding the role and accountability of foreign non-governmental organisations (NGOs) such as PATH and international funding agencies such as the Bill and Melinda Gates Foundation. We should also note that the HPV immunisation card given to children administered the vaccine carries the logos of the NRHM and of PATH. This raises questions about the role of the NRHM in this research, given that there is no mention of such "projects" in its mandate. One must also note the involvement of the ICMR in the approval and design of a project – for a foreign NGO to influence policymaking and public health needs by using Indian children as research subjects.

The ICMR guidelines on the principles of totality of responsibility state that:

...the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on *all those directly or indirectly connected with the research* or experiment including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, *inter alia*, the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use (emphasis added) (ICMR 2006a: 7).

The eagerness to welcome these vaccines is also evident in the memorandum of understanding signed between the ICMR and Merck in 2005, regarding trials

in India and the launch of Gardasil in the country – even before USFDA approval was obtained. Finally, there is the related question of the validity of the certificates of safety and worthiness given by professional bodies of doctors, such as the Indian Academy of Paediatrics, even when the drug's safety and efficacy were still under investigation.

None of the organisations, government, private or non-governmental, can be absolved of responsibility for the unethical research carried out in the name of demonstration projects.

#### Public Health Implications

Certain key facts about HPV infection and disease and the role of an HPV vaccine in the prevention of cervical cancer are relevant to any discussion of its introduction in India's public health programme.

Around 1,32,000 women in India develop cervical cancer every year, and 74,000 die of it (Bhatla and Moda 2009). The National Cancer Control Programme, formulated and funded by the MOHFW, has stressed the importance of implementing a community-based cervical screening programme, and also provides for funds to states to implement the cancer control programme, including cervical cancer screening. However, the programme has failed to have an impact.

In the absence of the organised screening programme, routine screening of asymptomatic women is almost non-existent in India. As a result, 70% of new cases of cancer of the cervix in India are diagnosed at stage III and higher, where treatment success rates are very low (Basu 2006). In the public sector, the facilities for pap smears are limited to tertiary care centres where the test is usually offered to women with symptoms of reproductive tract infections or advanced cervical cancer. Public institutions that perform pap smears do not have facilities for colposcopy or treatment at the pre-cancerous stage through cauterisation. Management of abnormal pap smears is limited to either a follow up visit (presumably to monitor for any progress from the pre-cancerous stage) or a hysterectomy to eliminate the need for follow-up, which is both risky and not indicated. Policy-makers do not realise the need for

prevention and treatment (Basu and Chowdhury 2009).

The HPV vaccine is apparently being introduced to address this gap in the public health system. However, a number of questions can be asked about the value of such an intervention.

First, how useful can the vaccine be in the National Immunisation Programme? It is estimated that the absolute risk of cervical cancer was 2.5/10,000/year, the absolute risk reduction from vaccination is 0.00025 and 4,000 girls would need to be vaccinated to prevent one death (Aneja and Puliye 2009).

Second, the decision to spend on a vaccine programme must also balance the risk of vaccination against the risk of the disease, and death from the disease and produce a high net health benefit by preventing morbidity and mortality from the disease. This is not the case with the HPV vaccine, with significant reported side effects and limited efficacy at best.

Third, even if the vaccine is proved to be safe, it is unaffordable. Even if it becomes affordable in the foreseeable future, is it really required in the UIP as the most effective way to prevent all cases of cervical cancer? Surely there are other methods of prevention, diagnosis, and treatment of HPV infection that are safer and more economical, keeping in mind the overall disease burden of various diseases and their management in the country.

Above all, vaccination is not a substitute for screening. Vaccinated women must continue to have regular pap tests, as the preventive effect of the vaccine on cervical cancer has not been demonstrated. Further, HPV infection is not the only cause of cervical cancer. Additionally, protection by the vaccines is shown only against certain subtypes and for a limited number of years (Lippman et al 2007). Many scientists feel that even in the best-case scenario, the HPV vaccination will require booster doses (Haug 2008). If booster doses are needed, it is not known how frequently they will be needed, or what the impact of the booster doses will be on the safety of the vaccine. Moreover, booster doses will increase the cost of vaccination, and pose additional implementation challenges to reaching women who need revaccination.

In fact, even if the HPV vaccine turns out to be very effective, if it is introduced in places where women are not fully covered by screening services, it will compete with limited budgets and affect existing limited budgets. The vaccine cannot be a substitute for comprehensive public health services. Health interventions of this sort should address causes of vulnerability, such as the absence of healthcare.

Thus, given the faltering existing cancer control programme, the imperative to carry on with routine screening (at an expenditure of not more than Rs 80-250 per screening per woman) even post vaccination, and the abysmally low public health expenditure, even the thought of introducing these vaccines into the public health system is irrational. International funding agencies such as the Global Alliance for Vaccines and Immunisation (GAVI) may be a major source of external assistance for the HPV vaccine as they have already included HPV vaccine in their Advanced Market Commitment plan (Basu and Chowdhury 2009). However, questions have been asked about the sustainability of GAVI's financial model and of such vaccination programmes in the countries that it seeks to help. One of the authors of this article has earlier raised doubts about whether the objective of protecting children against serious diseases will be achieved (Madhavi and Raghuram 2010).

## Conclusions

Clinical trials of two HPV vaccines in India, the circumstances of their marketing approval as well as their possible introduction into the public health system, raise a number of apprehensions about ethics, science, and regulation. It can be said with confidence that at least some of the trials for these vaccines violated established national and international ethical guidelines, and are of doubtful scientific value. The 23,000 girls in AP and Gujarat could not have given their informed consent to participate in the research, and they will not get lifelong follow-up after immunisation. Nor is it likely that this community will be able to afford the product when it does become available. The regulatory authorities permitted these

trials, possibly pressurised by drug companies and other powerful interests.

The content of Schedule Y of the DCA needs to be revised so that the stronger requirements and larger concerns of the ICMR guidelines and that of the Helsinki Declaration are reflected explicitly, forcing trial protocol documents in India to meet these requirements. This would ensure that rights of participants in clinical trials are made even more secure, and justifiable at that. The "window of opportunity" afforded in the DCA for entry of drugs into India without clinical trials or appropriate studies, under the label "approved for marketing", needs to be firmly shut. Exceptions may be made by a committee of experts only in specific cases of emergency or national interest, and the discussion leading to their decision should be made public.

All trials on marginalised and vulnerable groups should be banned – unless the marginality and vulnerability are objects of study, in which case the drug company must ensure that there is lifelong health insurance for the family of the trial subject, even as the drug or vaccine in question is given free of cost to the community in question for a specified period arrived at through consultation with the community. Research should be done in a way that respects the people and community on which it is conducted.

Given the concerns expressed about the vaccine's safety and efficacy, its introduction through a "demonstration project" should be viewed with concern. Is this a marketing tactic to find entry into the public health system? Surely our priority is to allocate the resources (approximately Rs 3,000 per course of the vaccine) to cervical screening rather than HPV vaccination.

The speed with which the HPV vaccine has been approved in India, within weeks of trials being conducted of doubtful scientific value; the unclear purpose and regulatory status of pre-approval "formative research"; the securing of the certificates of approval from professional organisations (PATH 2010) – these are evidence of the aggressive marketing strategies employed by the companies involved. All this is also a poor reflection of organisations like PATH, and their funders such as the

Bill and Melinda Gates Foundation, who, as part of their expressed mandate to fight disease, may be lending themselves to become uncritical accomplices in questionable policies.

Vaccines raise a special concern. The scientific community has a special responsibility to promote only those vaccines that are useful, and whose efficacy and safety are based on evidence. The regulatory authorities have a responsibility to ensure that new drugs and vaccines go through proper scientific evaluation before they are considered for approval. This case also underscores the need for a national vaccine policy that addresses public health interests, rather than those of the market, before introducing any new vaccine in the national immunisation programme, or even in the open market.

## NOTES

- 1 Brinda Karat, Member of Parliament in Rajya Sabha Calling Attention Proceedings, 22 April 2010.
- 2 The vaccines protect against certain types of the HPV, which is the source of a common sexually transmitted infection. HPV is a major causative agent in cervical cancer.
- 3 The team consisted of women's and health rights activists from Sama Resource Group for Women and Health, Jan Swasthya Abhiyan and Antra, who have been active in the campaign against the HPV vaccine. The report, *Preliminary Findings of Visit to Bhadrachalam: HPV Vaccine 'Demonstration Project' Site in Andhra Pradesh*, by Sarojini N B, Anjali S and Ashalata S (March 2010), is available on request from Sama: advocacyhealth@gmail.com.
- 4 Ghulam Nabi Azad in Rajya Sabha Calling Attention Proceedings, 22 April 2010.
- 5 Ibid.
- 6 Ibid.
- 7 Details of the approval process of both vaccines are available in USFDA 2009a and USFDA 2010.
- 8 Same as fn 4.
- 9 Susheela Singh, Anjali Sheno, Deepa Venkatachalam and Beenu Rawat.

## REFERENCES

- Aneja, H and J Puliyel (2009): "Selling Vaccines: Deciding on Who Can Afford HPV", *Indian Pediatrics*, 46: 647, <http://indianpediatrics.net/july2009/647.pdf>
- Bhatla, N and N Moda (2009): "The Clinical Utility of HPV DNA Testing in Cervical Cancer Screening Strategies", *Indian Journal of Medical Research* 130 (3): 261-65.
- Basu, M (2006): "The Relevance of Cervical Cancer Screening and the Future of Cervical Cancer Control in India in the Light of the Approval of the Vaccine against Cervical Cancer", *Indian Journal of Cancer*, 43(3): 139.
- Basu, P and D Chowdhury (2009): "Cervical Cancer Screening and HPV Vaccination: A Comprehensive Approach to Cervical Cancer Control", *Indian Journal of Medical Research*, 130: 241-46.
- CDSCO (undated): "Guidance for Industry on Submission of Clinical Trial Application for Evaluating Safety and Efficacy", Central Drugs Standard

- Control Organisation, Ministry of Health, Government of India, viewed on 30 July 2010 (<http://cdsco.nic.in/CDSCO-GuidanceForIndustry.pdf>).
- Dabade, G et al (2010): "Concerns Around the Human Papilloma Virus (HPV) Vaccine", Memorandum, *Indian Journal of Medical Ethics*, 7(1): 38-41.
- Dhar, A (2010a): "Centre Halts HPV Vaccine Project", *The Hindu*, 7 April, viewed on 30 July 2010 (<http://beta.thehindu.com/news/national/article391024.ece>).
- (2010b): "RTI Act Not Applicable to HPV Vaccine Project", *The Hindu*, 9 August, viewed on 9 August 2010 (<http://www.thehindu.com/news/article559462.ece>).
- Haug, C J (2008): "Human Papillomavirus Vaccination – Reasons for Caution", *New England Journal of Medicine*, 359: 861-68.
- ICMR (2006a): *Annual Report 2005-2006* (New Delhi: Indian Council of Medical Research), viewed on 30 July 2010 (<http://www.icmr.nic.in/annual/2005-06/hqds/overview.pdf>).
- (2006b): *Ethical Guidelines for Biomedical Research on Human Participants* (New Delhi: ICMR), viewed on 30 July 2010 ([http://icmr.nic.in/ethical\\_guidelines.pdf](http://icmr.nic.in/ethical_guidelines.pdf)).
- Jan Swasthya Abhiyan et al (2010): "Memorandum to the Health Minister on World Health Day Opposing HPV Vaccinations", 7 April, viewed on 30 July 2010 (<http://samawomensealth.wordpress.com/2010/04/08/memorandum-to-the-health-minister-on-world-health-day-opposing-hpv-vaccinations/>).
- Lippman, A, R Melnychuk, C Shimmin and M Boscoe (2007): "Human Papillomavirus, Vaccines and Women's Health: Questions and Cautions", *Canadian Medical Association Journal*, 177(5): 484-87.
- Madhavi, Y and N Raghuram (2010): "Crisis of Speculation: Donors Should Fund Only Locally Proven Vaccine Needs and Local Capacity Building", Rapid Response to P Moszynski (2010): "Drive to Vaccinate Children in Developing Countries Faces 'Acute Crisis' Because of High Costs", *BMJ*, 340: c2576.
- MOHFW (2005): "The Drugs and Cosmetics Act and Rules, as Amended up to the 30th of June 2005", Ministry of Health and Family Welfare, viewed on 30 July 2010 (<http://cdsco.nic.in/html/Drugs&CosmeticAct.pdf>).
- NIMS/ICMR: National Institute of Medical Statistics, Indian Council of Medical Research, "Clinical Trials Registry-India", <http://www.ctri.in/Clinicaltrials/index.jsp>
- Parliament Proceedings (2010): "Calling Attention to a Matter of Urgent Public Importance: HPV Vaccine Programme by PATH in Certain States of

- India", Rajya Sabha Synopsis of Debate, 22 April, viewed on 30 July 2010 ([http://164.100.47.5/newsynopsis1/Englishsessionno/219/Syn\\_%20Eng\\_%20Dated%2022\\_04\\_2010.pdf](http://164.100.47.5/newsynopsis1/Englishsessionno/219/Syn_%20Eng_%20Dated%2022_04_2010.pdf)).
- PATH (2010): "Update: PATH's HPV Vaccination Project in India", Program for Appropriate Technology in Health, press release 27 April, viewed on 30 July 2010 (<http://www.path.org/news/an100422-hpv-india.php>).
- (undated): "Shaping Strategies to Introduce HPV Vaccines in India; Formative Research Results from the HPV Vaccines: Evidence for Impact Project", viewed on 30 July 2010 ([http://www.rho.org/files/PATH\\_FRTS\\_execsumm\\_India.pdf](http://www.rho.org/files/PATH_FRTS_execsumm_India.pdf)).
- Sarojini, N B, Anjali, S and S Ashalata (2010): "Preliminary Findings of Visit to Bhadrachalam: HPV Vaccine 'Demonstration Project' Site in Andhra Pradesh" (New Delhi: Sama).
- Special Correspondent (2009): "Pilot Programme for Vaccination against Cervical Cancer Launched", *The Hindu*, 10 July, viewed on 30 July 2010 (<http://www.hindu.com/2009/07/10/stories/2009071059770500.htm>).
- Thacker, T (2010): "Ministry Admits Lapses in HPV Vaccine Trial", *The Indian Express*, 29 April, viewed on 30 July 2010 (<http://www.indianexpress.com/news/ministry-admits-lapses-in-hpv-vaccine-trial/612823/>).
- USFDA (2006): "FDA Licenses New Vaccine for Prevention of Cervical Cancer and Other Diseases in Females Caused by Human Papillomavirus: Rapid Approval Marks Major Advancement in Public Health", press release, 8 June, viewed 30 July 2010 (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108666.htm>).
- (2009a): Vaccines and Related Biological Products Advisory Committee (VRBPAC) Briefing Document Cervarix, Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant, 9 September, viewed on 30 July 2010 (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM181371.pdf>).
- (2009b): "FDA Approves New Vaccine for Prevention of Cervical Cancer", press release 16 October, viewed 30 July 2010 (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm187048.htm>).
- (2010): Vaccines, Blood and Biologics, Vaccines, Approved Products, Gardasil, last updated 9 July 2010, viewed on 30 July 2010 (<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/Approved-Products/ucm094042.htm>).
- USNIH (United States National Institutes of Health) [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

### Democracy after the Ayodhya Verdict

The Allahabad High Court's Ram Janma Bhumi Babri Masjid verdict has serious implications for the nature and functioning of India's democratic framework, and for the role of the judiciary in defending the secular basis of the Constitution. The judgement privileges the beliefs of the "people", leaving undefined who these "people" are, and in what historical context their beliefs were constructed. It goes beyond questions of law and imposes "a settlement" involving, among other things, partitioning of the disputed land. Most questionably, it ignores the illegality of the acts of 1949 and the demolition of the masjid in 1992.

Recognising the need to discuss and revisit the issues involved *The Social Scientist*, Sahmat and *Communalism Combat* are organising a symposium, "Fact and Faith: Democracy after the Ayodhya Verdict" from 6 to 8 December 2010 in Delhi. Apart from experts in various fields, a wide cross-section of people are being invited to participate in the symposium.

For further details please contact:

Safdar Hashmi Memorial Trust (SAHMAT)

29 Feroze Shah Road, New Delhi 110 001 • Telephone: (+91 11) 23381276 / 23070787

e-mail: [sahmat8@yahoo.com](mailto:sahmat8@yahoo.com)