The HPV Vaccine 'Demonstration Projects'

Following ethical concerns raised by the people's health movements, women's groups, human rights groups, child rights groups, public health networks etc. and Smt Brinda Karat, a Member of Parliament at a press conference on April 7th, 2010, the HPV vaccine 'demonstration projects' were suspended by the Ministry of Health and Family Welfare. The trials were conducted by the American NGO PATH in collaboration with the ICMR and the State Governments of Andhra Pradesh and Gujarat. Later the Ministry on April 15th, 2010 constituted an Enquiry Committee. The Committee included, Prof. S.S. Agarwal, former Director Sanjay Gandhi Postgraduate Institute of Medical Sciences; Dr. S.P. Agarwal, Former DGHS and

Dr. Suneeta Mittal, Head of Obstetrics and Gynaecology Department, AIIMS. The brief before the Committee was to look into 'the alleged irregularities in the conduct of studies using HPV vaccine by PATH in India'. An interim report by the Committee was made available to the media on February 21st, 2010 at a press conference called for by the campaign. However, the Committee's final report remains absent in the public domain till today.

The Committee's final report also follows the trend of the interim report in exonerating the responsible parties despite providing clear evidence of misconduct and violations. The Committee was also assisted by three expert members [Dr. Rani Kumar, Dean, AIIMS; Dr. A.K Dutta, Head of Pediatrics, Kalawati Saran Hospital and Dr. Y.K. Gupta, Head of Pharmacology, AIIMS] to look into various aspects of the projects including the linkages of the deaths with the vaccine and the ethics of the implementation of the projects. While the expert members have raised pertinent questions and ethical concerns, the Committee in its final recommendations and conclusions has in most cases chosen to ignore these findings. Some of the main issues that we would like to highlight here include:

1. Nature of the Projects – Ascertained Clinical Trials Violating the Drugs and Cosmetics Act (DCA)

PATH and ICMR have reiterated several times that the Demonstration Projects could not be classified as clinical trials: as they did not seek to evaluate the efficacy and safety of the vaccine and as no biomedical outcomes were being researched and no blood or other samples were drawn, and no therapies were tested. However, as Dr. Y. K. Gupta, observes in the Committee's report, the nature and objectives of these projects, makes it evident that they are in fact clinical trials, wherein the projects were a "study of a pharmaceutical product carried out in human participants" and "4 of 5 primary outcome measures proposed in the study related to evaluation of the safety of the vaccine in population setting." The very principles used to define a clinical trial by the CDSCO and the Schedule Y of the Drugs and Cosmetics Act, 1954 can be applied to the demonstration projects conducted by PATH.
Moreover, the Committee in the Section 7 of its findings [pg.73] has explicitly stated that it "is of the opinion that by whatever name you call it, the project proposal has been carried out as research on human participants. And as such it had to follow all the guidelines and statutory requirements applicable for research on human participants. Monitoring and management of Adverse Events/ Serious Adverse Events should have been more vigorously pursued."

If the demonstration projects were indeed clinical trials, the non-compliance of the requirements of Schedule Y of the Drugs and Cosmetics Act raises grave ethical and legal

concerns. Several clauses of the Act have been violated. The Ministry of Health and Family Welfare (MOHFW) therefore needs to take exemplary action on those violating the law of the land: in this case the concerned officials of the ICMR, the DCGI and the NGO PATH.

2. Selection of Study Area

Dr. Y.K. Gupta in his report to the Committee has specifically stated that the study has been carried out on "vulnerable population".However, the report once again falls short by stating that while the stratification (urban, rural and tribal) "seems appropriate, caution is required". The Committee in Section 7.5 (Page 75) has further stated that, "…. for better understanding of the research nature of the study and its impact on cancer prevention a higher strata/ better educated/ better aware population inclusion might have been more desirable. The tribal and more difficult areas could have been chosen in the later round. The standard of medical care in remote areas is generally not of the same level as in the urban areas. It would have been easier to provide proper medical care at urban district level for any SAE, particularly the life threatening SAE. It would have been better investigated to document the cause of the illness even if unrelated. The adequacy of existing AEFI system to measure 4 out of 5 primary endpoints also could have been better tested in the urban area first."
It has been categorically stressed that "everyone shall desist from research on tribal population, unless of specific benefit to them" (Pg 80:8.5). The Committee's recommendation to apply caution and safeguards while conducting trials on marginalized populations is a necessary and welcome one. However, the Committee appears to have taken too lenient a view of the violation of this very principle in the context of these demonstration projects, wherein the Committee's only suggestion is to undertake a review of ethics if the project was to continue.

3. Process of Obtaining Consent

In her findings, with respect to the process of obtaining consent and the inspection of the informed consent forms, Dr. Rani Kumar explicitly states "… from the numerical analysis it is obvious that the team involved in conduction (sic) of the study on HPV has been very casual in its approach and has ignored many ethical issues such as signatures of parent/guardian, witness, PI and discrepancy in the date of receiving the vaccine and date of signature (page 49)." Similarly, the Committee in its findings in Section 7.1 [Page-70] has also declared, "the most significant deficiency in the implementation of the project was the obtaining of consent". The Committee has observed (pg 72:7.1.4) that the ambivalent sentences in the consent form are tantamount to "covert inducement and indirect coercion" especially in the light of the high cost of the vaccine (~ Rs 9000 for three doses).

Also shocking in AP, is the Integrated Tribal Development Authority [ITDA] orders to the hostel wardens, headmasters and teachers to comply with the demands of the project and also facilitate the consent taking processes, particularly in the Ashram Paathshalas where these personnel were ordered to give mass consent (Page 51, Letter to Dr Kishore Chaudhury by Dr Rani Kumar dated 6thSeptember 2010). 2763 forms (out of a total of 14253) were signed by the Hostel Wardens/ Head Master in AP/.

The Committee, in section 7.1.1 [page 70] also mentions that, "this authorization runs contrary to the basic principles of obtaining consent as students cannot be considered to have full autonomy in front of their teachers/ Head Master. There is no express approval of the

Institutional Ethics Committees (Ices) of MNJIO&RCC, Hyderabad for this provision, nor is there any mention of it in the consent document."

It is extremely alarming that despite clear evidence regarding serious lacunae in such a fundamental aspect of any form of research, no action has been recommended against those involved in the designing and implementation of these projects nor against those ethics committees who approved of such a design.

4. Issues Related to Safety, Follow-up and Reporting of Adverse Events

The lacunae in the adverse event reporting system has been an issue of concern for the experts as well as in the discussions of the Committee. The Committee in its findings in Section 7.2 [page -74] explicitly states, "there has been direct contact with the human participants, they have administered an intervention which is not part of a prescribed prevention, and have expected adverse events. The Committee is of the view that in all investigational studies (irrespective of being done with non-licensed or licensed products), particularly those that deal with administration of new entities; monitoring, reporting and investigation of all adverse events – non-serious, serious or deaths – should be an integral part of the study and responsibility of the investigator. Adequate insurance cover for participants to include unforeseen/unexpected or even probable morbidity and mortality events should be a part and parcel of such studies.

In this context rule 122-e of the Drugs and Cosmetics Rules, 1945 provide that all vaccines shall be new drugs unless certified otherwise by the licensing authorities under Rule 21, and a new drug shall continue to be considered a new drug for the period of 4 years from the date of its first approval or inclusion in the Indian Pharmacopoeia, whichever is earlier."

Moreover, Dr. A.K. Dutta in his observations has mentioned several unacceptable and prolonged delays in the reporting of adverse events and deaths due to a lack of any independent monitoring systems. Further, although his observations state an unlikely link between the deaths of 7 girls and the vaccine, in 3 of these cases no conclusive evidence in this regard could be found. Further it is shocking that the study protocols did not include a separate component for the surveillance of adverse events with solely relying on the existing State run guidelines for the reporting of Adverse Events Following Immunization (AEFI). Particularly surprising is the lack of action taken by the DCGI and ICMR in the light of these delays.

We also welcome the Committee's recommendation: "…besides issuing directions, an active programme needs to be evolved for training investigators and sensitization of regulatory agencies to specially look for these aspects in any study involving human subjects. There is also need for specific and separate legislation covering all aspects of biomedical and health research involving human participants which should provide statutory status to ICMR ethical guidelines and harmonize separate provisions under GCP guidelines and Schedule Y of the Drugs and Cosmetics Act." [pg 81]

Although the Committee has quite forcefully condemned the laxity and also made sound recommendations in this regard, in their section on 'responsibilities' [pg 81] they once again absolve all the parties involved. Moreover, the Committee does not raise the important questions related to the number of girls who have dropped out of the study and their follow up.

5. Lack of Clarity in Finances

A lack of clarity regarding the finances and the financial contributions of the different parties involved, in the projects also reflects in the Committees observations and findings. The Committee has raised certain pertinent questions in their remark in section 7.5 [page 75] that states, "On the basis of market price of Rs. 3000 per dose the approximate cost of vaccinating 25000 girls would be aprox. Rs 250 million. What was the financial investment of ICMR and State Governments in the project is not provided. The State clearly provided the cold chain and manpower for immunization. But would it have done so if the vaccine was not free. There is concern about the hidden possibility of a hidden agenda to push this prohibitively expensive vaccine into the Indian Healthcare System. It might have been more prudent if the National Technical Advisory Group on Immunization (NTAGI) has deliberated on the study prior to its implementation and given its recommendations. The Ethics Committees should have looked into this aspect as well before approving the studies and a speaking mention should have been made in their approval."

6. Need for Insurance Cover for Study Participants

Further the Committee states that "concerns over the Insurance No provision has been made of an insurance cover for any unforeseen event or residual, morbidity, related, or unrelated to the intervention; which is a usual practice in trials with NCE/INDs. The Committee is of the view that since the HPV vaccine is a newly developed vaccine, even though licensed, there should have been a provision of insurance coverage for study participants. The need for an Insurance cover is even more since the vaccine is administered to normal healthy individuals that too adolescent girls." It also goes on to establish that "PATH has taken an insurance cover for itself". The absence of any mention of such insurance cover for participants in the study protocols raises concerns regarding inadequacies of the approval process and the responsibilities of the approval bodies.
However, once again the Committee has failed to build on these concerns later in the section on 'conclusions and recommendations' and 'responsibilities'.

7. Public Private Partnerships

Further, while the Committee has pointed out to the, "blurring of the distinction between the National Immunization Programme, as routine service activity versus the research nature of the HPV vaccination project" they have failed to levy any form of responsibility on either the State or PATH in this regard, merely advising caution for such partnerships in the future. Further although the Committee has commented on the role of the NRHM, it has failed to look into the other IEC material that has largely contributed to this blurring of distinction and has also in many ways mislead the parents of participants of the study.

Despite these cases of clear violations and foolproof evidence by the experts appointed, the Responsibility section of the report is the weakest with the Committee exonerating all involved in the project. Despite clearly highlighting the aspect of conflict of interest with the involvement of the two pharmaceutical companies, providing the vaccines free of cost, the Committee, fails to build upon these aspects later in the report.

Our Demands
In the light of the above, we demand that:

The DCGI be held accountable for the approval and licensing of such a study that was severely lacking in several clinical trial protocols as is required by the Drugs and Cosmetics Act and the ICMR's Ethical Guidelines on Biomedical Research on Human Participants. The multi-level violations particularly with regard to the selection of the study area, the lacunae in the research instruments, etc., – reflect the fact that the ICMR and its bioethics committees have been extremely lax in its role as technical supervisors and advisors.

Furthermore it also casts doubts on the objectivity, seriousness and thoroughness of the members of the advisory group and ethics committees who gave their approval to these projects without critically examining the protocols. Immediate action should be taken against all members of these committees along with those ICMR officials who were responsible for and associated with these projects.

Given the active engagement of the State governments and machinery in the implementation of the projects, immediate action must be taken against all those involved and further safeguards be put in place at the policy level to pre-empt such forms of exploitation in the future when similar projects run through public private partnerships.

These projects should not be restarted and immediate action be taken against the PATH officials involved, with all research findings being treated as null and void.
Bill and Melinda Gates Foundation the principal donor for these projects and the organization PATH, the principle investigator in this project, also largely responsible for its design and planning, take immediate onus of the various lacunae and provide compensation for all those affected by the vaccination.

All the participants of the projects for at least 4 years, as is prescribed by the Drugs and Cosmetics Act, for any adverse event, both serious and non-serious, with the immediate provision of any necessary treatment.

Given, the earlier concerns raised regarding the safety, efficacy and prohibitive costs of the vaccine, these vaccines must not be introduced under any circumstances in the public universal immunization programme, with increased efforts instead to promote and provide for screening facilities in areas of high incidence of cervical cancer.

A critical relook at the Drugs and Cosmetics Act and the ICMR's Ethical Guidelines for Biomedical Research on Human Participants to ensure that such violations do not recur, particularly given the booming clinical trial industry.

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Taken from Sama (A Resource Group for Women and Health) Website:
https://samawomenshealth.wordpress.com/2011/05/26/the-hpv-vaccine-%E2%80%98demonstration-projects%E2%80%99/