

Final Report of the Committee appointed by the
Govt. 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

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List of Acronyms/ Abbreviations

ACTREC	Advanced Center for Treatment, Research and Education, Navi Mumbai
AE	Adverse Event
AEFI	Adverse Event Following Immunization
AIDS	Acquired Immunodeficiency Syndrome
AIIMS	All India Institute of Medical Sciences, New Delhi
ANM	Auxiliary Nurse Midwife
AP	Andhra Pradesh
CORT	Centre for Operations Research and Training, Vadodra
DGHS	Director General Health Services
FIR	First Information Report (of the Adverse event by Medical Officer)
GSK	Glaxo Smith Kline Pharmaceuticals Asia Pvt. Ltd.
HPV	Human Papilloma Virus
ICMR	Indian Council of Medical Research, New Delhi
IND	Investigational new Drug
MSD	MSD (Merck Sharp Dhome) Pharmaceuticals Pvt. Ltd.
PATH	Programme for Appropriate Technology in Health, New Delhi
NCE	New Chemical Entity
PPP	Public Private Partnership
R	Rural
SAE	Serious Adverse Event
SGPGI	Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow
T	Tribal
U	Urban
UIP	Universal Immunization Programme

1. Executive Summary

A project titled “A Post-licensure observational study of HPV vaccination: Demonstration Project” was carried out by PATH in collaboration with the respective State Governments and the Indian Council of Medical Research in the Districts of Khammam, Andhra Pradesh and Vadodra, Gujarat from 2007 with the objective of ‘generating evidence that would enable policy makers to decide on possible public sector introduction of the HPV vaccine’. It was part of a Global Project, titled “HPV Vaccine: evidence for Impact”, which was funded by a grant from Bill and Melinda Gates Foundation. Besides India, the project has also been carried out in Peru, Uganda and Vietnam. The HPV vaccine for the project had been donated by the manufacturers, viz. GSK and MSD to PATH.

The study consisted of 3 phases. The first phase was ‘Assessing Introduction of HPV vaccines in India: Phase I formative study’. It was carried out by the National Institute of AIDS Research, Pune for PATH. This part of the study has been completed and the results have been published in February 2010. The second phase was of vaccinating all the eligible girls in 10-14 years age-group in 3 blocks each of the two districts. It has been completed (all the 3 doses) in the AP (13,791 girls), but in Gujarat only 9,637 out of 10,259 girls have received the third injection of the vaccine when the study was suspended in March 2010. The third phase was of assessing the coverage, acceptability, feasibility and cost of the HPV vaccine delivery. It is being carried out by CORT.

A report on the deaths of some girls who had received the HPV vaccine under the PATH project was published in the local newspapers. It drew the attention of the human rights activists and national leaders. Subsequently the matter was taken up by the Parliamentary Department-Related Standing Committee on Health & Family Welfare on Demand-for Grants of the Department of Health Research. Because of the concern of the public the study was suspended and an enquiry Committee was constituted by the Govt. 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.

The committee consisted of Prof. S.S.Agarwal, Former Director Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow and Advanced Center for Treatment Research and Education in Cancer, Tata Memorial Center, Mumbai, presently Senior Consultant in Medicine and Honorary Director, Academics and Research, Vivekananda

Polyclinic and Institute of Medical Sciences, Lucknow, as Chairman, and Dr. S.P. Agarwal, Former DGHS and presently Secretary General, Indian Red Cross Society, New Delhi and Dr. Suneeta Mittal, Prof. and Head Obstetrics & Gynaecology Department, All India Institute of Medical Sciences, New Delhi as members. The terms of reference of the committee were to enquire into:

- a) Link between the deaths and vaccination, if any, and
- b) Ethical Issues of subjecting children of marginalized populations to these studies, and investigations in children without appropriate consent.

The committee was assisted by the following experts:

- i) Dr. Rani Kumar, Dean, AIIMS
- ii) Dr. A.K.Dutta, Head of Pediatrics, Kalawati Saran Hospital
- iii) Dr. Y.K.Gupta, Head of Pharmacology, AIIMS

The committee has gone through the original papers related to the project, Experts report, key witness's evidence, and response to the queries raised by the Committee members. On the basis of examining of all the facts the committee is of the opinion that:

1. The deaths reported in the recipients of the HPV vaccine from the Khammam district in Andhra Pradesh and Vadodra district in the Gujarat were most probably unrelated to the vaccine. However, the cause of death in all the cases can not be established with certainty.
2. There has been no major violation of any ethical norm in the conduct of the study. However, the committee has observed several minor deficiencies in the planning and conduct of the study which in hindsight should be taken as learning lesson for further strengthening of clinical research in the country.

Detailed recommendations are given on pages - of this report for further action by the Government of India. Two issues that have emerged from the present enquiry, which need special emphasis, are:

- (a) Inclusion of vulnerable groups in the research study, and the process of consent taking, and
- (b) Identification and investigation of Adverse events, whether they be non-serious, serious or fatal

Besides issuing directions, an active programme needs to be evolved for training of investigators and sensitization of regulatory agencies to specially look for these aspects in any study involving human subjects. There is also a 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.

Background

A Global Project, titled “HPV Vaccine: evidence for Impact”, a population based, post-licensure study of HPV vaccine for prevention of Cancer cervix has been being carried out by PATH (Programme for Appropriate Technology in Health), an international NGO, in the districts of Khammam of Andhra Pradesh (AP) and Vadodra of Gujarat in India since 2007. It was implemented in collaboration with the Indian Council of Medical Research and State Governments of AP and Gujarat. Besides India, the project has also been carried out in Peru, Uganda and Vietnam. The project is funded by a grant from Bill and Melinda Gates Foundation and donation of HPV vaccine by the manufacturers, viz. GSK and MSD to PATH. The basic aim of the study was to evaluate strategies for delivery of the vaccine and its acceptance by the population. It may be highlighted that 4 of the 5 primary outcome measures proposed in the study related to evaluation of the safety of the vaccine in population setting. The information so derived is expected to be of useful to National Health authorities regarding incorporation of the HPV vaccine in the national programme. The timeline of various activities and approvals of the study is given in Appendix 1.

The study in India was carried out in 3 phases. The first phase was titled “Assessing Introduction of HPV vaccines in India: Phase I formative study”. It was carried out by the National AIDS Research Institute, Pune for PATH. This phase of the study has been completed and the results have been published in February 2010 (Appendix 2). The second phase titled “A Post-licensure observational study of HPV vaccination: Demonstration Project” was of vaccinating all the eligible girls in 10-14 years age-group in 3 blocks each of the two districts. It has been completed (all the 3 doses) in the AP, but in Gujarat only 9,637 out of 10,259 girls have received the third injection of the vaccine when the study was suspended in March 2010. The third phase is for assessing the coverage, acceptability, feasibility and cost of the HPV vaccine delivery. It is being carried out by CORT.

The project has been implemented by the State governments of AP and Gujarat using their state health machinery of the UIP. The main role of PATH has been in mobilization of the logistics and supervision of the project. The PI of the project from PATH was Dr. Martha Jacob, while State Health Commissioners have been the Co-PIs. The project has been carried out as PPP model with approval of the State Governments (Appendix 3 and 4). The ICMR has been involved with the project from the very beginning, primarily in the role of an advisor and facilitator (MOU in Appendix 5). Besides the State Govts., the project has the approval of the following authorities:

- i) A National Advisory Group constituted by the ICMR (List of members is given in Appendix 6).
- ii) The State Advisory Groups, of the AP and Gujarat constituted by the State Govts. (List of members is given in Appendix 7 and 8)
- iii) Health Ministry's screening Committee of the Govt. of India (Appendix 9 and 10)
- iv) DCGI – license for import of vaccine for trial, and trial protocol (Appendix 11)
- v) Institutional Ethics Committee of NARI for Phase I study (Appendix 12)
- vi) Institutional Ethics Committees, separately for the AP and Gujarat, for Phase 2 study (Appendix 13 and 14)
- vii) Western Institutional Review Board, based in Olympia, WA; an independent ethics committee in the United States (Appendix 15)

The HPV vaccination in the District Khammam, Andhra Pradesh was started in July 2009 and that in District Vadodra, Gujarat in August 2009. The vaccine used in AP is of MSD (Gardasil), and that in Gujarat is of GSK (Cervarix). A total of 14,091 girls, in the age range of 10-14 years, in AP have received the first dose of the vaccine. The second dose was received by 13,930 and the third dose by 13,791 girls. The corresponding numbers in Gujarat were 10,686, 10,259 and 9,637.

A report on the deaths of some girls who had received the HPV vaccine under the PATH project was published in the local newspapers. It drew the attention of the human rights activists and national leaders. A detailed press statement regarding the HPV vaccine project and deaths was issued by the Health Minister of Andhra Pradesh giving all the facts (Appendix 16) but it did not satisfy the critics. The matter was then taken up by the Parliamentary Department-Related Standing Committee on Health & Family Welfare on Demand-for Grants of the Department of Health Research. The record of the minutes of the meeting of the Parliamentary committee shows that the committee was concerned about non-observance of the DCGI guidelines which state that third phase trial cannot be conducted on children until a similar trial was conducted in adults (Appendix 17).

It was in this background that this enquiry Committee was constituted by the Govt. 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 (Appendix 18 and 19). The composition of the Committee and its terms of reference are given below:

3. Enquiry Committee Members

- i) Prof. Ranjit Roy Chowdhary, Chairman (15.04.2010 – 12.05.2010)
Former Chairman, INCLEN Board of Trustees & INCLEN Inc., and Distinguished Scientist, National Institute of Immunology, New Delhi
- ii) Prof. S.S.Agarwal, Chairman (13.05.2010-till end)
Former Director Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, and Advanced Center for Treatment Research and Education in Cancer, Tata Memorial Center, Mumbai; Presently Senior Consultant in Medicine and Honorary Director, Academics and Research, Vivekananda Polyclinic and Institute of Medical Sciences, Lucknow
- iii) Dr. S.P. Agarwal, Former DGHS and presently Secretary General, Indian Red Cross Society, New Delhi
- iv) Dr. Suneeta Mittal, Prof. and Head Obstetrics & Gynaecology Department, All India Institute of Medical Sciences, New Delhi

Terms of Reference

The Committee will investigate the following:

- a) Link between the deaths and vaccination, if any
- b) Ethical Issues of subjecting children of marginalized populations to these studies, and investigations in children without appropriate consent.

4. Conduct of the Enquiry

The background information about the PATH's project was provided by the ICMR. This included the following documents:

- i). Documents related to Study in Andhra Pradesh (Phase 2) including Protocol, copies of various approvals, and Notes of State Project Advisory Committee meetings etc. for AP (Supporting document 1)
- ii). Documents related to Study in Gujarat (Phase 2) including Protocol, copies of various approvals, and Notes of State Project Advisory Committee meetings etc. for Gujarat (Supporting document 2)
- iii). Minutes of the National Advisory Group meetings (Supporting document 3)
- iv). Operations Research study proposal (Phase 2) (Supporting document 4)
- v). Formative study details and Report (Phase 1) (Supporting document 5)
- vi). Other miscellaneous documents related to the study including copies of the notes on file, MOU between ICMR and PATH, etc.

The committee met 6 times on 21.4.2010, 30.4.2010, 31.5.2010, 22.6.2010, 27.9.2010 and 8.11.2010 (Minutes of the meetings are given in Appendix 20).

On basis of review of the provided documents, and deliberation of the committee, the committee members identified additional information to be obtained as detailed in the minutes of its various meetings. Replies to these queries were provided by the respondents which are appended under supporting documents (Supporting document 6).

The Committee invited key members of the project viz., the PI of the study from PATH, District Immunization Officers of the Khammam and Vadodra districts, the Chairman/Secretary of the IEC which reviewed and approved the projects in AP and Gujarat and a representative from the Office of the DCGI related to the project for examination. A record of the evidence provided by those who appeared before the Committee in its meeting on June 22nd, 2010 is placed along with the minutes of that meeting (Appendix 20).

This resulted in acquisition of voluminous data/records which required critical appraisal. For this purpose the assistance of the following experts was obtained vide Government order no. V.25011/160/2010-HR dt. June 30th, 2010 (Appendix 21):

- iv) Dr. Rani Kumar, Dean, AIIMS
- v) Dr. A.K.Dutta, Head of Pediatrics, Kalawati Saran Hospital
- vi) Dr. Y.K.Gupta, Head of Pharmacology, AIIMS .

These experts were given a defined brief to extract the required information from the given documents. Their reports are incorporated in the body of this report. The committee members had a detailed discussion with these experts at its meeting dated September 27th, 2010 the details of which are included in the minutes of that meeting (Appendix 20).

The reports of the Experts are given in Section 5 of this report.

5. Reports of the Experts

- (a) Report of Dr. A.K.Dutta
- (b) Report of Dr. Y.K.Gupta
- (c) Report of Dr. Rani Kumar

(a) Report from Dr. A.K. Dutta

Report of the analysis of Deaths and serious and minor AEFI in the project districts of Khammam (Andhra Pradesh) and Vadodara (Gujarat)

Executive summary

The demonstration project of HPV vaccine was launched by the PATH in collaboration with the Govt of Andhra Pradesh and Govt of Gujarat under the guidance of Indian Council of Medical Research. The project was initiated in three blocks each in Khammam district in AP and Vadodara district of Gujarat. The vaccination was given in 10-14 years old girls using Quadrivalent vaccine (Gardasil) in Khammam and Bivalent vaccine (Cervarix) in Vadodara district. It was planned as prospective post-licensure observational study on approximately 16,000 girls. The objectives of the study were:

- 1) To demonstrate suitable HPV vaccine delivery strategy for 10-14 years old adolescent girls
- 2) To raise community awareness of HPV, cancer of the cervix, and their prevention and
- 3) To gain experience in HPV vaccination and to build the evidence base of vaccine delivery strategies for future introduction of HPV vaccine into universal immunization programs.

The primary outcome measures included the following:

- 1) Number and percent of eligible girls fully vaccinated, partially vaccinated or not vaccinated at all according to vaccine delivery strategy
- 2) Number and percent of vaccinated girls experiencing serious adverse events, as reported spontaneously through routine mechanisms of UIP program
- 3) Number and percent of vaccinated girls' experiencing non-serious adverse events, as reported spontaneously through routine mechanisms of UIP program
- 4) Timeliness of reporting serious adverse events to local, state and National authorities, as per the usual UIP protocol and
- 5) Timeliness of reporting non-serious adverse events to local, state and National authorities, as per the usual UIP protocol.

A detailed protocol was made and ethical clearances from the appropriate authorities were taken. The study was initiated at both the states from August 2009. However, there were few deaths reported among the vaccinated girls from both the states which resulted in the temporary suspension of the project pending the investigation report. There were total 7 deaths, 5 from the AP and 2 from Gujarat. A detailed review of death cases were undertaken from the available records in the form of FIR, Clinic/hospital prescriptions/records and the autopsy. Out of the five deaths reported from Andhra Pradesh, two died due to consumption of organo-phosphorus poisoning (autopsy proven) and one died due to drowning in a well.

All the three girls died after 45, 97 and 49 days after the last HPV vaccine dose respectively. The fourth case developed symptoms 96 days after receiving the third dose of the vaccine and had died of unrelated disease which cannot be linked possibly to HPV. The fifth case had started symptoms 23 days after the last dose and possibly died of severe malaria after eight days of treatment in health facilities. Similarly at Gujarat, one case died of snake bite and the other case died of severe malaria. After reviewing all seven deaths (five deaths from AP in the Gardasil group and two deaths in Gujarat from Cervarix group), it has been observed that there is no common pattern to the deaths that would suggest that they were caused by the vaccine. In cases where there was an autopsy, death certificate, or medical records, the cause of death could be explained by factors other than the vaccine. The background death rates among girls 10-14 years of age in both Vadodora and Khammam districts did not show any increase rate. In fact in Vadodora district the death rate has significantly decreased in 2009 compared to the past years.

However the reporting system as per Govt of India surveillance of vaccine preventable disease guidelines, the notification was not done on time in two cases in AP and both the cases in Gujarat. There is no uniformity in the reporting system of AEFI in both the states. In the study no proforma was developed to monitor the AEFI nor there was any follow up of cases done. It is very surprising that the most common minor AEFI in any injectable vaccine is pain in the injection site of various degree. In AP, only ten girls after the first dose developed pain and none in second or third dose. In Gujarat none has reported pain following injection as minor AEFI. In both the states many minor AEFI has been combined e.g. nausea, vomiting, diarrhea and abdominal pain as one AEFI in AP and in Gujarat (Abdominal pain, vomiting and neurogenic pain due to injection) and (giddiness, jerky movement, neurogenic shock due to injection) has been clubbed together as one item in the description.

The primary end point of the study was to find out number of girls having serious and non serious adverse events following vaccination through routine UIP system. In this regard first of all routine system of reporting should have been verified in both the districts before designing the study. There is no dairy card based information record for assessing minor or major AEFI in the study protocol which seems unusual with such a large observational study.

There should have been some mechanism of insurance cover for the treatment of the vaccinated girls irrespective of their illness for a designated period of time. PATH has mentioned that there is an insurance cover for the organization but none was done for the girls in the study group.

Details of deaths that took place in Andhra Pradesh in the district of Khammam. (As per FIR)

1. Miss AAAAAAAAA, 14 years old girl daughter of Shri AAAABBB from PHC, Gowridevipeta, sub center Murmur and village Yeragutta of Bhadrachalam .She has been studying at Ashram School, Yeragutta. She has received the first dose of HPV vaccine (Gardasil) on 16.07.2009 in Ashram School, Yeragutta. During the process of community mobilization for second dose, the female health worker was informed that she has committed suicide by consuming insecticide on 29th August,2009

The girl was admitted on 29th August, 2009 with history of ingestion of some insecticide in a critical condition at 4 PM in the area hospital, Bhadrachalam and died at about 7 Pm on the same evening. She was at home at the time of consumption of the suspected poisonous substance. The detailed treatment record of the hospital is not available in the document. The postmortem of the case was performed. The viscera (stomach, intestine, Liver and kidney) was sent to the Andhra Pradesh Forensic Science Laboratories and the sample analysis report confirms the presence of organo-phosphorus insecticide poisoning (file no- WGL/TOX/998/2009 dated 17.11.2009). The FIR was prepared by Dr AAAACCC on 02.09.2009 and necessary formalities of reporting to higher authority were completed. Since there was no causal relationship with vaccine as the symptom occurred after 45 days of vaccine administration and definite history of ingestion of insecticide, further investigation was dropped by the district nodal officer Dr. AAAADDD.

2. Miss BBBBBBB, 11 years 8 months old girl daughter of ShrI BBBBCCCCCCCC from Kotha Colony, Bhadrachalam in Khammam district received the first, second and third doses of Gardasil on 21th July, 2009, 9th October 2009 and 22nd January 2010. After 96 days of the third dose of Gardasil on 29th April, 2010 the girl complained of severe headache and several episodes of vomiting and loss of consciousness at about 8.30 AM. The patient was taken to Swathi Children's hospital, Bhadrachalam in a critical and unconscious state. The doctor after examining the patient referred her to a higher center Gayathri Hospital at Kothagudem. The notes on FIR states that the condition of the patient on arrival at Gayathri hospital was very poor with feeble and rapid pulse and BP of 70/40 mm of Hg. The girl expired on 29th April at 10.30 AM. The probable diagnosis by the attending doctor was 1) Subarachnoid hemorrhage due to rupture of aneurysm 2) Intracranial space occupying lesion3) Anaphylactic shock 4) dehydration. The FIR was prepared by Dr. BBBBDDD on 20.05.2010 and duly signed by Dr. BBBBEEE, DIO. Detailed hospital records including investigations and treatment performed is not attached in the document.
3. Miss CCCCCC, 13 years old daughter of Mr.CCCCDDDDDDDD of Anjubaka village, Dummugudam Mandal, Bhadrachalam. She was studying at Kreguballi Ashram School and has received first and second doses of Gardasil vaccine on 19th July, 2009 and on 13th October respectively. She was due for her third dose. On January 21st, 2010, (after 97 days of the last dose of the vaccine) she was reported to have consumed poison

(Endosulphan) at home at about 9.30 AM. She was taken to Dummugudem civil Hospital at about 1.15 PM. In the civil hospital, she was given emergency treatment in the form of Decadron injection 2ml, Injection Dopamine, Injection Deriphylline and Injection Diazepam and stomach wash. She was also given oxygen inhalation. As her condition was not improving, she was referred to area hospital Bhadrachalam in an ambulance. However on the way to hospital the girl has expired at about 2.10 PM on 21st January, 2010. The area hospital at Bhadrachalam declared the girl as brought dead and the postmortem was performed on 22nd January, 2010. The FIR was made by Dr Balasudha on 29th January, 2010 and sent to DIO. The cause of death was poisoning and hence further investigation was not carried out. The preliminary autopsy report showed cause of death due to consumption of Organ o phosphorus insecticide poison. The viscera samples were sent to the Andhra Pradesh Forensic Science Laboratories at Red Hills, Hyderabad and the postmortem report confirms the presence of organo-phosphorus in the viscera thus confirming the diagnosis. Hence it can be clearly stated that the cause of death is not causally related to vaccine.

4. Miss DDDDDDD, 12 years old girl, daughter of Shri DDDDEEE of Appalanarshimapuram, Nelakundapalli, Khammam received the first dose of Gardasil on 20th July, 2009. She was due for her second dose and on community mobilization by the female health worker, it was informed that on 6th September, 2009. She had accidentally fallen in an open well (Granite quarry filled with water) and died due to drowning. This event occurred after 49 days of the first dose of vaccine. The female health worker informed the medical officer in charge of the PHC Nelakondapally. The Medical officer Dr. DDDDDFFF made an FIR and informed the DIO Dr. DDDDGGGGG on 07.09.2009. Since the case was not related to vaccination, hence further investigations were dropped.
5. Miss EEEEEEE, 13 years old girl, daughter of Shri EEEEEEEEEEEEEEEEE of Ganga Hussain Basti, Kothagudem received the first dose of Gardasil on 17th July, 2009. After 23 days of the vaccination she had developed fever on 1st August, 2009 and was treated by a local registered medical practitioner. She did not improve and was admitted in Kothagudem area hospital on 8th August with breathlessness and went into coma. She was then referred to Khammam civil hospital where she was given Inj Chloroquine, Injection Paracetamol, Injection Ranitidine, Injection Perinorm, Injection Gentamicin, Injection Deriphylline, Injection Decadron and Aminophylline drip. High risk consent was taken by the treating doctor. She did not improve with the treatment and expired on 8th August at 9 PM. The cause of death recorded as viral fever.

Deaths reported in the HPV project at Vadodara district of Gujarat as per FIR

1. Miss FFFFFFF, 10 years 4 months old girl, daughter of Shri FFFFGGGGGGG of village Pipalda Kawant of Vadodara received two doses of cervarix on 2nd September and 9th October respectively. The family had left the village after the second dose and migrated to Rajkot district for work. After 20 days of the last dose of Cevarix on 29th

October she complained of fever and headache since morning for which a nearby private practitioner was shown. She was given Inj Vitamin B complex and tablet paracetamol. The practitioner had suspected her to be a case of malaria and advised blood test. On 30th October again she visited the same doctor in a critical condition with Hb of 4gm/dl, TLC count of 46200 cells/cumm with neutrophil-71% and blood film was positive for P Vivax. The practitioner referred the case to nearby Govt CHC at Bhayabadar. The medical officer found that she was brought dead at 8 PM on 30th October, 2009. The cause of death has been mentioned as due to malaria with severe anemia. The medical officer Dr. FFFFHHHH investigated the case and finally opined that the girl died of malaria and severe anemia and informed the district RCH officer in FIR form whose signature is in the FIR on 25th March, 2010. In this case post mortem was not done.

2. Miss GGGGGGG, 15 years old girl daughter of GGGGHHHHHHHHHHHHHHHHHH of Nander, Bithli, Shinor of Barodara district received first and second dose of Cervarix on 9th September and 14th October, 2009 . The girl complained of mild fever, joint pain and headache on 15th October for which she was treated by a local private practitioner with tablet paracetamol, tablet ranitidine and tablet Liv-52 (herbal medicine for liver).She was asked to come for follow up after two days. She remained well and started working in the field. After 18th day of the second dose she had complained of pain in the leg and some insect bite locally and was not feeling well for which she did not go for work in the afternoon. She was not taken to the doctor for this ailment and rested at home. Her condition became very critical at night and on 2nd November at 7.30 AM 108 no ambulance service was called and shifted to CHC Motafolia. Her condition became very critical during the process of shifting with no recordable vital signs .The ambulance service people started CPR but the girl could not be revived and brought dead to the hospital..CHC doctor advised for postmortem but the family has refused. A diagnosis of snake bite was made as it is very common in the area and the insect bite which was refereed by the family was possibly due to bite by a poisonous snake. Dr GGGGIII made the FIR and sent the same to District child health officer Dr GGGJJJ on 31.12.2009. Dr. GK recorded his signature in the FIR on 02.01.2010. Since the death was not related to vaccine, further investigations not done.

Deaths following HPV vaccination in Andhra Pradesh and Gujarat (Table-1)

Name	Age in yrs	Date of event	Date of death	Date of notification	Following 1st/2nd/3 rd dose	Onset in days after last dose	Cause of death	Remarks
1. AAAAAAA (AP)	14	29 th Aug 09	29 th Aug 09	31 st August, 2010	1 st dose	45 days	Organophosphorus poisoning	Autopsy confirmed. Definitely not linked to vaccine. The date of notification of this case has been mentioned by the commissioner of health's mail to ICMR as 31 st August, 2009 by email dated 9 th June 2010 but in the FIR no date has been recorded
2. BBBBBBB (AP)	11 yrs 8 mths	29 th April 2010	29 th April 2010	20 th May, 2010	3 rd dose	96 days	? ICH /? ICSOL. Cause of death is uncertain	Diagnosis is uncertain. Unlikely to be linked with vaccine. The date of notification as per FIR is on 20.05.2010
3. CCCCCC (AP)	13 yrs	21 st Jan, 2010	21 st Jan, 2010	29 th jan, 2010	2 nd dose	97 days	Organo phosphorus poisoning	Autopsy confirmed. Definitely not linked with vaccine. The date of notification is on 29 th January, 2010 as per FIR.

4. DDDDDDD (AP)	12 yrs	6 th Sept, 2009	6 th Sept, 2009	7 th September,2 010	1 st dose	49 days	Drowning	Accidental fall in a well filled with water. Definitely not linked with vaccine
5. EEEEEEE (AP) 1.	13 yrs	1 st Aug, 2009	8 th Aug, 2009	9 th August,201 0	1 st dose	23 days	Fever of unknown origin	Possibility of Malaria, Typhoid or any other severe infection e.g. bacterial sepsis. Unlikely to be linked with vaccine. According to FIR the date of notification is on 4 th August and not on 9 th August.
6. FFFFFFF (Gujarat)	10 yrs 4 mths	29 th Oct, 2009	30 th Oct, 2009	22.03.2010	2 nd dose	20 days	Malaria with severe anemia	Unlikely to be linked with vaccine. The date of notification is very prolonged and possibly FIR was registered 5 months later.
7. GGGGGG (Gujarat)	15 yrs	1 st Nov 2009	2 nd Nov 2009	31.12.2010	2 nd dose	18 days	Snake bite	Definitely death is not linked to vaccine. The notification of death is delayed

Comments on deaths (Possible causes and whether any plausible link with HPV)

1. AAAAAAAA 14 years old girl had consumed Organo phosphorus insecticide which was proven by autopsy. The event had taken place 45 days after taking the first dose of the vaccine. The death cannot be attributed to Gardasil.
2. BBBBBB 11 yrs 8 months old girl received all three doses of Gardasil and was all right till 96 days after the last dose. On 29th April, 2010 she had sudden onset of severe headache and vomiting at 8.30 AM and lapsed into coma and died on the same day at 10.30 Am as per FIR. A detailed history of any head injury/any fever preceding the illness, any bleeding episode in the past would have been helpful in deciding about the cause of death in this case. Sudden history of severe headache and vomiting suggests evidence of raised intracranial tension which can be caused by a variety of causes. Reye's syndrome cannot be ruled out in this case. Reyes syndrome is characterized clinically by sudden onset of severe headache and intractable vomiting following subsidence of a mild viral fever. The cause of death in this case still remains unclear. However the event has taken place after 96 days of the last dose of the vaccine. It is very unlikely that the biological properties of HPV vaccine can lead to such plausible cause with an uneventful period of 96 days after the last dose. Following several other vaccines there is a possibility for development of acute demyelinating encephalomyelitis which usually would manifest within four weeks of the last dose of the vaccine. Therefore this diagnosis is also unlikely.
3. Miss CCCCCC, 13 years old girl had consumed organo phosphorus poisoning and died after 97 days of the last dose of vaccine. This cannot be linked with the administration of vaccine.
4. Miss DDDDDD, 12 years old girl received first dose of the vaccine and after 49 days accidentally fell in a well filled with water and drowned to death. The death cannot be attributed to be due to Gardasil.
5. Miss EEEEEEE, 13 years old girl developed fever 23 days after the first dose. She had attended the doctor and hospital but a diagnosis could not be made and died after 8 days of onset of symptoms. The diagnosis is uncertain and could be due to Malaria, Typhoid or any other causes of Fever of unknown origin. It is very difficult to co relate vaccine and the plausible mechanism of this event. This case did not present with clinical manifestations similar to acute demyelinating encephalomyelitis or GB Syndrome which are known to occur with the vaccine. Therefore it is unlikely that the death is related to the vaccine Garadasil.
6. Miss FFFFFFF who was 10 yrs and 4 mths old girl had received two doses of the vaccine Cervarix and developed fever and pallor 20 days after the second dose. She expired within two days of onset of symptoms. Her diagnosis was Severe malaria (Slide positive for plasmodium vivax) with severe anemia (Hb of 4 gm/dl) and a very high TLC count of 46,200/cumm. The death in this child is not linked to the administration of Cervarix.
7. Miss GGGGGG 15 years old girl had received two doses of the vaccine and after 18 days of the last dose was bitten in the leg by a venomous snake and died. The death cannot be attributed to be linked with Cervarix.

Analysis of nutritional status of the death cases in Khammam and Vadodara

Out of the total seven deaths reported following HPV vaccine (5 in AP) and (2 in Vadodara district) the anthropometry data of the three cases are not available indicating that probably it was not recorded. In the rest two cases at Khammam KS, 13 year old girl weighed 40 Kg and according to weight for age fell in 25th to 50th percentile. The other girl CAD, 12 years old with a weight of 30 kg falls in 5th to 10th percentile In Vadodara district, VML, 14 year old girl with weight of 37 kg was in the range of 10th to 25th centile and another girl JAR, 10 years of age weighed 24 kg and was in 5th to 10th percentile according to weight for age classification as per CDC growth chart. None of the girls where weight was recorded fell in the category of severe under nutrition.

Background mortality rate and comparison with causes related to HIV

The background mortality rate in Khammam and Vadodara due to poisoning, malaria, snake bite and other causes were verified as per the detailed records submitted. It was observed that during the year 2008, there was no death in the age group of 10 -14 years due to poisoning. However, in 2009 before the project of HPV vaccination started in the month of February itself there were two deaths due to poisoning. The record suggests that cases of poisoning, snake bites and malaria deaths are common among girls of the age of 10-14 years in the districts under review. Background death rate also suggests that there have not been any unusual causes or increase in the number of death.

Background death rate 10-14 years age girls in three blocks of HPV project (Khammam district)

Block	Population (2001 census)	2007	2008	2009(before vaccination, (Jan- July)	2009 9after vaccination (Aug-Dec)	2010
Thirumalayapalam	178886	1	1	0	1 (Death identified on trekking by health worker in HPV group)	2
Bhadrachalam	97311	0	0	1	5 (1 HPV)	1
Kothagudem	66465	0	0	0	1 (HPV given and death identified by health worker on trekking	0

Background death rate of 10-14 years old girls in three blocks (Vadodara district):

Block	Population (2009 dist. RCH report)	2005	2006	2007	2008	2009 (before start of HPV project-Jan- July)	2009 (after the HPV project-Aug- Dec)
Shinor block	74433	1	4	3	0	1	1
Kawant Block	189530	8	2	4	4	0	1
Dhaboi(urban)	60156	2	1	0	1	3	0

Comments on deaths

After reviewing all seven deaths (five deaths from AP in the Gardasil group and two deaths in Gujarat from Cervarix group), it has been observed that there is no common pattern to the deaths that would suggest they were caused by the vaccine. In cases where there was an autopsy, death certificate, or medical records, the cause of death could be explained by factors other than the vaccine. The background death rates among girls 10-14 years of age in both Barodara and Khammam districts did not show any increase rate. In fact in Badodara district the death rate has significantly decreased in 2009 compared to the past years.

So far in USA alone 29.5 million doses of Gardasil have been distributed and a total 16,140 episodes of adverse events have been reported. Non serious events comprised of 92% and the serious adverse events requiring hospitalization, death or disability consisted of 8% of the total AEFI cases.

As of May 31, 2010, there have been 53 U.S. reports of death among females who have received Gardasil. Twenty nine of these reports have been confirmed and 24 remain unconfirmed due to no identifiable patient information in the report such as a name and contact information to confirm the report. Confirmed reports are those that scientists have followed up on and have verified the claim. In the 29 reports confirmed, there was no unusual pattern or clustering to the deaths that would suggest that they were caused by the Cervarix vaccine. They also observed that the background death rate among the recipient of the vaccine was not more than the non vaccinated population of the same age group. Similarly following Cervarix vaccine trials till the lock out period of April 2008 in all ongoing and completed studies, there were 29 case fatalities among recipient of the vaccine. The independent data monitoring committee did not find the study vaccine related to death or serious adverse reaction and in UK alone more than 4 million doses of Cervarix has been distributed among school going girls.

Delay in notification of deaths:

From the case records (FIR) it has been observed that in most instances deaths have been reported late as per the AEFI surveillance of Govt of India guidelines. In AP, case number 1 and 2 in table 1, the dates of notification was not in accordance with GOI guidelines. In caseno.1, no date has been mentioned in the FIR form and in case no 2, notification of death as per FIR is after a lapse of one and half month. Similarly in Vadodora, in case no 5 the notification was done after 5 months of death and in case number 6,notification was done after more than one and half month (table1).

Serious adverse reaction following Gardasil other than death reported from Andhra Pradesh

1. HHHHHHH, 13 years old girl, daughter of Shri HHHIII of Bairuvunapalli, Pathabazaru, Nelakondapalli (M) Painampalli) dist. Khammam received first dose of Gardasil on 17.07.2009 at 12.30 AM. On the same day at about 4 PM she complained of pain abdomen and vomiting sensation. She was seen by a doctor at Nelakondapally primary health center and was given some antispasmodic and referred to Khammam district hospital. FIR was made by Dr HHHHJJJ reporting medical officer but the same has not been forwarded to DIO. The girl was discharged from the hospital.
No other serious adverse event following Gardasil has been reported from Andhra Pradesh.

Serious adverse reaction following Cervarix other than death reported from Gujarat

1. IIIIII aged 13 years daughter of Shri IIIJJJJJJJJJJJJJJJJJJJJ of Hanfeshwar Taluka Kawant had received Cervarix vaccine on 25.08.2009 at 14.10 hours and on the same day at 14.30 developed giddiness and jerky movements which lasted for about half an hour. An FIR form was filled up by Dr IIIKKKKKKKKKK on 25.08.2009 and sent to the nodal person Dr IIIILLL, DRCHO. The girl improved and no treatment was required.
2. JJJJJJ aged 12 years, daughter of Shri JJJJKKKKKKKKKKKKKKK of Hanfeshwar Taluka Kawant received Cervarix dose on 25.08.2009 at 14.30 hours and after 15 minutes developed nausea, pain in abdomen and vomiting once. She has recovered completely. An FIR was made by PHC doctor and sent to DRCHO.

Both the above cases where it has been reported as serious adverse reactions and FIR was sent cannot be considered as serious AEFI and should have been included as minor AEFI.

On detailed review of the existing AEFI surveillance system in both the districts under review, it is observed that the National surveillance of AEFI on Universal Immunization program was not very satisfactory with only one report of death from Vadodara district in 2007 and no report of any other form of adverse events following vaccination. It is expected that severe AEFI in the form of persistent inconsolable crying episode lasting for more than one hour, high fever of more than 40.5 degree centigrade, Seizure within seven days of

vaccination, encephalopathy within seven days of vaccination and transient shock like syndrome occur with whole cell pertussis component of DPT vaccination. Similarly from Khammam district in 2208, two deaths and in 2010 one death has been reported. There has been no severe form of AEFI besides death reported from both Khammam and Vodadara districts in their UIP surveillance report. In the routine surveillance report it is expected to have serious AEFI apart from death which is a rare event compared to other serious events. Following table shows the type of severe adverse reactions reported in the literature:

Serious adverse reactions following whole cell pertussis vaccine (DTwP)

Type of reaction	Incidence/million doses
Emergency department visit	72
Life threatening reactions	2.5
Hospitalization	16
Disabilities	1.4
Death	2.7
Seizure	13.4
Infantile spasm	0.39
Encephalopathy	0.78

Minor AEFI reported after HPV vaccine in the literature:

The most common adverse reactions reported during clinical trials of HPV vaccine were local reactions at the site of injection. These were most commonly pain (84%), swelling (25%), and erythema (25%). The majority of injection-site adverse experiences reported by recipients of quadrivalent HPV vaccine were mild to moderate in intensity. Fever was reported within 15 days of vaccination by 10% of vaccine recipients and 9% of placebo recipients. No serious adverse reactions have been reported. A variety of systemic adverse reactions were reported by vaccine recipients, including nausea, dizziness, myalgia and malaise. However, these symptoms occurred with equal frequency among both vaccine and placebo recipients. Syncope has been reported among adolescents who received HPV and other vaccines recommended for this age group.

AP serious and non serious AEFI Registry Summary report

S.No.	Type of reaction	Dose 1	Dose 2	Dose 3
1	Soreness, Redness and swelling	0	1	29
2	Fever, headache and body pain	8	42	189
3	GI Symptoms (Nausea, vomiting and abd. pain)	30	7	20
4	Itching	0	2	1
5	Joint pain (Arthralgia)	0	0	0
6	Anaphylaxis (shock)	0	0	0
7	Fits (Seizures)	0	0	0
8	Bleeding disorders(Thrombocytopenia)	0	0	0
	Total non serious AEFI	38 (0.27%)	52 (0.37%)	239 (1.37%)
	Total no of serious AEFI	0	0	0
	Total no. of doses	14091	13930	13791

Gujarat minor AEFI Registry summary report

S.No.	Type of AEFI	Dose 1	Dose 2	Dose 3	Total
1	Fever	6	0	0	6
2	Headache and giddiness	1	0	0	1
3	Vomiting	3	0	0	3
4	Giddiness	43	10	13	66
5	Headache	26	0	0	26
6	Giddiness ,Jerky movement, Neurogenic shock due to injection	1	0	0	1
7	Abdominal pain	5	0	0	5
8	Itching	1	0	0	1
9	Arm pain	10	0	0	10
10	Abdominal pain, vomiting, neurogenic shock due to injection	1	0	0	1
11	Death unrelated to vaccine	0	2	0	2
12	Menstrual bleeding	1	00	0	1
13	Rashes	0	0	1	1
	Total vaccine doses	10686	10259	9636	30582

1st and 2nd dose AEFI source – Dist. HPV monthly coverage reports
Third dose-Telephonic information from PHC

Comments on minor AEFI from both the states

There is no uniformity in the reporting system of AEFI in both the states. In the study no daily diary card was developed to monitor the AEFI nor there was any follow up of cases done. It is very surprising that the most common minor AEFI in any injectable vaccine is pain in the injection site of various degree. In AP, only ten girls after the first dose developed pain and none in second or third dose. In Gujarat none has reported pain following injection as minor AEFI. In both the states many minor AEFI has been combined e.g. nausea, vomiting, diarrhea and abdominal pain as one AEFI in AP and in Gujarat (Abdominal pain, vomiting and neurogenic pain due to injection) and (giddiness, jerky movement, neurogenic shock due to injection) has been clubbed together as one item in the description.

From the report submitted to the committee, it appears that the methodology of the study at both the places was not designed well to capture the AEFI. The vast majority (92%) of the adverse events reports following Gardasil vaccination in the United States of America where more than 29.5 million doses of the vaccine has been distributed till May 31st have included fainting, pain, and swelling at the injection site (the arm), headache, nausea, and fever. Fainting is common after injections and vaccinations, especially in adolescents. Falls after fainting may sometimes cause serious injuries, such as head injuries, which can be prevented by closely observing the vaccinated person for 15 minutes after vaccination.

Comments on study protocol:

The study has been designed very well except for the following shortcomings:

1. The primary end point of the study was to find out number of girls having serious and non serious adverse events following vaccination through routine UIP system. In this regard first of all routine system of reporting should have been verified in both the districts before designing the study. There is no dairy card based information record for assessing minor or major AEFI in the study protocol which seems unusual with such a large observational study.
2. There should have been some mechanism of insurance cover for the treatment of the vaccinated girls irrespective of their illness for a designated period of time. PATH has mentioned that there is an insurance cover for the organization but none was done for the girls in the study group.

(b) Report of Dr. Y.K.Gupta

प्रो. वाई. के. गुप्ता

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भेजषगुण विज्ञान विभाग
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Human Papilloma Virus Vaccines Demonstration Project

Report on Safety Aspects

By Dr. Y.K. Gupta

Background

Cervical cancer is a leading cause of cancer deaths amongst Indian women. Human Papilloma Virus (HPV) especially type 16/18 is an important cause of cervical cancers accounting for nearly 70% cervical cancers. Screening for cervical cancer using papanicolaou smear at regular intervals is the only proven means of early detection and timely management of HPV cervical cancers. The American College of Obstetricians and Gynecologists (ACOG) recommends screening for cervical cancers beginning biennial screening at age 21, regardless of sexual history. At age 30, screening every 3 years is recommended for women who have had 3 consecutive negative cytology screenings.

HPV vaccines have been developed which prevent HPV infection. Clinical trials have demonstrated 90%–100% efficacy of these vaccines in preventing precancerous cervical lesions attributable to HPV-16 and HPV-18. These vaccines, thus, may help in reducing the incidence of new cervical cancers by up to 70%. Currently only two HPV prophylactic vaccines are approved for use. Both the vaccines are available in US, Europe, Australia

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and Asia in over 100 countries including India. HPV vaccine is recommended as part of the National Vaccination Programme in US, UK, Australia and Netherlands. In US, the target population is 11-12 year old girls.

Pre-market Authorization safety data of HPV vaccines

A published pooled analysis of 11 clinical trials in nearly 30,000 female subjects who participated in phase II and III trials of HPV vaccine Cervarix suggested a favorable safety profile in women of all age groups. The common adverse events (AE) reported during clinical trials included injection site reactions, headache, fever, myalgia and gastrointestinal symptoms. Both the HPV vaccines appeared to be generally safe and well-tolerated. Pregnancies were reported in equal numbers in the vaccine and placebo groups and there was no increase in the incidence of congenital malformations, pregnancy loss or prematurity (Expert Opin Biol Ther 2010; 10(3): 477-487).

Phase IIIb study report of HPV Vaccine submitted by GSK (study conducted in India):

Total 176 female subjects aged 18 – 35 years received GSK HPV vaccine (three doses according to a 0, 1, 6 month schedule) and 178 female subjects received placebo in this randomized double blind manner. The incidence of any adverse symptom was higher in the HPV group as compared to the placebo group. This was mainly due to the local injection site symptoms. The most common general symptoms were fatigue, headache and fever and were similar in the two groups. However the most frequently reported unsolicited symptoms in the HPV group were infections and infestations (breast abscess, fungal infection, lymph node tuberculosis, nasopharyngitis, sinusitis and tonsillitis) with a

frequency of 3.4% in HPV group vs. 1.7% in placebo group and central nervous system disorders (headache and dizziness being more) with a frequency of 4.5% vs. 1.1% over the 30 day post vaccine observation period. No deaths were reported during the study.

Phase III study report of HPV vaccine submitted by MSD (study conducted in India):

A total of 108 female subjects in the age group 9 – 15 years received three doses of the HPV vaccine in this open label, non-randomized phase III study. The study report mentions that the most frequent adverse event was adverse injection site experience in the form of pain and tenderness of mild to moderate intensity which was more after first injection. The most common systemic adverse event was elevation in temperature observed in 23.15% subjects and was related to the vaccine. The next common adverse event was nasopharyngitis reported in 7.41% subjects. There were no deaths during the trial.

Post-market Authorization safety of HPV vaccines

(<http://www.cdc.gov/vaccinesafety/vaccines/hpv/gardasil.html> last accessed on 20th August 2010)

The post-marketing use of HPV vaccines has been monitored for safety in US by the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) using three systems i.e. the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD) Project and the Clinical Immunization Safety Assessment (CISA) Network. Following licensure in October 2009, VAERS had received three adverse event reports for Cervarix. By the end of May 2010, there were 16,140

VAERS reports of adverse events following Gardasil vaccination (licensed in US in 2006). The most common reports were due to syncope, local reaction at injection site, dizziness, nausea and headache. Of these 16,140 VAERS reports, 8% were considered serious and included syncope, Guillain-Barre Syndrome (GBS), blood clots and anaphylaxis. Although the reporting of syncope and venous thromboembolic events has been disproportional, the findings require further investigation and close monitoring. A 15-min observation after the vaccination was recommended by the CDC and FDA to monitor for anaphylaxis and syncope.

There have also been 53 US deaths reported following Gardasil vaccination. Of these, 29 reports were confirmed but there was no unusual pattern or clustering noted that would suggest causation by the vaccine. The clinical conditions present at the time of death (may or may not be related to vaccination) included viral infections, pulmonary embolism, cardiac events, diabetic ketoacidosis, seizures, acute GBS and drug overdose.

However there was no disproportionality in reporting of deaths or other serious adverse events as compared to other vaccines and hence no signal. The post-licensure safety profile is reported to be broadly consistent with safety data from pre-licensure trials and the benefit risk ratio was considered to be in favor of the HPV vaccine.

Periodic Safety Update Reports (PSUR)

Schedule Y mandates that the PSURs shall be submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two years – the PSURs need to be submitted annually. Licensing authority may extend the total duration

of submission of PSURs if it is considered necessary in the interest of public health. PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant. As defined by Indian Good Clinical Practice (GCP) Guidelines, a SAE is “an adverse event or ADR that is associated with death, inpatient hospitalization (in case the study was being conducted on out-patients), prolongation of hospitalization (in case the study was being conducted on in-patients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening”.

Cervarix Periodic Safety Update ReportInternational Birth Date: 18th May 2007DCGI approval Date: 10th Sept 2008

Date of Market Launch in India: XX March 2009

PSUR Cycle (India)	Schedule	PSUR submitted	Comments
1 st 6 months	XX Mar – XX Sept 2009	18 th Nov 2008 – 17 th May 2009 (4 th report)	PSUR submitted as per International Birth Date of
2 nd 6 months	XX Sept 2009 – XX Mar 2010	18 th May – 17 th Nov 2009 (5 th report)	Cervarix (18 th May 2007)
3 rd 6 months	XX Mar – XX Sept 2010	18 th Nov – 17 th May 2010 (6 th report)	Should have been submitted

GSK has also submitted the first three PSURs of cervarix that prepared before the launch of vaccine in India.

According to the summary of cervarix PSURs, approximately 9,924,980 doses were distributed since the launch of the vaccine. The number of subjects exposed to the vaccine is estimated to be between 3,308,326(considering all three doses were given) and 9,924,980(Considering that only one dose could be given). The exposure to Cervarix in India has not been mentioned. The manufacturer may be asked to provide this information.

After the launch of vaccine in India (March 2009), a total of 2419 reports were received (916 in 4th report and 1503 in 5th report) of which 3 were fatal. One death occurred due to streptococcal septicemia 24 days after an unspecified 2nd dose of cervarix and unclear causal relationship with the vaccine (4th report). Second death occurred within 75 minutes of one dose of cervarix which could be due to a serious underlying condition (5th report). The third death was an intrauterine death in which the mother was exposed to cervarix seven days before the estimated date of conception (5th report). The causal relationship with the vaccine is not clear. All the three death reports are from UK.

No fatalities have been reported from India (incidently not even those in the PATH demonstration project have been mentioned).

Gardasil Periodic Safety Update Report

International Birth Date: 1st June 2006

DCGI Approval Date: 4 July 2008 (amended on 1 Jul 2009 for prophylactic use in 27 – 45 year old females in addition to 9 – 26 year females)

PSUR Cycle (India)	Schedule	PSUR submitted	Comments
1 st 6 months	4 Jul 2008 – 3 Jan 2009	1 Jun 2008 – 30 Nov 2008 (5 th report)	PSUR submitted as per International Birth Date of Cervarix (18 th May 2007)
2 nd 6 months	4 Jan 2009 – 3 Jul 2009	1 Dec 08 – 31 May 09 (6 th report)	
3 rd 6 months	4 Jul 2009 – 3 Jan 2010	1 Jun 09 – 30 Nov 09 (7 th report)	
4 th 6 months	4 Jan 2010 – 3 Jul 2010	To be submitted	

In addition, MSD has submitted a summary of 4th PSUR (1 Dec 07 – 31 May 08)

PSUR (1 Jun 08 – 30 Nov 08): During this period, **syncope** was added to the list of side effects for the vaccine.

PSUR (1st Dec 08 – 31st May 09): During this period, **chills** was added to the list of side effects for the vaccine. Most common reports were of administration site reactions (53%). Next were 39% reports due to inappropriate vaccine administration followed by 30% reports of nervous system adverse events (headache, dizziness and syncope).

PSUR (1st Jun 09 – 30th Nov 09): During this period, **idiopathic thrombocytopenic purpura and acute disseminated encephalomyelitis** were added to the list of side effects for the vaccine. Six initial and one follow up reports with fatal outcome were reported during this period of which 2 reports, summarized in table, were due to an asthma attack 3 days after vaccination and convulsions 15 days after vaccination. The overall benefit-risk balance for the vaccine continued to be positive.

Post licensure study of HPV vaccination in India under PATH

India is considered to have nearly one fourth of the world's burden of cervical cancer which is expected to double by 2020. Considering the potential of HPV vaccines for primary prevention of cervical cancer, PATH initiated a five year project to advance prevention of cervical cancer. With the funding from Bill and Melinda Gates Foundation (BMGF), PATH selected four countries (India, Peru, Uganda and Vietnam) to increase the understanding of HPV vaccine introduction.

In India, PATH implemented the project in collaboration with ICMR and State Governments of Andhra Pradesh and Gujarat. The demonstration project has two components:

1. An observational study of post-licensure HPV vaccination through Universal Immunization Programme (UIP) and campaign mode; and
2. An evaluation of implementation of HPV vaccination through operations research in terms of coverage, acceptability, feasibility and cost.

Phase I (formative study) was conducted in India in collaboration with National AIDS Research Institute (NARI) in 2007. The study was carried out after being approved by the NARI scientific advisory committee, NARI Ethics Committee, State Government of Gujarat and Andhra Pradesh (AP) and Health Minister Steering Committee (HMSC). The objective of the formative study was to understand the socio-cultural milieu, policy environment and capacity of the health system for introduction of a new vaccine. The formative study suggested that the delivery of HPV vaccine programme requires public education and provider training. The three approaches suggested were: (i) merge HPV

vaccination with already established immunization services; (ii) package HPV immunization with adolescent health services or as part of a cancer control service; and (iii) deliver HPV vaccinations through either routine immunization services or a campaign using schools as sites for school-going girls and anganwadi or village health centers for non-school-going girls.

Comment: the protocol of the formative study mentions that based on predefined criteria, Maharashtra and Andhra Pradesh were selected for formative study (page 10 of HPV Vaccines Project: Formative Research). However the results mention that the study was conducted in **Gujarat instead of Maharashtra. The reason for the same is not clear.**

Phase II (Demonstration project)

Operations Research

Based on the results of the formative study, PATH conducted an operations research to demonstrate HPV vaccine delivery strategies for four components namely: coverage, acceptability, feasibility and cost. The study was carried out in Vadodara and Khammam district of Gujarat and AP respectively (where formative research was carried out). The study was approved by **PATH Research Ethics Committee for 10,000 subjects till September 9, 2010.**

Demonstration Project

The project started after being approved by the **Western Institutional Review Board, MNJ Institute of Oncology & Regional Cancer Center, local ethics committees in AP and Gujarat, DCGI and HMSC.** The overall goal of the project is to generate evidence

that would enable policy makers at national & state level to decide on the possible public sector introduction of the HPV vaccine.

Comments on PATH Demonstration Project

1. PATH describes the project as an observational study since it does not conform to the definition of a clinical trial established by CDSCO that “A prospective study.....behavior or nutritional strategies”. However, Schedule Y and Indian GCP Guidelines define clinical trial as “A systematic study of pharmaceutical products on human subjects (whether patients or non-patient volunteers) in order to discover or verify the clinical, pharmacological and/or **adverse effects**, with the object of determining their **safety and efficacy**”. The situation is not clear since:
 - a. Demonstrations project is a study of a **pharmaceutical product** carried out in humans.
 - b. Primary outcome of the study, as mentioned on page 9, HPV Vaccines: Gujarat Demonstration Project, includes
 - i. Number and % of vaccinated girls experiencing **serious adverse events**, as reported spontaneously through routine mechanisms of the UIP program
 - ii. Number and % of vaccinated girls experiencing **non-serious adverse events**, as reported spontaneously through routine mechanisms of the UIP program

2. The reporting of adverse events (both serious and non-serious) was to be done through routine mechanisms of UIP. The completeness of AE reporting in the UIP may vary because of possible differences in the level of training in different settings. Considering the background qualification and experience of the people involved in implementation of UIP, **underreporting of the non-serious AE is possible**. However **SAE**, particularly those taking place within a short period of vaccine administration, are unlikely to be missed.

3. The study has **also** been carried out in **“vulnerable population”**

The study has been carried out in 10 – 14 year old girls in three selected blocks in AP. These three blocks represent predominantly urban, predominantly rural and predominantly tribal population. **The study population is minor girls which also includes tribal girls.**

In order to implement HPV vaccination at in the public sector, the study required experience with HPV vaccination in different population structures and hence the stratification (urban, rural and tribal) **seems appropriate**. However, since the population under study is vulnerable, caution is required.

4. **Safety issues in the project protocol**

a. Exclusion Criteria, Page 11, (Gujarat Demonstration Project)

In this connection some question arise :

i. Any girl who is immune-compromised will be excluded

- How was the immune status of the participants assessed by the ANM, ASHA or Health Worker?
- How reliable is the history of 10 – 14 year old girls?
- Was any laboratory investigation carried out?

This is important as the prescribing information of the HPV vaccine specifically contra-indicates administration in immunocompromised subjects.

These issues could be addressed while revising the protocol for improvement..

- b. Training was provided to the ANM and health workers. Emergency kits were available and the drugs were reported to be as per WHO recommendations, were they able to handle serious adverse events (SAE) like anaphylaxis, cardiac arrest, seizures etc occurring at the site of vaccine administration?

Such adverse events may be rare but it is advisable to consider preparation for such situations through appropriate training of health workers in cardiopulmonary resuscitation. This training, on an ongoing basis, should be considered for UIP also.

5. Serious Adverse Events encountered in the study

a. SAEs in Gujarat

Other than two SAE, **two deaths** were reported from Gujarat on 2 Feb 09 and 30 Oct 09.

i. The 2 SAE reports are incomplete

- Case IDs are not present (One involving jerky movements possibly convulsions and one involving pain in abdomen)
- Details of vaccine are absent
- Details of adverse event are minimal
- Details of rescue medication used are absent

ii. SAE (IND (AEFI) – GJ/044) involving death”

- The report informs that the death occurred due to severe anemia and *P.vivax* infection. The attached medical opinion claims that the death occurred due to congestive cardiac failure secondary to anemia and severe malaria. **However clinical features of CCF have not been mentioned in the report. Moreover, no post-mortem report has been attached.**
- The SAE reporting timelines have not been adhered to.

iii. SAE (no case ID) involving death (possibly due to snake bite) – reported by Shivaji K. Kotwal

- Death occurred on 2/11/2009 during shifting to CHC. However the Institutional Ethics Committee for Human Research, Medical College and SSG Hospital, Baroda mentions that they were notified that the death occurred on 1/11/2009 vide letter dated 29/1/2010 (Annex D-G, Response to queries, N0-5). This seems to be error of pen and should be corrected and authenticated.
- The SAE reporting timelines have not been adhered to strictly.
- The report does not describe the site of bite, the presence or absence of fang marks and local wound condition. It also does not mention the presence of either neurotoxic symptoms (paralysis, head drop, ptosis etc) or hemotoxic symptoms (bleeding from wound/ DIC or hematuria etc). In the absence of such signs and symptoms of envenomation, causality assessment is difficult.

b. SAEs in Andhra Pradesh

Other than one SAE, five deaths have been reported from AP between 8 Aug 09 and 29 Apr 2010.

- i. The format of the First /information Report for SAEFI is not uniform.

ii. Death due to Subarachnoid hemorrhage: The cause of death has been attributed to aneurysm although no post mortem was carried out. The CIOMS report for the same mentions anaphylactic shock as an adverse reaction. However no details have been provided.

iii. Death due to viral fever:

- The causality term is 'possible' as infection occurred within 2 weeks following vaccination. Thus having a reasonable temporal relationship. Reports of infection following vaccination have also been mentioned in the Phase III Clinical trials and PSURs.
- The patient had high grade fever but she was not admitted due to lack of beds. She was given some treatment the record of which is not available.

It is advisable that a guideline/SOP be developed so that so subject is deprived of admission or medical treatment due to non availability of beds etc.

iv. Death due to poisoning (date of event: 21 Jan 2010): there is a discrepancy in the nature of poison.

- Case report mentions **endosulphan (which is an organochlorine)**. The case sheet and the SHO report mentions unknown poison whereas **the postmortem report mentions that the death occurred due to consumption of organophosphorous insecticide.**

This indicates the need for improvement in understanding insecticide poisonings by medical officers involved.

- The postmortem report has not been signed by the Civil Assistant Surgeon (as mentioned on the stamp).
- The SAE reporting timelines have not been adhered to.

Organophosphate and organochlorine are both commonly used pesticides. Hence the two are often loosely considered same in the community.

v. Death due to accidental drowning in well:

- The case record is incomplete. It just mentions that the subject accidentally fell in well and died.
- The preceding sequence of events is not mentioned.

It is unlikely that the accident happened due to vaccine induced dizziness. However it is difficult to establish or rule out with absolute certainty association of the event with the vaccine.

vi. Second death due to poisoning (unknown insecticide)

- The First Information Report does not mention the symptoms and signs of the patient at the time of admission.
- The post mortem report suggests organophosphate poisoning in which case typical OP poisoning signs and symptoms would

have been observed and specific antidote like atropine and pralidoxime should have been used.

- The SAE reporting timelines have not been adhered to.

Summary

Human papillomavirus infection is very common genital infection in women. Cervical cancer is a rare outcome of HPV infection. Yet cervical cancer is the most common type of cancer of women in India. The two HPV vaccines approved have the potential to prevent cervical cancer occurring due to most common types of HPV. These vaccines have been approved in more than 100 countries. Many countries have included catch-up HPV vaccination in the National Immunization programme.

The HPV vaccines have been demonstrated to be safe in the premarketing clinical trials. However, vaccine trials are designed to pick up adverse events that occur with a frequency of up to 1 in 10,000. Even more rare adverse events come to notice when the vaccine is used on a large scale. Careful surveillance is needed in the early post-marketing phase to detect these more rare adverse events. The two first generation HPV vaccines have been used in millions of women worldwide and the early post-marketing safety reports have been reassuring. No new cause of concern has been detected so far. The WHO's Global Advisory Committee on Vaccine Safety (GACVS) reviewed the post-marketing data on HPV vaccine in December 2008. The committee stated that the allergic reactions and syncope can occur after injection with HPV vaccine. However the usual safety precautions

should suffice. No evidence of previously undetected serious adverse events that were causally related to the vaccine was found. The post-licensure surveillance for Gardasil in the US by the Vaccine Adverse Event Reporting System (VAERS) reported that most of the adverse events following immunization of over 23 million vaccines were no greater than the background rates of other vaccines for this age group.

The goal of the demonstration project was to generate evidence that will enable introduction of HPV vaccine in the public sector in India. The demonstration project though observational in nature, may be considered as a clinical trial also. However it may not fit the classical description of a controlled clinical trial where rigorous patient monitoring mechanisms are usually employed.

Implementation of such large scale studies is difficult and some procedural deficiencies are likely (as pointed out in this report). **With an estimated sample size of 16,000, the study may miss adverse events that are non-serious in nature. It is however, more likely to pick up serious adverse events.**

The timely reporting of serious adverse events should be taken more seriously. The SAEs should have been reported to the Ethics Committees and the regulatory authorities by those concerned at appropriate times.

In light of the PSUR data submitted, the global safety profile of the HPV vaccines, the deficiencies pointed out in this report are unlikely to specifically affect outcome of the study. However, the experience with HPV vaccines in Indian population is limited. Hence, it is advisable that appropriate amendments be made in the protocol for identification of serious adverse events, training of health workers to manage serious adverse events, adherence to adverse event reporting timelines and greater emphasis on proper documentation.

The ethical issues involved in the project are being analyzed by other experts.

The experience emphasizes the need of to strengthen pharmacovigilance at all levels of the health care system.

(c) Report of Dr.Rani Kumar

December 2, 2010

STRICTLY CONFIDENTIAL

Subject: Alleged irregularities in terms of ethical issues involved during the conduct of the studies in AP and Baroda districts in India while giving Human Papilloma Virus vaccine to young girls between the age group of 10-14 years.

Dear Dr.Kishore Choudhry,

A detailed report on the above issue was submitted to the Chairman (Dr. S.S. Agarwal) of the Committee (copy enclosed). The meeting was held on 27th September at IRCS and the report was discussed in detail. The Chairman opined that numerical analysis of the 100 consent forms of AP and Baroda be done separately and it is as follows:

Andhra Pradesh

No. of Consent forms	Description
69	Signature of witness missing
4	Name of witness missing
2	Relationship with subject not mentioned
3	Signature of parent/guardian not done
2	Signature and name of parent not matching
2	Father is witness too
4	Name of PI is not mentioned

Apart from above, 6 monthly progress report of the project was supposed to be submitted to the ICMR. However, no mention of such a report is there.

Gujarat

The numerical in dates written is not in very legible handwriting and written in Gujarati/ English at different places. Therefore, it is very difficult to comment on dates of cosent, witness's signature and actual date of vaccination. However, it seems that the consent form signature and witness's signature are on the same date and vaccination is given within 10-20 days after that.

Serial numbers of forms are repeated, i.e. Sr.No.1 is given on 6 forms etc. Many forms have over writing and cutting etc. on serial numbers.

The name of parents/guardians given in the consent form and the name in signatures do not match in the following:-

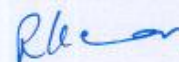
S.No.	Name
009	Rakshaben Kalabhai
018	Rathwa Rekhaben Kalubhai
126	Sartajbanoo Riaz Merchant
19	Rathwa Chetnaben

Also Gujarat State Advisory Group on Cancer cervix Prevention (GSAGCCP) was supposed to review the progress of prevention of cancer cervical activities in Baroda from time to time. But no mention of such an activity is there.

Thus from the above numerical analysis it is obvious that the team involved in conduction of the study on HPV had 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 vaccine and date of signature.

With regards,

Yours sincerely,



(Rani Kumar)

Dr. Kishore Chaudhry,
Scientist F,
ICMR, New Delhi.

6th September, 2010

SUB: HPV VACCINATION DEMONSTRATION PROJECT THROUGH IMMUNIZATION BY HPV IN GUJARAT AND ANDHRA PRADESH DISTRICT HEALTH DEPARTMENT AS A PART OF COLLABORATIVE PROJECT WITH PATH.

Dear Dr. Chowdhry,

This is with reference to your email dated 6th July 2010, regarding report on "HPV vaccination demonstration project in Gujarat and Andhra Pradesh District Health department as a part of collaborative project with PATH. I have gone through voluminous necessary papers in connection with the i) ethical issues and ii) AEFI related to the study, iii) 100 consent forms each from Andhra Pradesh and Gujarat; and iv) serious adverse events and actions taken thereon. I have made following observations:

Two states viz., **Andhra Pradesh (AP)** and **Gujarat** were selected for the Project. In Andhra Pradesh **Khammam** district and in Gujarat **Vadodara** district were chosen for the study. As per project protocol, school going girls through their schools and for non-school going girls through Anganwari, between the age group of 10-14 years, (belonging to rural, urban and tribal categories) were chosen for the study. After getting the consent from parent/ guardian/ warden in case of hostlers, were injected with Gardasil (generic name of drug), 0.5 ml dose intramuscularly at 0, 2, 6 months intervals (3 dose regime).

The subjects were observed for 15 min. to 30 min after vaccination for any minor/ adverse drug reactions and if any reaction ANM was informed at Primary Health Centre and necessary treatment was given.

For ethical clearance of the above subjects for HPV vaccine:

The Commissioner of Family Welfare GOAP and GOG gave **administrative sanctions for implementation of the cervical cancer prevention project** for formative research for data collection in Khammam District in Andhra Pradesh and Vadodara district in Gujarat wide letter dated 2nd March 2007 and 28.12.2007 respectively.

District Health administration, Gujarat **did not have its own system for ethical clearance for human research**, the Institutional Ethics Committee for Human Research (IECHR), Medical college Baroda was requested by one of the principal investigator, who was then Addl. Director (Family Welfare) to consider the project for ethical approval. The **IEFR Committee** was made by **Medical College, Baroda**.

Following the above administrative sanctions, the National AIDS Research Institute (NARI), **ICMR has approved the project** "Assessing introduction of HPV vaccine in India: Phase I formative study after discussing it in ethical committee vide letter dated 12.07.2007.

The Pamphlet on vaccination was available which says that the girls will be vaccinated only after receiving due permission and **consent from the girl and/ or her parents or guardians**. A witness needs to sign on consent form endorsing the parents'/guardians' signature.

Government of Andhra Pradesh, Tribal Welfare Department had issued a circular for vaccination in various schools instructing all **the hostel welfare offices and Head Masters of the Ashram Schools and hostels** under RRDA and Headmasters of Primary, UP and High Schools to cooperate in registration of eligible girls for vaccination of HPV and to **sign the consent forms on behalf of adolescent girls to have vaccine especially for hostellers** at Ashram Schools run by both government and private sector. This was done because contacting parent was difficult in the agency area.

According to ICMR guidelines, IEC committee should have the following criteria for its composition:

- (A) The Committee members of any IEC must have one legal expert/ retired judge as a member.
 - (i) IECHR, Medical College and SSG District Hospital Baroda **did not have legal person** as a member of the committee, however such legal member was added later.
 - (ii) IEC of GOAP does not mention the **composition of its committee** therefore its authenticity cannot be verified.
- (B) All IECs of the state should be **registered bodies**.

It is not clear whether IEC of Gujarat and Andhra Pradesh were registered bodies.

- (C) IEC is a **decision making body** which is supposed to meet periodically to evaluate progress of project and review serious adverse events (SAE) report.

No such meetings seem to have been held either in Gujarat or in AP. It was only after the reports which appeared in media in AP, that IEC meetings(s) was held.

INFORMATION ABOUT HPV VACCINE AND VOLUNTARINESS/ CONSENT OF THE PARTICIPANT/PARENT/GUARDIAN.

The following guidelines were to be followed before vaccination:

- (i) The girls will be vaccinated only after receiving **due permission** and **consent** from either the **girl** and/or her **parents** or **legal guardians**.
- (ii) A **witness** (who should be any full time government employee) is also required to sign on a separate form endorsing the parent's/guardian's consent.
- (iii) The consenting procedure must be obtained in the presence of Taluka Development Officer / Talati Secretary of Gram Panchayat by affixing the **photographs** or the copy of the **photo ID cards of the parents**.
- (iv) In the case of **hosteller at Ashram School** (run by Government & Private Sector in AP), government of Andhra Pradesh, Tribal Welfare Department had issued a circular instructing all Welfare officers and Head Masters of the Ashram Schools and hostels under PRDS and headmasters of Primary, UP and High School to **sign the consent forms on behalf of adolescent eligible girls for HPV vaccination**. This was done because contacting parent was difficult in the agency area and in AP.
- (v) **The signature of the vaccinator (Investigator)** should be taken.

After going through each consent form separately (100 each in case of AP & Gujarat), the following observations are made:

Neither the proper procedure of information about HPV vaccine has been followed (as in remote places of AP, it was done on phone or through village messengers) nor consent statement has been followed properly for the following reasons:

- (i) Has the guardian/warden been given **written permission/authority by the parents to sign** on behalf of their girls?
- (ii) On many forms **witness has not signed** and if those forms which are signed, it is not clear if they are signed by full time government employees.
- (iii) Neither the **photograph nor the photo ID card** of parents/ guardians/ wardens is pasted on consent form.
- (iv) On many forms **investigator has not signed**.
- (v) In some forms signature of parent/guardian is **not matching** with their name.
- (vi) The **date of vaccination is much earlier** than the date of signature of parents/ guardian in the consent form.
- (vii) In some forms, **the name is of father but signature is of probably mother** (lady's name).

Thus all the consent forms have been very **carelessly filled** and are **incomplete** and **probably inaccurate**. The full explanation, role, usefulness, and pros and cons of vaccination have not been properly provided to parents/ guardian as in some cases (hostellers) , this has been done on telephone or through messengers.

From the above facts it is not clear **how correct** is it **ethically** to have vaccinated such girl participants.

ADVERSE EFFECTS FOLLOWING HPV VACCINATION AND ACTION TAKEN THEREON:

According to **Non-serious AEFI registry report**, minor symptoms in the form of fever, headache, giddiness, vomiting, abdominal pain, itching, arm pain, menstrual bleeding, rashes, etc. were noted and were treated accordingly.

In AP after 1st dose, 31 cases out of 14091 (0.27%), 52 cases out of 13930 (0.37%) after 2nd dose and 13 cases out of 9639 (1.13%) after 3rd dose of vaccine were reported for minor symptoms which were treated accordingly..

In Gujarat after 1st dose, 97 cases out of 10686 (0.9%), 13 cases out of 10259 (0.1%) after 2nd dose and 14 cases out of 9637 (0.13) after 3rd dose of vaccine were reported for minor symptoms which were treated accordingly.

Minor AEFI Registry Summary Report

No. of cases & %	After 1 st dose	After 2 nd dose	After 3 rd dose
Gujarat	97/10686 (0.9%)	13/10259 (0.1%)	14/9637 (0.1%)
A.P.	38/14091 (0.27%)	52/13930 (0.37%)	13/9637 (0.13%)

No serious AEFI were reported in AP. In Gujarat two girls were hospitalized due to AEFI and treated, recovered and discharged. Two cases died of which cause of death of one was **P.virex malaria** and for other it was **snakebite**.

Thus from the above data it can be inferred that HPV vaccine probably did not give rise to markable adverse effects and **deaths did not appear to be related to vaccination**.


(Rani Kumar)

6. Findings of the Committee

6.1. 'Link between Deaths and vaccine' in girls from Khammam and Vadodra districts in the cohort immunized with HPV vaccine under the PATH project

- 6.1.1 A total of 7 deaths have been reported, 5 from Khammam in AP and 2 from Vadodra in Gujarat, amongst all those who received the HPV vaccine (14091 in Khammam and 10686 in Vadodra).
- 6.1.2 A summary of all the deaths is given in Table no.1. Photocopies of Medical records, FIRs (First Information Reports), Postmortem reports and Forensic analysis are given in Appendix 22.
- 6.1.3 There was no temporal or spatial clustering of the deaths. All the girls who died received the vaccines at different centers, lived in different villages and died at different times.
- 6.1.4 Three girls died after the 1st injection (22, 44 and 48 days later), 3 died after the 2nd injection (19, 21 and 100 days later-after the 2nd injection) and 1 died after the 3rd injection (97 days later-after the 3rd injection).
- 6.1.5 In two cases there was history of consumption of poison in Khammam, AP (44 days after the 1st injection in one case and 100 days after the 2nd injection in the second case). The death has occurred within 3 and 5 hours after the onset of symptoms. In both cases autopsy was done. Chemical examination of the viscera (stomach) confirmed the presence of poison in both the cases. In one case symptoms supportive of insecticide poisoning are recorded.
- 6.1.6 In one case there was history of accidental drowning in the pond (48 days after the 1st injection). No autopsy was done in this case.
- 6.1.7 In two other deaths from Khammam (one after 22 days after 1st injection and the other after 97 days following 3rd injection) the alternate cause of death was not established with certainty. One case had fever for 7 days before death (without any other symptoms) and one case had sudden onset of headache with vomiting and

unconsciousness and died within 2 hours. The relationship of this clinical picture to vaccine reaction is not apparent.

- 6.1.8 In Gujarat 2 deaths have occurred, one after 19 days and the other after 21 days of second injection. These cases were from 2 different blocks, Shinor and Kawant. One child has received the vaccine on 9th October and the other on the 14th October, 2009. One of these cases is reported to have hemoglobin of 4gm% and was positive for P.vivax. Both died within a day from the onset of symptoms. No autopsy or other investigations were done in these cases. Their cause of death remains uncertain. The inclusion of the child with such severe anemia was in contravention to the inclusion/exclusion criteria laid down for the study.
- 6.1.9 Recording, reporting and investigation of deaths was done as per GOI Guidelines for Reporting and Management of Adverse Events Following Immunization (AEFIs). Both the MOs and DIO/DRCHO considered that the deaths were not related to vaccine and therefore did not ask for Detailed Investigation.

Dr. A.K.Dutta, on basis of review of First Information Repots, Post-mortem examination reports, and available medical records of all the deaths in the study area, has opined that 'there is no common pattern to the deaths that would suggest that they were caused by the vaccine' (see Reports of Experts).

- 6.1.10 The investigators have placed total reliance on the routine state machinery for Reporting and Management of Adverse Events Following Immunization (AEFIs). This included Serious Adverse Events and Deaths as well. This plan was conceived and approved by all the advisory groups in spite of identification of following end-points as 'Primary outcomes' of the study:
- (a) Number and percent of vaccinated girls experiencing serious adverse events, as reported spontaneously through routine mechanisms of the UIP program
 - (b) Number and percent of vaccinated girls experiencing non-serious adverse events, as reported spontaneously through routine mechanisms of the UIP program
 - (c) Timelines of reporting serious adverse events to local, state and national authorities, as per the usual UIP protocol; and

- (d) Timelines of reporting non-serious adverse events to local, state and national authorities, as per the usual UIP protocol

No independent mechanism was set up to cross verify the adequacy of the routine state program.

Dr. Dutta has identified that the reporting of non-serious AEs is grossly under represented. This raises questions about the accuracy of SAEs as well. Also, delay in recording, reporting and investigation of deaths could have been due to sole dependence on this mechanism even in a research study. This is a significant lapse in the execution of the study.

6.1.11 There was no control group in the study; hence, no comparison can be made with the number and causes of death in a comparable group. The information on background death rate due to all causes in this population group is not reliable. For example in the three project sites (population of 342662) and 4 non-project sites (population 2222750) in district Khammam only 42 deaths (including those in the vaccinated group) have been reported in girls between 10-14 years from 2007 to 2010 (data provided by DM&HO, District Khammam) whereas national death rate in this age-group is approximately 1 per 1000 (including both boys and girls). Hence this data can not be used for comparison. The record of causes of death in the data available does show that poisoning is relatively common in the 10-16 year age group in this area in recent years.

6.1.12 Internationally, as of January 31, 2010 forty-nine deaths have been reported in the US against approx. 28 million doses of Gardasil vaccine distributed in the US. Out of these 28 deaths have been traced. According to CDC there was no common pattern or clustering of the deaths that would suggest that the deaths were caused by the vaccine. In the US the CDC and FDA have been monitoring the post-marketing safety of the vaccine. The clinical conditions present at the time of death (which may or may not be related to vaccination) included viral infections, pulmonary embolism, cardiac events, diabetic keto-acidosis, seizures, acute GBS and drug overdose. In the Vaccine Adverse Event Reporting System (VARES), there have been 16140 VARES reports until the end of May 2010. Of these 8% have been considered serious; including syncope, Guillain-Barre syndrome, blood clots and anaphylaxis. A 15 minute

observation period has been recommended by the CDC and FDA to monitor for syncope and anaphylaxis following immunization. The same has been followed in the present study.

6.1.13 In case of Cervarix, 9.9 million doses have been distributed. After March 2009 a total of 2419 reports have been received of AE of which 3 were fatal. All 3 death reports are from UK. The causal relationship with vaccine has not been established. The serious AE have included idiopathic thrombocytopenia and acute disseminated encephalomyelitis. Dr. Y.K.Gupta, on the basis of review of Periodic Safety Update Reports (PSURs), has opined that ‘overall benefit-risk balance for vaccine continues to remain positive’ (see Reports of Experts, Section 5).

6.2 Ethical Issues of subjecting children of marginalized populations to these studies, and investigations in children without appropriate consent.

6.2.1 Studies in Children (Adolescent girls)

6.2.1.1 The project was targeted to cover girls in the age-group of 10-14 years as the HPV vaccine is primarily beneficial for prevention of HPV infection. This is in accordance with the WHO’s position paper on HPV vaccines (Weekly Epidemiological Record 15:118-131, 2009). According to this paper:-

“Models predict that vaccination programmes for young adolescent females (defined as being roughly within the range of 10-13 years) will substantially reduce the incidence of cervical cancers associated with vaccine-related HPV types if coverage is high (>70%) and vaccine-induced protection lasts \geq 10 years. ...Depending on assumptions related to vaccination and screening programmes, vaccination could reduce the life-time risk of cervical cancer by 35-80%.”

The Indian Academy of Pediatrics has recommended the HPV vaccine to be given to adolescent girls (10-12 years of age) and FOGSI (Federation of Gynecologists and Obstetricians of India) to girls between 12-16 years of age.

The Drugs Controller General of India has given the permission to market Cervarix - HPV Vaccine of M/s Glaxo Smith Kline (GSK) - for the following indication:

“It is indicated in females from 10-45 years of age ...” (Appendix 23), and to Gardasil – the HPV vaccine of M/s Merck Sharp and Dohme for “...girls and women 9-26 years of age...” (Appendix 24).

Since the project being carried out by PATH was a post-licensure study, the use of the HPV vaccine for approved indication, and recommended usage was justified.

Further it was clearly mentioned in the project proposal which was evaluated by the Ethics Committees. The Ethics Committees have examined and approved the study since the intervention was likely to be directly beneficial to the participants. This was also approved by the Project Advisory Committees and Health Minister’s Screening Committee.

6.2.1.2.1 According to Schedule Y, studies in Pediatric populations can be carried out under following conditions:

- i) The timing of pediatric studies in the new drug development program will depend on medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate age group. 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.
- ii) If the new drug is for disease predominantly or exclusively affecting pediatric patients, clinical trial data should be generated in the pediatric population except for initial safety and tolerability data, which will usually be obtained in adults unless such initial safety studies in adults would yield little useful information or expose them to inappropriate risk.
- iii) If the new drug has a potential for use in pediatric patients – pediatric studies should be conducted. These studies may be initiated at various phases of clinical development or after post marketing surveillance in adults if a safety concern exists. In cases where there is limited pediatric data at the time of submission of application – more data in pediatric patients would be expected after marketing authorization for use in children is granted.
- iv) If the new drug is major therapeutic advance for the pediatric population – the studies should begin early in the drug development, and this data should be submitted with the new drug application.

- v) Pediatric subjects are legally unable to provide written informed consent, and are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/legal guardian. However, all pediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand. Where appropriate, pediatric participants should additionally assent to enroll in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form.
- vi) For clinical trials conducted in the pediatric population, the reviewing ethics committee should include members who are knowledgeable about pediatric, ethical, clinical and psychological issues.

6.2.1.2.2 According to GCP guidelines of the Government of India and ICMR guidelines:

- a) Children will not be involved in research that could be carried out equally well with adults
- b) The purpose of research is to obtain knowledge relevant to health needs of children. For clinical evaluation of a new drug the study in children should always be carried out after the phase III clinical trials in adults. It can be studied earlier only if the drug has a therapeutic value in primary disease of children
- c) A parent or legal guardian of each child has given proxy consent
- d) The assent of the child should be obtained to the extent of the child's capabilities such as in the case of mature minors, adolescents etc
- e) Interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child subject must be justified in relation to anticipated risks involved in the study and anticipated benefits to the society
- f) The risk presented by interventions not intended to benefit the individual child subject is low when compared to the importance of the knowledge that is to be gained

6.2.1.2.3 Further, according ICMR Guidelines

..Many of the prophylactic vaccines are given to pediatric group. The guidelines to conduct the clinical trial on investigational vaccines are similar to those governing a drug trial...

6.2.1.2.4 In accordance with the regulatory provisions *Phase III bridging studies were carried out in India before licensing of the vaccine by the Drugs Controller General of India*, since the vaccine was already approved and marketed outside India. Two such studies were carried out in India. One involved 176 female subjects between 18-35 years of age for the GSK vaccine and the other 108 girls between 9-15 years of age for the MSD vaccine. The reports of these studies are given in Appendix 25 and 26, respectively. **Thus not only the requirement of assessing the safety and efficacy of the vaccine in adults prior to use in children has been fulfilled, the data on adolescent girls has also been acquired. As such there was no violation of any laid down guidelines for use of new drug/vaccine in the Pediatric age group.** On the strength of both the Indian data and also the international data the DCGI has approved the use of the vaccine in adolescent age group.

6.2.2 Inclusion of the children of marginalized populations

6.2.2.1 Selection of States, Districts and Blocks in the study

The selection of the States for inclusion in the study was carried out in consultation with the National Advisory Committee of the ICMR. The following criteria have been listed:

- (a) Routine immunization coverage of the State being similar to national average
- (b) Experience with introduction of new vaccine such as Hepatitis B vaccine
- (c) Commitment of the State to Adolescent health and cervical cancer prevention
- (d) Expressed willingness to participate in the project

Initially the States of Andhra Pradesh and Maharashtra were chosen for the study. Subsequently because of lack of response from the State, the state of Maharashtra was replaced by the state of Gujarat.

Among the states the districts were chosen in consultation with the State Advisory committees. The criteria for selection were:

- (a) Percentage of married girls less than 18 years old
- (b) Percentage of children aged 12-35 months old who had received full vaccination
- (c) Percentage of women visited by ANMs or health workers
- (d) Literacy rate, and
- (e) Percentage of school drop-out in grades 1-5

Districts with average performance were short listed and the list was discussed with State government. From this list the District Khammam in Andhra Pradesh and District Vadodra in Gujarat were selected.

In each district, three study blocks were identified based on distribution of urban, rural and tribal populations. In Khammam, Andhra Pradesh the three blocks were Kothagudem (predominantly urban), Thirumalaypalem (predominantly rural) and Bhadrachalam (predominantly tribal). In Vadodra, Gujarat the three blocks were Dabhoi (urban), Shinor (rural) and Kawant (tribal).

Thus, except for selection of one predominantly tribal block out of the 3 blocks in each district (without any assigned reason) the choice of the study sites was reasonably objective. All the overseeing committees have approved this arrangement. However, in hindsight the selection of populations for such a study could have been more objectified. The ability to understand and comprehend research nature of the study, ability to provide well informed consent, and availability of quality medical care to attend to any AEs, particularly SAEs, might also have been taken into consideration.

6.2.2.2 Selection of Eligible girls for vaccination in the selected blocks

The goal was to immunize **all eligible girls** in the age group of 10+ to <15 who were resident or attending school in the selected block. The objective was to include both school-going and non-school-going girls in the defined age group in the study. The exclusion criteria were:

- (a) Non residents (visitors during the vaccination period)
- (b) Any girl who is pregnant or immune compromised, has a history of bleeding disorders, allergy to vaccine components or previous allergic reactions to other vaccines; or experiencing high fever at the time of vaccination.

The responsibility of determining the eligibility was that of the ANM and was required to be carried out prior to administration of the vaccine.

No information has been provided about the efficiency/efficacy of this screening. The data on no. of girls excluded for various reasons would be known after the final analysis.

No information has been collected on socio-economic status of the beneficiaries. It was not the criteria for inclusion or exclusion.

As a surrogate marker the committee has asked the investigators to provide the information about the SC/ST status, and public/private status of the schools, of the girls in the age group of 10-14 years in the block – all eligible girls, those who consented and those who were immunized. The data is given in Table no. 2 and 3.

Preliminary analysis shows that girls from both private and public schools were enrolled in the study. But the no of private schools was considerably less than that of public schools. In Andhra Pradesh 9405 girls from the public schools were immunized compared to 3395 from private schools. Corresponding numbers for Gujarat were 4216 and 3039.

As far as caste wise distribution is concerned, in AP amongst those who received the 1st dose of the vaccine 22% were SC, 31% were ST and 47% were others. Corresponding numbers in Gujarat were 4%, 72% and 24%. However these proportions were the same for the total population as well, indicating that **there was no systemic bias in immunization of girls of any one particular group.**

6.2.3 Investigations in children without appropriate consent

6.2.3.1 The investigators have followed a very elaborate procedure for obtaining consent (see Appendix 27).

A copy of the information sheet provided to the parents/legal guardians for providing consent in English, and regional languages, duly approved by the local Institutional Ethics Committees, is placed at Appendix 28. A copy of the brochure used for creating awareness is placed at Appendix 29.

According to investigators, in Andhra Pradesh, Signatures of one parent were obtained on 9543 forms, thumb impression of one parent on 1948 forms and signatures of Hostel Warden/Head Master as Guardian in 2763 forms.

The consent by the Hostel Warden/Head Master was given on basis of the circular issued by the Dy. Director, Tribal Welfare Department, Khammam (Appendix 30).

The legality of the signing by the Hostel Warden/Head Master in Andhra Pradesh needs to be examined by an appropriate authority.

In Gujarat one parent has signed on 6217 forms, has provided thumb impression on 3944 forms and Legal guardian has signed or put thumb impression on 545 forms.

According to investigators no body was immunized without consent.

According to Protocol verbal assent of the girls was obtained at the time of immunization by the ANM/Female Health Worker. Since it was a verbal assent, there is no record of the same. Adequacy of this process of assent is questionable.

6.2.3.2 The investigators were asked to submit 100 consent forms, chosen randomly, for both AP and Gujarat for independent verification.

The report of the expert shows that there were several discrepancies in the submitted consent forms (see Report of Dr.Rani Kumar, Section5). This raises concern about actual implementation of the consent process.

Local ethics committees need to be mandated to provide closer supervision of consenting process.

Table 1 (Part 1)

1	2	3	4	5	6	7
State	Demo ID	Initials	Age	Name of village/Town/Block/ District where subject lived	Name of school/Ashram/Anganwadi where immunized	Name of sub center/PHC/other from where vaccine was taken
AP	57/09	Kas	13	Kothagudem/ Khammam	Ramchandra Govt. high school	Kothagudem UFWC
AP	03/09	SsK	14	Yerragattu/ Bhadrachalam/ Khammam	Yerragattu - Ashram School	PHC Gowridevpeta
AP	33/09	MsL	12	Appalarshimpuram/ Tirumalayapalem/ Khammam	Government high school, Appalanarsimhapuram	PHC Nelakondapalli
AP	104/09	KS	13	Angipaka/ Bhadrachalam/ Khammam	Kreguballi ashram school	PHC Narsapur
AP	05/09	CaD	12	B. R Colony/ Bhadrachalam/ Khammam	Govt. school Kothacolony	PHC Nellipaka
GJ	10/09	VmL	14	Bithi/ Shinor/ Vadodara	Subcenter - Bithli	PHC Simli
GJ	044/09	JaR	10	Pipalda/ Kawant/ Vadodara	Anganwadi Center - Pipalda	PHC Pipaldi

Table 1 (Part 2)

1	2	3	8	9	10	11	12	13	14	15	16
State	Demo ID	Initials	Dose I			Dose II			Dose III		
			Lot No.	Diluent	Date of Vaccination DOSE I	Lot No.	Diluent	Date of Vaccination DOSE II	Lot No.	Diluent	Date of Vaccination DOSE III
AP	57/09	Kas	876	No diluent needed for HPV Vaccine	17-Jul-09	NA	No diluent needed for HPV Vaccine	Did not receive dose II	NA	No diluent needed for HPV Vaccine	Did not receive dose III
AP	03/09	SsK	876	No diluent needed for HPV Vaccine	16-Jul-09	NA	No diluent needed for HPV Vaccine	Did not receive dose II	NA	No diluent needed for HPV Vaccine	Did not receive dose III
AP	33/09	MsL	876	No diluent needed for HPV Vaccine	20-Jul-09	NA	No diluent needed for HPV Vaccine	Did not receive dose II	NA	No diluent needed for HPV Vaccine	Did not receive dose III
AP	104/09	KS	876	No diluent needed for HPV Vaccine	19-Jul-09	876	No diluent needed for HPV Vaccine	13-Oct-09	NA	No diluent needed for HPV Vaccine	Did not receive dose III
AP	05/09	CaD	876	No diluent needed for HPV Vaccine	21-Jul-09	876	No diluent needed for HPV Vaccine	9-Oct-09	876	No diluent needed for HPV Vaccine	22-Jan-10
GJ	10/09	VmL	AHPVA050AG	No diluent needed for HPV Vaccine	9-Sep-09	AHPVA050AG	No diluent needed for HPV Vaccine	14-Oct-09	NA	No diluent needed for HPV Vaccine	Did not receive dose III
GJ	044/09	JaR	AHPVA050AG	No diluent needed for HPV Vaccine	2-Sep-09	AHPVA050AG	No diluent needed for HPV Vaccine	9-Oct-09	NA	No diluent needed for HPV Vaccine	Did not receive dose III

Table 1 (Part 3)

1	2	3	17	18	19	20	21	22
State	Demo ID	Initials	Date & time of first symptoms	Presenting Symptoms	Investigation reports	Medical care received - Place, qualification of doctor, date - time	Date/time of death	Date of Autopsy
AP	57/09	Kas	Date: 1-Aug-09, Time: 6:00 pm	Fever mild in nature not associated with chills & rigour or vomiting or headache	Area Hospital case record	Seen by Registered Medical Practitioner (RMP) on 4-Aug-09. On 7-Aug-09 seen at Area Hospital Kothagudem. On 8-Aug-09 admitted to Area hospital Kothagudem.	Date: 8-Aug-09, Time: 9:00 pm	Not done
AP	03/09	SsK	Date: 29-Aug-09, Time: Around 4:00 pm	History of consumption of unknown insecticide	None	Admitted to Area Hospital Bhadrachalam on 29-Aug-09 where she expired.	Date: 29-Aug-09, Time: 7:00 pm	30-Aug-09
AP	33/09	MsL	Date: 6-Sept-09, Time: 2:00 pm	Accidentally fallen in a well in a field	None	None	Date: 6-Sept-09, Time: 2:00 pm	Not done
AP	104/09	KS	Date: 21-Jan-10, Time: 9:00 am	Convulsions, froth coming from mouth & nose. Consumed insecticide	Dummugudem Civil Hospital case record	Taken to Dummugudem Civil Hospital at 1:15 pm and provided treatment, but as she didn't recovered she was referred to Area Hospital Bhadrachalam - on the way she expired.	Date: 21-Jan-10, Time: 2:10 pm	22-Jan-10
AP	05/09	CaD	Date: 29-April-10, Time: 8:30 am	Headache with sudden onset of vomiting & loss of consciousness	ECG done (report not available)	Taken to Swathi Children Hospital Bhadrachalam on April 29th 2010 in unconscious state and was referred to Kothagudem town Gyathri Hospital - she was declared dead after ECG at 10:30 am.	Date: 29-April-10, Time: 10:30 am	Not done
GJ	10/09	VmL	Date: 1-Nov-09, Time: afternoon	Feeling unwell .History of insect bite ?	Pre Hospital Care Record, 108 Emergency Services	CPR was provided by paramedical medical staff of 108 emergency services around 7.30 am on 2 Nov 2009, during her transportation from residence to CHC Motafofaliya , Shinor.	Date: 02-Nov-09, Time: 8:00 am approx	Not done
GJ	044/09	JaR	Date: October 29, 2009, Time: 10:00 am	Fever & Headache	Lab report and CHC case record	Seen by local practitioner around 10:00 am on 29-Oct-09, Bhyavadar village, district Rajkot and had her blood tests done and found low Hb level (4:00 gms/100 ml), WBC count – 46200 cells/cu mm, Neutrophils – 71% with Plasmodium vivax positive. She was referred to higher center (CHC Bhayavadar, Rajkot) on 30-Oct-09, around 8.00 pm. The CHC medical officer examined the girl and found that she was brought dead (expired on her way to CHC). MO took secondary opinion from a local private practitioner, MBBS, DCH before declaring death of the girl.	Date: 30-Oct-09, Time: 8:00 pm	Not done

Table 1 (Part 4)

1	2	3	23	24	25	26	27	28	29	30
State	Demo ID	Initials	Date/time of death	Date of Autopsy	Autopsy report with date	Date reported to MO/DIO by ANM	Date reported to PATH (by district health worker)	Date of information to Ethics Committee	Date of information to Manufacturers	Date of information reported to DCGI
AP	57/09	Kas	Date: 8-Aug-09, Time: 9:00 pm	Not done	NA	9-Aug-09	13-Oct-09	29-Jan-10	29-Jan-10	29-Jan-10
AP	03/09	SsK	Date: 29-Aug-09, Time: 7:00 pm	30-Aug-09	17-Nov-09	31-Aug-09	15-Oct-09	29-Jan-10	29-Jan-10	29-Jan-10
AP	33/09	MsL	Date: 6-Sept-09, Time: 2:00 pm	Not done	NA	7-Sep-09	10-Sep-09	29-Jan-10	29-Jan-10	29-Jan-10
AP	104/09	KS	Date: 21-Jan-10, Time: 2:10 pm	22-Jan-10	1-Apr-10	28-Jan-10	28-Jan-10	3-Feb-10	1-Feb-10	3-Feb-10
AP	05/09	CaD	Date: 29-April-10, Time: 10:30 am	Not done	NA	7-May-10	7-May-10	28-May-10	11-May-10	28-May-10
GJ	10/09	VmL	Date: 02-Nov-09, Time: 8:00 am approx	Not done	NA	24-Dec-09	24-Dec-09	29-Jan-10	15-Jan-10	29-Jan-10
GJ	044/09	JaR	Date: 30-Oct-09, Time: 8:00 pm	Not done	NA	13-Mar-10	13-Mar-10	25-Mar-10	17-Mar-10	25-Mar-10

Table 2

	Andhra Pradesh			Gujarat		
	Listed	Consented	Vaccinated 1st dose	Listed	Consented	Vaccinated 1st dose
Schedule	3241	3150	3123	644	470	468
Caste	(22%)	(22%)	(22%)	(5%)	(4%)	(4%)
Schedule	4445	4350	4294	9013	7660	7652
Tribe	(31%)	(31%)	(31%)	(71%)	(72%)	(72%)
Others	6847	6754	6674	2979	2576	2566
	(47%)	(47%)	(47%)	(24%)	(24%)	(24%)
Total	14533	14254	14091	12636	10706	10686

Table 3

	Andhra Pradesh				Gujarat			
	K(U)	T(R)	B(T)	Total	D(U)	S(R)	K(T)	Total
Govt								
No. Schools	6	119	114	239	9	42	165	216
Listed girls	1319	4796	3478	9593	413	770	4085	5268
1st dose	1299 (98.5%)	4688 (97.8%)	3418 (98.3%)	9405 (98.0%)	356 (86.2%)	670 (87.0%)	3190 (78.1%)	4216 (80.0%)
Private								
No. Schools	7	14	14	35	18	13	11	42
Listed girls	1801	915	795	3511	1424	1060	913	3397
1st dose	1781 (98.9%)	858 (93.8%)	756 (95.1%)	3395 (96.7%)	1232 (86.5%)	991 (93.5%)	816 (89.4%)	3039 (89.5%)
Total	3080	5546	4174	12800	1588	1661	4006	7255
Govt %	42.17	84.53	81.89	73.47	22.42	40.34	79.63	58.11
Private %	57.82	15.47	18.11	26.52	77.58	59.66	20.37	41.89

7. Deficiencies identified by the Committee in the planning and conduct of HPV vaccine study in India by PATH

7.1 The most significant deficiency in the implementation of the project was the obtaining of consent.

7.1.1 This included authorization by the Govt. of Andhra Pradesh; through a circular issued by the Dy. Director, Tribal Welfare Department, Khammam; of the Hostel Welfare Officers and Head Masters of TW Ashram Schools and Hostels under TTDA and Head Masters of Primary, UP and High Schools "... to sign the consent forms on behalf of the adolescent girls to have vaccine especially for hostellers at Ashram schools run by both Govt. & Private Sector" (Appendix 30).

The legality of this authorization would need to be examined by law experts. Various Ethical Guidelines applicable in India provide as follows:

- i) Pediatric subjects are legally unable to provide written informed consent, and are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/legal guardian. (Schedule Y as revised in 2004 under Drugs and Cosmetics Rules 1945)
- ii) A parent or legal guardian of each child has to give proxy consent. (ICMR Guidelines and GCP Guidelines)

There is no mention in these guidelines whether legal guardian can give consent even when parent is alive, and whether Hostel Welfare Officer/Head Master can be given the authority to serve as 'legal guardian' by a Dy. Director's circular. The argument that Hostel Wardens and Head Masters normally exercise this authority for medical treatment under emergency and for routine immunization etc. (since parents are not easily accessible) can not be applied to 'research' vaccination which can wait for parental consent.

Even the Protocol for Andhra Pradesh (HPV03 Version 2.0 06/11/09) which was considered by the Ethics Committee does not mention about the circular. Page 20-21 of the Protocol mentions that teachers will play a primary role to explain and obtain consent but does not say that Hostel Welfare Officers and Head Masters will be signing the consent. 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 IEC of MNJIO&RCC, Hyderabad for this provision, nor is there any mention of it in the consent document. As per information provided by the PI 2763 forms (out of a total of 14254) were signed by the Hostel Warden/Head Master in AP.

As per ICMR Guidelines “adequate justification is required for the involvement of subjects such as prisoner, **students**, subordinates, employees, service personnel etc. who have reduced autonomy as research subjects (students highlighted by us)”.

7.1.2 In addition to this ?wrongful authorization, there was general laxity in obtaining of consent as given in the report of Dr. Rani Kumar. Although write-up in the protocol is quite extensive but its exact implementation on ground has been the casualty. Considering the fact that the study included vulnerable population special care should have been taken about obtaining of consent. In hindsight an independent check on the adequacy of understanding in the study population would have been desirable since it was a vulnerable population. In fact this approach has been adopted in another Phase I HIV vaccine trial carried out by NARI.

7.1.3 No provision in the protocol has been made of obtaining proper assent of the participants in the information sheet/consent sheet (page 96-97 of the protocol), although it is mentioned in the IEC material. Schedule Y guidelines of the Drugs and Cosmetic rules provide as follows:

“... all paediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand. Where appropriate, paediatric participants should additionally assent to enroll in the study. Mature minors and adolescents *should personally sign and date a separately designed written assent form...*”

Page 23 of the protocol says that the assistant/ANM will check that the girl “assents to receive the vaccine” and will be “reminded of what she is vaccinated for”. This is not adequate assent in the spirit of the above guidelines as any acceptance without full information is meaningless.

7.1.4 Two statements in the consent form, viz.,

“You will not be **charged** for your daughter to receive the vaccine”

“...Refusal to participate **will not involve any penalty or loss of benefits** to which you are otherwise entitled”

may be considered to be covert inducement and indirect coercion particularly since the cost of the HPV vaccine is quite high (about Rs 9000/- for 3 doses).

7.1.5 No provision has been made of an Insurance cover for any unforeseen event or residual morbidity, related to or unrelated to the intervention; which is a usual practice in trials with NCEs/INDs. The committee is of the view that since 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.

7.1.6 The committee observed that the Ethics Committee of Gujarat study has been more effective in ensuring better consent, and therefore perhaps in a better position to have confidence of the study population. The Gujarat IECHR has required that the consent be taken ***in front of a full time government employee*** so the parents were requested to come to Primary Health Center or Sub-center for signing the consent. In Gujarat only 545 out of 10706 consent forms were signed by the legal guardians, who did not in any way had any influence over the children.

7.2 Second major deficiency of the study was total reliance on the State AEFI programme to measure four of the five Primary outcomes of the study without an independent verification (page 11 of the protocol), as highlighted in the report of Dr.A.K.Dutta. Gross inadequacy of AEFI programme is shown by the decimal rates of reported AEs even for the local reactions. The prevalence of minor AE in AP, following Gardasil, was 0.29% after the 1st dose (14091), 0.37% after the second dose (13905) and 1.37% after the third dose (13791).

This has also led to delay in reporting of SAEs and deaths and their inadequate investigation which precipitated the crisis in the execution of the study. The deaths in the vaccinees in the AP that have occurred on 17.7.2009, 10.9.2009, 13.10.2009 and 15.10.2009 were not taken cognizance until 29.1.2010. In hindsight, the investigator and the advisory

groups should have been more sensitive to the possibility of occurrence of such events and their impact on the programme. Even if it was a post-licensure study a mechanism for independent verification of rates and timings of reporting of AE should have been built-in in the project.

The investigator has tried to justify that no additional system was set up to investigate the cause of death (or for that matter any AE) for the following reasons:

- i) This is not a clinical trial as per definition of clinical trial given by CDSO
- ii) The study used DCGI-approved vaccine and dosages
- iii) No biological specimens were collected
- iv) The study is not assessing efficacy or safety of the vaccines
- v) The vaccines are licensed in India, available in the private market and are recommended by IAP and FOGSI.

The investigators have variously labeled the research project carried out by them as Observational study, Demonstration study, Epidemiological study etc. to establish that the study is not a clinical trial.

The committee 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 AE/SAE should have been more vigorously pursued.

In fact the investigators have followed exactly the same procedures as are required for any clinical trial/clinical research viz.

- i). Writing a research proposal defining the Aims and Objectives of the study
- ii). Laying down a plan of study, including criteria of inclusion and exclusion from the study
- iii). Describing the Primary and Secondary end points and their measurement
- iv). Taking approval of the Scientific and Ethics committees, and
- v). Publishing their results.

Further *there has been direct contact with the human participants, they have administered an intervention which is not part of 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 shall be part and parcel of all such studies.

In this context Rule 122-E of the Drugs and Cosmetics Rules, 1945 provides that all vaccines shall be new drugs unless certified otherwise by the Licensing authority under Rule 21, and a new drug shall continue to be considered as new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia, whichever is earlier.

7.3 In hindsight the planning of the study could have included a control to provide background rates of morbidity/mortality in the population. In our country routine reporting is not adequate for research purposes. But the committee also recognizes logistic problems related to inclusion of control group. It needs to be debated how a reliable database may be created for this purpose, prior to or concurrent with, the conduct of such a study.

7.4 The third problem with the project was that partnership of the State govt. in the project led to *blurring of the distinction between the National Immunization programme, as routine service activity, versus the research nature of the HPV vaccine project.* While such studies must be carried out in collaboration with State health authorities, extra care needs to have been exercised to ensure that an average person could have appreciated the difference. This should serve as a lesson for public-private-partnership programmes in future.

7.5 One debatable issue is the selection of the districts/blocks in the two States for the study. Although detailed justification and procedure for selection has been provided in the protocol, as well as in the paper published on the data of Phase 1 study (The Open Vaccine

Journal 2010, 3:96-107), the fact remains that the selected population for vaccination had considerably higher % of the tribal population than the national or state average (26.47% in Khammam and 26.56% in Vadodra compared to national average of 8.1%, AP average of 6.6% and Gujarat average of 14.8%). Also, giving 1/3 weightage to tribal group in the study design (Urban, Rural and Tribal) may be questioned. While on one hand difficult to reach and more socio-economically backward population may be more deserving target population for HPV vaccine prophylaxis, but 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 also have been better investigated to document the cause of the illness even if unrelated. The adequacy of existing AEFI system to measure 4 of the 5 primary endpoints also could have been better tested in the urban area first.

The report of Dr.Y.K.Gupta indicates that preparedness to tackle acute illnesses that led to death in the remote areas was not up to the mark.

- 7.6 No information has been provided regarding funding of the project except that it was global study funded from the Bill and Melinda Gates Foundation and that the vaccine has been donated by the manufacturers free of cost. On the basis of market price of Rs 3000/- per dose approximate cost of vaccinating 25000 girls would be approx. 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 a concern about the possibility of hidden agenda to push this prohibitly 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.

7.7 The committee finds that a crisis like situation was created by the publication of reports of deaths in HPV vaccine recipients in the media. Various factors that contributed to it could have been:

- i) lack of anticipation and preparedness to counter adverse coverage
- ii) lack of full investigation of the cause/s of death/s probably due to late detection of deaths
- iii) lack of adequate medical facilities in the interior to diagnose and treat acute emergency conditions
- iv) lack of proper communication and timely provision of data on background deaths in the population in the target population.

8. Conclusions and Recommendations

8.1. The post-licensure study of HPV vaccine carried out by PATH in India was quite well designed, and an adequately documented study. It was an ambitious project to vaccinate approximately 25-30000 adolescent girls in two States of the country, which it achieved to considerable extent. The study had the necessary approvals from the required agencies; including National and State level Advisory Committees, Institutional Ethics Committees of the States, DCGI and Health Ministry's Screening Committee. The project has been executed by the health department machinery of the State governments with due approval of the State. Considerable time and effort has been invested in getting all the approvals. ***But the same can not be said for its actual implementation. In hindsight, the Committee has identified several deficiencies in the planning as well as implementation of the project which led to the crisis requiring suspension of the study.*** However, there is no major deficiency for which the responsibility could be fixed on any individual or agency. A collective effort is required to raise the standards of clinical research – one in the arena of implementation of bioethical guidelines and the other in the monitoring and investigation of Adverse Events Following Immunization to raise public confidence.

8.2 A total of seven deaths (5 in Andhra Pradesh out of 14091 recipients of the Gardasil vaccine, and 2 in Gujarat out of 10686 recipients of the Cervarix vaccine) have been reported following HPV vaccination. ***These deaths were most probably unrelated to the vaccine, as there was no characteristic and uniform pattern of illness preceding the death, or temporal/spatial clustering.*** In addition an alternate cause of death, in form of suicide by organophosphorus poisoning in two cases (proved at autopsy), drowning in one case and malaria in another case were identified in the FIR prepared by the investigating Medical officer. The report was reviewed by the District Immunization Officer/District Reproductive and Child Health Officer of the State. The illness in the remainder 3 cases also did not conform to vaccine induced reaction or illness. An alternate diagnosis of snake bite, viral fever and acute CNS illness was considered for these cases but in the absence of definitive pathological or post-mortem examination these diagnoses can not be accepted with certainty. The DIO/DRCHO did not consider the necessity for further investigation. This is in conformity with the SOPs of the AEFI monitoring protocol of the Govt. of India.

In the absence of a control group it is not possible to say whether there were excess deaths in the vaccinated group or not. An attempt has been made to collect the data on

background deaths from routine mortality reporting system from the same area for the current and previous years. The overall death rate during the period of vaccination is not significantly different supporting the contention that reported deaths are independent of the HPV vaccination.

Internationally, as of January 31, 2010 forty-nine deaths have been reported in the US against approx 28 million doses of the Gardasil vaccine distribution. Out of these 28 deaths have been traced. According to CDC there was no unusual pattern or clustering to the deaths that would suggest that they were caused by the vaccine.

While at this juncture there is no specific issue about the safety of the vaccine that has emerged from this study, there is a need for continued pharmacovigilance of the HPV vaccine. The DCGI should consider reiterating the rule 122-E through an appropriate mechanism that all vaccines, in particular the HPV vaccine, shall be treated as new drug for four years from the date of their approval in India. All research studies (whether a clinical trial or not) involving administration of a new drug (vaccine), even after licensing, should proactively monitor (e.g., a diary system, a telephonic contact or a home visit provision etc.) and investigate of all adverse events, more so the SAE and deaths irrespective of their appearing or not appearing to be related to the vaccine (Action: Research funding agencies and Institutional Ethics Committees). The DCGI may also review steps that may be taken for assuring safety of licensed products, and application of the provisions of Phase IV post-marketing surveillance of HPV vaccine (Action: DCGI).

One of the major deficiencies of the study was inadequacy of the preparation for tackling SAEs and deaths, whether related or unrelated to the vaccine. The deaths came to notice after a long gap of their occurrence, mainly when the preparations were afoot for the next round of vaccination. And then no independent body of experts analyzed the cause of death. The scientific committees will have to be more vigilant to this aspect.

It should not be forgotten that if something can go wrong then it will definitely go wrong. The wisdom is in incorporating multiple layers of defense in anticipation.

8.3. The inclusion of 10-14 years old girls in the study is fully justified as it is the primary target group for HPV vaccination for prevention of Cancer cervix. Necessary bridging trials,

in both adults and adolescent girls, have been carried out in India as required under the Drugs and Cosmetics Act before the licensing of the two HPV vaccines by the DCGI. The license issued by the DCGI permits the use of the vaccine for 9-40 years age group. There is enough data internationally on the use of these vaccines in adolescent girls and several countries have incorporated the HPV vaccination in their national program for this age group. This is the recommendation of WHO, IAP and FOGSI as well. Thus, use of HPV vaccine in adolescent girls is a standard practice. As such ***there has been no violation of the general ethical principle of testing in adults first before use in children.*** This principle applies to testing before approval by the licensing authority. Once the licensing authority has approved the product it is used as per terms of approval – whether in clinical practice or further trials if needed. Further, there are several exceptions to the general principle which provide trial to be carried out in children in special circumstances.

8.4. The selection of the study sample viz., State, District, Blocks, and eligible subjects within the chosen blocks was done according to a defined plan which was approved by the Advisory groups, both at the State and National level, as well as by the Institutional Ethics Committees. ***There was no specific targeting of any particular group or class except that the plan called for including a predominantly urban, rural and tribal block in each selected district.*** From those blocks all eligible girls, both in the Govt. and Private schools and also those who were not going to schools and consented to participate in the study were included in the study without any bias. The committee has obtained the data which shows that a significant number of girls from Private schools and non-tribal communities were also enrolled in the study.

As such there is no major ethical violation in the conduct of the study in the way it has been done. As a general rule pilot study should be representative of future programme and therefore to include three sites, one predominantly urban, one rural and one tribal. However, in hindsight the veracity of this plan can be debated. The alternate view is that while for replicability of the data the sample should be representative; the logistic considerations shall also be kept in mind while selecting the site and population for study. In particular literacy, education, available infrastructure and standards of healthcare might have been taken into consideration. Thus if it was impractical to take consent of parents in predominantly tribal area such an area might have been excluded from the study. It may be

worthwhile incorporating these considerations in future while planning such trials to enhance public confidence and avoid precipitation of crises in public health programmes.

8.5. ***The legality and morality of the circular of the Government of Andhra Pradesh authorizing the Hostel Wardens and Head Masters to sign the consent on behalf of the minor girls included in the study is questionable.*** In view of this Enquiry Committee for an elective health promoting activity, particularly which is a subject of research, this step was perhaps counterproductive. In this context the step taken by the ICHER of Vadodra, Gujarat of requiring the consent by the parents/guardian to be signed in front of a permanent/regular Government employee is an interesting improvisation of assuring that consent taking is carried out in the right spirit.

The committee stresses that everyone shall desist from research on tribal population, unless of specific benefit to them.

8.6. The committee noted that no provision has been made of an Insurance cover for any unforeseen event (including death) or residual morbidity related to the intervention for vaccine recipients in this study which is the usual practice for trials with NCEs/INDs. The committee is of the view that since HPV vaccine is newly developed vaccine, even though licensed, there should have been a provision of insurance coverage for study participants. The need is even more since the vaccine is administered to normal healthy individuals. This deserves to be made an essential requirement in future studies.

The committee has been informed that PATH has taken an insurance cover for itself. It may be explored whether any relief can be provided to the unfortunate families under this policy.

8.7. The study was carried out in close collaboration with the State Governments of the Andhra Pradesh and Gujarat. The State's health machinery was actively involved in the execution of the project. While it was important and useful for the success of the project, and is commendable; the Committee is of the view that it might have led to blurring of the distinction between routine, national immunization programme and research nature of the HPV vaccination study being carried out under the initiative of PATH. ***It is important for***

Public Private Partnership programmes to be extra vigilant and ensure that the Authority of the State is not misrepresented.

8.8. There is a need for specific and separate legislation covering all aspects of Biomedical and Health Research involving Human Participants, and eliminating overlaps such as definition of clinical trial/clinical research etc. that exist in Schedule Y of Drugs and Cosmetics Act Rules, GCP guidelines of the Central Govt. and ICMR guidelines etc., and that are likely to come in future. It shall be made clear that any research involving human participants, by whatever name it is called, shall adhere to the directions given by this legislation. The two issues that have emerged from the present enquiry, which need special emphasis, are:

- a. Inclusion of vulnerable groups in the research study, and the process of consent taking***
- b. Identification and investigation of Adverse Events, whether they be non-serious, serious or fatal***

Besides issuing directions, active training of investigators and sensitization of regulatory agencies such as funding agencies and IECs shall be made mandatory.

Responsibility

1. It is true that deaths have occurred in the recipients of the HPV vaccine under the PATH study in AP and Gujarat, and it is also true that a lot of negative vibe has been generated against this project due to mal-handling of the entire situation, but the committee has not been able to identify a single event, individual or agency which can be held entirely accountable for it. However, some deficiencies in the implementation of the project did occur which have been detailed in the report. These deficiencies noted by the committee should serve as a lesson for strengthening clinical research in future rather than starting any punitive or disciplinary proceedings.

The deficiencies do not appear to be willful or fully anticipatable. In hindsight these deficiencies should be taken as learning experience. The committee recommends that these lessons be incorporated both in the ongoing, proposed to be started and future research studies in general and in new vaccine trials in particular so that public trust in the vital

national immunization programme is restored and enhanced. These recommendations are not entirely new, but were not strictly adhered to in the current project.

2. The development of HPV vaccines has provided a new opportunity for prevention of Cancer cervix, which is an important health burden for the women of our country. HPV vaccination is not to replace the cancer cervix screening programme, but to supplement it. However since the vaccine is expensive, an element of cost-effectiveness and determination of competing health immunization priorities should have been addressed by the study. The fact that the vaccine for the study was provided by the manufacturers free of cost does raise the concern about undeclared conflict of interest since the results of the study may be used to influence the decision by the Government. Again since there does not appear to be any overt mal-intention, no responsibility can be fixed on one person. However, any programme focusing on vaccination should also be targeting on public education for cancer cervix screening.

Recommendation regarding restarting of stopped/pending studies

Regarding suspended study being carried out by PATH, there is no sense in pursuing the remainder part of the 2nd phase study as the window period for the 3rd dose is already crossed. The 3rd phase of Operational research shall be allowed to be continued as it is going to provide the most useful information and does not involve any further vaccination.

The committee understands that along with the study under reference, some other studies which were already underway or planned to be carried out using HPV vaccine were also stopped. *The committee recommends that each study shall be re-reviewed, both scientifically and ethically, in light of the observations and findings of this Inquiry committee before restarting these studies.* In particular we recommend that each review should be speaking in nature, and not just a blanket yes or no.

9. Appendices

- Appendix 1 - Timeline of various approvals etc.
- Appendix 2 - Paper published in the Open Vaccine Journal on results of Phase I study
- Appendix 3 - Approval letter/s of the State Govt. of AP
- Appendix 4 - Approval letter/s of the State Govt. of Gujarat
- Appendix 5 - MOU between PATH and ICMR
- Appendix 6 - List of members of the National Advisory Group constituted by the ICMR
- Appendix 7 - List of members of the State Advisory Group of Andhra Pradesh
- Appendix 8 - List of members of the State Advisory Group of Gujarat
- Appendix 9 - Letter of Approval of the HMSC for Andhra Pradesh
- Appendix 10 - Letter of Approval of the HMSC for Gujarat
- Appendix 11 - Letter/s of Approval/License from DCGI
- Appendix 12 - Letter of Approval of IEC of NARI for Phase 1 study (with list of members)
- Appendix 13 - Letter of Approval of IEC of AP (with list of members)
- Appendix 14 - Letter of Approval of IEC of Gujarat (with list of members)
- Appendix 15 - Letter/s of Approval of the Western Institutional Review Board (with copy of the Information for Consent and Consent sheet)
- Appendix 16 - Press note issued by the Health Minister of AP following report in Deccan Chronicle
- Appendix 17 - Minutes of the Standing Committee of the Parliament
- Appendix 18 - Letter of the DHR appointing the Enquiry Committee
- Appendix 19 - Letter of the DHR appointing Dr. S.S.Agarwal as Chairman
- Appendix 20 - Minutes of the Enquiry Committee meetings (21.4.2010, 30.4.2010, 31.5.2010, 22.6.2010, 27.9.2010, 8.11.2010)
- Appendix 21 - Letter of DHR appointing experts to assist the Enquiry committee
- Appendix 22 - Photocopies of the Medical records, FIRs, Postmortem reports and Forensic analysis reports
- Appendix 23 - Copy of the License issued by the DCGI to GSK
- Appendix 24 - Copy of the License issued by the DCGI to MSD
- Appendix 25 - Report of the Bridging clinical trial (Phase III) on Gardasil prior to licensing
- Appendix 26 - Report of the Bridging clinical trial (Phase III) on Cervarix prior to licensing
- Appendix 27 - Procedure laid down to be followed for obtaining consent
- Appendix 28 - Information sheet for obtaining consent as approved by the Ethics committees
- Appendix 29 - Information brochure for creating awareness
- Appendix 30 - Letter issued by the Dy. Director Tribal Welfare Department, Khammam authorizing Wardens/Head Masters to sign the consent

10. Supporting documents

- Supportive doc 1 - Protocol of study at AP (including other papers-spiral bound sent to the Committee by the ICMR)
- Supportive doc 2- Protocol of study at Gujarat (including other papers-spiral bound sent to the Committee by the ICMR)
- Supportive doc 3- Minutes of the National Advisory Group Meetings
- Supportive doc 4- Operations research study proposal
- Supportive doc 5- Formative study Report (Phase 1)
- Supportive doc 6- Queries asked by the Enquiry Committee and replies by respective respondents