REPORT OF CENTRAL TEAM FOR ASSISTANCE IN INVESTIGATION OF SERIOUS AEFI CASES IN KERALA (4th-6th Feb 2013)

Introduction

15 deaths were reported from Kerala from December 2011 –January 2013. A central team was formed (circular no T13020/11/2011-CCV dated 23rd Jan 2013-Annexure 1) to investigate the spurt of serious AEFI cases (including death) from Kerala in Dec 2012. The team comprised:

1. Dr MK Agarwal: DC Immunization, GoI
2. Dr NK Arora: Chairman, National AEFI Committee,
3. Dr Sujeet Jain: AEFI focal person, WHO country office
4. Dr Madhur Gupta: Technical Officer , Pharmaceuticals WHO Country office
5. Dr Jyoti Joshi Jain, Sr Advisor-Immunization safety, ITSU-PHFI
6. Ms Visala: Deputy Drug Inspector, DCGI office

Dr Arora was unable to attend due to urgent personal reasons and DCGI office directed Mr V S Prabhakran, Drugs Inspector South Zone office, Chennai and Mr P B Prasad from the local office in Kerala to attend.

The team conducted a 3 day visit and met various officials in context of the AEFI deaths. This report presents activities undertaken by the investigation team, discussions with the State AEFI committee members and other state officials, review of the vaccine management and injection safety practices at cold chain points and sample health facilities and community investigation. The report concludes with analysis of available information and further suggestions to complete the investigation.

Field activities undertaken during the visit

On the first day (4th Feb 2013) the team met senior officials including the following:

a. Shri Rajeev Sadanand, Principal Secretary Health
b. Dr M Beena, Mission Director, NRHM Kerala
c. Dr P K Jameela, Director, Directorate of Health Services
d. Dr N Sreedhar, Additional Director Family Welfare & State Program Manager, Kerala
e. Dr Asha Raghavan, Surveillance Medical Officer- Kerala, WHO

The team led by Dr Agarwal met Shri Rajiv Sadanand (Principal Secretary-Health, Kerala) who urged the team to conduct a conclusive AEFI investigation and validate vaccine safety to reassure the country and the state as otherwise it might lead to roll back of the introduction in the state.

He stated that the autopsy specimens of some of the cases have been preserved and expressed the need for national level support in sending these samples for further tests in national / international labs (AIIMS/NCDC/CDC Atlanta) to be conclusive regarding cause of death. These tests may include pathological autopsy, immunofluorescence etc. as recommended by the state AEFI committee.

Dr Agarwal assured the Principal Secretary that all possible aspects of investigation will be reviewed with the Kerala State AEFI committee in the meeting called today on a case by case basis to ascertain the cause and reassure the immunization program of vaccine safety.

Findings of the team

The team together with the members of the Kerala State AEFI committee (Annexure II) then reviewed the cases in detail (Anexure III) and classified them further based on the available investigation documents including the PIR and DIR of cases. This included review of cases reported with pentavalent vaccine and 2 other vaccines namely, *Infanrix* (DTaP, acellular pertussis in DPT and non-Hib containing vaccine) and *Easyfour* (quadrivalent vaccine DPT+Hib). The discussion with the State AEFI committee members on reported AEFI deaths was put in context with the following background.

1. *Haemophilus Influenzae* type B is one of the leading causes of acute respiratory infection, pneumonia and meningitis in India and through govt. UIP program it is made available to all strata of society free of cost.
2. The vaccine has already been used in the private sector since more than a decade.
3. Introduction of any new vaccine in the routine program is accompanied by an increased sensitivity of AEFI surveillance and hence increased reporting. (Example of Sri Lanka where the vaccine was stopped due to increased AEFIs being reported and then restarted in the routine immunization program when the deaths were not found to be vaccine-related)
4. Introduction of pentavalent vaccine in the routine UIP program in Kerala too was accompanied by awareness and capacity building activities of health workers including structured training on AEFI reporting which also contributed to better AEFI reporting from the state.
5. Profile of AEFIs expected with DPT vaccine is similar to that expected with Pentavalent vaccine due to the DPT+Hib+Heb B combination.
6. Timely receipt of PIR (within 7 days of FIR) and DIR(within 90 days of FIR) at national level is of prime importance to aid any state AEFI investigation and enables better support to the state level from the national AEFI committee and AEFI surveillance program.

2. The summary conclusions of the discussion and analysis in the meeting were as follows:
    a. Total 15 deaths were reviewed of which 13 had received pentavalent vaccine, 1 *Easyfour* (quadrivalent) vaccine and 1 had received non Hib containing *Infanrix* vaccine.
    b. Of the 14 Hib containing vaccines, coincidental causes identified in 7 cases, 6 classified as unknown and classification of 1 was still pending due to lack of reports.
    c. The Paediatricians (including the IAP representative and the Professor from Paediatrics department, Thiruvanthapuram Medical College& SATH noted :
        i. There has been a notable decrease in the no. of bacterial pneumonias and meningitis cases seen in the Paediatric population which may possibly be due to the inclusion of Hib containing pentavalent vaccine in the UIP.
        ii. AEFIs reported with pentavalent were higher as intense training and reporting has been undertaken with the new vaccine whereas the AEFIs seen with older vaccines (DPT/ Hepatitis B) even though occurring in the

field were hardly reported eg. Seizures are routinely seen with DPT in the field but are seldom reported whereas seizures with Pentavalent are being reported and creating apprehension about the vaccine.

iii. 60-70% of the deaths were reported in early morning hours, during the cold season (Dec 11, Dec 12 -Jan 13) which is typical of Sudden Infant Death Syndrome (SIDS) but lack of definitive scientific literature on background rates of SIDS make it difficult to compare pre and post vaccination scenarios.

iv. Temporality of vaccination with death cannot be established as a causal relationship since it may also be possible that in the child had a subclinical infection (therefore no obvious signs and symptoms) and it aggravated in cold conditions, led to Bronchiolitis and death. This may be the reason for death due to pulmonary edema (manifesting as blood from the nose and in some post mortem findings of blood in respiratory tract).

d. Screening for inborn errors of metabolism (IEM) will soon be started in Kerala and it may be useful to screen children who may not be immune-competent for vaccination as per routine immunization program.

It was decided to conduct a field investigation and community interviews for the case from Pathanamitta (90km from Thiruvanthapuram) on 5th Feb and another case in Thiruvanthapuram on 6th Feb. Based on the discussion the specific recommendations for the state are as follows:

Recommendations for causality assessment of AEFI deaths

1. **Timely sharing of PIR and Post Mortem reports:** Though the state has a competent and active AEFI surveillance field network, there is delay in sharing AEFI investigation reports. This results in needless delays in central support, gaps in data collection and case closure. The State Program Manager was requested to ensure timely sharing of reports including PIRs (within 7 days of FIR to the national and state level simultaneously. The post mortem reports of the cases had also not been shared for some cases and in some of the cases Post mortem could not be conducted. This would have been useful for final classification of AEFI cases. Timely PIR reports, post mortem and possibly pathological autopsies (collaboration between Pathology and Forensic department) will be useful to finally classify AEFI and reassure the public and policymakers about the vaccine.
2. **Pathological autopsy:** Since the Post mortem samples of the cases are still preserved, a detailed histo-pathological examination of these should be done in the state/another premier institute in an effort to localise the antigen responsible for the hypersensitivity reaction as reported in PM.
3. **Specialised forensic tests**: Higher expertise may be sought to conduct other specialized tests on these specimens which can help to identify the other possible causes of death.
4. **International expertise**: on these AEFI death cases maybe sought to aid investigation and know if such similar cases have been encountered elsewhere.

1. Case reviewed: [redacted] from Pathanamitta district

Field team composition: Central team along with state officials which included

1. Dr Ajitha – RCH officer Pathanamthitta
2. Dr Asha Abraham, Paediatrician, Thiruvella Taluk Hospital
3. Dr Anu: Junior Administrative Medical Officer
4. Dr Asha Raghavan, SMO TVM
5. Dr Rajiv, PHC Medical officer
6. ANM , LHV and other PHC health staff

Case summary: 1 month, 20 days old female baby born full term by normal vaginal delivery on 6th November 2012, vaccinated on 26th December 2012 with first dose pentavalent and OPV vaccine in Kaviyoor PHC at 12.00noon. Fever and crying started by 8.00pm same day and paracetamol syrup as given in the night and twice(morning and evening) next day. Baby was breast fed at 2.45am on 28/12 and was found dead by mother at 4.30am with blood stained discharge from nose.

Vaccines used for immunization: The child was give pentavalent vaccine (Manufactured by Serum Institute of India batch number 124P1033A and OPV (manufactured by Bharat Immunologicals and Biologicals batch number P 213) Pentavalent vaccine vial was a 10 dose vial. 8 other children have been vaccinated from the same vial

Other medications given: Paracetamol syrup was given to the child manufactured by Medicamen Biotech, Batch no. HL 12040 , exp: 1/20/2014 (The PHC also stocked PCM syrup from Vivek Pharma , Batch no. PC512018, exp 5/14). These were informed to the local drug inspector for further batch analysis and investigation.

Review of cold chain and injection practices at PHC : The cold chain equipment and vaccine storage practices were noted and the cold chain monitoring records were reviewed. The temperature of the ILR was +4degrees and the freezer showed -20 degree temperature. The monitoring records were regular and updated. No immunization session was being conducted on the visit day

Epidemiological review of cases: 8 other cases had been vaccinated with the vial and all no adverse outcome in the cases had been reported. This child was the 6th child among the children who were immunized that day (within the last doses of the vial and the RI session of the day) all of whom are reported healthy.

PHC Medical officer, Dr Rajiv confirmed that there were no unusual illnesses reported in the area, including any febrile illnesses.

Family interview:

Dr Asha Abraham (Paediatrician fom Block hospital) interviewed the mother and mother-in-law and translated for the benefit of other team members. It was noted that:

1. The baby was a second child, with an elder male sibling. FTNVD of female baby born on 6/11/2012, birth wt 3.5kg and had received 1st dose Pentavalent vaccination at the Kaviyoor PHC.

2. There was no h/o any pre -existing illness including respiratory illness) or significant family history for seizure/ tradition of consanguineous marriage.
1. Mother described swelling on the leg and baby made grunting sounds during the day following vaccination along with reluctance to feed. She gave 4 drops of PCM syrup (using h her finger) in the evening and twice the following day. The PCM syrup was still available with the family and had been used subsequently for the elder sibling. Mother reports that by the time of the night time feed the next day, baby was better and keen for the feed. However, after the feed early morning feed mother slept off and when she woke she found the baby cold, clammy. On lifting the baby from the bed three drops of frank blood dropped from the nose on the front part of the chest (? Pulmonary edema? Aspiration following subtle seizure ? SIDS)
2. Baby slept beside the mother in a separate mosquito net on the same bed.
3. No observation of visible seizure/ cyanosis/pallor /vomiting seen in the child.
4. The child was rushed to a private hospital and seen by the ENT specialist who did not advise any autopsy and so no Post mortem was conducted.

The case was classified in the Unknown, unclassifiable category by the team.

Discussion:

2. Case reviewed: [redacted], Thiruvanthapuram district

The team visited the PHC Anakudy in Thiruvanthapuram district to review another serious AEFI case of seizure following pentavalent vaccine. The central team was accompanied by Dr Asha Raghavan (WHO SMO,TVM) and Dr Jayshree V (Deputy DHS, FW) from the Directorate and in addition met the following officials:

1. Dr. Salim :Block Medical Officer
2. Dr Santosh: Medical officer of additional PHC
3. ASHA/ANM and other health staff at the PHC
4. The cold chain session at the PHC was observed and the following observations were noted:
    a. The cold chain temperature monitoring records were updated and ILR and deep freezer showed temperature within recommended limits.
    b. The due list was not prepared routinely by the ASHA worker to assist in efficient use of multi dose vials
    c. The time of opening of the JE vaccine vial was not recorded. This is important as the vaccine has to be used within 2 hours of opening and then discarded.
    d. Used syringes with needles intact were lying on the table unattended. The hub cutter was kept on another table away from the vaccine site.
5. Mother of case (baby [redacted]) who described that child was given 1st dose Pentavalent and OPV at one and half months of age at 11.00AM and by evening 8.00 PM had developed fever, signs of seizure (eye rolling and neck floppiness). No family h/o seizures reported. Child was rushed to private hospital and referred to govt. medical college, Thiruvanthapuram). The child was admitted for 2 days at the medical college hospital and no further episodes of seizures were noted. The patient was advised DTaP for subsequent vaccination (procured from Nidhi stores at MCH campus) . DTaP and HepB were given at

SATH and there was no history of any recurrence of seizures. Measles at 9months was administered at the same PHC. Baby is well and thriving.

Case classified as vaccine reaction (seizures due to whole cell perstusis component of the DPT) in Pentavalent vaccine.

Recommendations for routine immunization practices in the PHC were made as follows:

1. Due list should be compiled by each ASHA and shared with the ANM to predict patient load and ensure efficient utilization of vaccine and good immunization coverage.
2. Re training and supervision of ANM on safe disposal of needles and syringes should be done to prevent needle stick injuries.
3. Time of opening of JE vials should be stressed to ensure potent vaccine is provided to the community
4. Vaccine batch no.s and expiry date should be recorded against each child's record to ensure good record keeping and easy, simple traceability.

Conclusion and Recommendations:

Based on the discussion with the state AEFI committee, state officials and the field visits undertaken the team gave the following recommendations specifically for these cases and in the long term for improved AEFI surveillance:

1. **Immediate:**
    a. Timely sharing of AEFI reports including PIR and DIR and other detailed investigation of cases in the field should be done.
    b. 4 batches of pentavalent vaccine have been used in these cases. The vaccine quality reports of some of the death cases were sent by the district for analysis. CDSCO may initiate a quality review of pentavalent batches implicated in light of the severe outcome to ascertain if production quality was up to the mark.
    c. International expertise should be requested through WHO to assist in further investigations (forensic tests, pathological autopsies, lab tests etc) to ascertain other possible causes of death and assure vaccine safety.
    d. Capacity building of state AEFI committees to undertake a thorough and informed causality assessment of reported cases based on the PIR and DIR reports.
    In fact, the following interventions are planned for 2013-14
    - Training of trainers at national level for conducting causality assessment based on the new recommended methodology is planned from 11-14 March in Delhi.
    - Technical AEFI Collaborating Centre is planned to be established with Pediatrics department of Lady Hardinge Medical College to review state reports and assist the national level in regular, timely case investigation.
    - It is planned to conduct a capacity building workshop of group of representatives from State AEFI Committee to enable better AEFI investigation and causality assessment.
2. **Long term**
    a. An infant death audit review comparing cause of death (specially death in age of 1-6 month olds) and immunization history may be conducted by some of the tertiary

care hospitals. Such a study may be conducted in another state too for comparative purposes.

b. Further research studies on SIDS and its incidence and predisposing factors may be documented to ascertain the background rates for SIDS.
c. Research studies may be instituted to determine background rates for vaccines used in the national immunization program and/ or reference parameters defined for background rates based on countries with similar epidemiological and demographic profile.

3. Other UIP related activities undertaken during the visit were as follows:

1. Review of Regional Vaccine Store (RVS) in District Medical Office campus, Thiruvanthapuram

On 4th Feb 2013, evening at 4.00 pm the cold chain equipment, temperature monitoring records for ILRs, walk-in-cooler (WICs) were reviewed and the responsible staff were met. This RVS stores and supplies, vaccines of UIP to 4 districts in the state – Thiruvanthapuram, Kollam, Pathanammitta and Allepy.

The temperatures records of the ILR, freezer and Walk-in-cooler (WIC), the stock register of RVS and VVM status of vaccines in the store were reviewed and the following observations were made:

- Cold chain temperatures were within normal limits
- Pentavalent vaccine was stored in the ILR whereas the WIC had un utilized space where this vaccine should be stocked to ensure continuous adequate cold chain conditions..
- Non- standard icepacks (received from the manufacturer with vaccine shipment) were found stored in the freezer and are strictly not recommended for use in UIP either for storage or transport in the cold chain..
- There was only 1 voltage stabiliser to support the ILR and the freezer.
- Cold chain handler had not received training since Aug 12 and expressed a need for refresher training.

Kerala specific recommendations for improving quality of UIP program performance are as follows: recommendations:

1. **Hiring of Consultant –Child Health** : The state Program Management Unit can request for hiring 2 consultants- A Maternal Health Consultant and a Child Health Consultant using the budget resources of NRHM. The Terms of Reference for the Child health should include Immunization and specifically AEFI surveillance to aid timely reporting and follow up of AEFI cases.
2. **Cold chain supplies:** Based on the visit to the cold chain store, the following recommendations were made :
    a. The state program manager was requested to send an email requesting for the following supplies
        i. Estimated no. of ice packs required for storage(in the RVS) and vaccine transport under the UIP and DC(Imm) assured its sanction and procurement.
        ii. Voltage stabilizer for ILR.

b. State deptt shared that there was large quantity of short expiry Pentavalent vaccine (exp. Nov 13) and based on annual utilization rates it may be unutilised. National level will check if supplies beyond required stocks can be shared with other states.
c. Data for National Cold chain Management Information Systems (NCMIS) was requested to be shared by end of the month to enable preparation of state wise reports before the National EVM is undertaken.