

Meeting 22.04.2013 in the Room of Dr. S K Panda. AIIMS

Present were:

Professor S K Panda

Dr N K Arora

Professor AP Dube

Dr. Jyoti Joshi PHFI,

Dr Rakesh Kumar

Dr Jacob Puliyel

Dr. NK Arora opened the meeting saying the purpose of meeting to share & discuss AEFI from TN & Kerala experience from 2011. He said that there were 2 causality assessments after November 2012. Dr. Satinder Aneja's office and Lady Harding Medical College was the nodal organizations for AEFI cases. An immunization technical support unit has been set up at PHFI to augment immunization services in the country.

The 2nd causality assessment meeting decided to have postmortem tissue reassessed by Dr Panda. Postmortem had been done in 4 cases and tissue was available in 3. He said that today's agenda was to discuss the reports and to decide where we go from here.

Dr. Arora asked Dr. Jyoti Joshi to share minutes of previous meetings.

Dr. Rakesh Kumar said data was current up to February 2013.

2 hand-outs were provided to the committee, entitled

1. Draft Minutes of meeting of causality assessment meeting held at LHMC on 15-Feb,13
2. Technical update on reported deaths following administration of Pentavalent vaccine

These are attached at the end of these minutes

The rest of the meeting was spent with Dr Jyoti Joshi reading the draft minutes and discussing it.

1. Reported deaths (AEFI cases) are sporadic from different part of the state, there is no clustering, and adverse events have not been reported from other children who have received the vaccine from the same vials. Programme errors therefore appear unlikely.

Dr Panda asked to know details of the process for manufacture of the vaccine with full details of **all the components and the analytic reports at each stage in the process of manufacture from the company.**

2. In 8 cases, death was reported after 1st dose, in 4 cases – after 2nd dose, in 1 case- after 3rd dose and in case- (Easy4 – not known). Eleven infants were females.

Dr Puliyel pointed out that there were twice as many deaths after the first dose and 8 times as many as after the 3rd dose and this suggests this is not 'random death' occurring coincidentally with vaccine. Puliyel pointed out that drug reaction is likely to be picked up mostly with first dose.

He said that SIDS deaths rate was actually a little higher in the 3rd month compared to 2nd month so there should have been more deaths after the second dose that is given in the third month than after the first dose given in the second month.

He said the same pattern of more reactions after the first dose was seen with intussusceptions with rotavirus vaccine which vaccine was withdrawn when 15 kids developed intussusception (although no child had died).

Dr Arora however felt the numbers were not big enough to make decisions.

Dr. Panda asked for death rates where components of the Pentavalent vaccine DPT Hib and Hep B are given separately. Dr Joyti Joshi said 400,000 doses of Pentavalent vaccine have been administered and that was the denominator for the deaths.

Dr. Puliyel pointed out that number of dose is not relevant but the death per children fully immunized. **He pointed out that the hand-out stated that 4000,000 children had been immunized. Dr. Jyoti Joshi apologized for the error.**

Dr. Puliyel said Dr Jyoti Joshi must inform the AEFI committee of this mistake too and correct all the records. Dr Jyoti Joshi agreed to do this. **Dr. Panda expressed surprise that the PHFI**

Comment [R1]: (As 3 dose are needed per child it means less than 130,000 children had been immunized - and 19 had died. This death rate is higher than the deaths in Kerala in the first 6 months where 5 kids died where 40,000 had been immunized)

unit could not give the information on number of children vaccinated readily and asked that this be brought to the next meeting

3. Eleven deaths occurred beyond 12 hours of administration of the vaccine and in 2, vaccine was administered in less than 12 hours (within 5-6 hrs) before the death. In one child interval between vaccine administration and death was not available.

Dr. PuliyeI asked for data on when the first symptoms of reaction were noticed in each of the children after vaccination.

He asked why data on death before and after 12 hours was being presented as this is not mentioned in any SOP on AEFI surveillance. He said a child can be kept alive for a week on a ventilator and that is meaningless for AEFI surveillance.

Dr Panda showed the committee the WHO website asking for time of onset of symptoms happening in the first 48 hours after vaccination. He said criteria of death in '12 hours after vaccination' was not mentioned anywhere.

Dr. Panda said that a excel sheet with time of onset of each symptom must be presented at the next meeting of this committee.

4. In six cases, co-morbidities were present that could have contributed to death.

Dr. PuliyeI asked what the co-morbidities were in each case and whether it was sufficient to cause death. Dr. Jyoti Joshi said she didn't have exact list but one child had a cardiac condition, one was preterm and malnourished and a third had a diaphragmatic hernia with other congenital abnormalities.

Dr. PuliyeI wanted to know the condition of the child with heart disease on day of vaccination before administration of the vaccine. Was the child having just a cardiac murmur or was the child in cardiac failure and gasping before the vaccine was administered. Dr. A P Dube said that even if the child had not received the vaccine he would have died of his heart disease. Dr Panda

pointed out that if such a child who was gasping and going to die in any case in 12 hours, was administered this vaccine it suggests a serious programme error. The AEFI committee had certified no programme error had occurred.

Dr Puliyel pointed out that if the child had a non significant cardiac murrer, it is not sufficient reason for death. Otherwise instructions must be sent to all centers that no child with a cardiac murmer must be vaccinated with Pentavalent vaccine as they are at risk of death in 24 hours.

Regarding child with malnutrition as co-morbidity, Dr Puliyel pointed out that the majority of children in India are malnourished and asked if malnutrition was to be a contraindication for immunization

Regarding baby who was born prematurely Dr. Puliyel said that the vaccine was given at 6 weeks and asked what gestational age at birth was a risk of death with pentavalent vaccine.

It was agreed that details of all these 6 children with co-morbidities would be presented to this committee at the next meeting, to examine if they were coincidental or sufficient cause for death .

5. The clinical manifestations, age group, season, and time of the death in 8 infants were consistent with presumptive diagnosis of SIDS (Sudden Infant Death Syndrome).

Dr. Puliyel asked how a presumption was of SIDs was made.

He asked what the above statement meant.

He said all babies vaccinated are infants, so as the age group is appropriate for diagnosis of SIDS will it be sufficient to say all the children died of SIDS.

In the same way - season. There is no winter in Kerala. Just because a few more children died between December and February and SIDS happens more in winter is that sufficient to say all the deaths (summer and winter deaths) are all SIDS.

It was the same with the sex predilection he said.

Dr Dube said that as the child had been put to bed and died at night in its sleep it must be SIDS.

Dr Arora asked why there were more post vaccination deaths at night if they were not because of SIDS.

Dr Puliye said that the children had received a vaccine earlier in the day and the children were febrile and was put to be breathless and it cannot fit SIDS criteria by any stretch of imagination.

Dr Arora and Dr Dube said they were Pediatricians and that they make a diagnosis of SIDS when any child is brought dead to the hospital and a clear diagnosis cannot be made.

Dr Panda and Dr Puliye disagreed and said the very fact that the child had been vaccinated that day make SIDS untenable.

Dr Arora said that a Norwegian paper showed death on day of vaccination had been reported as SIDS. He said there was no data on SIDS from India. He said a fourth of all infant deaths in India could be SIDS.

Dr Puliye pointed out that the Scandinavian paper showed that these were very rare deaths. He said that under no circumstance can the SIDS rate in the state of Kerala be higher than the IMR of the State. He said that in the 24 hours on the day of vaccination, the rate of death was 4 times the post neonatal IMR of Kerala.

Dr. Panda said we must assume this the death are due to vaccine and investigate if that is true. We must say that these were deaths associated with vaccine that need investigation.

Dr Arora said we must not say the deaths were associated with vaccine, but merely that there were deaths that must be investigated. He said a case control study was planned looking for exposure to vaccine in the children dying to provide this answer.

Dr Puliye read out the causality assessment criteria on page 17 of the SOP for AEFI of the Government of India. He said that the committee was mandate to follow the SOP and he read that vaccine is 'Very likely or certainly the cause of AEFI' if there is a plausible time relationship between AEFI and vaccination and if no alternate cause was found. Dr Arora agreed that all deaths were within a plausible time (or else it would not have been brought up to the committee) and there was no alternate cause but he said that for developing countries a new

algorithm was being mooted where the first step for attributing causality involves identification of mode of death – whether anaphylaxis etc. The next step was to establish relation to vaccine and in the third step only causality as in Brighton classification will be considered.

Dr Puliyel asked if this protocol was peer reviewed and published to which Dr Arora said no. It was decided that the SOP of AEFI of GoI must be followed by this committee.

Dr Rakesh Kumar asked that if we are to assume vaccine is cause of death until proved otherwise all deaths will be said to be vaccine related. Dr Puliyel said that Pentavalent vaccine is given only on 3 days in the life of the infant. Assuming a 2 day window it makes 6 days around vaccination. Pentavalent vaccine is not given in remaining 359 days. Deaths on those days will not be presumed to be vaccine related. The question is whether the death rate in those 6 days with vaccine is higher than in the remaining 359 days.

Dr Panda said that while there was concern that vaccine was causing deaths in 2 states and we are still investigating them why did the Govt of Delhi and 6 other states start the pentavalent vaccination programme?

A fresh death in Karnataka on 19/4/13 was also mentioned.

Dr Dube said that that was the Governments decision and he was not responsible. Dr Panda reiterated that this was unacceptable.

Dr Arora summarized the data that needs to be brought to the next meeting in 2 weeks time.

Draft

Minutes of meeting of causality assessment meeting held at LHMC on 15-Feb,13

- All the 14 death cases following pentavalent vaccination in Kerala were discussed and analysed during the meeting. The draft Kerala report by the central team and state AEFI causality assessment report was also reviewed.
- References from Brighton, Nelson and other research articles were reviewed.

To summarise:

1. Reported deaths (AEFI cases) are sporadic from different part of the state, there is no clustering, and adverse events have not been reported from other children who have received the vaccine from the same vials. Programme errors therefore appear unlikely.
2. In 8 cases, death was reported after 1st dose, in 4 cases – after 2nd dose, in 1 case- after 3rd dose and in case- (Easy4 – not known). Eleven infants were females.
3. Eleven deaths occurred beyond 12 hours of administration of the vaccine and in 2, vaccine was administered in less than 12 hours (within 5-6 hrs) before the death. In one child interval between vaccine administration and death was not available.
4. In six cases, co-morbidities were present that could have contributed to death
5. The clinical manifestations, age group, season, and time of the death in 8 infants were consistent with presumptive diagnosis of SIDS (Sudden Infant Death Syndrome)
6. There is also seasonality in death cases: 5 cases were during April – October while 9 cases were during December – February (cooler months).
7. Post mortem was done in 4 cases. The tissues from these children should be subjected to more detailed analysis for histopathology, immunological, molecular and toxicology testing to complement our current understanding and help in arriving at a more specific diagnosis in the context where deaths have occurred. These tissue samples may be sent to institutions like AIIMS, New Delhi and possibly WHO/CDC for further testing (if required).
8. From the available tissues, possibilities of genetic studies may be explored to determine association with SIDS.
9. All cases had received PCM prior to death. PCM related hypersensitivity although rare in children < I year, the possibility needs to be investigated.
10. A request to CDSCO may be sent for vaccine quality audit.

Finally, the overall assessment of the 14 reported deaths by causality assessment committee, it appears that the vaccine is unlikely to be contributing to the cause of these deaths. However, the causality assessment committee shall meet again to review the detailed investigations from PM cases.

Technical update on reported deaths following administration of Pentavalent vaccine
(With comments of J Puliyl made after the meeting of 22 April 2013)

1. Government of India introduced a liquid pentavalent into the routine immunization schedule on 14 December 2011 to replace the DPT and Hepatitis B vaccines and introduce Hib vaccine. Since its introduction, about 400,000 children have received the vaccine in 2 states: Kerala and Tamil Nadu.
2. Within India, the national Technical Advisory Group on Immunization (NTAGI) ‘strongly recommended that Hib vaccine should be immediately introduced in India’s UIP’ and the Indian Academy of Pediatrics (IAP) stated in 2012 that “(the committee of immunization) strongly supports the Government of India’s efforts to introduce the vaccine in all the states of the country.”
3. A total of 79 AEFI cases reports with Penta vaccine of which 19 are death (24%) and 60 cases (76%) are of hospitalization.
4. Annual breakup is as follows:

Comment [R2]: This is 400,000 doses

Year	Death	Hospitalization	Total
2011	1	4	5
2012	14	42	56
2013	4	14	18
Total	19 (24%)	60 (76%)	79

5. The states reporting the 22 death are as follows:

Year	State	AEFI death reported
2011	Kerala	1
2012	Kerala	10
	Tamil Nadu	4
	Total	14
2013		
	Kerala	3
	Haryana	1
	Total	4
	GRAND TOTAL	19

Comment [R3]: Add death in Karnataka 19/4/13
Total 20 deaths to date 25/4/13

6. Causality classification of AEFI deaths is as follows:

S No.	State	Program error	Vaccine reaction	Injection reaction	Coincidental	Unrelated	Total
1	Kerala	0	0	0	6	8	14
2	Tamil Nadu	0	0	0	4		4
3	Haryana	0	0	0	1		1
	India	0	0	0	11	8	19

Comment [R4]: Appears to mean any death they decide cannot be called SIDS (or perhaps babies who had so called co-morbidities)

Comment [R5]: These are perhaps what they want to call SDS deaths

7. AEFI deaths reported following pentavalent vaccine in Kerala state were reviewed by state AEFI committee and a central team was also sent to facilitate the process. The cases were further reviewed by the causality assessment subcommittee of the National AEFI committee which confirmed that for the 14 reported deaths, 6 had co morbidities and 8 other cases were unrelated to the vaccine. It reported

- a. For the 14 penta related AEFI deaths there is seasonality in death cases with almost a third of the deaths having been reported during the cooler period from December – February.
- b. The clinical manifestations, age group, seasons, and time of the death in 8 infants were consistent with presumptive diagnosis of SIDS (Sudden Infant death Syndrome). Post-mortem samples are available from 4 cases and the central investigation team has requested for a more detailed analysis for histopathology, immunological, molecular, toxicology and genetic testing to complement current **understanding** and help in arriving at a more specific diagnosis in the context where deaths have occurred and to determine association with Sudden Infant Death Syndrome. (SIDS).
- c. All cases received PCM prior to death, PCM related hypersensitivity although rare in children < 1 year; the possibility needs to be **investigated**.

Comment [R6]: This will be path breaking indeed!!

Comment [R7]: Interesting association indeed

Finally, the overall assessment of the 14 reported deaths by causality assessment committee; it appears that the vaccine is unlikely to be contributing to the cause of these deaths. However, the causality assessment committee shall meet again to review the detailed investigations from PM cases.

8. As directed further histo-pathological analysis of the post mortem samples of 3 cases was sought at Pathology Department AIIMS, Delhi under the leadership of Dr S K Panda had a review meeting was conducted soon after.
9. The histopathological review concluded that the deaths were due to vasogenic shock. The cause of the shock could however not be determined with the current evidence available and the previous conclusion of the causality committee **holds**.
10. Haemophilus influenza type B (Hib) is a bacterium which causes severe pneumonia, meningitis and other life-threatening conditions in children less than five years of age. Conjugate Hib vaccine has proven to be one of the best tools to prevent infections caused by Hib vaccine globally. WHO recommends Hib conjugate vaccines for all children, noting “in view of their demonstrated safety and efficacy, conjugate Hib vaccine should be included in all routine infant immunization programmes”. Although safe and effective, the Hib vaccine was available to only a small portion of children in India through the private sector.
11. These deaths though sad and unfortunate, are sporadic from different parts of the state. There is no clustering, and adverse events have not been reported from other children who have received the vaccine from the same vials.

Comment [R8]: It seems Dr Panda was not helpful at all

Technical update on reported deaths following administration of Pentavalent vaccine

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