EDITORIALS

AEFI and the pentavalent vaccine: looking for a composite picture

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Georg Christoph Lichtenberg's reference to "a knife without a blade, for which the handle is missing" has been illustrated recently by Broomberg and Oliver Chanarin (1). In his work, *Jokes and their Relation to the Cognitive Unconscious*, Freud suggested that the "knife without a blade which has no handle" is as absurd or funny as a "frame without a picture" (2). The joke is, of course, on the viewer who looks for something where there is nothing shown . This editorial examines the investigations into the deaths that followed the use of the pentavalent vaccine (DPT+hepatitis B+H influenza b vaccine). Most of them reveal nothing and remind one of Broomberg and Oliver Chanarin's work of art.

On May 4, 2013, the ministry of health of Viet Nam suspended Quinvaxem, the pentavalent combination used in that country, after it had caused 12 deaths and nine non-fatal serious adverse events (3). On investigating the reactions caused by the vaccine, the World Health Organization (WHO) reported that the nine non-fatal cases could correspond to known vaccine reactions, but the fatal cases were not related to the use of the vaccine. "Quinvaxem was prequalified by WHO … no fatal adverse event following immunisation (AEFI) has ever been associated with this vaccine," the report asserts, wrongly.

The term "AEFI" merely denotes a temporal relationship (not necessarily a causal relationship) between immunisation and adverse events, and a "fatal AEFI" is any death that occurs soon after vaccination. The fact that 12 children died soon after immunisation has not been disputed in the report. It is therefore patently wrong and misleading to conclude that "no fatal AEFI have ever" been associated with the vaccine. According to local news reports, all the babies who died had been in good health prior to vaccination, but hours after receiving the vaccine, they began wailing loudly, and had convulsions and serious trouble breathing. They died shortly afterwards (4).

The deaths in Viet Nam represent only a small fraction of the problem. By now, serious adverse reactions and deaths have been reported following the use of other brands of the pentavalent vaccine in a number of countries.

The background

The Global Alliance for Vaccines and Immunisations (GAVI) and WHO recommended the use of this pentavalent vaccine in developing countries to replace the DPT vaccine. The underlying reason (as described on the GAVI website) was to be able to increase the uptake of the hepatitis B and Hib vaccines in these countries (5) by piggybacking these on a well-accepted EPI vaccine, ie DPT (6).

This combination vaccine is not licensed for use by the Food and Drug Administration (FDA) in the USA, nor is it used in other developed countries. Thus, there is little information on its adverse effects from countries with strong drug regulatory systems. It is to be noted that the Parliamentary Committee on Health and Family Welfare in India has recommended that the Central Drugs Standard Control Organisation (CDSCO) should subject drugs to intense scrutiny if they are relevant to the needs of countries like the USA, Canada, the UK and other countries in the EU, Australia and Japan, but have not been cleared for use there (7). The pentavalent vaccine would fall in this category.

The Brighton Protocol

When serious adverse events follow immunisation, the WHO recommends that investigations be carried out by experts using its Brighton protocol (8). Only clinical events which have a plausible relationship with the time of the administration of the vaccine and which cannot be explained by concurrent disease or other drugs or chemicals are classified as "very likely" related to the vaccine. An AEFI for which there is an alternative explanation is classified only as "possibly related" to the vaccine. A clinical event whose relationship with the time of the administration of the vaccine makes a causal connection improbable, and which could be explained by underlying disease or other drugs or chemicals is classified as "unlikely" to be related to the vaccine.

Before being introduced in India, the pentavalent vaccine had been used in Bhutan (9), Sri Lanka (10) and Pakistan (11). In each of these countries, there were unexplained deaths soon after immunisation. Bhutan, in fact, stopped the immunisation programme after four infants died (9). It was later persuaded to restart the programme by the WHO, which suggested that the deaths were probably due to coincidental viral meningo-encephalitis. The reintroduction of the vaccine was followed by another four deaths.

Bhutan no longer uses the pentavalent vaccine. The Director of Public Health, Dr Ugen Dophu, noted that there were no more cases of meningo-encephalitis among infants the year after the vaccine was withdrawn (12).

Deaths following the use of the vaccine resulted in the suspension of the immunisation drive in Sri Lanka as well. A WHO committee investigated the deaths. The full report of this committee was made available to the Delhi High Court (13). The report said that although the committee could find no alternative cause for the deaths (which would suggest that the vaccine was very likely to be the cause of the reactions and deaths), the deaths were 'unrelated' to the immunisation. The committee did not substantiate why it thought the reactions were 'unrelated' to immunisation (10).

The experience in Pakistan was similar. The events surrounding the deaths following the administration of the vaccine were revealed by Professor F Mansoor, an expert on the committee investigating the deaths. One child died within half an hour of receiving the vaccine and two others died within 12–14 hours. No alternative cause of death was found in any of the cases. Two of the deaths were attributed to sudden infant death syndrome (SIDS), probably because the babies died after sunset, but the "experts were not sure of the third case." In no case was the vaccine blamed (11).

Given this background, when the pentavalent vaccine was proposed to be introduced in India, the National Technical Advisory Group on Immunisation (NTAGI) mandated that it be introduced in the immunisation programmes of two states (Tamil Nadu and Kerala) to begin with so that its safety could be monitored. The data from this experiment would be reviewed one year later, before introducing the vaccine into other states (14).

There were some protests in Kerala against the plan to introduce the vaccine there. To allay public anxiety, the state government set up the Noel Narayanan Committee (15). In its report, the committee recommended that the government collect data on each child 48 hours after immunisation. This report strengthened the reporting of AEFI in the state and thus, more cases of AEFI were reported from Kerala than from Tamil Nadu.

In the first six months after the introduction of the vaccine in Kerala, 40,000 children were vaccinated and five of them died of AEFI. By the end of a year, 14 children had died. Several academicians and public health specialists wrote a letter to the health secretary, expressing their concern about these deaths (16). The Central Government set up a committee to investigate the deaths (17).

Death from co-morbid conditions

When the number of children who died had been four, it was reported that two had died of co-morbid conditions. The press noted that the authorities had neither specified what the co-morbid conditions were, nor explained why the doctors had administered the vaccine to children who were so sick (18). After 14 babies had died, it was claimed that co-morbid conditions were responsible for six of the deaths. Some details of these co-morbid conditions were made available through the Right to Information Act of 2005:

1. One child had a ventricular septal defect (VSD) and a patent ductus arteriosus (PDA), but there was no suggestion that the child was in cardiac failure before the vaccination, which would have explained his/her death on the day of immunisation.
2. Another co-morbid condition recorded was prematurity. In India, babies with a birth weight of less than 2 kg qualify as premature, but this baby's birth weight was 2.4 kg. Further, the baby would have been 6 weeks old at the time of the vaccination and it is unlikely that prematurity would have been the cause of the infant's death on the day of immunisation.
3. One child was reported to have Down's syndrome and multiple congenital deformities. The multiple deformities were bilateral talipes.
4. One child's co-morbidity was his mother's "psychiatric illness."
5. One child had documented upper respiratory tract infection but died after suffering from high fever and convulsions within 16 hours of the vaccination. According to the AEFI committee, the child died of "pre-existing lung infection."

None of these qualifies as a "sufficient alternative cause" for the deaths. Mothers in Kerala, which has a high literacy rate, seldom take their children for immunisation if they are very sick.

As for the remaining deaths, no alternative explanation was available (other than the fact that the babies had received this vaccine a few hours earlier). They were all clubbed as death due to SIDS.

SIDS and AEFI

All sudden deaths in infancy are not cases of SIDS. SIDS, by definition, is the death of an infant that is not predicted by the infant's medical history, and which remains unexplained after a thorough forensic autopsy and detailed investigation of the death scene (19). There are certain features common to all the deaths discussed in this editorial: the children had received the pentavalent vaccine, which in most cases, was followed by a high fever and excessive crying and in some, convulsions before the child died. The use of the term SIDS in a generic manner to describe deaths following vaccination, when the autopsy has suggested hypersensitivity and shock, is misleading and unfortunate.

There is, however, a precedent for AEFI being legitimately classified as SIDS. One needs to have a clear understanding of this so as to be able to distinguish when the term SIDS is being used improperly.

SIDS in the USA

In the USA, adverse events following vaccines are reported to the Vaccine Adverse Events Reporting System (VAERS). This system logs all AEFI reported by the public and healthcare providers (20). Following an analysis of the data from 1991 to 2001, it was found that all the deaths reported as being caused by AEFI were, in fact, due to SIDS (21). These are the data that are often cited inappropriately to suggest that all deaths after vaccination are caused by SIDS.

Out of every 10,000 cases of vaccination in the USA, 1.14 cases of AEFI were reported to the VAERS. Deaths accounted for 1.4% of the reports of AEFI (20). There were 0.016 deaths due to AEFI (occurring mostly within two weeks of the vaccination) per 10,000 vaccinations. A clinical research team followed up on all the deaths reported to the VAERS. All except one death (of a 28-year-old) were due to SIDS. The frequency of these deaths was compatible with the rate of the occurrence of SIDS in the USA. The number of deaths reported to the VAERS after 1992–1993 reflected the overall decrease in the prevalence of SIDS in the USA after the implementation of the 'Back to Sleep' campaign.

The USA has one of the highest SIDS rates in the developed world, that is, in the developed countries where such data are available. In the USA, 0.5 deaths occur due to SIDS per 1000 live births (22). Given this rate, if all infants are vaccinated every day during the first year of their life (365 vaccinations on 365 days), then out of every 1000 babies subjected to such intensive vaccination, 0.5 will die by chance of SIDS on the day of the vaccination. If children receive only one vaccine in the year, the chance of death from SIDS on the day of the vaccination is 0.5 per 365,000 children. As for death on the day the child receives the first dose of the pentavalent vaccine, there will be one death per 720,000 infants vaccinated.

Probability of SIDS in Kerala

After six months of the trial in Kerala and after five babies had died (four after the first dose of the vaccine), we considered the probability that a cluster of SIDS following immunisation had occurred by chance.

The infant mortality rate in Kerala is 12 to 13 per 1000 and neonatal mortality, 6 to 7 per 1000 (23). The post-neonatal infant mortality rate of 6 per 1000 during 337 days (365 – 28 days of the neonatal period) is 0.0178 per day per 1000 children. If we include all causes of death, only 0.712 deaths may occur among 40,000 children on the day of the vaccination, by chance. In the case of the deaths following the pentavalent vaccine, the estimated SIDS rate is five times greater than the all-cause mortality rate of the state. Using the Poisson probability theory, the occurrence of four deaths among the vaccinated (40,000 vaccinated for the first time) is highly inconsistent with the background picture of mortality rates (24).

SIDS deaths form a small part of the total mortality and cannot logically exceed the overall age-specific mortality.

The majority of deaths after the administration of the pentavalent vaccine have followed the first dose. This pattern of the adverse events taking place predominantly after the first dose also suggests that these are not random events, nor can they be explained by SIDS, which actually peaks in the third month of life (when most babies are likely to be getting their second dose of immunisation).

The balance sheet: lives saved through immunisation

The vaccine is used to prevent deaths from invasive Hib disease, i.e. Hib meningitis and Hib pneumonia. (The benefits related to the possibility of hepatitis B occurring much later in life are not studied here.) The WHO uses the incidence of Hib meningitis to estimate the burden of Hib disease in the community (25). The incidence of Hib pneumonia is said to be 5–10 times higher than that of Hib meningitis. However, the mortality associated with it is only about 1%, compared to 10% in the case of Hib meningitis (26, 27).

From the figures above, we can estimate the mortality from Hib (pneumonia and meningitis) by doubling the mortality from Hib meningitis in the country. The largest empirical evaluation of Hib meningitis in India (Minz study) found that the incidence of Hib meningitis was 7 per 100,000 children under 5 (28). Given the mortality rate of 10%, 175 children among the year's birth cohort of 25 million would die of Hib meningitis over the next five years. Assuming that an equal number die of Hib pneumonia, a total of 350 lives will be lost to Hib pneumonia and meningitis over the next 5 years by vaccinating one birth cohort in India.

If the birth cohort of 25 million were immunised and 1 per every 8000–10,000 of the babies vaccinated were to die of AEFI, about 3125 children would die from AEFI. It is apparent that to save 350 lives from Hib disease, 3125 children will die from the adverse effects of the vaccine.

AEFI reports and desired course of action

Many of the adverse events that follow vaccination are not caused by the vaccine but are merely coincidental events. Yet in 1999, when the administration of the rotavirus vaccine was followed by an increase in the rate of intussusceptions from 1 per 10,000 children immunised to 2 per 10,000, the vaccine was withdrawn voluntarily by the manufacturers after just 15 children developed

intussusceptions (29). In developed countries, product liability is a strong disincentive that prevents the marketing of drugs once serious adverse effects have been reported.

The autopsies of the children who died after the administration of the pentavalent vaccine showed that they had died of a hypersensitivity reaction. The deaths associated with this vaccine have been sporadic, meaning that thousands have had no reaction to it. This follows the pattern of anaphylaxis reactions, which develop in only a very few people. However, if a drug is known to have caused this form of fatal reaction, it is not permissible to give the medication to anyone without first testing for sensitivity. An example of such testing is the penicillin skin test and doctors who administer penicillin without testing are liable for negligence. No such test is carried out before administering the pentavalent vaccine.

Ethics and vaccine safety

The advice of experts to the government needs to be evaluated in retrospect. If it does not show evidence of due diligence, their advice should not be sought in the future. DeLong's detailed analysis of conflicts of interest in research on vaccine safety could be relevant in this context (30).

The CDSCO, which is responsible for licensing new drugs, post-marketing surveillance and ensuring that the "product-insert" is up to date and reflects all the facts, must also monitor the regulatory status of the product in other countries. The Drug Controller of India is duty-bound to exercise the powers vested in him to zealously protect the lives of children.

The product-insert of the Pentavac PFC used in India (31) states: "In a study conducted on PENTAVAC, the frequency of local and systemic reactions was not higher with subsequent doses and was well within the range of other DTP-containing vaccines." The fact that the vaccine has caused deaths in India and other countries, as well as the fact that it has been withdrawn in Bhutan and Viet Nam, is not mentioned. The product-insert is less than truthful.

Vaccines are meant to save lives. The public will cease to trust its healthcare providers if unscientific recommendations are accepted and this will have grave consequences for public health in the future. It is the health of the public rather than the viability of the pharmaceutical industry that must take precedence.

Twenty-one babies have died in India following immunisation with the pentavalent vaccine. If Bhutan and Viet Nam have been capable of taking action, there is no reason why India cannot act similarly. It has become imperative to protect the lives of children who are potential victims of the pentavalent vaccine. One hopes that the authorities entrusted with safeguarding the interests of the public will act decisively and in a transparent manner to rebuild the confidence of the public.

The international organisation involved in the investigation of AEFI all over the world is WHO. It is in the best position to discern the pattern of deaths across countries where the vaccine has been used. There is a need for WHO to look at the composite picture rather than deal with the issue in the context of individual countries.

Trivialising all these deaths as coincidental deaths, or deaths due to SIDS, amounts to obscuring the real picture. As with Lichtenberg's humour at the expense of his audience, the butt of this cruel joke are the parents and the general public who were looking for answers as to why their children died and perhaps hoping that other children will not suffer a similar fate.

Post script

The report of the meeting of June 12, 2013 of the 'Global Advisory Committee on Vaccine Safety review of pentavalent safety concerns in four Asian countries' has been published now. (It is available from: http://www.who.int/vaccine_safety/committee/topics/hpv/GACVSstatement_pentavalent_June2013.pdf).

The report provides more data on the deaths following pentavalent vaccine. The deaths in Pakistan were not included in this report.

Sri Lanka introduced Crucell in January 2008. After five deaths by April 2009, the vaccination programme was suspended. It was reintroduced in 2010. Between 2010 and 2012, there were 14 additional deaths following the vaccine, taking the total number of deaths in Sri Lanka to 19. In six of the 19, a congenital heart disease was reported.

Bhutan introduced pentavalent vaccine from Panacea (Easyfive) in September 2009. After five cases reported as encephalopathy (other reports have mentioned that four of them died), the vaccine was withdrawn in October 2009. Subsequently, it was reintroduced and there were four more deaths.

India introduced pentavalent vaccine from Serum Institute of India (Pentavac) in December 2011. Up to the first quarter of 2013, 83 serious AEFI were reported, some of which were associated with fatality. (Other reports had counted 21 deaths).

Viet Nam introduced Crucell in June 2010. By May 2013, 27 deaths had been reported and nine of the deaths following vaccination occurred betweeen December 2012 and March 2013. The vaccine has been suspended there.

Including the three deaths in Pakistan, a total of at least 70 deaths have taken place in five countries associated with different brands of the pentavalent vaccine.

Note *Some of the material used in this editorial has been published previously on the author's BMJ blog page.*

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