

Since 2008, *Haemophilus influenza* type b (Hib) vaccine has increasingly been introduced into Asian countries immunisation programmes. Hib vaccine has mainly been introduced as a combination pentavalent vaccine, which has replaced the traditional DTwP or DTPwP-HepB vaccines. As expected with the introduction of a new vaccine, there has been increased attention to serious adverse events following immunization (AEFI) and this presented challenges in several countries from the WHO Southeast Asian (SEAR) and Western Pacific (WPR) regions. At the 12-13 June 2013 meeting of the Global Advisory Committee on Vaccine Safety (GACVS), four countries that introduced pentavalent vaccines from 3 different manufacturers presented their experience.

Sri Lanka introduced the pentavalent vaccine from Crucell in January 2008. Within 3 months, 4 reports of deaths and 24 reports of suspected hypotonic-hyporesponsive episodes (HHE) prompted regulatory attention and precautionary suspension of the initial vaccine lot. A subsequent death that occurred with the next lot in April 2009 led the authorities to suspend pentavalent vaccine use and resume DTwP and HepB vaccination. Bhutan introduced pentavalent vaccine from Panacea in September 2009. The identification of 5 cases with encephalopathy and/or meningo-encephalitis shortly after pentavalent vaccination prompted the authorities to suspend vaccination on 23 October 2009. Subsequently 4 additional serious cases related to vaccine administration were identified and investigated. India introduced pentavalent vaccine from Serum Institute of India in the two states of Tamil Nadu and Kerala in December 2011. This was followed up with expansion of vaccine usage in the states of Goa, Pondicherry, Karnataka, Haryana, Jammu and Kashmir, Gujarat and Delhi during the second half of 2012 to the 1st quarter of 2013. To date, 83 AEFI cases, some of which were associated with fatality, have been reported after vaccine introduction from some states. Vietnam introduced pentavalent vaccine from Crucell in June 2010. Through May 2013, a total of 43 serious AEFI cases were investigated, including 27 fatalities. Following receipt of reports of 9 deaths following vaccination between December 2012 and March 2013, health authorities suspended use of the vaccine.

In each country the serious AEFIs were reviewed with independent national and international experts. Based on those reviews, none of the fatal cases could be classified as having a consistent causal association with immunization. In Sri Lanka, after a comprehensive investigation and review, the same pentavalent vaccine product was re-introduced in 2010. Since then and up to 2012, another 14 deaths were reported among infants who had received the Crucell pentavalent vaccine. In addition, 6 of 19 infant deaths were found at autopsy to have severe congenital heart disease. Following this finding, in Sri Lanka children with known severe congenital heart disease are now vaccinated under close medical supervision, and no additional deaths among these children have since been reported in temporal association with pentavalent vaccine administration. In Bhutan, following a similar investigative process, the vaccine was reintroduced in 2011. Vietnam is currently reviewing clinical, epidemiological and vaccine quality issues. All three countries have also actively managed public communication about the observed events and their public health implications.

GACVS identified several common features among the countries that experienced significant vaccine safety concerns following pentavalent vaccine introduction. In all countries, the vaccination program is well established and achieves high coverage (India introduced the vaccine in states with high vaccine coverage). Vaccine introduction was accompanied with very thorough training of health care staff about the benefits and risks of the vaccine. In Sri Lanka and Bhutan, discontinuation and resumption of pentavalent vaccine use did not significantly modify the pattern of serious AEFI reports. Several limitations were noted in all four countries. Incomplete clinical information significantly complicated the causality assessment. For some cases, additional clinical information allowed another cause of death to be identified. For other cases, there was insufficient clinical information to allow the cause of death to be ascertained, including the possibility of sudden infant death syndrome (SIDS).

The diagnosis of SIDS requires clinical information and a thorough post-mortem examination (as described in the Brighton Collaboration case definition) that is not available in many instances. As peak incidence of SIDS occurs in early infancy, a close temporal relationship between SIDS and receipt of pentavalent vaccine is expected by simple chance. GACVS emphasized the need for thorough investigation of any reported serious AEFI and the importance of establishing standard investigation procedures. In the case of SIDS in particular, the possibility of conducting autopsies or at least investigating and documenting rapidly the circumstances of death and collecting specimens and other clinical evidence was highlighted.

New vaccine introductions associated with increased reports of deaths and other serious AEFI present a challenge to immunization programs with respect to their ability to properly assess, manage and communicate about serious vaccine safety concerns. Identification of serious AEFI, including death is expected in temporal relationship with any infant vaccine even if no adverse events are causally associated with the vaccine. The findings of the investigations and expert reviews of deaths following pentavalent vaccine in the four countries are reassuring although not all cases could be fully ascertained due to incomplete evidence. The importance of thorough clinical investigation of AEFI (e.g., lumbar puncture and cerebro-spinal fluid examination for patients with suspected meningoencephalitis), and of adequate evaluation of deaths following vaccination including autopsy to identify underlying conditions and any potential alternative causes of death was demonstrated by the experience of those countries.

In the context of evaluating a safety signal, it is important that countries understand their own infant mortality rates and underlying causes. If a particular serious AEFI is identified as a concern, additional epidemiological studies should be conducted to ascertain factors that can be used to evaluate the evidence for risk hypotheses. SIDS, among other causes of infant mortality would benefit from detailed epidemiological studies. This is particularly important when new vaccines such as

those against Hib, pneumococcus and rotavirus are introduced in resource-poor countries and where there is increased attention to safety concerns. GACVS also emphasizes the fact that in a context of decreasing risk related to vaccine preventable diseases and increasing attention to AEFI, the capacity of all countries that introduce new vaccines to rapidly assess and communicate using a risk communication approach should be reviewed and enhanced accordingly.

In conclusion, pentavalent vaccine introduction in Asian countries has illustrated how legitimate increased attention to AEFI can pose new challenges to national decision-makers. The review of the experience of four countries, their willingness to openly discuss all case information with external experts, the consistent causality assessment conclusions reached in all countries and the thoroughly managed reintroduction of pentavalent vaccines in Sri Lanka and Bhutan are valuable examples of the successful maturation of national vaccine safety systems. Pentavalent vaccines, provide tremendous public health benefits related to the ability to protect against five major health problems in a single shot. Currently pentavalent vaccines from 5 different manufacturers are prequalified by WHO and considered to be safe, effective and of assured quality.