Global Advisory Committee on Vaccine Safety (GACVS)

Report on GACVS meeting

June 2012

World Health Organization

Thiomersal in vaccines

- 1999: As a precaution, the US Public Health Service and American Academy of Pediatrics called for thiomersal to be removed from vaccines given to young infants as rapidly as possible.
- 2002 – 2008: Data reviewed by GACVS established that ethyl mercury is rapidly excreted from the body (< 30 days of vaccination) even in premature and LBW infants.

Thiomersal in vaccines
Review of new publications

- 28 publications from 2008 to 2012.
- Epidemiological studies that examined the relationship between thiomersal receipt and several health outcomes:
  - Three ecological studies suggesting an association between thiomersal and neurodevelopmental disorders found to be fraught with methodological flaws.
  - The continuous increase in the number of cases of autism diagnosed in the USA despite removal of thiomersal from most vaccines strongly argues against a causal association.
  - All other high quality epidemiological studies reviewed, in different countries, failed to identify any association with neurodevelopmental disorders.
- Recently published studies confirm that in all populations including pre-term and low birth-weight babies the half-life of ethyl mercury in blood is between 3 and 7 days.

Thiomersal in vaccines
GACVS conclusions

- The quantitative risk assessment framework reviewed indicated that:
  - Animal or human toxicity studies suggest that the levels of ethyl mercury attained in the blood and brain from cumulative doses of vaccines do not reach toxic levels, making it biologically implausible for any relation between thiomersal in vaccines and neurological toxicity.

- Based on the current evidence:
  - Available evidence strongly supports the safety of the use of thiomersal as a preservative for inactivated vaccines.
  - No additional studies of the safety of thiomersal in vaccines are warranted
  - Consideration of additional evidence suggestive of the contrary should be based on studies using the same high standards of epidemiological and causal inference.

Thiomersal in vaccines
GACVS conclusions

- Thiomersal allows millions of people worldwide to have access to life-saving vaccines and to date, no other safer and equally efficacious alternative has been identified for many vaccines.

Aluminium adjuvants

- The GACVS reviewed 2 published papers alleging that aluminium in vaccines is associated with autism spectrum disorders

- These 2 studies were considered seriously flawed because:
  - They are based on ecological comparisons of aluminium content in vaccines and rates of autism spectrum disorders and in general, ecological studies cannot be used to assert a causal association.
  - Incorrect assumptions about known associations of aluminium with neurological disease, uncertainty of the accuracy of the autism spectrum disorder prevalence rates in different countries.
  - Issues with accuracy of vaccination schedules and resulting calculations of aluminium doses in different countries.

Aluminium adjuvants

- A US FDA risk assessment model that incorporate the most recently published data on aluminium in vaccines was reviewed.
- The FDA analysis indicates that the body burden of aluminium following injections of aluminium-containing vaccines never exceeds safe US regulatory thresholds based on orally ingested aluminium even for low birth-weight infants.

Aluminium adjuvants GACVS Conclusions

- This comprehensive risk assessment further supports the clinical trial and epidemiological evidence of the safety of aluminium in vaccines.
- Ongoing research on pharmacokinetics of aluminium in vaccines should be encouraged as a means of further validating and improving this model.

Vaccine safety in pregnancy and lactation

- Optimal protection against preventable diseases that pose a higher risk for disease and death in pregnant woman and their offspring should be balanced against the risk of adverse outcomes that theoretically could affect the fetus.
- GACVS established a subgroup to review available data on the use of vaccines in pregnancy.
- The group complemented the review conducted in June 2008 on the accumulated safety data for rubella-containing vaccines when inadvertently administered to pregnant women.
- GACVS concluded that:
  - The data remain very reassuring for the use of rubella vaccines during pregnancy, with no evidence of adverse fetal outcomes identified.
  - Protection of mothers at risk and their young infants will be critical to contain infections.

Use of influenza vaccines during pregnancy

- The committee reviewed the safety data available for influenza vaccines from clinical trials, observational studies, and spontaneous reporting.
- A review of spontaneous reports found no increased risk of adverse pregnancy outcomes when compared to background rate.
- The data confirm the safety of non-adjuvanted trivalent inactivated seasonal influenza vaccines in pregnancy:
  - The safety profile was comparable to seasonal influenza vaccine in non-pregnant adults.
  - Positive effects in their infants, including the reduction of low birth weights, and a significant decrease in influenza related pneumonia.

Causality assessment of Adverse Events following Immunization

- In December 2010, a working group was established to review the 2005 aide-mémoire and develop a simple, objective, adaptable and evidence-based method suitable in different resource settings.
- After concluding a thorough review of the most innovative methods available for determining causation for drugs and biologicals, an algorithm that incorporates additional elements of causation was designed.
- This was harmonized after the Clinical Immunization Safety Assessment (CISA) network's newly developed algorithm and the new definition of AEFI proposed by the Council for International Organizations of Medical Sciences (CIOMS)

Causality assessment of Adverse Events following Immunization

- The assessment classifies the AEFI as consistent or inconsistent with an association with the immunization, or indeterminate due to lack of evidence.
- The new WHO proposed method allows:
  - the National Committees for AEFI case review and causality assessment.
  - to screen serious cases.
  - the objectiveness of the assessment.
  - Cases deemed incomplete are directed towards additional case investigation and review.
  - Creating a repository of all AEFI cases for future signal detection and additional epidemiological studies.
- GACVS recognizes its limitations to previously unknown AEFIs due to insufficient information.
- GACVS recommended its speedy dissemination.

Core variables for AEFI monitoring

- For collection of harmonized data on AEFI, in collaboration with a network of countries and independent experts, a preliminary list of core variables was proposed.
- This list was subsequently compared with the reporting forms from the UMC to verify which variables are captured by the current reporting forms.
- It became apparent that:
  - Vaccine safety monitoring needs specific tools.
  - The current web-based interface for reporting of suspected drug reactions (VigiFlow) should be modified and adapted for AEFI reporting.

Core variables for AEFI monitoring

- It was recognized that for the purpose of signal detection, data collection tools should remain simple
  - 22 core variables should be collected for any AEFI (basic information) of which 10 were identified as critical.
  - An additional 33 variables were found of interest for a more detailed case review (advanced information).

Vacciflow

- "VacciFlow" will be developed as the adaptation of drug-specific VigiFlow 4.2 to facilitate the entry of vaccine-related AEFI data including immunization programme errors by both the national regulatory authority and the immunization programme staff:
  - To explore possibility of incorporating this new interface with minimal computer capabilities and mobile phone technology.
  - There will be 3 flexible levels enabling national and subnational level users to analyse and use the data available.
  - WHO-ART dictionary to be incorporated to standardize the terminology.