

Global Advisory Committee on Vaccine Safety (GACVS)

**Report on GACVS meeting
December 2012**

Topics Discussed

- Safety profile of varicella vaccines.
- Risk of narcolepsy and Guillain-Barré syndrome (GBS) with influenza vaccines.
- Safety aspects of dengue vaccines.
- Progress on implementation of the Global Vaccine Safety Blueprint through the Global Vaccine Safety Initiative (GVSI).



Varicella vaccines

- Post-licensure review of the safety of varicella vaccine including the Varivax® (Merck) vaccine in USA.
- Review included
 - Summary of the 2011 US Institute of Medicine (IOM) report (addressed 15 potential adverse events from 1950 to Dec 2010).
 - Literature review from December 2010 to October 2012.
 - Review of key post-licensure observational studies from the US Centers for Disease Control and Prevention and Merck.

Varicella vaccines – safety findings.

- IOM identified convincing evidence in support of a causal relationship with the vaccine (not quantified) for:
 1. Disseminated varicella infection (widespread chickenpox rash).
 2. Disseminated varicella infection resulting in pneumonia, meningitis or hepatitis.
 3. Vaccine strain viral reactivation (appearance of chickenpox rash months to years after vaccination).
 4. Vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis.
 5. Anaphylaxis.
- In addition, IOM identified 10 events with insufficient evidence to assess causality.
- With combination vaccines MMRV, an increased risk of febrile seizures after vaccination among children aged 12–23 months, compared with children receiving separate MMR and varicella vaccination was found.
- No cases of congenital varicella syndrome during 16 years of vaccine use (data do not support a signal of an increased risk of spontaneous abortion or birth defects).



GACVS conclusions and recommendations

● Questions to be clarified

- Whether varicella vaccination increases the risk of shifting varicella disease to older age groups.
- Whether risks from currently available varicella vaccines remain similar to those described earlier.
- What the risk–benefit ratio of varicella vaccine use would be in low and middle income countries (LMICs) with a high proportion of undetected immunocompromised people.

● GACVS recommended

- Additional data are needed to determine the full safety profile if it is to be deployed in LMICs.
- Conducting surveillance for varicella disease to assess the effectiveness.
- Enhanced vaccine adverse event monitoring if varicella vaccine is introduced in LMICs.

Pandemic influenza vaccines contd...

Narcolepsy

- Pandemrix® (Glaxo-SmithKline) association with abrupt juvenile narcolepsy has been confirmed in 5 countries (Finland, Ireland, Norway, Sweden and France).
- Low absolute risk but high relative risk (ranging from 6.6 in Sweden to 13.0 in Ireland).
- Existing Pandemrix vaccine doses have expired.

GBS

- GACVS reviewed the published and unpublished active surveillance studies that monitored GBS cases during influenza A(H1N1)pdm09 pandemic vaccination from Canada, France, Germany, Sweden, the UK and the USA as well as a multinational European Union study and a global study.
- Some studies have shown a relative incidence of GBS of 2.28 to 3.76 following both non adjuvanted and adjuvanted influenza A(H1N1)pdm09 pandemic vaccines.

GACVS conclusions

Pandemic influenza vaccines

- Narcolepsy

- Research should continue to better characterize the possible underlying biological mechanisms of this association especially since new vaccines will be required to protect against future pandemics.

- GBS

- Overall, the data available are compatible with a small increased risk of GBS after influenza A(H1N1)pdm09 vaccination that is substantially lower than that observed following the 1976 swine influenza vaccination campaign in the USA.

Live attenuated dengue vaccines

- Recombinant live dengue virus vaccines
 - To date, no serious vaccine-related events documented in 41,700 subjects who have participated in different phases of the tetravalent vaccine trials.
 - No excess cases of dengue fever or severe dengue attributable to the vaccine virus demonstrated.
- GACVS
 - Agreed that the safety profile observed up to date is encouraging (efficacy to protect against dengue remains a critical factor to be confirmed).
 - Recognized several challenges:
 - Harmonization of dengue case classifications.
 - Consensus on the follow-up to monitor vaccine-mediated enhanced severe disease.
 - Adverse events of special interest are rare (i.e., neurotropic or viscerotropic disease from the yellow fever vaccine virus backbone).
 - Severe dengue from natural infection by incomplete vaccine protection.

Live attenuated dengue vaccine

- GACVS concurs with the 2008 WHO recommendations to guide the development of dengue vaccines:
 - Long-term follow-up of vaccinated and unvaccinated cohorts (to determine the safety of dengue vaccines when exposed to several natural infection cycles).
 - Storage of adequate samples of sera and peripheral blood mononuclear cells for future studies on protection conferred by dengue vaccines.
 - Post-licensure studies to provide estimates of the long-term effectiveness against multiple dengue virus serotypes.
 - Assess the risk of vaccine virus escape and any herd effects of vaccination.
 - Establish whether booster immunization is needed and
 - Indicate any potential age shifts in dengue presentations.



GACVS Recommendations

Live attenuated dengue vaccine

- GACVS identified several approaches that should be considered in designing those studies
 - Collection of background dengue surveillance data.
 - Use of phased introduction (e.g., stepped wedge designs).
 - Use of case-control and case-only methods (to detect rare early adverse events) and
 - Epidemiological exploration of signals.

Global Vaccine Safety Initiative (GVSI)

- The GVSI has identified activities through a portfolio to achieve the strategic goals of the blueprint through a broad network of stakeholders.
- Currently, the portfolio includes >80 activities:
 - Prioritized based on their expected impact, feasibility and desirability.
 - Provides initiators, managers and donors of each activity with due recognition for their respective roles.
 - Resource for all stakeholders in global pharmacovigilance to help identify ongoing efforts, allow for better synergies, minimize duplications and enable resource mobilization.

Global Vaccine Safety Initiative

- GACVS identified that GVSII should outline the role of WHO in:
 - Involving regional and national immunization technical advisory groups with vaccine safety assessment and communication efforts.
 - Use of existing academic and educational institutions to expand vaccine safety training resources.
 - Engagement of vaccine producers in promoting information exchange and
 - Development of a roster of vaccine pharmacovigilance experts.
- GACVS proposed an analysis of:
 - How the needs for vaccine safety can best be addressed and
 - Development of an accountability framework for all stakeholders.
- The role of GACVS with respect to the GVSII will remain at the consultancy and advisory level and identifying a system of prioritization with a focus on meeting the needs of LMICs



Discussions planned for GACVS

June 2013

- Safety of pentavalent DTwP-HepB-Hib conjugate vaccines
- Safety of varicella and herpes zoster vaccines
- Immunization during pregnancy
- Safety monitoring of Yellow fever vaccines during mass campaigns in sub-Saharan Africa
- Safety of Japanese encephalitis vaccine
- Update on HPV vaccines

