# Global Advisory Committee on Vaccine Safety (GACVS)

## Report on GACVS meeting

## June 2013



World Health Organization

# Topics Discussed

- Pentavalent vaccine in 4 Asian Countries
- Zoster vaccine safety and varicella vaccine safety in immunocompromised populations
- Immunization during pregnancy
- Yellow fever vaccine safety during mass immunization campaigns in sub-Saharan Africa
- Safety profile: Japanese encephalitis vaccines
- Update: human papillomavirus vaccines
- Update: pandemic influenza vaccine (Pandemrix®) and narcolepsy

# Progressive pentavalent vaccine introduction in 4 Asian Countries

- Sri Lanka (Crucell, Jan 2008):
  - Within 3 months, 4 deaths and 24 suspected HHE: precautionary suspension of initial lot.
  - 1 death following immunization April 2009: vaccine suspended, DTwP and Hep B resumed.
- Bhutan (Panacea, Sep 2009)
  - 5 cases of encephalopathy and/or meningoencephalitis lead to suspended vaccination 23 Oct 2009. (Subsequently, 4 serious AEFI were identified and investigated).
- India (Serum Institute of India, Tamil Nadu and Kerala, Dec 2011; Goa, Pondicherry, Karnataka, Haryana, Jammu and Kashmir, Gujarat and Delhi from Q3 2012 – Q1 2013)
  - To date, 83 AEFI cases reported, some associated with mortality.
- Vietnam (Crucell, Jun 2010 - May 2013)
  - 43 serious AEFI investigated, including 27 with fatal outcome.
  - Following 9 deaths following vaccination reported Dec 2012 - March 2013: vaccine suspended.

# GACVS analysis of common features among countries experiencing significant vaccine safety concerns

- Vaccination programmes are well established and achieves high coverage
- Vaccine introduction was accompanied by thorough training of health-care staff on benefits and risks of vaccine
- Sri Lanka and Bhutan: discontinuation and resumption of pentavalent vaccine did not significantly modify pattern of serious AEFI with previously utilized vaccines
- Limitations in all 4 countries:
  - Incomplete clinical information complicated causality assessment.
  - For some cases, additional clinical information allowed another cause of death to be identified.
  - For other cases, insufficient clinical information made it impossible to rule out SIDS, which could have occurred coincidentally

# GACVS conclusions and recommendations

- New vaccine introductions associated with increased serious AEFI challenge immunization programmes in terms of assessment, management and communication
- Serious AEFI can occur with any infant vaccine even if no adverse events are causally associated with the vaccine.
- Investigations and expert review results in all 4 countries are reassuring although not all cases could be fully assessed (incomplete case information)
- Thorough clinical investigation of AEFI and evaluation of deaths following vaccination incl. autopsy to identify underlying conditions and any potential alternative causes of death, is essential.
- Carefully managed reintroduction of pentavalent vaccines in Sri Lanka and Bhutan are valuable examples of successful maturation of national vaccine safety systems
- Pentavalent vaccines provide great public health benefits, protecting against 5 major threats to health in a single injection.
- WHO prequalified pentavalent vaccines from 5 different manufacturers are considered to be safe, effective and of assured quality.

# Zoster vaccine safety and varicella vaccine safety in immunocompromised populations

- **Zoster vaccine safety**: FDA provided 7-year safety update of Zostavax® summarizing:
  - post-licensure observational studies conducted by CDC and Merck (total of >190 000 vaccinated study subjects, no new safety signals)
  - literature review from date of licensure (May 2006) - Feb 2013,
  - analysis of 12,000 reports from VAERS (May 2006 - Feb 2013): 1057 were considered serious (most frequently: herpes zoster, pain, and rash)

- FDA data mining using disproportionate analysis: AEFI predominantly due to:
  - vaccine failure (i.e. herpes zoster despite vaccination),
  - accidental exposure and
  - inappropriate administration (i.e. use in subjects younger than ≤50 years).

- In summary: although safety data on the subpopulation of individuals aged ≥80 remains limited, no new safety risks have been identified or confirmed since initial licensure.

# Zoster vaccine safety and varicella vaccine safety in immunocompromised populations

- **Varicella vaccine safety**: Studied because diseases from wild type VZV are more severe and fatal in persons with defects in cell-mediated immunity
- Study groups: children with cancer, HIV, and post-organ transplant (all but one group in developed countries).
- Varicella vaccine contraindicated/only to be used with strict protocol in leukaemia patients.
- Two doses of varicella vaccine are effective and safe in preventing varicella in children with HIV with CD4 T-cell count ≥15%. Case reports described other immunocompromised children due to natural killer T-cell deficiency discovered after vaccination.
- In countries with routine childhood varicella vaccination programmes, children are likely to be vaccinated without known immune deficiency states (esp. undetected and untreated HIV infection) **A risk benefit analysis should therefore be considered before introducing varicella vaccination.**

# Immunization during pregnancy

- December 2011, SAGE asked GACVS to review current evidence on the safety of vaccinations in pregnant and lactating women.
- GACVS prioritized vaccines for review as per:
  - potential to reduce morbidity for the pregnant woman and her fetus;
  - use (or projected use) in vaccination campaign settings, which have the potential for inadvertent vaccination of pregnant women.
- Data included: interventional, non-interventional studies & spontaneous reporting systems.

# GACVS conclusion on immunization during pregnancy

- No evidence of adverse pregnancy outcomes from the vaccination of pregnant women with inactivated virus, bacterial, or toxoid vaccine.
  **Pregnancy should not preclude women from immunization with assessed vaccines if indicated**.

- Live vaccines may pose a theoretical risk to the fetus. Substantial literature available describing the safety of live attenuated vaccines (e.g. on monovalent rubella, combined MMR, and oral polio vaccines) indicate no significant adverse effects to the fetus.
  **Contraindication of MMR vaccines is considered purely precautionary. Inadvertent vaccination with MMR-containing vaccines is not considered an indication for pregnancy termination.**

- Benefits of vaccinating pregnant women generally outweigh potential risks of exposure to a particular infection to the mother or her fetus/newborn if the vaccine is unlikely to cause harm.

- Using selected vaccines in pregnancy improves maternal health and benefits the neonate.

# Yellow fever vaccine safety during mass immunization campaigns in sub-Saharan Africa

- In 2006, the Yellow Fever Initiative led by the WHO in partnership with UNICEF and GAVI was launched to control the increasing resurgence of Yellow Fever to reduce the risk of epidemics in sub-Saharan Africa.
- The recent (2007–2010) preventive yellow fever (YF) vaccination campaigns in West and Central African countries enabled GACVS to review surveillance of AEFIs in Benin, Burkina Faso, Cameroun, Guinea, Liberia, Mali, Senegal, Sierra Leone and Togo.
- In all, 38 million doses of the vaccine were administered, and 3116 AEFIs were observed: (2952 non-serious and 164 serious).
  - Of the serious AEFIs, 22 were classified as related to the YF vaccine, 142 not related.
    - Of the 22: 6 clinical cases resembled acute neurotropic disease (YEL-AND), 5 clinical cases resembled acute viscerotropic disease (YEL AVD). A further 11 involved hypersensitivity reactions.
    - Attack rates per 100 000 vaccinated people obtained from the study therefore were 0.016, 0.013 and 0.029 for YEL-AND, YEL-AVD and hypersensitivity reactions respectively.
    - These rates were lower than those seen with recipients of a first dose of YF vaccine in more developed settings.

# GACVS recommendations: Yellow fever vaccine safety during mass immunization campaigns in sub-Saharan Africa (2)

- Conducting a pharmacovigilance study in a resource-limited setting faces enormous challenges.
- Enhanced vaccine safety monitoring, including additional resources to provide adequate capacity and expertise, should be included in planning vaccination campaigns.
- Criteria for case definitions are very strict and difficult to apply appropriately in such settings. **More operational criteria could be proposed that would be adapted to local clinical practice or that additional dedicated efforts be conducted to meet existing criteria.**
- There is a need to put standard operating procedures or tiered instructions in place to strengthen pharmacovigilance and address technical and logistic issues.
- Clinical and laboratory findings even if limited should be more systematically correlated with post-mortem examinations.

# Safety profile of Japanese encephalitis vaccines

- GACVS considered recent data on the safety profiles of 2 inactivated Japanese encephalitis (JE) vaccines a cell culture based on live attenuated SA 14-14-2 JE vaccine.

- SA 14-14-2 is produced by Chengdu Institute of Biological Products, licensed 25 years ago, worldwide >400 million doses administered. GACVS previously found this vaccine to be generally safe.
  - Philippines and Sri Lanka: Studies on a few hundred children found only mild reactions.
  - India: in 19 adults no evidence found of viraemia up to 2 weeks administration.
  - Chinese Centre for Drug Evaluation: During 2009–2012 6024 AEFI reported (70 severe: febrile convulsions, thrombocytopenic purpura and encephalitic/ meningitic illness of which one was considered vaccine related). 4 recorded deaths, none considered related to vaccination.

# GACVS conclusion: Safety profile of Japanese encephalitis vaccines

- Although there was no evidence of a safety signal, the number of events recorded in the AEFI reporting system was low given that >70 million doses of vaccine have been administered.
- Studies in immunocompromised populations, particularly individuals with HIV, should be carried out with new inactivated vaccines, starting with those with CD4 T-cell counts >200.
- Overall, GAVCS noted that the live attenuated and the inactivated vaccines based on SA-14-14-2 appear to have an excellent safety profiles.
- There is need for building post-marketing surveillance systems in countries where disease is endemic and vaccines are used, and currently only limited data are collected post-licensure.
- More detailed study is requried of safety in pregnant women, on viral shedding of the live vaccine, the implications for the efficacy and safety of the vaccine in infants with high maternal antibodies against JE virus.

# Update on human papillomavirus vaccines from the United States, Australia, Japan and the manufacturers of Cervarix® (GSK) and Gardasil® (Merck).

- United States (extension of spontaneous reports to VAERS and completed and planned studies from the Vaccine Safety Datalink).
  - data from VAERS now includes >50 million doses distributed and the profile has not changed since the review in 2009
  - Reported adverse events not identified at the time of the first review: syncope and venous thromboembolism (VTE).
  - VSD did not find any increased risk of Guillain-Barré syndrome or stroke.
- Australia, a new programme targeting males started in February 2013 and data are starting to become available.
  - To date, with almost 7 million doses distributed, the previously investigated concern of increased anaphylaxis was not confirmed.
  - There are no further concerns regarding demyelinating disease or other chronic conditions also investigated earlier by the expert group.
- Surveillance from the 2 manufacturers found no signals suggesting any necessary revisions to product labelling.

# GACVS conclusion on safety review of human papillomavirus vaccines

- **GACVS continues to be reassured by the safety profile of the available products.**
- Anaphylaxis and syncope have been addressed through further studies and appropriate revisions were made to the product labelling.
- Serious adverse events that have been reported as potential signals have been investigated in more detail, including Guillain-Barré syndrome, seizures, stroke, venous thromboembolism, anaphylaxis, and other allergic reactions – many using rapid cycle analysis in the VSD in the United States.
- Surveillance of pregnancy outcomes among women inadvertently vaccinated during pregnancy through spontaneous reports and registries have not detected any adverse outcomes above expected rates.
- The cases of chronic pain being reported from Japan deserve specific mention. To date there is little reason to suspect the HPV vaccine, however, careful documentation of each case and a thorough search for a definitive diagnosis should be made.

# Update on pandemic influenza vaccine (Pandemrix®) and narcolepsy

- Previously reviewed data included studies on the use of monovalent A(H1N1)pdm09 vaccine in Finland, Sweden, Ireland, the UK and France - all demonstrated an increased risk of narcolepsy following Pandemrix® vaccination in children and adolescents.
- GACVS reviewed newly available national care register data from Finland on safety of Pandemrix® vaccine in adults.
- From 2009 – 2011 comparison of incidence rates indicated a 3–5-fold (after sensitivity analysis 2–4-fold) risk of narcolepsy among vaccinated compared to unvaccinated adults (8 months post vaccination; thereafter, no increased risk observed).
- Reports from Sweden, France and Finland concur that young adults have an increased risk of narcolepsy after Pandemrix® vaccination.
- GACVS acknowledges this finding suggesting a possible risk of narcolepsy among adults, although it remains lower than that seen among children.
- Further follow-up research is required to confirm the strength of the observed association and size of the risk and urges to continue research to identify the underlying biological mechanisms of this association.

# Upcoming Agenda Topics

- December 2013
  - Rotavirus vaccine
  - Recombinant Japanese encephalitis virus vaccine
  - Pandemic influenza vaccine
  - Inactivated polio vaccine
  - Vaccine safety surveillance manual

- June 2014
  - RTS,S malaria vaccine