Global Advisory Committee on Vaccine Safety (GACVS)

Report on GACVS meeting

June 2014

World Health Organization

Safety profile of a novel live attenuated rotavirus vaccine

- Rotavac was licensed in India in January 2014
- The vaccine is derived from a naturally attenuated human neonatal strain containing 1 bovine segment (G9P[11]) originally isolated from an asymptomatic infant at the All India Institute of Medical Sciences in 1988
- The strain was further studied by Indian and U.S. investigators, with safety trials conducted in adults and children in the U.S. and licensed to Bharat Biotech International (Hyderabad, India)

Safety profile of a novel live attenuated rotavirus vaccine

- A randomized, double-blind, placebo-controlled Phase 3 study with active monitoring for safety in 4532 infants who received the rotavirus vaccine and 2267 placebo recipients
- No imbalance noted between the ROTAVAC and placebo groups with respect to adverse events, death or intussusception
- 11 confirmed cases of intussusception; no case occurred within 30 days of vaccination.
- The observed incidence of confirmed intussusception was 94 per 100 000 child-years (95% CI: 41–185) among vaccinated infants and 71 per 100 000 child-years (95% CI:15–206) among those who received placebo.

Safety profile of a novel live attenuated rotavirus vaccine – GACVS conclusions

- Based on the experience with similar vaccines,
  - it will be important that additional data be collected in order to assess the risk of intussusception as well as to identify any other rare adverse events that may occur.
  - the infrastructure of sentinel sites that exists in India should be utilized for continued intussusception surveillance in order to fully characterize the safety profile of this new rotavirus vaccine.

Safety profile of a recombinant hepatitis E vaccine

- It is manufactured by Xiamen Innovax Biotech, Xiamen China. It was approved by the Chinese Food and Drug Administration in 2011 and has been available since October 2012.

- The efficacy and safety of the vaccine was evaluated in the Jiangsu Province of China in a randomized, double-blind, controlled Phase 3 clinical trial in >112 000 healthy subjects 16–65 years of age irrespective of anti-HEV antibody status.

- Study participants were randomized 1:1 to receive either Hecolin (n = 56 302) or a licensed hepatitis B vaccine (n = 56 302) administered through intramuscular injection in 3 doses (0, 1 and 6 months). Participants were followed for 19 months.

Safety profile of a recombinant hepatitis E vaccine

- Overall, safety data derived from Phase 1, 2 and 3 clinical trials suggested that the vaccine was well tolerated.
- Short-term (72 hours) local and systemic solicited adverse event data obtained from the "reactogenicity subset" that participated in the Phase 3 clinical trial showed more frequent local adverse events in the Hecolin group compared to the active control group.
- The solicited systemic adverse events and unsolicited adverse events occurred at similar rates between study groups.

Safety profile of a recombinant hepatitis E vaccine

- The vaccine appeared to be well tolerated in pregnant women with rates of adverse events similar to those observed in matched non-pregnant women. However, the overall sample size was too small to allow a conclusive statement on the safety of Hecolin in pregnant women and their babies.
- The safety of Hecolin was also evaluated in HBsAg-positive persons and the data are reassuring; however, the analysis subset did not include persons with ongoing liver disease as this was an exclusion criterion for the trial.

GACVS Conclusions - Safety profile of a recombinant hepatitis E vaccine

- Available safety data on Hecolin derived from Phase 1, 2 and 3 clinical trials in healthy subjects are reassuring.
- Further studies need to be conducted in paediatric subjects, the elderly, persons with underlying diseases or conditions, when given concomitantly with other vaccines and those inadvertently vaccinated in pregnancy.
- Phase 4 post-marketing study be conducted once the vaccine is in more widespread use

Meningococcal A conjugate vaccine during pregnancy

- Meningococcal A conjugate vaccine (MenAfriVac, manufactured by the Serum Institute of India), is a lyophilized group A conjugate vaccine developed under the Meningitis Vaccine Project.

- The GACVS had been following the vaccine from its initial Phase 1 and 2/3 clinical trials through to licensure and the first mass immunization campaigns. At the last update, in June 2011, over 50 million doses had been administered.

- At each update, the GACVS continued to be reassured of its ongoing safety

Meningococcal A conjugate vaccine during pregnancy

- Inadvertent vaccination in pregnancy throughout the early phases had not revealed any concerns.
- GACVS supported WHO's technical guidance that MenAfriVac should be offered to pregnant and lactating women from the African meningitis belt during any stage of pregnancy or lactation.
- GACVS recommended to follow up women in antenatal or obstetric clinics, and to monitor pregnancy outcomes by making comparisons with unvaccinated pregnant women.

Meningococcal A conjugate vaccine during pregnancy

- The Navrongo Health Research Centre, Ghana, followed up a mass vaccination campaign that was held between 9 and 19 October 2012, targeting individuals between 1 and 29 years of age including pregnant women.

- During this campaign, some pregnant women elected not to receive the vaccine, providing an opportunity to evaluate the safety of the meningococcal A vaccine by comparing the rates of pregnancy- related outcomes in vaccine recipients, with rates among unvaccinated pregnant women.

- In addition, a matched historical control group was assembled to document pregnancy outcomes in a time period before the immunization campaign.

Meningococcal A conjugate vaccine during pregnancy

- A total of 1730 pregnant women were vaccinated during the campaign, while 919 pregnant women elected not to be vaccinated. A total of 3551 pregnant women were in the historical unvaccinated control group.

- There was no significant difference in any of the pre-specified outcomes between women who had received the meningococcal A conjugate vaccine and those who had not, either in the concurrent or historical comparison groups.

GACVS conclusions: Meningococcal A conjugate vaccine during pregnancy

- Overall, in the almost 4 years since MenAfriVac was rolled out no concerns have been identified regarding its use in pregnancy.
- As with other inactivated vaccines, neither pregnancy nor lactation are contraindications for vaccination in situations of increased disease risk.
- Given the emerging evidence of the effectiveness of this meningococcal A conjugate vaccine more permissive language in the package insert may be warranted.

Preparing for malaria vaccine introduction

- The development of recommendations for post-licensure safety assessment of malaria vaccines is an important preparatory step to provide early implementing sites
  - with sufficient time for planning, training and improving or developing surveillance systems.
  - establishment of active surveillance for events of special interest, thereby providing background rates
- Safety guidance would be developed alongside effectiveness and impact guidance in harmonisation for use by the public sector to assist them to conduct independent studies.

Preparing for malaria vaccine introduction

- To allow detection and evaluation of signals for rare unexpected events as well as assessment of events of interest from clinical trials,
  - the main components should cover on-going strengthening of routine systems for reporting adverse events following immunization (AEFIs), stimulated passive reporting in selected settings, such as health demographic surveillance system sites and
  - active follow-up for specific events of interest using suitable epidemiological designs.
  - consideration of feasibility (for example, use of case definitions adapted to local clinical practice).
  - following up vaccine recipients with innovative mechanisms such as diary cards, issuing of mobile telephones or identifying patients through hospital admissions.

Fifteen years of GACVS: challenges and opportunities

- After the first GACVS meeting on 14–15 September 1999, the committee has met twice yearly and convened by telephone conference more frequently when needed.
- The Committee's regular reports are published soon after each meeting in the WHO Weekly Epidemiological Record, while urgent reports are posted separately on-line. >100 reports related to vaccine safety issues have been produced.
- GACVS has also looked into capacity building aspects of global vaccine pharmacovigilance, provided advice on the development of the Global Vaccine Safety Blueprint and is now advising on the development of specific tools for vaccine safety monitoring, including the classification of AEFI, core data elements, and indicators for surveillance systems.

GACVS considerations: Looking forward

- The Committee's independence and high level of individual expertise maintain the credibility and impact of its advice.
- A transparency policy needs to be developed with a view to providing more specific information on how conclusions were reached.
- How can the communication of GACVS work products be improved?
- Although GACVS work is well established and recognized, it is critical to remain mindful of current vulnerabilities in the context of the evolving global vaccination landscape that requires a continuous adjustment of methods and processes.

Topics for December 2014

- Risk-management plans for:
  - Malaria vaccine.
  - Dengue vaccine.
- Safety of ZEBOV vector vaccines.
- Performance indicators for AEFI surveillance.
- Events of special interest for monitoring and evaluation of immunization in pregnancy
- Criteria for Vaccine Safety Net.