

Global Advisory Committee on Vaccine Safety (GACVS)

Report on GACVS meeting

June 2015

Vaccine Safety Net (VSN)

- Identify websites that provide useful, reliable information about vaccine safety and meet quality of content standards
- GACVS work group updated evaluation criteria
- 15000 visitors per year on WHO VSN homepage
- Currently 35 sites listed and 10 under evaluation
 - 10 languages
 - 16 countries
- Proposed upgrades
 - VSN logo
 - Create network of expertise
 - Survey of sites web metrics
 - Explore social networks and mobile device applications



Observed rates of adverse reactions

- WHO information on priority vaccines maintained since 2000
 - Vaccine-specific information sheets developed in 2012
 - Support WHO position papers
 - Describe known adverse reactions, with expected rates, and addresses major AEFI
- Methodological review
 - Enhance systematic approach to literature review and evaluate quality of evidence
 - Main challenge – Rare events and post-marketing assessment cannot be addressed by randomized clinical trials
 - Need for alternative tools for assessing the quality of observational studies
 - GACVS work group will propose specific safety questions that warrant systematic reviews (severe reactions and others of special interest)
 - Updated information sheets will be accompanied by summary tables, on the model of position papers

Two candidate Ebola virus vaccines (data as at June 2015)

● ChAd3 EBO-Z

- In clinical development since September 2014
- Phase 1 studies data available
- Dose-ranging 10E10 to 10E11 viral particles per dose
- Dose-related reactogenicity observed
 - Injection-site pain
 - Fever within first 24 hours, resolving rapidly
- Transient decrease in lymphocytes and platelet counts
- No serious adverse events documented

Two candidate Ebola virus vaccines (data as at June 2015)

● VSV-ZEBOV

- In clinical development since October 2014
- Phase 1a/b studies data available
- Dose-ranging 3×10^3 to 3×10^6 pfu per dose
- Non-specific dose-related reactogenicity
 - Injection-site pain
 - Systemic symptoms (fever, malaise, flu-like) within first 72 hours
- Viraemia (PCR) up to 2 weeks
- Vaccine virus in saliva and urine in a few subjects
- Arthralgia, arthritis, dermatitis, rash and cutaneous vasculitis at varying frequency during 2nd week (more frequent with higher age)
- Vaccine virus identified in joints and skin
- Joint reaction not dose dependent, lasted for 2-3 weeks, some persistent
- No serious adverse events documented

Two candidate Ebola virus vaccines VSV-ZEBOV update and GACVS conclusions

- Mid-August update with manufacturer in preparation for SAGE working group
 - New study with higher titers up to 10E8 pfu per dose still blinded but only mild reactions and few systemic reactions
 - Preliminary data among children aged 4 years and older with similar reactogenicity profile
 - Data from phase 2/3 still limited to serious AEFI, none classified as vaccine related
- GACVS conclusions
 - Safety profile of both vaccines so far reassuring
 - Insufficient or no data for several important sub-groups (pregnancy, lactation, chronic conditions, HIV infection, children)
 - Safety monitoring to continue for now under study conditions

Preparing for RTS,S introduction

- Two safety signals from Phase 3 trial discussed at December 2014 meeting
 - Meningitis
 - Febrile convulsions (resolved with no sequelae)
- Meningitis signal
 - Various aetiologies, no temporal clustering
 - More frequent in 5-17 months cohort
 - Will require further assessment post Phase 3
- Data on HIV positive children
 - N=200, age 6-17 weeks
 - No other safety signal identified

Preparing for RTS,S introduction

- Malaria vaccine work group to develop guidance for post-licensure safety surveillance
 - Adverse events of special interest require specific approaches tailored to local clinical settings
 - Theoretical concern for auto-immune disorders (AID) related to use of new adjuvant
 - No evidence or risk from experimental or human data
 - Numerous practical constraints for establishing AID surveillance (few cases diagnosed in sub-Saharan Africa and epidemiology largely undetermined)
- *GACVS advises not to recommend monitoring for AID with possible revision if new evidence becomes available (passive surveillance or use of the same adjuvant with other vaccines)*

RTS,S and cerebral malaria

- Post-hoc analysis conducted after GACVS
- Excess number of cerebral malaria cases among RTS,S recipients compared to controls ($p=0.03$) in children first vaccinated at 5-17 months of age
 - In first 20 months
 - In both vaccinated groups after booster
 - Higher CFR than other severe malaria cases
 - More cases in areas with high malaria transmission
- Very few cerebral malaria cases consistent with meningitis
- Cerebral malaria does not explain severe malaria rebound effect

→ *New signal identified that warrants further monitoring in post-licensure studies*

CYD-TDV dengue vaccine

- Previously reviewed by GACVS in December 2012 and December 2014
 - Long-term follow-up data presented (NEJM 2015;373:1195-206)
 - Higher risk of hospitalized dengue among vaccine recipients aged 2-5 years in Asian study (RR=7.45, 95%CI 1.15-313.80)
 - Protective effect among vaccine recipients aged ≥ 9 years in Asian study (RR=0.57, 95%CI 0.18-1.86) and Latin American study (RR=0.53, 95%CI 0.25-1.16)
- Revised indication for administration at 9-60 years of age

CYD-TDV dengue vaccine

● GACVS recommendation

- Importance of understanding potential factors associated with increased risk among young children from Asian study
- Assess if protective effect among older age groups is sustained over time
- Assess risk of dengue hospitalization over time among older subjects who were serologically naive at the time of vaccination
- Pursue follow-up of controlled trial in both regions
- Need for additional information on co-administration with other age-appropriate vaccines
- Assess vaccine safety among pregnant women and immune-compromised individuals
- Generate additional safety data among older age groups (Phase 3 trials were conducted among subjects up to 16 years of age)

Topics for December 2015

- Vaccine safety signals in UMC data base
- Mass psychogenic reactions following vaccination
- HPV vaccines and autonomic disorders
- Update on narcolepsy and pandemic influenza vaccines
- Safety of smallpox vaccines