

Global Advisory Committee on Vaccine Safety (GACVS)

**Report on the GACVS meeting
of
December 2015**



Topics Discussed

1. RTS,S malaria vaccine
2. Safety of smallpox vaccines
3. Safety of HPV vaccines
4. Influenza A (H1N1) 2009 pandemic vaccine /narcolepsy
5. Anxiety-related clusters of adverse events
6. Vaccine related signals from the Uppsala Monitoring Centre



RTS,S malaria vaccine

- GACVS updated on the RTS,S/AS01 vaccine following SAGE and MPAC (October 2015)
 - Key recommendation that pilot studies be implemented to address questions concerning efficacy and safety.
- GACVS had previously reviewed 3 safety issues
 - Generalized convulsions shortly after vaccination
 - Risk of meningitis of various etiologies.
 - Increased number of “cerebral malaria” cases in vaccinees
 - All-cause mortality in girls



GACVS: RTS,S malaria vaccine

- GACVS agreed that there were safety signals requiring further evaluation.
- GACVS recommended that committee members be involved in the safety aspects of the design of the pilot studies given these signals which require further assessment.
- In light of the protocols being developed, GACVS deferred further recommendations for safety guidance.

Safety of smallpox vaccines

- The Committee was provided with updated safety information for 1st, 2nd and 3rd generation vaccines
 - Preparation for informed decisions regarding emergency vaccine stockpiling and future use.
- Detailed safety information was provided for
 - the currently licensed replicating 2nd generation ACAM2000
 - non-replicating 3rd generation Imvanex/Imvamune vaccines.



GACVS: Safety of smallpox vaccines

- Overall, no new safety concerns observed with the ACAM2000 and Imvanex/Imvamune vaccines.
 - Both immunogenic and protective against lethal orthopoxvirus challenge in animal models.
- However there is little safety information in:
 - Pregnancy
 - Pediatric populations
 - By ethnicity
- GACVS noted that in the absence of circulating smallpox, these vaccines should not be used in pediatric populations.



Safety of HPV vaccines

- GACVS has followed HPV vaccine safety since 2007
 - Initial safety data post licensure, including planned studies
 - Issues arising: anaphylaxis, vaccination in pregnancy, reports of vaccine component-related events
 - **GACVS has found no safety issues altering recommendations**
- At this meeting, GACVS reviewed new reports concerning autoimmune conditions
 - A retrospective cohort study from the French ANSM on autoimmune conditions and HPV vaccine in >2million girls
 - Postural Orthostatic Tachycardia Syndrome (POTS)
 - Update on Japan's suspension of proactive recommendation
 - Arising from reports suggestive of Complex Regional Pain Syndrome (CRPS)



GACVS: Safety of HPV vaccines

- Symptoms of CRPS and POTS overlap with Chronic Fatigue Syndrome
 - A published study of CFS reported no association with HPV vaccines.
 - Other reviews of pre- and post-licensure: no evidence.
- French study: no signal with autoimmune disease except for GBS
 - Small risk (~1 per 100,000 vaccinated) not seen in other studies
- Review by Japan's national expert committee suggested the concerns unfounded
 - Still not possible to reach a consensus to resume HPV vaccination
- **GACVS remains concerned that policy decisions based on weak evidence continue to cause harm**
 - Continued pharmacovigilance will ensure that evidence is available
 - HPV vaccines remain a communications challenge, not a safety one

Influenza A (H1N1) 2009 pandemic vaccine and narcolepsy

- GACVS has continued to review the association between the 2009 H1N1 influenza vaccine and narcolepsy.
 - Pandemrix® displayed evidence of risk in adults that needed further research to confirm
 - Further research also needed to identify underlying pathophysiological mechanisms
- Overall, studies have produced consistent results for the risk following Pandemrix®
 - Risk following Arepanrix ® present but lower magnitude (Canada)
- GACVS reviewed more recent papers and heard evidence regarding putative mechanisms

GACVS: Influenza A (H1N1) 2009 pandemic vaccine and narcolepsy

- GACVS looked at potential biases such as
 - media attention
 - delays from onset to diagnosis in unvaccinated vs vaccinated
- GACVS also discussed autoimmune mechanisms, such as the close association with HLA type DQB1*0602.
 - Cross-reactivity of T-cells and antibodies to vaccine antigens and hypocretin receptors has been documented but is also found among healthy controls.
- GACVS therefore concluded that at this stage:
 - evidence of an association was clear.
 - evidence for a cross-reactive pathogenic mechanism remains limited

Clusters of anxiety-related reactions following immunization

- Reported in media, social media, and scientific literature
- Many countries across the globe
 - Rural; Urban; Low, middle, high income
- Mostly school-age, girls>boys, rapid onset with “spread”
 - New vaccine, new program, change in routine
- Response varies and impacts vaccination programme
 - Public confidence/coverage decreased, fear among providers,...
- Prevention (ideal) but rapid/careful responses are key

GACVS: Clusters of anxiety-related reactions following immunization

- Practice guidelines for anxiety reactions and event recognition
 - Standardized case definitions
 - Research on effective communication
- Training on AEFI management
 - Management guidelines
- GACVS sub-committee on AEFI-related Immunization Anxiety Reactions
 - Evidence-based prevention and intervention strategies
 - Review paper planned related to anxiety reactions, taxonomy

Vaccine safety signals from the Uppsala Monitoring Centre (UMC) database

- The UMC publishes “Signal” – targeted to the PV community.
 - Recent signals documented HPV (GI) and rabies vaccines (EM)
 - Database on vaccines is mainly US and European
 - Concern expressed by agencies and manufacturers
- GACVS was presented with an overview of UMC methods and tools, a statistical perspective on its signal detection, and methods used by the US/FDA and EMA.
- The UMC methods are sound, but only 8.5% of reports involve vaccines and there are limits to causality conclusions from these data.

GACVS: Vaccine safety signals from the Uppsala Monitoring Centre database

- Signals by the UMC's large international database are useful
 - Potential will only increase as data sources improve
- The preliminary nature of reports in the “Signal” publication have evoked concerns but can be mitigated with input
- The UMC has in the past had a focal point for vaccines, and was a member of GACVS
- GACVS recommended a strengthened process of collaboration with UMC to leverage additional expertise
 - From GACVS and partner agencies, and additional data analyses
 - FDA and EMA, who have access to more complete ICSR information
- GACVS Secretariat will liaise with UMC to identify opportunities for such collaboration.

Topics for June GACVS meeting

- New health products vigilance initiative (BMGF)
- Serious AEFI during pentavalent series in South India
- Harmonized definitions for safety monitoring during pregnancy
- Dengue vaccine safety (tentative)
- Multi-country collaboration proof-of-concept study