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
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)
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
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