HPV vaccines: past, present and future safety issues undertaken by the Global Advisory Committee on Vaccine Safety

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(…here as chair, GACVS)
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Global vaccine safety, monitoring and response system

Global capacity building and harmonized tools
- Brighton Collaboration
- CIOMS/WHO working group
- Training providers

Global analysis and response
- GACVS
- Other global or regional advisory bodies

National AEFI surveillance, investigation and response
- National regulatory authority
- National Immunization Programme
- AEFI review committee
- Other support groups

Global signal, evaluation and detection
- WHO PIDM
- Global vaccine safety data link
- Other partners

Product monitoring
- Vaccine manufacturers
- Licensing authorities in country of manufacture
- Procurement agencies
Global Advisory Committee on Vaccine Safety (GACVS)

- Established 1999
- 14-member committee with broad expertise in their personal capacity
  - Coordinated by WHO/EMP/SAV
- Independent, authoritative, scientific advice to WHO/IVB on vaccine safety issues of global or regional concern
  - promptly, efficiently, with scientific rigor
- Decisions and recommendations based on best available evidence

Reporting to: Strategic Advisory Group of Experts (SAGE) on Immunization

Nov 2006: GACVS will look at the vaccination of adolescents and the occurrence of coincidental conditions, such as autoimmune diseases, that could lead to allegations of associations with immunization when HPV or other adolescent vaccinations are introduced.

Apr 2007: IVB’s HPV Expert Advisory Group, in collaboration with WHO’s experts from relevant departments, should review evidence for a future WHO HPV vaccine position paper and identify outstanding questions about safety, efficacy and delivery, with a view to presenting this to SAGE for future consideration.
Safety of human papillomavirus vaccines

Committee reports
- 22 January 2016 - Safety of HPV vaccines (from meeting of 2-3 December 2015)
- 14 February 2014 - Human papillomavirus vaccines safety (HPV) (from GACVS meeting of 11-12 December 2013)
- 19 July 2013 - Update on human papillomavirus vaccines (from meeting of 12-13 June 2013)
- 7 August 2009 - Safety of human papillomavirus vaccines (from meeting of 17-18 June 2009)
- 30 January 2009 - Safety of human papillomavirus vaccines (from meeting of 17-18 December 2008)
- 20 July 2007 - Safety of human papillomavirus vaccine (from meeting of 12-13 June 2007)

Statements
- ▼ GACVS Statement on Safety of HPV vaccines - 17 December 2015
  - pdf, 112kb
- ▼ GACVS Statement on the continued safety of HPV vaccination - 12 March 2014
  - pdf, 173kb
- ▼ GACVS Safety update on HPV Vaccines, Geneva - 17 December 2013
  - pdf, 19kb
- ▼ GACVS Safety update on HPV Vaccines - 13 June 2013
  - pdf, 230kb

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GAVS meetings related to HPV


Pregnancy  Syncope  Mass P/S  Anaphylaxis  Autoimmune  Aluminum  POF  CRPS  MS  VTE  CDD  GBS  Vasculitis  POTS

Doses:  60M  175M  200M
Countries:  109  130
Timeline: Events, Issues, Allegations

- **Past (2007-2009) – from request by SAGE**
  - Early post market surveillance
  - Vaccination in pregnancy
  - Anaphylaxis, Syncope
  - Mass “psychogenic” or “sociogenic” events

- **Present (2013-2015) – new allegations and studies**
  - *Aluminum adjuvants (2012)*
  - Guillain Barre syndrome, multiple sclerosis, autoimmune disease
  - Primary ovarian failure
  - Japan cases of chronic pain, CRPS
  - HPV DNA
  - POTS
Early post market experience

- Meetings of June, 2007, Dec 2008 (additional data)
- Pre-licensure trials and PMS from both manufacturers and the EMA, FDA and CDC
  - Common events included injection site and muscle pain
- Long term up to 6 years, including pregnancy
- No concerns with safety profile

- GACVS advice: surveillance for rare events, background rates, enhance capacity in LMIC, establish registries
Anaphylaxis / Syncope

- New studies discussed in Dec 2008
- Brotherton et al. NSW Australia* – 7 cases of anaphylaxis after 269,000 doses.
  - Higher than expected (2.6 vs 0.4/100K), but no sequelae
- Syncope risk identified in PMS – recommendations to adhere to waiting period (15min) strengthened
- Risk of anaphylaxis not confirmed

Vaccination in pregnancy

- Early data presented in 2007
- Manufacturers developed pregnancy registries
  - Presented Jun 2009 and June 2013
  - Early monitoring as well as more recent similarly found no differences between vaccinees and controls or background rates of events

- GACVS comment (2009):
  - Data on the inadvertent administration shortly before pregnancy or during pregnancy are reassuring but insufficient to rule out a small effect, in particular if conception occurs shortly after vaccination. More data encouraged
Sociogenic/psychogenic illness and mass vaccination

- Report from Australia of an event in 2007*
  - 26/720 girls 12-17 reported symptoms of dizziness, syncope and neurological complaints
  - Nothing organic found on examination and investigation
- Such events are reported during mass vaccination clinics
  - Not unique to vaccination
  - Appropriate investigation, management and communication is key
- “Minimising the risk of this phenomenon should routinely be considered when planning mass vaccination campaigns.”*

Other post market surveillance

- VAERS data presented in Jun 2013
  - Slade et. al 2009 (~23M doses, published after 2009 Jun mtg)
  - Updated information from VAERS (now ~56M doses)
    - Included data on syncope and VTE

- VSD rapid cycle analysis
  - No increased risk of pre-specified Guillain-Barré syndrome, seizures, stroke, VTE, anaphylaxis/other allergic reactions...

- Australia data:
  - New program in males – reports reassuring
  - Early reports of chronic conditions investigated by an expert group: no concerns
CRPS and chronic pain

- Cases thought CRPS reported from Japan (8M+ doses distributed)
  - Few in other countries
- Patient groups: patients and parents reporting persistent pain
  - Review by an expert committee could not ascertain causality due to lack of information and no definitive diagnosis
- Only “Proactive Recommendation” suspended, not availability
- Little reason to suspect vaccine – but GACVS urged documentation of cases to guide proper diagnosis and treatment
  - None of the evidence presented altered recommendations GACVS has made
- Despite various committees finding no association of symptoms with vaccination, Japan has been unable to restart their program
Aluminum adjuvants

- Papers appeared in the fall of 2011 questioning the safety of Al adjuvants and suggesting a relationship with autism
  - GACVS reviewed the papers and an FDA risk assessment of Al
  - Serious weaknesses were identified in the studies
  - Nevertheless, the authors extended their work to HPV vaccines
- (Extended shortly after to HPV vaccine “publications”)

- The FDA risk assessment found no increase in cumulative absorbed doses of aluminum in infants on routine schedule
  - GACVS: Pharmacokinetic and immuno-toxicology on-going and should be encouraged to further validate and improve this model
GBS, MS, Autoimmune disease

- Early report of central demyelinating disease
  - Paper emerged prior to Dec 2008 meeting: Sutton et al. CNS demyelination and quadrivalent vaccine. Multiple Sclerosis, 19 September 2008 (epub)

- Studies since had not found any associations between HPV vaccines and MS or GBS, or autoimmune disease
  - Included register-based study in Sweden and Finland (300,000 vaccinated)
  - US VSD rapid cycle (mentioned earlier)

- French authorities compensated a case of MS in a 15yr old girl despite ANSM determining relationship doubtful

- ANSM undertook a retrospective cohort study of 14 conditions
  - an association only with GBS (within 3mo): 1 per 100,000 vaccinated children.
  - No association with MS or overall autoimmune disease
HPV DNA fragments and VLPs

- Parent group sounded “alarm” about HPV DNA in the vaccine

- HPV 16 L1 VLPs
  - Binding to cerebral vasculature with resultant “vasculitis”

- HPV 16 L1 DNA fragments bound to aluminum
  - Release of TNF and immune mediated cytokine reaction

- The presence of HPV DNA is not unexpected
  - The quantities insufficient to cause any of the postulated effects

- Autopsy results have not shown abnormalities, and no inflammation
POTS

- Postural orthostatic tachycardia syndrome
  - Unclear/heterogeneous etiology and not well characterized
  - Onset difficult to define

- Overlaps with chronic fatigue syndrome, which has not been found associated with vaccination

- Issue raised in certain geographic locations

- Pre- and post-licensure data find no evidence of association

- Reviewed extensively by the EMA

- Further studies ongoing
Primary ovarian failure

- POF is mostly idiopathic, and incidence is as high as 1/10,000 age 15-29y and 1/1,000 to age 40
- Evidence presented is solely in case reports
  - Wide variation in time to onset
- Publication “bias”, Ideology rather than evidence *
- Subject of a statement by “ACP”
  - Among allegations noted by GACVS

GACVS sub-group: Immunization Anxiety-Related Reactions

A not insignificant proportion of the public fear needles...

- Guidelines document
  - Key definitions, risk factors, consequences, interventions, proposed research
  - Case/country examples
- Review ongoing (CDC)
  - Epidemiological and social media aspects of mass psychogenic illness
Summary/Discussion

- GACVS summary
  - Profile has remained reassuring throughout the reviews
  - GBS, VTE, seizures, stroke, anaphylaxis and vaccination in pregnancy have not been issues
  - Policy decisions based on weak evidence result in real harm when safe and effective vaccines are not used
  - Continued pharmacovigilance will be important to ensure that concerns related to HPV vaccines can be addressed with the best possible evidence

- Work in progress examining anxiety-related events following immunization
15 year contributions paper: some conclusions

- Need for independent review of (often limited) evidence and provide recommendations...
  - Challenge of transparency yet confidentiality of information presented
- Need and recognized value in support
- Relevance for effective communication exemplified by safety concerns resolved at the scientific and policy levels
  - Yet continue to surface as public concerns