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

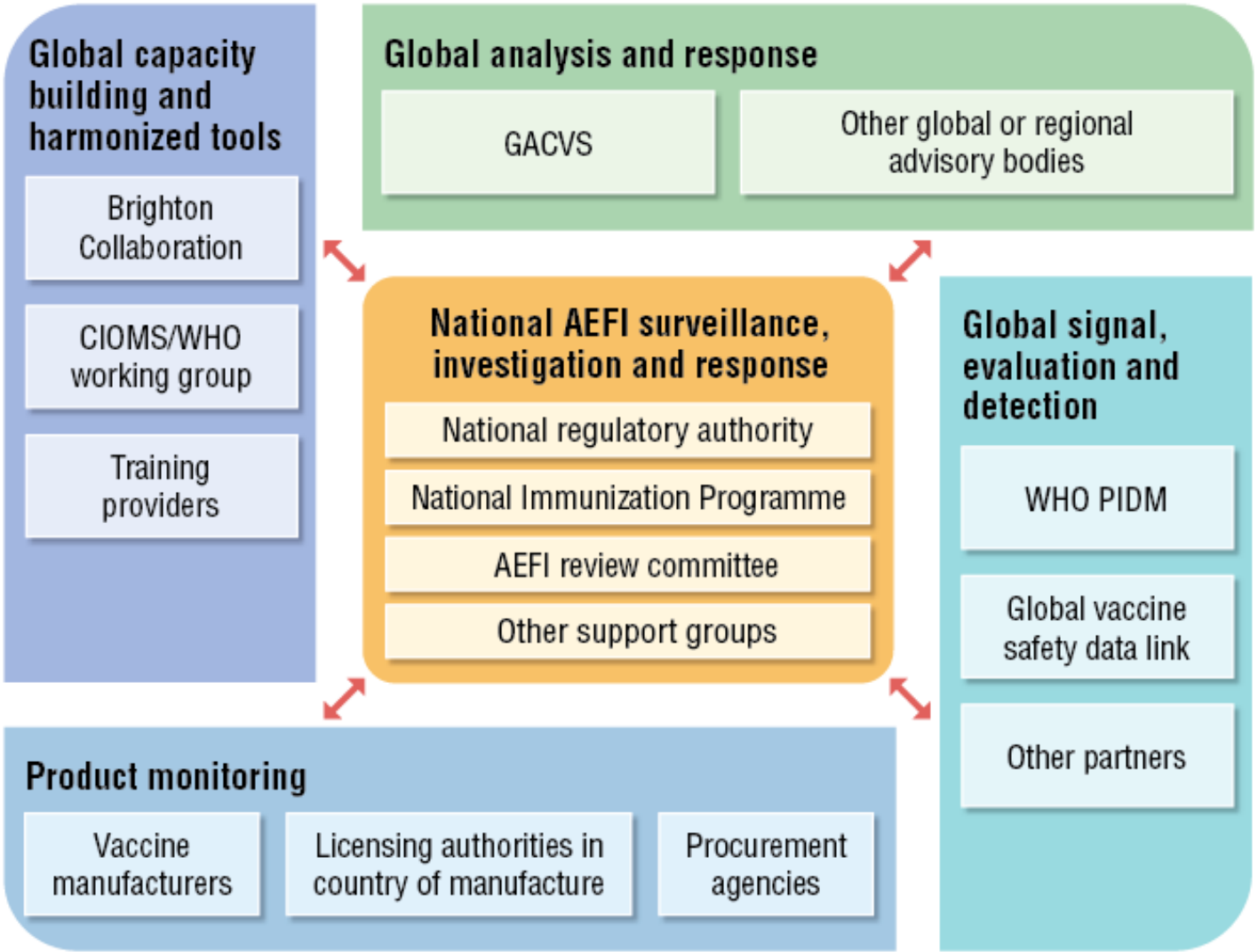
Robert Pless MD MSc

(…here as chair, GACVS)

HPV Prevention and Control Board, Antwerp, Jun 27, 2016

World Health Organization

Global vaccine safety, monitoring and response system



World Health Organization

Global Advisory Committee on Vaccine Safety (GACVS)

http://www.who.int/vaccine_safety/committee/en/

- 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.

World Health Organization

Topics

Here is a list of topics covered in our committee meetings.

- AEFI
- Adjuvants
- BCG vaccines
- Bell's Palsy following intranasal vaccination
- Dengue vaccines
- Diphtheria, tetanus and pertussis vaccines
- Ebola virus vaccines
- GACVS' Anniversary
- Global Vaccine Safety Blueprint
- Hepatitis A
- Hepatitis B vaccines
- Hepatitis E vaccines
- Hexavalent vaccines
- Human papillomavirus vaccines
- Immune overload
- Influenza vaccines
- Japanese encephalitis vaccines
- Malaria vaccines
- Measles vaccines
- Menactra meningococcal vaccine and Guillain-Barré Syndrome
- Meningococcal A conjugate vaccine
- MMR vaccines and autism
- Monitoring vaccine safety
- Mumps vaccines
- Pentavalent vaccine
- Pharmacovigilance
- Pneumococcal vaccines
- Poliovirus vaccines
- Pregnancy and lactation
- Residual cellular DNA in vaccines
- Rotavirus vaccines
- Smallpox vaccines
- Thiomersal and vaccines
- Transmissible spongiform encephalopathies
- Varicella Zoster virus
- Vaccinating adolescents and young adults
- Vaccine formulations
- Vaccines produced on yeast
- Vaccine Safety Information
- Yellow fever vaccines

Safety of human papillomavirus vaccines

Committee reports

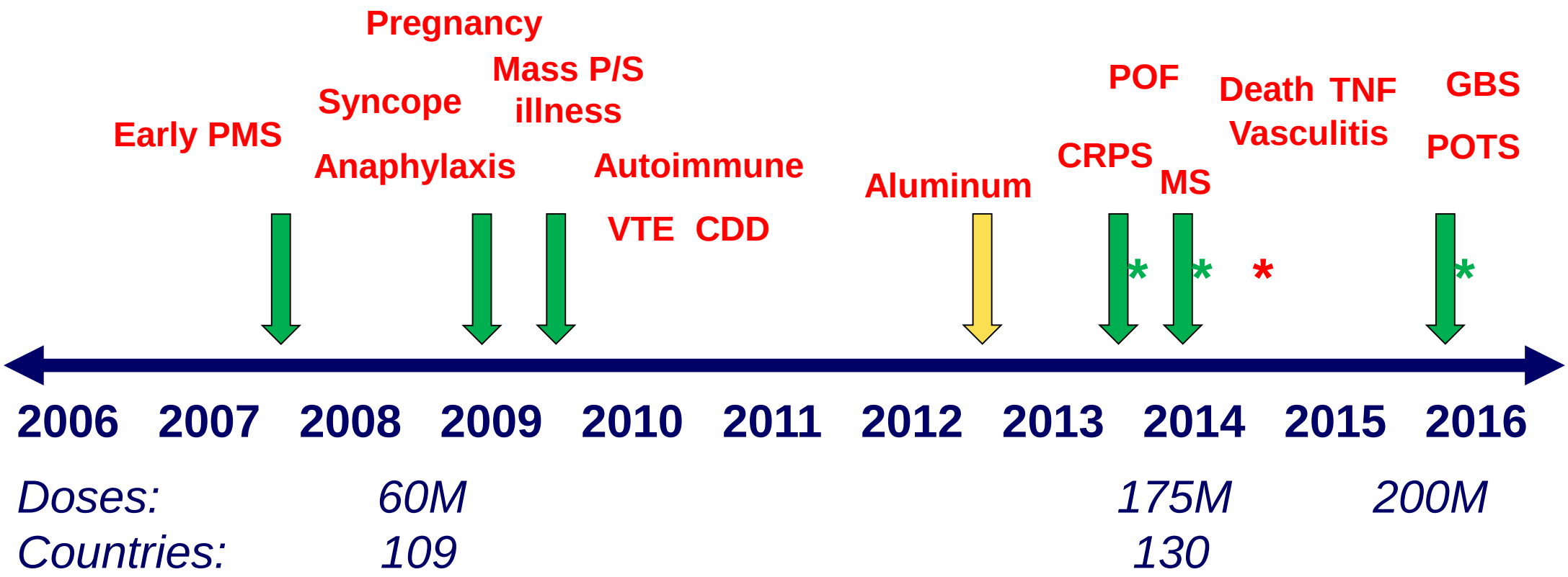
- 22 January 2016 - Safety of HPV vaccines (from meeting of 2-3 December 2015)
- 14 February 2014 - Human papillomavirus vaccines safety (HPV) (from GACVS meeting of 11-12 December 2013)
- 19 July 2013 - Update on human papillomavirus vaccines (from meeting of 12-13 June 2013)
- 7 August 2009 - Safety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

Page last updated: 22 January 2016

GAVS meetings related to HPV



World Health Organization

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

Brotherton J, et al. Anaphylaxis following quadrivalent human papillomavirus vaccination. CMAJ 2008: 179.

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.”*

* Buttery JP, Madin S, Crawford NW, Elia S, La Vincente S, Hanieh S, Smith L,Bolam B. Mass psychogenic response to human papillomavirus vaccination. Med JAust. 2008 Sep 1;189(5):261-2.

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”)

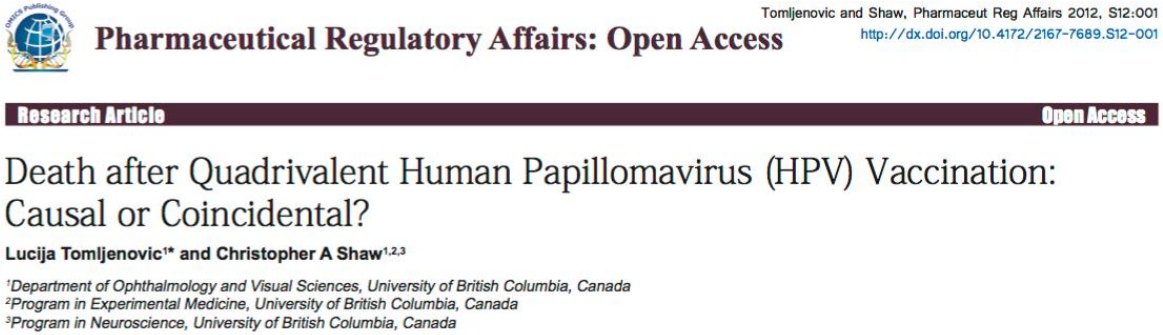
- The FDA risk assessment found no increase in cumulative absorbed doses of aluminum in infants on routine schedule
  - GACVS: Pharmacokinetic and immuno-toxicology on-going and should be encouraged to further validate and improve this model

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



Tomljenovic and Shaw, Pharmaceut Reg Affairs 2012, S12:001
http://dx.doi.org/10.4172/2167-7689.S12-001

Pharmaceutical Regulatory Affairs: Open Access

Research Article Open Access

Death after Quadrivalent Human Papillomavirus (HPV) Vaccination: Causal or Coincidental?

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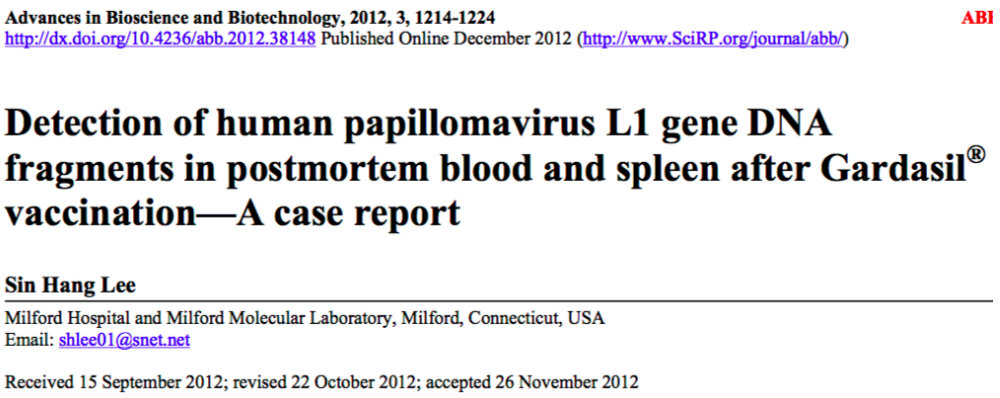

Advances in Bioscience and Biotechnology, 2012, 3, 1214-1224
http://dx.doi.org/10.4236/abb.2012.38148 Published Online December 2012 (http://www.SciRP.org/journal/abb/)

ABI

Detection of human papillomavirus L1 gene DNA fragments in postmortem blood and spleen after Gardasil® vaccination—A case report

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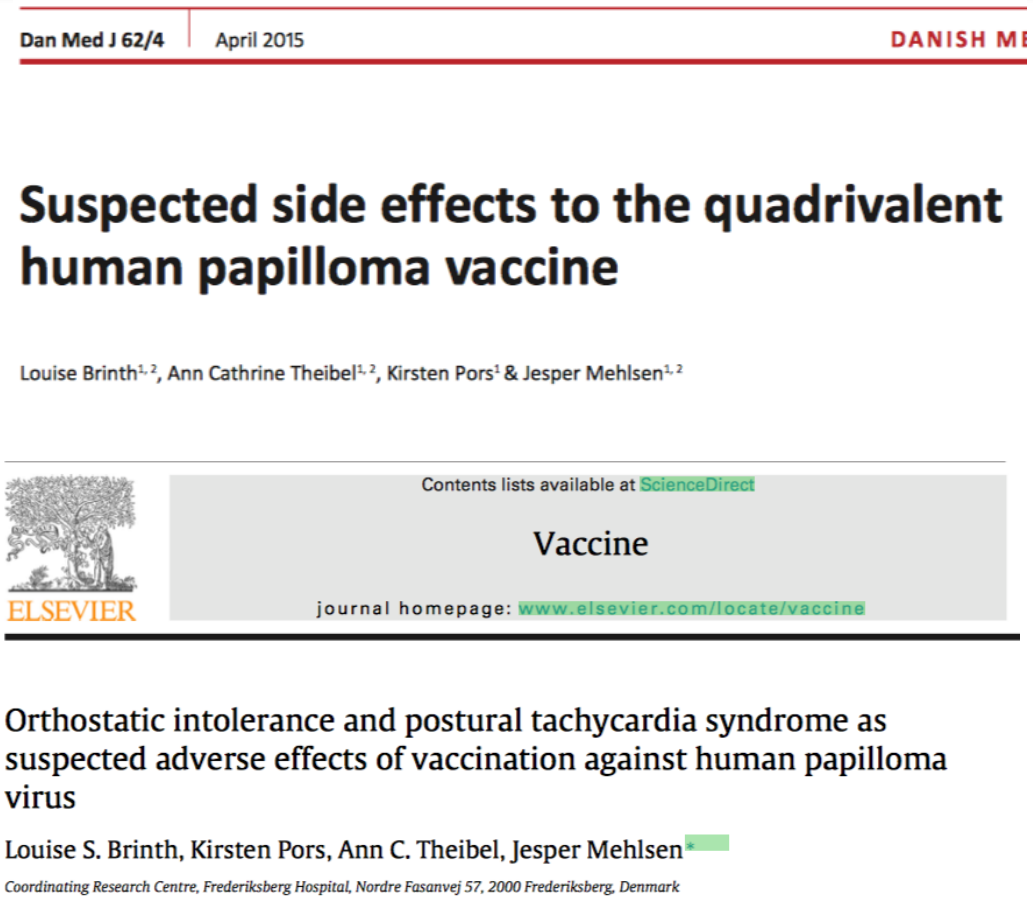
Received 15 September 2012; revised 22 October 2012; accepted 26 November 2012

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



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Suspected side effects to the quadrivalent human papilloma vaccine

Louise Brinth[1,2], Ann Cathrine Theibel[1,2], Kirsten Pors[1] & Jesper Mehlsen[1,2]

ELSEVIER

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus

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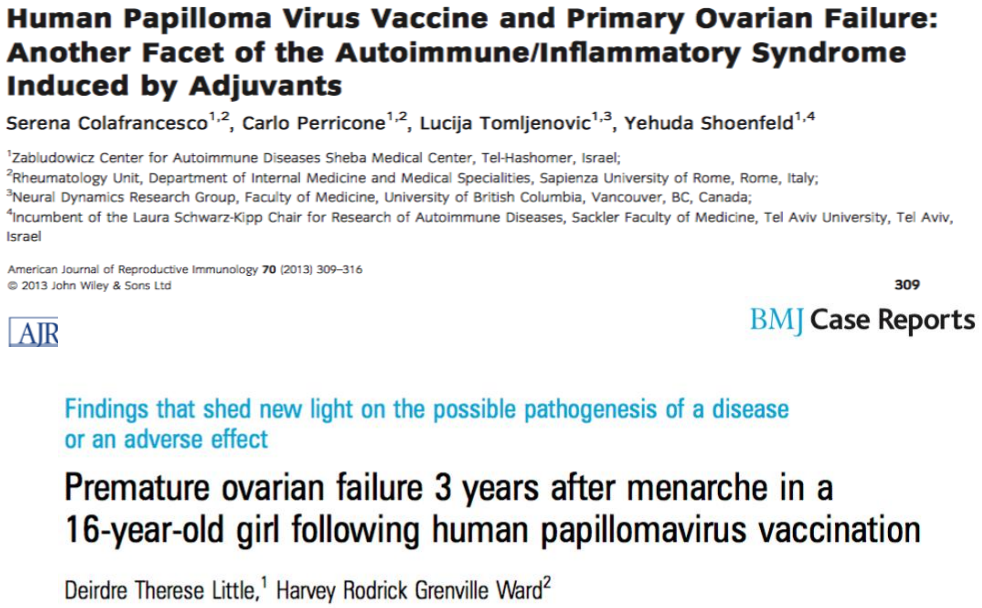
Primary ovarian failure

- POF is mostly idiopathic, and incidence is as high as 1/10,000 age15-29y 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



Human Papilloma Virus Vaccine and Primary Ovarian Failure: Another Facet of the Autoimmune/Inflammatory Syndrome Induced by Adjuvants

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AJR

BMJ Case Reports

Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Premature ovarian failure 3 years after menarche in a 16-year-old girl following human papillomavirus vaccination

Deirdre Therese Little,[1] Harvey Rodrick Grenville Ward[2]

* Hawkes D, Buttery JP. Human papillomavirus vaccination and primary ovarianinsufficiency: an association based on ideology rather than evidence. Curr OpinObstet Gynecol. 2016 Feb;28(1):70-2

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

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Contributions and challenges for worldwide vaccine safety: The Global Advisory Committee on Vaccine Safety at 15 years☆

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ABSTRACT

In 1999, the Global Advisory Committee on Vaccine Safety (GACVS) was established by Organization (WHO) to provide independent scientific advice on issues relating to the and immunization. Fifteen years onward, we conducted a multi-faceted review to ev reach and challenges facing GACVS, including the role GACVS plays in informing global, member state vaccine policy. The methods included measures of organizational structu themes approached, and a discussion by previous and current members to evaluate future challenges. Given the increasing range of data sources and the deployment of n the Committee is facing the complex task of identifying the best available evidence for on vaccine safety. To help meet the increased demand for public transparency in decisi structured methodology for evidence-based decisions is evolving. GACVS also prom and capacity building for timely and accurate risk assessment; risk communications countries maintain and, if needed, rebuild public trust in vaccines; and advocacy for gaps in vaccine safety capacity globally.

Vaccine. 2016 Jun 17;34(29):3342-9.

- 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