Vaccine Safety – HPV

Helen Petousis-Harris, PhD
National Immunisation Workshop
Sept 2017
• How vaccine safety is monitored
  – Clinical
  – Post licensure
• The example of HPV
Clinical development is a step-wise process

- **Phase I**
  - Safety and immunogenicity
  - 10’s

- **Phase II**
  - Safety, immunogenicity, dose ranging
  - 10’s – 100’s

- **Phase III**
  - Safety, efficacy, immunogenicity
  - 1000’s – 10,000s

**Biological licence application**
- Inspection of facilities
- Lot release
- ...
Pre-licensure studies for new vaccines

Novel vaccine

Randomised Controlled Trial (RCT)
(placebo saline and/or adjuvant only)
e.g. HPV or Rotavirus

New formulation or design

- Compare with existing vaccine
- Always RCT
- Big enough to exclude relatively rare adverse events
- Big enough to show protection against endpoints
- E.g. pertussis, flu, pneumo
- Exceptions
Adverse Events and Adverse Reactions - there is a **REALLY** big difference between these two

**Adverse Event Following Immunisation (AEFI)**
Any untoward event which follows immunisation, not necessarily caused by the immunisation

**Vaccine Reaction**
An event caused by the administration of a vaccine
What causes AEFI?

<table>
<thead>
<tr>
<th>Cause-specific type of AEFI</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine product-related reaction</td>
<td>An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.</td>
</tr>
<tr>
<td>Vaccine quality defect-related reaction</td>
<td>An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.</td>
</tr>
<tr>
<td>Immunization error-related reaction (formerly “programme error”)</td>
<td>An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.</td>
</tr>
<tr>
<td>Immunization anxiety-related reaction</td>
<td>An AEFI arising from anxiety about the immunization.</td>
</tr>
<tr>
<td>Coincidental event</td>
<td>An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists, and anxiety.</td>
</tr>
</tbody>
</table>

Note: “Immunization” as used in these definitions means the use of a vaccine for the purpose of immunizing individuals. “Use” includes all processes that occur after a vaccine product has left the manufacturing/packaging site – i.e. handling, prescribing and administration of the vaccine.
Adverse Reaction

Vaccine product-related reaction

DEFINITION: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.

Example: Extensive limb swelling following DTaP vaccination
Adverse Reaction

Vaccine quality defect-related reaction

DEFINITION: An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.

Example: *Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine.*
Adverse Reaction

Immunisation error-related reaction

DEFINITION: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.

Example: Brachial neuritis after poor injection technique and wrong site of injection
Adverse Reaction

Immunisation anxiety-related reaction

DEFINITION: An AEFI arising from anxiety about the immunisation.

Example: Vasovagal syncope - fainting
Adverse Event

DEFINITION: An AEFI that is caused by something other than the vaccine product, immunization error or immunisation anxiety

Example: A fever occurs at the time of the vaccination (temporal association) but is in fact caused by the flu
Vaccine safety – background rate

- **Observed rate**
  - Total number of cases reported per 1000 vaccinated children
  - Detected in clinical trials or post licensure studies

- **Background rate**
  - Occur per 1000 unvaccinated children
  - Recorded prior or simultaneously to vaccination

- **Vaccine reaction rate**
  - (related to vaccine)
  - \( \text{Vaccine reaction rate} = \text{Observed rate} - \text{Background rate} \)

Example – Fever following vaccination

- Knowing the background rate is essential!!

<table>
<thead>
<tr>
<th>Table II—Fever after MMR vaccination or placebo injection in 581 twin pairs: Mean no of children affected per day and mean rate per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after injection</td>
</tr>
<tr>
<td>1-6</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>---</td>
</tr>
</tbody>
</table>
| **Mild fever** 
(≤38.5°C rectal): |
| MMR | 190 | 163 | 196 | 168 | 222 | 191 | 206 | 177 | 180 | 155 |
| Placebo | 187 | 162 | 194 | 166 | 196 | 169 | 193 | 166 | 181 | 156 |
| Difference | 3 | 1 | 2 | 2 | 26 | 22 | 13 | 11 | -1 | -1 |
| **Moderate fever** 
(38.6-39.5°C rectal): |
| MMR | 9 | 8 | 34 | 29 | 42 | 36 | 21 | 18 | 7 | 6 |
| Placebo | 9 | 7 | 13 | 11 | 10 | 9 | 10 | 9 | 9 | 8 |
| Difference | 0 | 1 | 21 | 18 | 32 | 27 | 11 | 9 | -2 | -2 |
| **High fever** 
(>39.5°C rectal): |
| MMR | 1 | 1 | 7 | 6 | 15 | 13 | 5 | 4 | 2 | 1 |
| Placebo | 1 | 1 | 3 | 3 | 1 | 1 | 1 | 0 | 1 | 1 |
| Difference | 0 | 0 | 4 | 3 | 14 | 12 | 4 | 4 | 1 | 0 |
### TABLE I—SYMPTOMS AND SIGNS CAUSED BY MMR VACCINATION AND DAY OF PEAK OCCURRENCE

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Maximum difference in rate* (%)</th>
<th>CI95%</th>
<th>Peak frequency (days after vaccination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local erythema (&gt;2 cm)</td>
<td>0.8</td>
<td>0.1–1.4</td>
<td>2</td>
</tr>
<tr>
<td>Other local reaction</td>
<td>0.4</td>
<td>0–1.4</td>
<td>2</td>
</tr>
<tr>
<td>Mild fever (≤38.5°C rectal)</td>
<td>2.7</td>
<td>0–6.1</td>
<td>10</td>
</tr>
<tr>
<td>Moderate fever (38.6–39.5°C)</td>
<td>2.9</td>
<td>1.6–4.3</td>
<td>9</td>
</tr>
<tr>
<td>High fever (≥39.5°C)</td>
<td>1.4</td>
<td>0.7–2.1</td>
<td>10</td>
</tr>
<tr>
<td>Irritability</td>
<td>4.1</td>
<td>2.1–6.1</td>
<td>10</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2.5</td>
<td>1.4–3.6</td>
<td>11</td>
</tr>
<tr>
<td>Willingness to stay in bed</td>
<td>1.4</td>
<td>0.5–2.3</td>
<td>11</td>
</tr>
<tr>
<td>Generalised rash</td>
<td>1.6</td>
<td>0–3.0</td>
<td>11</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2.1</td>
<td>0.9–3.2</td>
<td>10</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>0.8</td>
<td>0.2–1.3</td>
<td>7–9</td>
</tr>
<tr>
<td>Peripheral tremor</td>
<td>0.4</td>
<td>0–0.9</td>
<td>9</td>
</tr>
<tr>
<td>Cough and/or coryza</td>
<td>-1.5†</td>
<td>-4.6–1.6</td>
<td>9</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>-0.8†</td>
<td>-1.6–0</td>
<td>7–8</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.7</td>
<td>0–1.7</td>
<td>11</td>
</tr>
</tbody>
</table>

*Between MMR group and placebo group.
†More in placebo-injected children.
Vaccine safety – modern approaches

- Post-licensure clinical trials and Phase IV surveillance studies
- Large linked databases
- Passive safety surveillance
- Clinical centres

Pre-licensure clinical trials
Pharmacovigilance
The WHO Programme for International Drug Monitoring – est 1968

- Thalidomide 1957
- 10,000 cases of phocomelia worldwide including NZ

Phocomelia – where hands and feel attached close to trunk, limbs under developed or absent
Note – the FDA never approved thalidomide

- Canadian pharmacologist and physician
- Kelsey refused to approve thalidomide because of inadequate evidence for safety
- Despite constant pressure from the company
- The ‘near miss’ resulted in revision of regulations 1962
  - “substantial evidence’ of safety required

Frances Oldham Kelsey, Ph.D., M.D.
1914 - 2015
THE PIDM mothership is in Uppsala Sweden
There are 125 national pharmacovigilance centres collecting spontaneous reports.
Vaccine safety is monitored at many levels - Global

WHO and SAGE

• 14 multidisciplinary members
• Nominated by Director of WHO Department of Essential Medicines and Health Products
• Determine causal relationships
• Ad hoc task forces inlc. urgent matters
• Provide recommendations to assist WHO, governments and international organisations

Also:
FDA
CDC
EMA
MedSafe
Etc...

NIPs

Provide advice

WHO Global Advisory Committee on Vaccine Safety

Basic sciences

Epidemiology

Collaboration with experts
Passive surveillance generates hypotheses

Vaccine safety

Post-licensure clinical trials and Phase IV surveillance studies

Large linked databases

Clinical centres

Passive safety surveillance

Pre-licensure clinical trials
Global examples of passive surveillance systems - VAERS

• United States

• Vaccine Adverse Event Reporting System (VAERS) est. 1990
  – Sponsored by CDC and FDA
  – Disseminated to the public
  – HPs required to report
  – Claim to fame – Rotashield and intussusception 1999
  – ~30,000 reports annually
Global examples of passive surveillance systems - VAESCO

• Europe

• Pharmacovigilance in European Economic Area (EURDAVIGILANCE), est 2001
  – Sponsored by European Medicines Association and National Competent Authorities
  – Mandatory reporting
  – Disseminated to the public
  – Claim to fame - narcolepsy
Global examples of passive surveillance systems - TGA

• Australia
• Office of Product Review of the Therapeutic Goods Administration (TGA)
  – Voluntary reporting of AEFI by HPs and consumers
  – Mandatory reporting from sponsors
  – Coordinated approach from states and territories
    • ACT, NSW, NT, QLD, SA, VIC and WA
    • SAFEVIC and SA have enhanced systems
  – Routine reporting via NCIRS and ATAGI
  – Published in Communicable Diseases Intelligence
  – Claim to fame – febrile convulsions
New Zealand’s passive reporting system - CARM

• Centre for Adverse Reaction Monitoring (CARM)
  – Based in Dunedin, UoO
  – Reports provided to MARC/Medsafe
• Very small population
• Claim to fame – highest reporting rate in the world
Hypothesis testing
Summary - cornerstones of vaccine pharmacovigilence

Signal detection
- Passive surveillance
- Anecdote

Development of causality hypothesis
- Develop a question about a possible causal association

Testing of causality hypothesis
- Test the hypothesis using appropriate epidemiological method

E.g. Microcephaly in Brazil and maternal Tdap

E.g. VSD
The example of 4HPV

Examining pre-licensure vaccine safety and efficacy
Reported HPV coverage rates
Selected years in two time periods

Source: Brotherton et al. 2016
What people say, what people think. Facebook public page
There are four key approaches to establishing vaccine safety:

- **Pre-licensure clinical trials**
  - 00,000s

- **Post-licensure clinical trials**
  - 000s – 00,000s

- **Post-licensure surveillance**
  - Passive: 000,000,000s
  - Active: 000,000s – m’s

Generally by comparing vaccinated with unvaccinated
Scientific evidence on the safety of quadrivalent HPV vaccine

From pivotal trials and post-licensure surveillance 2002 - 2015
There are four key approaches to establishing vaccine safety:

1. **Pre-licensure clinical trials**
   - 00,000s

2. **Post-licensure clinical trials**
   - 000s – 00,000s

3. **Post-licensure surveillance passive**
   - 000,000,000s

4. **Post-licensure surveillance active**
   - 000,000s – m’s

Generally by comparing vaccinated with unvaccinated.
First came the HPV4 pivotal trials to 2006

• Safety evaluated in placebo-controlled double blind trials in 22 countries
  – Placebo aluminium adjuvant OR saline
  – 11,778 vaccinated/9686 unvaccinated

• Local & systemic events
  – Detailed diary card 14 days
  – Long term follow up >800 days

• Safety during pregnancy
**Systemic events** among females aged 9-23 years 1-15 days after any vaccination with GARDASIL® vaccine

<table>
<thead>
<tr>
<th>Adverse Event (1-15 days PV)</th>
<th>GARDASIL® (n=5088)</th>
<th>Placebo (n=3790)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia*</td>
<td>13.0%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.7%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6.4%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3.6%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.4%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Cough</td>
<td>2.0%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Toothache</td>
<td>1.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>URTI</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Malaise</td>
<td>1.4%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>1.1%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

* 4.0% to 4.4% receiving vaccine reported fever over 38ºC after any dose. Slightly more than placebo (3.1% to 3.8%)

Food and Drug Administration, Clinical Review of Biologics License Application for Human Papillomavirus 6, 11, 16, 18 L1 Virus Like Particle Vaccine (S. cerevisiae) (STN 125126 GARDASIL), manufactured by Merck, Inc, D.o.V.a.R.P.A. Vaccines Clinical Trial Branch, Office of Vaccines Research and Review, Centre for Biologics Evaluation and Research, Editor. 2006, Food and Drug Administration.
The proportion of systemic events comparable in each group

<table>
<thead>
<tr>
<th>Event</th>
<th>Gardasil (n=1165)</th>
<th>Saline placebo (n=594)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any systemic event</td>
<td>541 (46.4%)</td>
<td>260 (44.5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>221 (19.0%)</td>
<td>110 (18.8%)</td>
</tr>
<tr>
<td>Fever</td>
<td>100 (8.6%)</td>
<td>45 (7.7%)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>52 (4.5%)</td>
<td>24 (4.1%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>43 (3.7%)</td>
<td>21 (3.6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>38 (3.3%)</td>
<td>22 (3.8%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>38 (3.3%)</td>
<td>17 (2.9%)</td>
</tr>
<tr>
<td>Nasopharyngitis (a cold)</td>
<td>34 (2.9%)</td>
<td>22 (3.8%)</td>
</tr>
<tr>
<td>Myalgia (muscle pain)</td>
<td>30 (2.6%)</td>
<td>10 (1.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 (2.2%)</td>
<td>18 (3.1%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25 (2.1%)</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Arthralgia (joint pain)</td>
<td>21 (1.8%)</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>19 (1.6%)</td>
<td>14 (2.4%)</td>
</tr>
</tbody>
</table>
Serious adverse events – all safety studies

- Vaccine related serious events occurred in <0.1% (1/1000) of persons.
- Proportion similar in vaccine and placebo groups
- 7 persons had events possibly, probably or definitely related to vaccine or placebo
  - 5 among the GARDASIL® recipients (bronchospasm, gastroenteritis, headache, vaginal haemorrhage, severe site reaction)
  - 2 among the placebo group
- Death
  - 10/11778 (0.08%) GARDASIL® group (none vaccine-related)
  - 7/9686 (0.07%) Placebo group
  - Non prescription drug overdose, MVA, suicide, DVT, sepsis, cancer, arrhythmia, asphyxia
Previous 7 GACVS reviews found no signals of concern

- **2007**: Pre and post data; 2007 no issues of concern identified, 2008 report of anaphylaxis from Australia, 2009 syncope added to label of one product; data on inadvertent use in pregnant women limited but no issues identified.

- **2008**:

- **2009**: 2013 Cases of chronic pain reported from Japan; no similar signal from other countries. 2013 Cases of multiple sclerosis reported from France, but no increase in risk seen in multiple studies

- **2013**: 2014 No evidence of harm from aluminium or DNA fragments in vaccines
GACVS activities and conclusions from December 2015

Review of data on association between HPV and autoimmune diseases

No overall association, weak signal for GBS (H1N1?)
Additional epidemiological studies found no signal

Proposed safety signals from VigiBase

Committee proposed a closer role for GACVS in VigiBase signalling

POTS and CRPS discussed

Available evidence, including EMA review found no indication for an association. The committee also acknowledged that the perceived associations continue to disrupt vaccine programmes.

Denmark planning additional study
However........
<table>
<thead>
<tr>
<th>Condition</th>
<th>GARDASIL® n=11778</th>
<th>Days post last dose</th>
<th>Placebo n=9680</th>
<th>Days post last dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>4</td>
<td>373, 8, 90, 800</td>
<td>3</td>
<td>2, 342, 798</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>1</td>
<td>19</td>
<td>1</td>
<td>202</td>
</tr>
<tr>
<td>Sepsis, DIC</td>
<td>1</td>
<td>359</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia, sepsis</td>
<td>1</td>
<td>625</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>1</td>
<td>578</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arythmia</td>
<td>1</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convulsion, drug use</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicide</td>
<td></td>
<td>2</td>
<td>200, 517</td>
<td></td>
</tr>
<tr>
<td>Asphyxiation</td>
<td></td>
<td>1</td>
<td>256</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL (%)</strong></td>
<td><strong>10 (0.08%)</strong></td>
<td></td>
<td><strong>7 (0.07%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** no causal link has been shown between GARDASIL® vaccination and any cause of death
Since licensure in 2006 >270 million doses HPV vaccine distributed

  - Anaphylaxis 1.7/million
  - Syncope common

- Deaths
- New onset chronic disease
- All SAEs
- Medically significant events

- Guillain-Barre Syndrome
- CRPS
- POTS
- Ovarian failure
What are those stories on the internet about....

Complex Regional Pain Syndrome (CRPS)
Postural Orthostatic Tachycardia Syndrome (POTS)
Primary Ovarian Failure...
• >15,000 received ≥1-dose HPV9
• Pregnancies were followed to outcome (n=2950)
• Safety outcomes followed for 7 – 72 months
• New medical conditions collected at each visit
  – 2 developed CRPS, both related to a previous injury
  – 2 developed POTS, one case >3 years after vaccination
There are four key approaches to establishing vaccine safety

- **Pre-licensure clinical trials**
  - 00,000s

- **Post-licensure clinical trials**
  - 000s – 00,000s

- **Post-licensure surveillance passive**
  - 000,000,000s

- **Post licensure surveillance active**
  - 000,000s – m’s

Generally by comparing vaccinated with unvaccinated
Observational studies to 2016

Passive and active surveillance
Post licensure studies - most compare outcomes in vaccinated with unvaccinated

<table>
<thead>
<tr>
<th>System or review (country)</th>
<th>Year of Publication</th>
<th>Number of doses evaluated</th>
<th>Description</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
</table>
| VAERS (US)                 | 2009                | N/A                       | Summary of 12,424 VAERS reports following 4-HPV between 2006–2008 | Spontaneous reporting; data mining for disproportionality reporting | No disproportionality reporting; no unvaccinated observed: no new concerns observed.
| Vaccine Safety Datalink (US) | 2011            | 600,558                   | Large database used for active surveillance and research; safety assessment of 9 pre-specified health outcomes among females vaccinated recipients aged 9–26 years | Cohort design with weekly sequential analyses of electronic medical data | No statistically significant increase in risk for the outcomes monitored; non-significant elevated risk detected for VTE.
| Institute of Medicine review (US) | 2011       | N/A                       | Review of available 4-HPV safety data | Review of published studies, case reports, and surveillance systems | No evidence to support association among 12 outcomes; anaphylaxis causally associated with 4-HPV syncope associated.
| Post-marketing commitment to FDA (US) | 2012      | 346,972                   | General safety, VTE, neurologic, death | General safety, VTE, neurologic, death | General safety, VTE, neurologic, death |
| Post-marketing commitment to FDA (US) | 2012      | 346,972                   | Autoimmune | Assessment of 6 different autoimmune outcomes following 4-HPV among 211 cases and 875 controls aged 14–26 years | No increased risk for combined endpoint of six autoimmune disorders.
| VAERS (US)                 | 2013                | N/A                       | Review of 25,176 VAERS reports following 4-HPV between 2006–2014 | Spontaneous reporting; data mining for disproportionality reporting | No increased risk for VTE.
| Register-based cohort study (Denmark and Sweden) | 2013   | 696,420                   | Autoimmune, Neurologic, VTE | Case-control study with recruitment of cases and controls through registries | No increased risk for VTE.
| VAERS (US)                 | 2014                | N/A                       | General safety | Review of 25,176 VAERS reports following 4-HPV between 2006–2014 | No increased risk for VTE.
| Pharmacoepidemiologic General Research Extension (France) | 2014  | N/A                       | VTE | Assessment of VTE following 4-HPV among women aged 18–24 years | No increased risk for VTE.

Outcomes include autoimmune, neurological, blood clots, CNS, CRPS, other specified conditions....

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</tr>
</thead>
<tbody>
<tr>
<td>Register-based cohort study [Denmark and Sweden]</td>
<td></td>
<td></td>
<td>Assessment of multiple sclerosis and other demyelinating diseases of the central nervous system among females aged 9–26 years</td>
<td>Cohort design using data linked to national registers</td>
<td>No association with the development of multiple sclerosis and other demyelinating diseases</td>
</tr>
<tr>
<td>Vaccine Safety Datalink (US)</td>
<td>2015</td>
<td>1,240,000</td>
<td>Assessment of VTE among adolescents and young adults aged 9–26 years</td>
<td>Self-controlled case series; cases confirmed by medical record review</td>
<td>No increase risk for VTE</td>
</tr>
<tr>
<td>Sentinel System (US)</td>
<td>2015</td>
<td>1,423,390</td>
<td>Assessment of VTE among females aged 9–26 years</td>
<td>Self-controlled risk interval design; cases confirmed by medical record review</td>
<td>No increased risk for VTE</td>
</tr>
<tr>
<td>VAERS (US)</td>
<td>2015</td>
<td>N/A</td>
<td>Review of 21 CRPS-related VAERS reports following 4v-HPV between 2006 and 2015</td>
<td>Spontaneous reporting: clinical review of CRPS cases</td>
<td>Lack of evidence to suggest an association; data suggest CRPS following HPV vaccine is rare</td>
</tr>
<tr>
<td>Post-marketing commitment to FDA (US)</td>
<td>2015</td>
<td>N/A</td>
<td>Review of 4,919 reports of pregnancy following 4v-HPV between 2006–2012</td>
<td>Voluntary reporting to pregnancy registry</td>
<td>Data were reassuring with no elevated reporting of adverse pregnancy outcomes</td>
</tr>
<tr>
<td>VAERS (US)</td>
<td>2015</td>
<td>N/A</td>
<td>Review of 147 VAERS pregnancy reports following 4v-HPV between 2006 and 2013</td>
<td>Spontaneous reporting: data mining for disproportional reporting</td>
<td>No unexpected patterns fetal adverse events after 4v-HPV</td>
</tr>
<tr>
<td>Vaccine Safety Datalink (US)</td>
<td>2016</td>
<td>1,355,535</td>
<td>Evaluation of deaths among individuals aged 9–26 years</td>
<td>Case-centered method; medical record review</td>
<td>Rate of death was lower than the national expected rate of death in this population</td>
</tr>
</tbody>
</table>

Abbreviations:
- CRPS - Chronic Regional Pain Syndrome
- FDA - Food and Drug Administration
- HIV - Human immunodeficiency virus
- 4v-HPV - Quadrivalent Human Papillomavirus vaccine
- VAERS - Vaccine Adverse Event Reporting System
- VTE - Venous thromboembolism

Sources:
Reviewed in 2017 by GACVS

- A systematic review (GRADE)
  - All SAEs, medically sig conditions, NOCD, deaths
  - 75,697
  - Very high level of evidence
- UK self controlled case-series, VAERS and VSD
  - GBS
  - 10.4 million doses, 60 million doses, 2.7 million administered
- Denmark and Sweden
  - Autoimmunity
  - >3 million 18-44
  - Unmasking of celiac disease
- Cohort study from Denmark
  - 540,805 pregnancies
- VSD
  - >92,000 pregnancies
- New data from Japan
  - Nationwide epidemiological survey
Significant clinical and observational data support the positive safety profile of HPV vaccines

- No increased risk for serious events
  - Exception syncope (fainting) at time of injection
- HOWEVER – positive impact on disease seen in countries using vaccine including NZ!
Lead Fluoride Antibiatics Vaccines Pesticides GMO

Still THINK it's just genetics?

www.thinkingmomsREVOLUTION.com

Balloons Tubesocks Testicles Bunnies Strippers Dromedaries

We can make CRAP up too.

www.facebook.com/RtAVM
Big Pharma only want my money, so I'm not vaccinating

Big Petroleum only want my money, so I'm not using any transport

Big Electricity only want my money, so I'm not using any electrical equipment

Big Supermarkets only want my money, so I'm not doing any shopping

Big Water Company only want my money, so I'm not drinking any water

Big Telecoms only want my money, so I'm not using a phone
You mean to tell me that...
A billionaire presidential candidate couldn’t hide a campaign derailing video.

AND...
The most powerful spy agency in the world couldn’t protect their secrets from a low-level employee.

Yet you still want me to believe...
there is a mass pro-vaccine conspiracy spanning numerous government agencies, humanitarian charities, and countless medical professionals and scientists.

Via Refutations to Anti-Vaccine Memes