Adverse Events Following Immunisation

(common, uncommon, shockin’ rare, and how do we know their likely cause?)

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Portiuncula Hospital, Sept. 18, 2017
Definitions

• Adverse Event (AE)
  .. untoward medical occurrence...during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment

• Adverse Reaction (ADR, AR)
  Response to a drug which is noxious and unintended..
Definitions

**Adverse Event Following Immunisation (AEFI)**

Any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine

Can be an unfavourable or unintended sign, abnormal laboratory finding, symptom or disease
## Known Adverse Reactions

<table>
<thead>
<tr>
<th>More Common (&gt;1 in 100)</th>
<th>Less Common (&lt;1/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Redness</td>
<td>• Encephalitis</td>
</tr>
<tr>
<td>• Swelling, nodule</td>
<td>• Paralysis</td>
</tr>
<tr>
<td>• Pain</td>
<td>• Arthritis</td>
</tr>
<tr>
<td>• Fever, irritability, loss of appetite</td>
<td>• Allergic reaction</td>
</tr>
<tr>
<td>• Nausea, D+V</td>
<td>• Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>• Febrile seizure</td>
</tr>
<tr>
<td></td>
<td>• Fainting</td>
</tr>
<tr>
<td></td>
<td>• Narcolepsy</td>
</tr>
<tr>
<td></td>
<td>• Death</td>
</tr>
</tbody>
</table>
Causes of AEFIs

**Vaccine product-related reaction**
- very common (>10%): site pain, swelling
- uncommon (1/100-1/1,000): headache, fever
- rare (1/1,000-1/10,000): febrile seizure (MMR)
- very rare (<1/10,000): anaphylaxis

**Vaccine quality defect-related reaction:** manufacture, storage

**Immunisation error-related reaction:** inappropriate usage, prescribing, administration, needle

**Immunisation anxiety-related reaction:** syncope, hyperventilation

**Coincidental:** AEFI caused by something other than above
Causes of Coincidental AEFI

• Pre-existing or newly acquired illness
• Emergence of a genetically programmed disease
• Exposure to other drug or toxin prior to the event
• Surgical or other trauma that leads to a complication
• Coincidental infection present/incubating/not apparent at time of vaccination
• Spontaneous occurrence (event without known risk factors)
Your Role in Vaccine safety

• Storage and Handling
• Timing and Spacing
• Administration Issues
  • Equipment
  • Injection site recommendations
  • Identify contraindications
• Education
• Report and treat AEFIs
Pre- and post-marketing Safety Assessment
Vaccine Safety Studies

PHASE I
- Safety
- May not involve target population
- 10-100 subjects

PHASE II
- Safety, immunogenicity, dosing in target population
- 100 to 200 subjects

PHASE III
- Safety, immunogenicity, duration of immunity, concomitant use, efficacy
- 1000s to 10,000s

PHASE IV
- (Post-marketing) Safety and effectiveness
- N > 100,000
Benefit-risk Balance

Cohort

With Vaccination

- Adverse Events
  - Immune
    - Infected
    - Not Infected
  - Susceptible
    - Infected
    - Not Infected

No Adverse Events

- Immune
  - Infected
  - Not Infected

- Susceptible
  - Infected
  - Not Infected

Without vaccination

- Infected
  - Not Infected
Numbers needed to test for increased relative risk of an adverse event

<table>
<thead>
<tr>
<th>Background rate in general population</th>
<th>Rate In Vaccinated Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-fold higher</td>
</tr>
<tr>
<td>1 in 10,000</td>
<td>141,000</td>
</tr>
<tr>
<td>1 in 100,000</td>
<td>1,238,000</td>
</tr>
<tr>
<td>1 in 1,000,000</td>
<td>12,951,500</td>
</tr>
</tbody>
</table>

Hierarchy of Evidence

- Systematic Reviews and Meta-analyses
- Randomized Controlled Double Blind Studies
- Cohort Studies
- Case Control Studies
- Case Series
- Case Reports
- Ideas, Editorials, Opinions
- Animal research
- In vitro ('test tube') research
Pharmacovigilance (PhV)

Detection, assessment, understanding, prevention of ARs

Objectives:
- prevent harm
- promote safe, effective use
Why Pharmacovigilance?

• No vaccine is 100% safe
  Rare events require huge numbers to detect

• Benefit/risk balance changes over time
  • as incidence falls - e.g. VAPP and oral polio vaccine
  • as society becomes more critical
Why Pharmacovigilance?

• Identify previously unrecognized ARs (new, frequent, severe)

• Identify subgroups of patients at particular risk of ARs

• Continue surveillance to ensure benefits/harms balance remains acceptable

• Confirm or refute false-positive signals that arise
### MMR vaccine and Measles (1m children <5 yrs)

<table>
<thead>
<tr>
<th>MMR vaccine</th>
<th>Measles infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 children have febrile fits</td>
<td>10,000 have febrile fits</td>
</tr>
<tr>
<td>25 have thrombocytopenia</td>
<td>330 have thrombocytopenia</td>
</tr>
<tr>
<td>1-3 have anaphylaxis</td>
<td>0 will have anaphylaxis</td>
</tr>
<tr>
<td>1 may have encephalitis</td>
<td>2,000 may have encephalitis</td>
</tr>
<tr>
<td>0 will have SSPE</td>
<td>10 will have SSPE</td>
</tr>
</tbody>
</table>
## Pertussis Disease v. Pertussis Vaccine

### Pertussis

<table>
<thead>
<tr>
<th>Condition</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pneumonia</td>
<td>5</td>
</tr>
<tr>
<td>(12% in &lt;6/12)</td>
<td></td>
</tr>
<tr>
<td>• Convulsions</td>
<td>1.4</td>
</tr>
<tr>
<td>• Encephalopathy</td>
<td>0.2</td>
</tr>
<tr>
<td>• Death (83% &lt;3/12)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### Pertussis Vaccine

<table>
<thead>
<tr>
<th>Reaction</th>
<th>DTwP</th>
<th>DTaP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pain</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>• Cry&gt;3 hrs</td>
<td>0.4</td>
<td>0.04</td>
</tr>
<tr>
<td>• High fever</td>
<td>0.24</td>
<td>0.04</td>
</tr>
<tr>
<td>• Convulsion</td>
<td>0.02</td>
<td>0.007</td>
</tr>
<tr>
<td>• Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Days</td>
<td>RR</td>
</tr>
<tr>
<td>---------------</td>
<td>------</td>
<td>-----</td>
</tr>
<tr>
<td>MMRV (N=83,107)</td>
<td>7-10</td>
<td>6.1</td>
</tr>
<tr>
<td>MMR + V (N=376,354)</td>
<td>7-10</td>
<td>4.4</td>
</tr>
<tr>
<td>MMR (N=145,302)</td>
<td>7-10</td>
<td>4.3</td>
</tr>
<tr>
<td>Varicella (N=107,744)</td>
<td>9-14</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Outpatient Fever Visits Among 12-23 Month Olds after First Dose Vaccine: VSD Automated Data 2000-2008*
Common symptoms in a paired twin study (MMR v. Placebo)
### What do rare, very rare mean?

<table>
<thead>
<tr>
<th>Frequency of known injury*</th>
<th>What else is this common?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1,000 to 1/100,000</td>
<td>Having quadruplets</td>
</tr>
<tr>
<td>– Fainting or collapse</td>
<td></td>
</tr>
<tr>
<td>– Febrile seizure</td>
<td></td>
</tr>
<tr>
<td>– Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>1/100,000 to 1/1,000,000</td>
<td>Getting struck by lightning</td>
</tr>
<tr>
<td>– Serious allergic reaction</td>
<td></td>
</tr>
<tr>
<td>– Arthritis</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 in a million</td>
<td>Winning the lottery</td>
</tr>
<tr>
<td>– Encephalitis</td>
<td></td>
</tr>
<tr>
<td>– Paralysis</td>
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*highest rate for any childhood vaccine
AEFI – Cause or Coincidence?

All health problems after vaccination

Caused by the vaccine
Correlation is not Causation

• **Correlation**: the extent to which two or more variables fluctuate together

• **Cause**: one event is the result of the occurrence of the other event
Criteria of Causality at Population level

- **Temporal**: exposure must precede AEFI
- **Strength of association**: statistically significant (not chance occurrence)
- **Dose-response relationship**: increasing exposure increases risk of AE
- **Consistency of evidence**: similar results in studies using different methods, settings
- **Specificity**: the vaccine is only known cause of the AEFI
- **Plausibility and coherence**: association between vaccine and AEFI plausible and consistent with current knowledge of biology of vaccine and AEFI
Criteria of Causality in an Individual

- Usually not possible to establish *definite* causal relationship between AEFI and vaccine based on single report
- Important to try (may identify product-related AEFI; false attribution may result in reduced vaccine uptake
- Seldom possible to get straightforward answer
- Systematic consideration of all possible causes of AEFI necessary to conclude that evidence is consistent
Possible Causes of Coincidental AEFI

- Pre-existing or newly acquired illness
- Emergence of a genetically programmed disease
- Exposure to other drug or toxin prior to the event
- Surgical or other trauma that leads to a complication
- Coincidental infection present/incubating/not apparent at time of vaccination
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Benefit-risk Balance

Remember:

• Medicines tested in trials (selected, relatively few subjects)

• Then used in patients who differ from trial subjects
  (age, diseases, other medicines, genetic, nutrition,.... )
Minimising Immunisation Errors

- Right patient
- Right vaccine and diluent
- Right time (age, interval, expiry)
- Right dose
- Right site
- Right route
- Right needle
- Right documentation