Adverse Events Following Immunisation

Castlebar, Nov. 8, 2013
Kevin Connolly
Outline of presentation

Definitions
Safety assessment
Timing of reactions
Causality-real and coincidence
Errors
Occasional diversions
Abbreviations

- **ADR**- adverse drug reaction
- **AE**- adverse event
- **AEFI**- adverse event following immunisation
- **AESI**- adverse event of special interest
- **SAE**- serious adverse event
- **SUSAR**- suspected unexpected serious adverse reaction
Adverse Event Following Immunization (AEFI)

• Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
AEFI-coincidence or Vaccine Injury?

All health problems after vaccination

Health problems caused by the vaccine
Bradford-Hill criteria for causation (does A cause B?)

- **Strength of association.** How large is the effect?
- **Consistency of association.** Has the same association been observed by others, in different populations, using a different method?
- **Specificity.** Does altering only the cause alter the effect?
- **Temporal relationship.** Does cause precede effect?
• **Biological gradient.** Is there a dose response?
• **Biological plausibility.** Does it make sense?
• **Coherence.** Does the evidence fit with what is known regarding the natural history and biology of the outcome?
• **Experimental evidence.** Are there any clinical studies supporting the association?
• **Reasoning by analogy.** Is the observed association supported by similar associations?
What is a serious AE?

- Fatal
- Life-threatening
- Permanently/significantly disabling
- Requires hospitalisation
- Causes Congenital abnormality
- Requires intervention to prevent permanent impairment or damage
Pre- and Post-marketing Testing

- Preclinical - assure no major side effects
- Clinical trials
- After approval (MA), samples of each lot of vaccine tested for safety, potency, and purity.
## Clinical Trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-license</td>
<td>Safety, in healthy adult volunteers (10-20)</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Safety and immunogenicity in target population (100-200)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Protective efficacy in target population (large)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Pharmacovigilance to detect (rare) AEs</td>
</tr>
<tr>
<td>Post-license</td>
<td></td>
</tr>
</tbody>
</table>
Timing of Vaccine Reactions

• **Inactivated vaccines**: generally within 48hrs

• **Live vaccines**: according to time for virus to replicate
e.g. MMR:
  - measles (fever, rash) in 6-11 days
  - rubella (stiffness or arthritis) in 2\(^{nd}\) week
  - mumps (parotid swelling) in 3\(^{rd}\) week
    (may occur up to 6 weeks)
AEFIs: potential sources

- Manufacturing potency issues
  - over-attenuation of live vaccines
    - instability over time
    - reconstitution, mixing interferences
- Storage issues (cold chain)
- Administration issues
  - technique
  - concommitant administrations
- Patient profile
  - age, weight, immune deficiency
- Environmental
  - epidemiology: strain variation
Errors in manufacture

– Use of wrong diluent
– Transmission of pathogens
– Incomplete inactivation of virus or bacterium (vaccine is virulent)
Role of Administrator in vaccine safety

• Storage and Handling
• Timing and Spacing
• Administration Issues
  – Equipment
  – Injection site recommendations
  – Identify contraindications
• Education
• Report and treat AEFIs
# Needle Size

<table>
<thead>
<tr>
<th>Colour</th>
<th>Gauge</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange</td>
<td>25</td>
<td>16 mm</td>
</tr>
<tr>
<td>Blue</td>
<td>23</td>
<td>25 mm</td>
</tr>
<tr>
<td>Green</td>
<td>21</td>
<td>40 mm</td>
</tr>
</tbody>
</table>

- **25mm** needle is preferable and suitable for most
- **16mm** only recommended for <2.5-3kgs, sc, id
- **40mm** may be needed in heavier adults
Frequency of reactions

- Very common: >10%
- Common: 1-10%
- Uncommon: 1/100-1/1,000
- Rare: 1/1,000-1/10,000
- Very rare: <1/10,000
# Known Vaccine AEs

<table>
<thead>
<tr>
<th>More Common</th>
<th>Less Common</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(More than 1 in 100)</strong></td>
<td></td>
</tr>
<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, nausea, D+V.</td>
<td>• Allergic reaction</td>
</tr>
<tr>
<td></td>
<td>• Coagulopathies</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>
Anaphylaxis: Treatment In the Community

Anaphylaxis is likely if a patient who, within minutes of exposure to a trigger (allergen), develops a sudden illness with rapidly progressing skin changes and life-threatening airway and/or breathing and/or circulation problems.

1. Get help
   Call ambulance

2. Assess airway, breathing, and circulation

3. Sternal, wheeze, respiratory distress or clinical signs of shock

   For hypovolemia, lie patient flat with legs raised (unless respiratory distress increased)

4. Epinephrine 1:1000 (1mg/ml) IM

   - 0-5 years: 0.15ml (150 micrograms)
   - 6-12 years: 0.3ml (300 micrograms)
   - >12 years: 0.5ml (500 micrograms)
   - Adult: 0.5ml (500 micrograms)

   These ≥ 100 laps can be given IM (use 2G, 3mm needle)

5. Repeat every 5-10 mins, up to 3 doses
   Remember urgency of hospital transfer

1. Ambulance will be equipped with oxygen, Salbutamol and fluids.
2. If profound shock judged immediately life threatening, give CPR/BLS if necessary.
3. If respiratory distress present, elevate head.
4. Epinephrine maximum effect 10 minutes after IM injection.

Suggested Anaphylaxis Kit

- The availability of protocols, equipment, and drugs necessary for the management of anaphylaxis should be checked before each vaccination session

- Copy of “Anaphylaxis: Treatment in the Community” from Immunisation Guidelines for Ireland
- 3 x 1ml ampoules of epinephrine (1:1000, 1mg/ml)
- 3 x 1ml syringes
- Needles: 3 x 16mm, 3 x 25mm, 3 x 40mm
- 1 pocket mask
- Sphygmomanometer (optional)
- Stethoscope (optional)
- Pen and paper to record time of administration of epinephrine.

The kits should be kept closed to ensure the drugs are not exposed to light and stored at room temperature. The kits require regular verification to replace drugs before their expiry date.
## What Do We Mean by “Less Common”?

<table>
<thead>
<tr>
<th>Frequency of known injury*</th>
<th>What else is this common?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 1,000 to 1 in 100,000</td>
<td>Having quadruplets</td>
</tr>
<tr>
<td>- Fainting or collapse</td>
<td></td>
</tr>
<tr>
<td>- Seizure from vaccine caused fever</td>
<td></td>
</tr>
<tr>
<td>- Blood clotting problems</td>
<td></td>
</tr>
<tr>
<td>1 in 100,000 to 1 in a million</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>Less than 1 in a million</td>
<td>Winning the lottery</td>
</tr>
<tr>
<td>- Encephalitis</td>
<td></td>
</tr>
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<td>- Paralysis</td>
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*Injury rates differ for different vaccines; this table shows the highest rate for any childhood vaccine.
## Pertussis

<table>
<thead>
<tr>
<th>Reaction</th>
<th>DTwP</th>
<th>DTaP</th>
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</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>
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</tr>
<tr>
<td>Convulsions</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>Limpness</td>
<td>0.07</td>
<td>-</td>
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### Pertussis

#### Pertussis Complications in Infants

<table>
<thead>
<tr>
<th>Condition Reported</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>~50</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
</tr>
<tr>
<td>Convulsions</td>
<td>1.6</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>0.4</td>
</tr>
<tr>
<td>Death</td>
<td>1.6</td>
</tr>
</tbody>
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#### Pertussis vaccine

<table>
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Why monitor AEFIs?

• No vaccine 100 % safe
  – Safety profile established in prelicensure trials
  – Detectable frequency depends on numbers studied
    (rule of 3)
    Rare events require huge numbers

• Risk / benefit balance changes over time
  – as incidence falls: VAPP, TB
  – as society becomes more critical ...
Reporting AEFIs

- 1-10% are reported
- 90-99% are not reported
- Safety is provisional at time of licencing - Rotashield, Vioxx, Pandemrix, etc
- If in doubt, write one out
- Every report is important
The Seven Rights of Immunisation

• Right patient
• Right vaccine, diluent
• Right time (age, interval, expiry)
• Right dose
• Right site
• Right route
• Right documentation
AEFI: “a medical incident ....after an immunisation, causes concern, and believed to be caused by immunisation”.

• Does not restrict type of event (other than being a health consequence)
• Does not limit the time after immunisation,
• Does not attempt to determine causality

The belief that immunisation was responsible may be correct, incorrect, or impossible to assess
Safety and Efficacy

Safety: “Relative freedom from harmful effect... when prudently administered, taking into account the character of the product in relation to the condition of the recipient at the time.”

Quality: “Relative freedom from extraneous matter in the finished product,...”

Efficacy: “Specific ability of the product ... to effect a given result.”

(N.B. differs from effectiveness).
### OPD Fever Visits by 12-23 Month Olds after First Dose

VSD Automated Data 2000-2008

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Days</th>
<th>RR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRV (N=83,107)</td>
<td>7-10</td>
<td>6.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>MMR + V (N=376,354)</td>
<td>7-10</td>
<td>4.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>MMR (N=145,302)</td>
<td>7-10</td>
<td>4.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Varicella (N=107,744)</td>
<td>9-14</td>
<td>1.2</td>
<td>0.06</td>
</tr>
</tbody>
</table>
• **Biological gradient.** Is there a dose response?
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Alleged associations
all unproven

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vaccine</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological damage</td>
<td>DPT</td>
<td>Scotland</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>Hepatitis B</td>
<td>Canada</td>
</tr>
<tr>
<td>SIDS</td>
<td>DPT</td>
<td>France</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Hepatitis B</td>
<td>France</td>
</tr>
<tr>
<td>Autism</td>
<td>MMR</td>
<td>UK</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>Thimerosal</td>
<td>USA</td>
</tr>
</tbody>
</table>
What Causes AEFI?

**Vaccine** – due to vaccine’s inherent properties

**Programme Error**

**Injection reaction** - anxiety or pain of injection

**Unknown** - cause cannot be determined