Adverse Events Following Immunisation

Kevin Connolly
Limerick, Sept. 22, 2016
Outline

• Abbreviations, Definitions
• Adverse Event (AE), Adverse Reaction (AR) or coincidence?
• How are AEs recorded?
• How are ARs are identified?
• Frequency of ARs
Abbreviations

• **AE**- adverse event
• **AR**- adverse reaction
• **AEFI**- adverse event following immunisation
• **SAE**- serious adverse event
Definitions

• **Adverse Event**
  Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment

• **Adverse Drug Reaction**
  A response to a drug which is noxious and unintended, ...
Definitions

**Adverse Event Following Immunization (AEFI)**

Any untoward medical occurrence which follows immunisation 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
Immunisation Error-related Reaction

An adverse event following immunisation that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
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 AEFIs

<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>
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<tr>
<td></td>
<td>• Fainting</td>
</tr>
<tr>
<td></td>
<td>• Narcolepsy</td>
</tr>
<tr>
<td></td>
<td>• Death</td>
</tr>
</tbody>
</table>
## What is “Less Common”?

<table>
<thead>
<tr>
<th>Frequency of known injury*</th>
<th>What else is this common?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1/1,000 to 1/100,000</strong></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><strong>1/100,000 to 1/1,000,000</strong></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><strong>&gt; 1 in a million</strong></td>
<td>Winning the lottery</td>
</tr>
<tr>
<td>– Encephalitis</td>
<td></td>
</tr>
<tr>
<td>– Paralysis</td>
<td></td>
</tr>
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<td>– Death</td>
<td></td>
</tr>
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</table>

*highest rate for any childhood vaccine
Presenting Risk Information

1. A serious reaction occurs about 1 to 3 times per 10,000 doses

2. About 1 to 3 children out of 10,000 will experience a serious reaction

3. This vaccine rarely causes serious reactions - about 1 to 3 children out of 10,000 who receive it

4. This vaccine is very safe - 9,997 children out of 10,000 will experience no significant adverse reaction
AEFI - Coincidence or Vaccine Injury?

All health problems after vaccination

Health problems caused by the vaccine
What Causes AEFIs?

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

**Programme, administration**

**Injection reaction** - anxiety, pain

**Unknown** - cause cannot be determined
AEFIs: potential sources

• Manufacturing potency issues
  - over-attenuation of live vaccines
  - instability over time
  - reconstitution, mixing interferences

• Storage issues

• Administration issues
  - technique
  - concomitant administrations

• Patient profile
  - age, weight
  - immune deficiency e.g. AIDS

• Environmental
  - epidemiology: strain variation
AEFIs: potential sources

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Is this an AE or an AR?
AEFIs: potential sources

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Timing of Vaccine Reactions

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

- **Live vaccines**: according to time for organism to replicate

  MMR: - mini-measles 6-11 days (SSPE years)
    - rubella 2\textsuperscript{nd} week
    - mumps 3 to 6 weeks
  
  BCG: days - 12 months +
Minimising Errors

• Right patient
• Right vaccine and diluent
• Right time (age, interval, expiry)
• Right dose
• Right site
• Right route
• Right documentation
Vaccine Safety Studies

PHASE I
- Safety, tolerability
- 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 immune response, concomitant use, efficacy
- 1000s to 10,000s

PHASE IV
- Safety and effectiveness; occurs after licensure
- N > 100,000
Why Monitor AEFIs?

• No vaccine is 100% safe
  Safety profile established in pre-license trials
  Rare events require huge numbers to detect

• Risk / benefit balance changes over time
  • as incidence falls-e.g. VAPP with oral polio vaccine
  • as society becomes more critical
Pharmacovigilance

Science and activities relating to the detection, assessment, understanding and prevention of adverse effects

Objectives:
- preventing harm from adverse reactions
- promoting safe and effective use of medicinal products
Number needed to test for increased risk of an AE

<table>
<thead>
<tr>
<th>Background rate in general population</th>
<th>2-fold higher</th>
<th>10-fold higher</th>
<th>100-fold higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 10,000</td>
<td>141,000</td>
<td>5,500</td>
<td>500</td>
</tr>
<tr>
<td>1 in 100,000</td>
<td>1,238,000</td>
<td>53,500</td>
<td>2,500</td>
</tr>
<tr>
<td>1 in 1,000,000</td>
<td>12,951,500</td>
<td>532,500</td>
<td>23,500</td>
</tr>
</tbody>
</table>

Benefit-risk balance

- Medicines may have unintended, harmful effects.
- Active substance tested in trials
- Licenced only if benefits outweigh risks
- Used in patients who may differ from the study population, e.g. age or additional diseases
- Important to identify any new risk ASAP, and to take measures to minimise risk and promote safe and effective use
Pharmacovigilance by Pharmaceutical Companies

• Legal obligations to continuously collect data and conduct pharmacovigilance
• Data must be sent to authorities within defined timelines
• Any emerging concern about the benefit-risk balance has to be notified immediately.
• Authorities may request further investigations, including formal studies.
• Authorities may update product information and implement other safety measures
Is Sequence Consequence?

A

Exposure
(Vaccine, Drug, Diet, Occupation etc)

Time

B

Disease

• Direct and only cause?
• One of multiple potential causes?
• Co-factor/indirect cause, trigger?
• Coincidental?
Correlation is not Causation

Ice Cream and Drowning Scatter, 2006

Drowning Deaths

Log Ice Cream Production

Spurious Correlations, tylerviggen.com
Divorce rate in Maine correlates with Per capita consumption of margarine

Correlation: 99.26% (r=0.992558)

Sources: National Vital Statistics Reports and U.S. Department of Agriculture
US spending on science, space, and technology correlates with Suicides by hanging, strangulation and suffocation

Correlation: 99.79% (r=0.99789126)

Sources: U.S. Office of Management and Budget and Centers for Disease Control & Prevention
Number of people who drowned by falling into a pool correlates with Films Nicolas Cage appeared in

Correlation: 66.6% (r=0.666004)

Sources: Centers for Disease Control & Prevention and Internet Movie Database
Criteria of Causality (Bradford Hill)
The Bad Dog Ate the Cat

- Temporality - occurs after, change in incidence over time
- Biological Plausibility - biological mechanism can make causality more plausible
- Dose - Response Relationship
- Association (strength of) - measured using RRs and ORs
- Consistency - similar results from different studies, researchers, populations, times
Adverse Reaction to Lectures

The Nodder

zzz

Bliss

The Ghost Writer

zzz

*Scribble Scribble*

Systems Failure

*SNORE*

zzz
Reporting AEFIs

• <10% are reported
• Up to 99% are not reported
• Safety is provisional at time of licencing - Rotashield, Vioxx, Pandemrix, HRT
• Every report is important
• If in doubt, write one out
Report an Issue

Reporting Safety and Quality Concerns

If you are concerned that you have had a side effect to a medicine, or experienced a problem with any other type of healthcare product regulated by the HPRA, you may need to contact your healthcare professional who can advise on any treatment that may be needed. They can also report the issue to the HPRA on your behalf.

If you wish to directly report issues relating to the use or quality of healthcare products you can use the HPRA’s online reporting service. Anyone can report issues relating to the safety and quality of healthcare products to the HPRA. This includes patients, carers, other members of the public and healthcare professionals.

Please note that in completing a report form, we understand that you are consenting to the information provided, including your contact details, to be stored securely by the HPRA. Your contact details will be used solely for the purposes of interaction with you regarding the report submitted. For the purposes of complying with our statutory and legal reporting requirements, summary details of this report (excluding personal information) may be shared with other bodies also involved in monitoring activities in accordance with HPRA obligations and data protection requirements. This ensures that the information is available to all relevant parties. The right exists to request a copy of personal data held by the HPRA and to have any inaccuracies in such data corrected or deleted.

Online Report Forms

The following forms can all be completed using the HPRA online reporting system:

Human Medicine Adverse Reaction
R.E.G.R.E.T.

“Reactions and effects of Gardasil resulting in extreme trauma”
“R.E.G.R.E.T. set up by parents of Irish teenage girls who have developed serious health problems after entering secondary school. These parents are certain that the HPV vaccine (Gardasil) is the cause of their daughters' otherwise unexplained illness.”

One is entitled to one’s beliefs and feelings, but not to one’s own science
Problems with REGRET’S Beliefs

• Sampling, recall, susceptibility bias
• Incidence of CFS in population, in trials, after introduction of HPV vaccines
• EMA, WHO assessment

The overwhelming body of scientific evidence is that there is no causative association between HPV vaccines and POTS, CFS or CRPS
Remember..........

Incidence of HPV-related cancers
Effectiveness of HPV vaccine
Estimated Impact of HPV Vaccination

In the 9 years since HPV vaccine introduced:

- HPV Genital infection reduced by 64 - 85%¹
- CIN2 + 3 reduced by 75% ²

¹ US, Australia
Estimated Impact of no HPV Vaccination

- Currently 500,000 girls <15 in Ireland; if none are vaccinated:
  - 3,500 will develop cervical cancer
  - 1,000 will die from cervical cancer

- 80% uptake would prevent 1600 cases of cancer and 500 deaths
The End
Unsure if applause is because I was good

or because I have shut-up