Are vaccines safe?

2017

Vaccine Advice for Clinicians Service (VACCSline)
Learning objectives

• Explain the stages of clinical trials
• Describe how vaccine safety continues to be monitored post-licensure
• List possible adverse events post vaccination
What questions may you expect a parent or patient to ask you relating to vaccine safety?
How do we know vaccines are safe?

- Clinical trails prior to licencing – safety, identify expected adverse events
- Post-licensing surveillance
- Protocols and Stand Operating Procedures for their storage and administration
Phases of Clinical Trials

**Phase I:**
Small group of people (20-80)
Safety – safe dose and identifying side effects

**Phase II:**
Large group (100-300)
Effectiveness & Safety

**Phase III:**
Larger group (1,000-3,000)
Effectiveness, monitor side effects
Compare to commonly used treatment

**Phase IV:**
Post marketing
Post licensure “studies”

- Vaccine effectiveness – reduction in disease, herd immunity

- Adverse events (phase 4 surveillance)
  - Larger number of people vaccinated
  - Diverse range of people vaccinated
  - Manufacturing problems (National Institute for Biological Standards and Control (NIBSC))
Vaccine Production

- National Institute for Biological Standards and Control (NIBSC) routinely batch test vaccines
- Manufacturing problems - withdraw batches
# Adverse events

<table>
<thead>
<tr>
<th>Medications</th>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Given to sick people</td>
<td>• Given to healthy people</td>
</tr>
<tr>
<td>• Predominantly to elderly</td>
<td>• Given to young people</td>
</tr>
<tr>
<td>• Influence on immune system, if any, inhibitory</td>
<td>• Stimulating immune system</td>
</tr>
<tr>
<td>• Designed to have short lived</td>
<td>• Designed to have long lasting effect</td>
</tr>
<tr>
<td>• Minor AE’s likely to be tolerated</td>
<td>after single or few doses</td>
</tr>
<tr>
<td>• Individually prescribed</td>
<td>• Minor adverse effects may not be tolerated</td>
</tr>
<tr>
<td></td>
<td>• Universally recommended</td>
</tr>
</tbody>
</table>

For vaccines:
- Increased likelihood of coincidental association
- Increased difficulty in establishing association

(Slide courtesy of Dr. Matthew Snape)
WHO classifications of AEFIs

• programme-related
• vaccine-induced
• coincidental
• unknown.

Causality assessment of adverse events following immunization. WER 2001;76:85-89
Programme related

- expired vaccine
- wrong intervals
- wrong route
- too much, too little or no diluents
- wrong dose
- prepared incorrectly
- incorrect storage

Contraindications ignored
Common vaccine induced AEFIs

Local adverse reactions

- Usually early, mild and self limiting
- Pain, swelling and redness at the injection site
- Common with DTaP containing vaccines (5-25%)
- Less common with MenC, flu, pneumococcal

Systemic reactions:

- Fever, malaise, myalgia, irritability, headache and loss of appetite
- Hours (usually within 48 hours) with inactivated vaccines
- Later with live vaccines – dependent on viral replication
- Fever/rash 7-10 days; parotitis 3 + weeks post MMR
FIGURE 5 Symptom onset

A. Fever
B. Diarrhoea
C. Rash
D. Fever, rash or diarrhoea

Onset, d after MMR1

Percent of children

LeBaron, C. W. et al. Pediatrics 2006;118:1422-1430 (Slide courtesy of Dr. Matthew Snape)
Local redness 24 hours after immunisation

*How would you advise a parent if they asked you about this reaction? Could it happen again?*

Photos courtesy Karen Ford
Routine use of antipyretics

Managing common vaccine-induced AEFIs

Whilst paracetamol and ibuprofen can lower the duration of fever and reduce distress, there is no evidence that they prevent febrile convulsions. It is not therefore recommended that these drugs are used routinely to prevent fever following vaccination as there is some evidence that prophylactic administration of antipyretic drugs around the time of vaccination may lower antibody responses to some vaccines (Prymula et al., 2009).

From online green book

Exception: Men B if given with primary immunisations under one year of age give prophylactic paracetamol
Men B & paracetamol use

- Routinely when Men B is given with other infants immunisations up to one year of age
- Give 2.5 ml of paracetamol (120mg/5ml):
  - With or shortly after vaccination
  - 2 further doses spaced 4-6 hours apart

Aim: to decrease occurrence of high fever rates > 38 degrees following administration of MenB with other routine infants imms (50-80% - around 2 out of 3 infants)
Prophylactic paracetamol reduced fever rates without affecting the immune response to Men B or the other routine infant immunisations when given together
Men B and paracetmol

- MenB and Paracetamol mock consultation
Vaccine specific AEFI

- Intussusception is a naturally occurring condition of the intestines
- Incidence begins to rise after 6 months of age
Vaccine specific AEFI: Intussusception

- Research from some countries suggests that Rotarix® may be associated with a very small increased risk of intussusception.

- Data from observational safety studies performed in several countries indicate that rotavirus vaccines carry an increased risk of intussusception, mostly within 7 days of vaccination. Up to 6 additional cases per 100,000 infants have been observed in the US and Australia against a background incidence of 33 to 101 per 100,000 infants (less than one year of age) per year, respectively. (Rotarix SPC https://www.medicines.org.uk/emc/medicine/17840)

Even with this small potential risk, the benefits of vaccination in preventing the consequences of rotavirus infection outweigh any possible side effects.
Details of Vaccine Specific AEFI’s

http://www.medicines.org.uk/emc/search

Summary of Product Characteristics


VACCSline
Allergic reactions; Anaphylaxis

• Very rare

1997 – 2003 – 130 reports to MHRA (no deaths)
117 million doses of all vaccines

• 0.65 per million immunisations

• Potentially life threatening
### Distinguishing anaphylaxis from other reactions

<table>
<thead>
<tr>
<th>Syncope</th>
<th>Anxiety attack</th>
<th>Breath holding episode</th>
<th>Anaphylaxis</th>
</tr>
</thead>
</table>
| **(Faint)** | Good central pulses but may be bradycardic  
Respiration continues  
Pallor  
Warm skin  
Unusual in preschool children  
No upper airway oedema  
No itching  
Patient regains consciousness when lying down | May appear fearful  
Usually tachycardic  
Hyperventilation  
Pallor  
Complain of tingling of face and extremities  
Complain of feeling light-headed, dizzy or numb | Mainly in young children  
Generally distressed/ crying prior to episode | Poor central pulses, usually sinus tachycardia  
Possible apnoea, especially in children  
Upper airway oedema, sneezing  
Bronchospasm, may be audible expiratory wheeze or stridor  
Urticarial lesions  
Itching  
Sense of impending doom  
Flushing/sweating  
Cold skin  
Patient does not revive when lying down |

Anaphylaxis may appear fearful and usually tachycardic. It often involves hyperventilation, pallor, and complaint of tingling of face and extremities, as well as complaint of feeling light-headed, dizzy or numb. Anaphylaxis is mainly seen in young children and is generally accompanied by distress/crying prior to the episode.

In contrast, syncope, or fainting, may have good central pulses but may be bradycardic. Respiration continues, and pallor, warm skin, unusual in preschool children, no upper airway oedema, and no itching are common. The patient regains consciousness when lying down.

Anxiety attacks may have patients appear fearful, usually tachycardic, often with hyperventilation, pallor, and complaint of tingling of face and extremities. They generally complain of feeling light-headed, dizzy or numb, and may briefly become unconscious during which breathing returns.

The table above highlights the differences between anaphylaxis, anxiety attacks, and syncope to help distinguish between these conditions.
Potential triggers to anaphylaxis

• Egg proteins (yellow fever, Epaxal (Hep A) and influenza vaccines)

• Thiomersal (some flu in the past seasons and hep B vaccines)

• Antibiotics (neomycin, streptomycin and polymixin B)

• Stabilisers and other vaccine components (yeast, gelatin)

• Toxoid (DTaP, Td)
Reporting AEFI’s

Drug and device alerts
Drug Safety Update
Report a problem with a medicine or medical device
Medical devices regulation and safety
Marketing authorisations, variations and licensing guidance
Patient information leaflets and summaries of product characteristics
Herbal and homeopathic medicines
Good practice, inspections and enforcement
Clinical trials and investigations
Blood regulation and safety


VACCSline
The Yellow Card Scheme: guidance for healthcare professionals

What to report

Medicines

For established medicines and vaccines you should report all serious suspected ADRs, even if the effect is well recognised.

We are particularly interested in receiving Yellow Card reports of suspected ADRs:

- in children
- in patients that are over 65
- to biological medicines and vaccines
- associated with delayed drug effects and interactions
- to complimentary remedies such as homeopathic and herbal products

See what to include in your Yellow Card of an adverse drug reaction (PDF, 73.8KB, 3 pages).

See specific areas of interest for adverse drug reactions reporting (PDF, 65.8KB, 2 pages).

https://www.gov.uk/the-yellow-card-scheme-guidance-for-healthcare-professionals#how-to-report
### What is the MHRA?

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work and are acceptably safe. When any possible problem is found, the MHRA takes prompt action to protect the public and reduce risk.

For more information about the MHRA:

- Visit: [www.mhra.gov.uk](http://www.mhra.gov.uk)
- Email: info@mhra.gsi.gov.uk
- Tel: 020 3080 6000

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### Reporting Adverse Drug Reactions to the Yellow Card Scheme

Healthcare professionals are asked to help improve medicines safety by reporting suspected Adverse Drug Reactions (ADRs) to the Yellow Card Scheme. Please support the scheme by following the these reporting guidelines.

- Please report all suspected ADRs for new medicines (identified by the black triangle ▼ symbol).
- Please report all serious suspected ADRs for established vaccines and medicines, including unlicensed medicines, herbal remedies, and medicines used off-label.
- If you are unsure, please report anyway.

Help make medicines safer for everyone.

[www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)

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#### Reporting Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Category</th>
<th>Reporting Requirements</th>
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<tr>
<td><strong>All Suspected ADRs</strong></td>
<td>Please report all suspected ADRs for new medicines (identified by the black triangle ▼ symbol).</td>
</tr>
<tr>
<td><strong>All Serious ADRs</strong></td>
<td>Please report all serious suspected ADRs for established vaccines and medicines, including unlicensed medicines, herbal remedies, and medicines used off-label.</td>
</tr>
<tr>
<td><strong>Other medicines/vaccines</strong></td>
<td>If you are unsure, please report anyway.</td>
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**VACCSSline**
Continuous safety review

Information of a possible signal of a safety concern pooled from many sources

MHRA
Commission of Human Medicines
JCVI

Available evidence reviewed and action to investigate further taken e.g formal epidemiological studies

Epidemiological databases

Post marketing safety studies

Medical Literature
Reassure parents/patient about vaccine safety...

- Rigorous safety system for vaccines that continues post-licensure and after their introduction into the routine schedule