Safety monitoring of vaccines

Jeremy Labadie MD
vaccine safety specialist
Vaccines

- vaccines are special
- immunization programmes
- pharmacovigilance & vaccines
- vaccines & AEFI
- causality assessment of AEFI
- UMC and AEFI
Vaccines

Vaccines are special

ADR

AEFI = Medical incident that takes place after an immunization which causes concern and is believed to be caused by immunization (WHO)
Vaccines are special

- biologicals
  - GMP, WHO requirements
- production variability
  - Lot / Batch release
- fragile
  - temperature (cold chain), sunlight
Vaccines are special

- **Summary of Product Characteristics:**
  - pharmacokinetics data: immune responses
  - pharmacodynamics data: absent

- Vaccines are difficult to regulate

NRA functions relating to vaccines

1. Marketing authorization and licensing activities
2. Post-marketing surveillance (including AEFI surveillance)
3. NRA lot release
4. Laboratory access
5. Regulatory inspections
6. Oversight of clinical trials
Vaccines

Vaccines are special

59 countries have a functional NRA to regulate vaccines (2010):

Adapted from: http://www.who.int/phi/news/Presentation14.pdf
Vaccines

Vaccines are special

- preventive health care
  (most cost effective public health intervention)
- vaccines usually given to healthy individuals
- administered by trained person
- uniform dose & frequency (immunisation schedule)
- low tolerance for adverse reactions
- large number of vaccinations – potentially many coincidental events
Vaccines

Vaccines are special

- Combination vaccines (Hexavalent: diphtheria, tetanus, acellular pertussis, haemophilus influenzae type B, poliovirus and hepatitis B)

  Causality assessment?

- Simultaneous administration of vaccines

  Causality assessment?
Vaccines

vaccines are special

- lot-by-lot surveillance
- need for vaccine distribution data
- programmatic used products
  - childhood immunisation programme
  - occupational immunisation programme (health care professionals, military)
- programmatic errors
Vaccines

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**Vaccines**

Expanded Programme on Immunization

**Vaccines and schedule**

- **BCG, OPV:** at birth
- **DPT, OPV, Hepatitis B:** 6 - 10 - 14 weeks
- **Measles:** 9 months

- In some countries: yellow fever, rubella, *Haemophilus influenzae* type B, pneumococcal and meningococcal vaccines

- Tetanus toxoid to women at/before child bearing age
Evolution of Immunization Programme and Prominence of Vaccine Safety

**Programmatic Errors:**
- bacterial abscess
- severe local reaction
- high fever or sepsis
- BCG lymphadenitis
- toxic shock syndrome
- clusters of AEFI s

From RT Chen, CDC
Evolution of Immunisation Program and Prominence of Vaccine Safety

From RT Chen, CDC
Vaccines

public perception: BENEFIT < RISK

UK: Whole cell pertussis vaccine & neurological damage
Vaccines

public perception: BENEFIT < RISK

UK: Measles, Mumps, Rubella (MMR) vaccine & autism
public perception: **BENEFIT > RISK**

problems
• media seeking controversy
• consumer groups internet!

  *parents of vaccine-injured(??) children*

solutions
• official immunization information:
  - handling of vaccine safety concerns
  - vaccine risk communication
  - educate healthcare professionals
Vaccines

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Vaccines

pharmacovigilance & vaccines

spontaneous reporting system [SRS]

• separate for vaccines:
  Australia, Denmark, India, Italy, Mexico, USA, ……

• SRS for all drugs [vaccines included]:
  France, New Zealand, Sweden, United Kingdom, Netherlands …..

lack of communication:

  drug (ADR) - vaccine (AEFI)
  NRA/PV - NI P/ EPI
Vaccines

Potential objectives for AEFI Surveillance System

- detect, correct, and prevent programme errors
- identify problems with vaccine lots or brand
- prevent false blame from coincidental events
- maintain confidence by properly responding to parent/community concerns while increasing awareness (public and professional) about vaccine risks
- generate new hypotheses about vaccine reactions that are specific to the population
- estimate rates of occurrence on AEFI in the local population, compared with trial and international data

⇒ improving coverage, effectivity and safety
Vaccines

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Vaccines

classification of AEFI

- **vaccine reaction**
  event caused or precipitated by the vaccine when given correctly; caused by inherent properties of the vaccine

- **programmatic error**
  caused by error in vaccine preparation, handling, or administration

- **coincidental event**
  happens *after* immunization but **not** caused by it – a chance association

- **injection reaction**
  event from anxiety about or pain from the injection itself rather than the vaccine

- **unknown**
  whose cause can not be determined
**Vaccines**

**immune response & AEFI**

**common ADR concepts?**
- de-challenge?
- re-challenge?
- allergic reaction?

**vaccine specific ADR concepts?**
- autoimmune disease?
- allergic constitution?
Vaccines

age & AEFI

• age specific immune responses
  [polysaccharide vaccines immunogenic > 2 years of age]

• age specific infectious disease risks
  [Mumps infection complications in adolescents & adults]

• age specific AEFI
  - HHE [first year of life]
  - febrile convulsions [first 5 years of life]
Vaccines

AEFI notification

- vaccine (type)
- manufacturer
- lot number
- expiry date
- shipped from..... to ........
- route / site of administration
- time to onset
- nr. of previous doses
- vaccinated at ...?
# Vaccines

## AEFI Notification

### Special Reporting Form (Example Canada)

### Report of Adverse Events Following Immunization (AEFI)

<table>
<thead>
<tr>
<th>1a. Unique episode #</th>
<th>1b. Region #</th>
<th>2. Impact Lin:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

### Patient Identification

<table>
<thead>
<tr>
<th>First name</th>
<th>Last name</th>
<th>Health number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Address of usual residence:</th>
<th>Postal code:</th>
<th>Phone: ( ) - (ext #: )</th>
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<tbody>
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</table>

<table>
<thead>
<tr>
<th>Information Source: First name:</th>
<th>Last name:</th>
<th>Relation to patient:</th>
</tr>
</thead>
<tbody>
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</table>

### Contact info, if different:

<table>
<thead>
<tr>
<th>Phone: ( ) - (ext #: )</th>
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<tbody>
<tr>
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</tbody>
</table>

### Information at Time of Immunization and AEFI Onset

<table>
<thead>
<tr>
<th>4a. At time of immunization</th>
<th>4b. Medical history (up to the time of AEFI onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date vaccine administered:</td>
<td>Concomitant medication(s)</td>
</tr>
<tr>
<td>Date of birth: YYYY / MM / DD</td>
<td>Known medical conditions/allergies</td>
</tr>
<tr>
<td>Age:</td>
<td>Acute illness/injury</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>Female</td>
</tr>
</tbody>
</table>

### Immunizing Agent

<table>
<thead>
<tr>
<th>Immunizing agent</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Lot number</th>
<th>Dose #</th>
<th>Dosage/unit</th>
<th>Route</th>
<th>Site</th>
</tr>
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<tbody>
<tr>
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</tr>
</tbody>
</table>

### Immunization Errors

<table>
<thead>
<tr>
<th>Did this AEFI follow an incorrect immunization?</th>
<th>Did an AEFI follow a previous dose of any of the above immunizing agents (Table 4c)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

### Impact of AEFI, Outcome, and Level of Care Obtained

<table>
<thead>
<tr>
<th>7a. Highest impact of AEFI: (Choose one of the following)</th>
<th>7b. Outcome at time of report:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did not interfere with daily activities</td>
<td>Death *</td>
</tr>
<tr>
<td>Interfered with but did not prevent daily activities</td>
<td>Permanent disability/incapacity *</td>
</tr>
<tr>
<td>Prevented daily activities</td>
<td>Not yet recovered *</td>
</tr>
</tbody>
</table>

### Level of care obtained: (Choose one of the following)

<table>
<thead>
<tr>
<th>Unknown</th>
<th>Non</th>
<th>Telephone advice from a health professional</th>
<th>Non-urgent visit</th>
<th>Emergency visit</th>
<th>Required hospitalization (days)</th>
<th>OR</th>
<th>Resulted in prolongation of existing hospitalization (by days)</th>
<th>Date of hospital admission</th>
<th>Date of hospital discharge</th>
<th>Date of hospital discharge</th>
<th>Date of hospital discharge</th>
</tr>
</thead>
</table>

### Treatment received: (Provide details of all treatments including self treatment, in section 10)

<table>
<thead>
<tr>
<th>7d. Treatment received:</th>
<th>No</th>
<th>Unknown</th>
<th>Yes</th>
</tr>
</thead>
</table>

### Reporter Information

<table>
<thead>
<tr>
<th>Setting:</th>
<th>Physician office</th>
<th>Public health</th>
<th>Hospital</th>
<th>Other, specify:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phone:</td>
<td>( )</td>
<td>( )</td>
<td>(ext #: )</td>
<td>( )</td>
</tr>
<tr>
<td>Address:</td>
<td>City:</td>
<td>Prov/Terr:</td>
<td>Postal code:</td>
<td>Date reported: YYYY / MM / DD</td>
</tr>
<tr>
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</tr>
</tbody>
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Vaccines

causality & AEFI

• in short: can it? did it? will it?

AIDÉ MEMOIRE

Purpose: This aide-mémoire serves as a guide to a systematic, standardized causality assessment process for serious adverse events following immunization (including clusters). It is intended to be used by staff at the national (or first sub-national) level.

AEFI causality assessment overview

All reported AEFIs require verification of the diagnosis, coding, review, collation and storage; if an AEFI is serious, it requires triage for systematic, standardized causality assessment. Many AEFIs, and their reporting, may not be concerned with causality, and may not

Routine AEFI review and triage

All AEFIs need to be screened and triaged by trained immunization programme staff to determine the subsequent steps needed (follow up, action, addition to database, analysis, reference for systematic causality assessment, etc.).

AEFI must be reviewed to verify the diagnosis and the timing with respect to immunization, and to classify them on the basis of standardized national case definitions.¹

¹ Standardized case definitions for some AEFIs are available from the Brighton Collaboration at (http://www.brightoncollaboration.org). Use of these definitions is

WORLD HEALTH ORGANIZATION

ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI): CAUSALITY ASSESSMENT
Vaccines: cause of AEFI?

- antigen
- adjuvans [aluminium salts, ASO3, AS04, MF59]
- preservative [thimerosal]
- stabilisor [gelatine]
- antibiotics [neomycin]
- others - ph
  - osmolarity
When is "fever" FEVER?

*Some studies with >1 cut off

Case definitions for AEFI

Nr of Studies (N=120)*
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Global monitoring of AEFI

Global analysis and response
- GACVS
- Other global or regional advisory bodies

National AEFI surveillance, investigation, and response
- Immunization programme
- Regulatory authority
- AEFI review committee
- Other support groups

Global signal detection and evaluation
- WHO PIDM
- Global vaccine safety data link
- Other partners

Product monitoring
- Vaccine manufacturers
- Licensing authorities in country of manufacture
- Procurement agencies

Global capacity building and harmonized tools
- WHO and partners
- Brighton Collaboration
- CIOMS/WHO working group

Product monitoring
Improving global monitoring of vaccine safety: A quantitative analysis of adverse event reports in the WHO Adverse Reactions Database

Megan Letourneau, George Wells, Wikke Walop and Philippe Duclos

Vaccine, Volume 26, Issue 9, 26 February 2008, Pages 1185-1194
## Top 10 drugs in <1 year of age

<table>
<thead>
<tr>
<th>Reported drug</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria and tetanus toxoids and pertussis</td>
<td>7724</td>
<td>6714</td>
</tr>
<tr>
<td>Poliovirus vaccine live oral</td>
<td>6524</td>
<td>5681</td>
</tr>
<tr>
<td>Haemophilus B conjugate vaccine</td>
<td>6315</td>
<td>5467</td>
</tr>
<tr>
<td>Hepatitis B vaccine</td>
<td>3243</td>
<td>2898</td>
</tr>
<tr>
<td>Diphtheria/Tetanus/Pertussis/Haemophilus B vaccine</td>
<td>2375</td>
<td>2070</td>
</tr>
<tr>
<td>Poliomyelitis vaccine inactivated</td>
<td>1430</td>
<td>1281</td>
</tr>
<tr>
<td>Measles, mumps and rubella vaccine</td>
<td>963</td>
<td>894</td>
</tr>
<tr>
<td>Varicella virus vaccine, live</td>
<td>831</td>
<td>773</td>
</tr>
<tr>
<td>Palivizumab</td>
<td>681</td>
<td>521</td>
</tr>
<tr>
<td>Haemophilus influenzae B</td>
<td>661</td>
<td>620</td>
</tr>
</tbody>
</table>
UMC and AEFI

AEFI reports \((n = 246,877)\) versus ‘Other’ reports \((n = 2,440,241)\)

Improving global monitoring of vaccine safety: A quantitative analysis of adverse event reports in the WHO Adverse Reactions Database Megan Letourneau, George Wells, Wikke Walop and Philippe Duclos

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UMC and AEFI

Global PMS Network

Members (12)
Albania, Brazil, China, India (1 State), Iran, Kazakhstan, Mexico, Senegal, Sri Lanka, Tunisia, Uganda, Vietnam

Uppsala Monitoring Centre (UMC)
WHO Collaborating Centre for International Drug Monitoring

Network Secretariat & Management Group
WHO (HQ, Regions), UMC
UNICEF + PAHO Revolving Fund
Representation of Member Countries

Technical Oversight Committee
• Funding source: Gates Foundation PQ grant (approx 3.8 million USD)
UMC and AEFI

Global PMS Network: Expected outputs

- Improved reporting and analysis of vaccine safety data at global level
  - Quality of data
  - WHO-UMC tools and resources for vaccines
  - Signal generation
- Improved assessment of causality
  - Investigation capacity
  - Individual case causality assessment
  - Assessment of signals (special studies as needed)
UMC and AEFI

Pharmacovigilance training course 2001
Safety Monitoring of a New Pentavalent Vaccine in the Expanded Programme on Immunisation in Ghana

Alexander N.O. Dodoo,1 Evonna Renner,2 Adrianus C. van Grootel,1 Jerry Labadie,3 Kwadwo O. Antwi-Agyei,4 Selasie Hayibor,1 Johannes Addison,1 Victoria Paapoe2 and Augustina Appiah-Danquah1

1 Centre for Tropical Clinical Pharmacology & Therapeutics, University of Ghana Medical School, Accra, Ghana
2 Department of Child Health, University of Ghana Medical School, Accra, Ghana
3 Netherlands Pharmacovigilance Centre Lareb ‘s-Hertogenbosch, The Netherlands
4 The Expanded Programme on Immunization, Ghana Health Service, Accra, Ghana

Abstract

Background and objective: Safety monitoring of vaccines used in expanded programmes on immunisation is important in all countries, including those with limited resources. As the rates of target diseases decrease, parents become less accepting of even minor common adverse events. Identification, detection, prevention and appropriate communication of adverse events following immunisation (AEFI) are therefore essential to preserve the integrity of immunisation programmes and protect public health. The objective of this study was to document the occurrence of common minor AEFI associated with a newly introduced pentavalent vaccine for routine immunisation in Ghana’s expanded programme on immunisation.