Specificities of Vaccine Pharmacovigilance

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Lessens learned from vaccine safety issues

1926: Diphtheria toxin incomplete inactivation
1929: BCG contaminated strain leading death of 72 infants
1942: YF vaccine - stabilizer (human albumin) contaminated with Hep B
1955: Cutter incident (incomplete inactivation of polo vaccine)
1997: HepB vaccination and demyelinating disease
1999: RotaShield and intussusception
2010: Pandemrix and narcolepsy
Vaccine Pharmacovigilance Definition (WHO)

The science and activities relating to the detection, assessment, understanding, prevention and communication of adverse events following immunization (AEFIs) or any other possible vaccine or immunization-related problems.

Vaccine Pharmacovigilance also known as Vaccine Safety
Vaccine Pharmacovigilance is a key global public health function

PV has a vital role in Public Health

- to ensure patient safety
- to prevent or reduce harm of medicines
- to improve the use and benefit of medicines

Public trust in vaccine safety is key for successful immunization programs
Vaccine Pharmacovigilance is a key global public health function

Specific aims of PV are

• to collect good quality data on medicines and their safety
• to improve public health by evaluating and monitoring safety
• to contribute to the assessment of the benefit, risk and effectiveness of medicines.
Vaccine Pharmacovigilance in Industry

Vaccine Pharmacovigilance is a key responsibility for all vaccine manufacturers

- **Legally responsible** for the vaccine quality, safety and efficacy
- **Shared responsibility**, not only a regulatory requirement
- **Proactive vaccine safety surveillance** during the whole life-cycle
Why Vaccine Pharmacovigilance?

- To protect the vaccinated individuals as well as the population from harm
- To ensure lot-related safety
- To ensure ongoing effectiveness
- To ensure continuous positive benefit risk ratio
- To clarify signals from individual AEFIs
- To be able to react to changes of the benefit risk balance
- To protect the vaccine from false positive signals
- To respond to safety crisis
Important specific - Vaccines versus Drugs

Vaccines: Higher safety standards expected

Vaccines
- given to healthy populations, all ages
- preventive aim
- biological products with complex compositions
- de- and re-challenge negligible for assessment
- mainly immunological considerations
- short duration of exposure with a long time for response
- minor adverse events are important (can jeopardize acceptance or indicate program error)
- may cause the illness they are meant to prevent (e.g., VAPP)

Drugs
- given to sick populations, mainly adults
- therapeutic aim
- chemical products with many drug classes
- de- and re-challenge important for assessment
- mainly pharmacological considerations
- longer duration of exposure with shorter time for response
- minor adverse events rarely important
# Main differences between Vaccines and Drugs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Small molecule drugs</th>
<th>Prophylactic vaccines</th>
<th>Implication for vaccine Pharmacovigilance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>• Well defined products • Low batch variability</td>
<td>• Complex biologicals • Batch-related variability • Potential contamination with adventitious agents (from cell banks, substrates etc.) • Can contain live attenuated organisms</td>
<td>• Batch-related safety surveillance • Monitoring for infections</td>
</tr>
<tr>
<td>Indication and administration</td>
<td>• Largely therapeutic • Administration triggered by disease or condition</td>
<td>• Prophylactic • Administration «imposed» by, recommended or mandatory vaccination schedules</td>
<td>• Usually co-suspect vaccines according to vaccination schedules • Timing of administration of childhood vaccines may coincide with peak period or onset of conditions (e.g., sudden infant death, autism) • Low risk tolerance</td>
</tr>
<tr>
<td>Population</td>
<td>• Patients, mainly adults</td>
<td>• Healthy subjects, largely children</td>
<td>• Low risk tolerance in healthy and vulnerable population</td>
</tr>
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# Main differences between Vaccines and Drugs

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<tr>
<td>Exposure</td>
<td>• Often chronic</td>
<td>• Large segments of population are exposed</td>
<td>• Low case volume</td>
</tr>
<tr>
<td></td>
<td>• Dosage varies depending on disease severity</td>
<td>• Exposure to very few single doses at fixed dosage in a given population</td>
<td>• High impact of safety issues</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>• Concepts of dose-dependency, de-challenge, re-challenge usually not applicable</td>
</tr>
<tr>
<td>Benefit-risk perception</td>
<td>• Individual benefit easy to perceive</td>
<td>• Individual benefit (i.e., not contracting disease) usually not perceived</td>
<td>• Low risk tolerance</td>
</tr>
<tr>
<td></td>
<td>• Risk acceptance depends on disease severity and expectation of benefit</td>
<td>• Population benefit (i.e., herd immunity/protection) rarely perceived</td>
<td>• Challenge of appropriate safety communication</td>
</tr>
<tr>
<td></td>
<td>• Risk acceptance can be high for serious conditions</td>
<td>• Low risk acceptance by parents for their children</td>
<td>• Impact of individual serious or fatal cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lack of vaccine confidence problematic across various cultures</td>
<td>• Preparedness for vaccine confidence crisis</td>
</tr>
<tr>
<td>Lack of effect</td>
<td>• Affects individual patient</td>
<td>• Vaccination failure decreases herd protection / affects population</td>
<td>• Product-specific assessment of vaccination failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Expedited reporting of cases</td>
</tr>
</tbody>
</table>
Perceived Benefit and Acceptance of Risks


Vaccines
Preventive treatments
Drugs / Therapeutics

Size of the treated population
Perceived benefit of treatment
Acceptance of adverse reactions
Focus of Vaccine Safety Surveillance

- Intensive investigation of rare adverse events
- Case definitions for case ascertainment (i.e., Brighton Case Definitions)
- Long-term follow up in post-marketing setting
- Adverse events affecting acceptability of immunization
- Age-relatedness of AEs / safety in different target groups
- Methods of assessing causality of serious and rare adverse events
- Batch-relatedness of adverse events
- Safety surveillance in pre-licensure/post-licensure
- Vaccine risk communication
AEFI: any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The AE may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.
Adverse Events following immunization AEFI
Reaction to vaccine

Different vaccines are prepared with different types of antigens, using different scientific methods:
- Attenuation
- Inactivation,
- Fragmentation
- Conjugation
- Recombination DNA technology

Some vaccines include components to enhance immune response, such as adjuvants, e.g.
- Aluminum salts
- Monophosphoryl lipid A (MPL)
- AS01/AS02/AS03 /AS04
- MF59
- CpG 1018 Adjuvant

Adjuvants are part of the benefit –risk equation

Added for stability of conservation:
- Preservatives
- Stabilizers
Cause-specific Definitions

**Vaccine product-related reaction**
AEFI caused or precipitated by the vaccine when given correctly, and due to one or more of the inherent properties or quality defects of the vaccine.

**Vaccine quality defect-related reaction**
AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects (defined as any deviation of the vaccine product as manufactured from its set quality specifications) of the vaccine product including its administration device as provided by the manufacturer.

**Immunization error related reaction**
AEFI caused by inappropriate vaccine handling, prescribing and administration, and thus by its nature is preventable.

**Immunization anxiety-related reaction**
AEFI arising from anxiety about immunization (may include anticipated pain or other fears related to the vaccine(s) or its administration).

**Coincidental event**
- AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
**Vaccine reaction rate**

**Observed rate**
Total number of observed adverse events in a cohort of e.g., 10,000: observed AE rate is 6/10,000

**Background rate**
Number of observed adverse events in an unvaccinated cohort (not related to vaccination) e.g., background rate 4/10,000

**Attributable rate**
(Vaccine reaction rate)
Number of observed AEFIs in a vaccinated cohort related to vaccination e.g., attributable rate 2/10,000

**Attributable rate (Vaccine reaction rate) = Observed rate – Background rate**
Vaccination Failure (Lack of Effect)
Causes of vaccination failures

<table>
<thead>
<tr>
<th>Type of failure</th>
<th>Causes</th>
</tr>
</thead>
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<tr>
<td><strong>Failure to vaccinate</strong></td>
<td></td>
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<tr>
<td>Usage-related</td>
<td>- Administration error (wrong route, dose, diluent)</td>
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<tr>
<td></td>
<td>- Vaccination schedule not adhered to</td>
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<tr>
<td></td>
<td>- Wrong storage (out of cold chain)</td>
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<td></td>
<td>- Expired vaccine used</td>
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<tr>
<td>Program-related</td>
<td>- Suboptimal recommendation (number and time points of doses - primary and booster)</td>
</tr>
<tr>
<td></td>
<td>- Vaccine shortage</td>
</tr>
<tr>
<td><strong>Vaccine failure</strong></td>
<td></td>
</tr>
<tr>
<td>Host-related</td>
<td>- Immunodeficiency, immnosuppressive therapy, health status</td>
</tr>
<tr>
<td></td>
<td>- Waning immunity, age-related decrease in immune response</td>
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<tr>
<td></td>
<td>- Low/Non-responders</td>
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<tr>
<td></td>
<td>- Interference (antibodies or infection)</td>
</tr>
<tr>
<td>Vaccine-related</td>
<td>- Vaccine not 100% efficacious</td>
</tr>
<tr>
<td></td>
<td>- Incomplete coverage of strains, variants, mutants</td>
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<tr>
<td></td>
<td>- Vaccine-vaccine interactions (co-administered vaccines)</td>
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<td></td>
<td>- Manufacturing related (batch variation, quality defect)</td>
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</tbody>
</table>

Vaccination Failure (Lack of Effect)
Assessment of efficacy related cases

Vaccines are not 100% effective. Vaccination failure is not an event, but an assessment based on vaccine specific guidelines.

Diseases attributed to vaccines - without attributed causality

Examples:

- Autoimmune disorders
- Diabetes mellitus type I
- Graves’ disease
- Multiple sclerosis / neuro-inflammatory diseases
- Neuro-developmental disorders (e.g., ADHD, autism, etc.)
- Rheumatoid arthritis
- Systemic lupus erythematosus
Adverse events of special interest (AESIs) in Vaccine Pharmacovigilance

A pre-identified and pre-defined medically significant event that has the potential to be causally related with a vaccine product that needs to be carefully monitored and confirmed by further specific studies.
Adverse events of special interest AESIs

**Examples:**

- Anaphylaxis
- Encephalopathy / encephalitis
- Neurological disorders (e.g., Guillain Barré syndrome, Bell’s palsy)
- Aseptic meningitis
- Vasculitis
- Thrombocytopenic purpura
- Vaccine-enhanced disease (e.g., COVID-19 vaccines, Dengue vaccines)
Immunization, Disease Rates and Public Concern

- Public concern about disease (1)
- Increasing coverage (2)
- Increased public concern about vaccine safety (3)
- Lack of evidence-based safety data (4)
- Loss of confidence (5)
- Resumption of confidence (6)

Chen, CDC 1996, adapted by Kohl / Loupi 2004

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“Don’t think of it as getting a flu shot. Think of it as installing virus protection software.”

Thank You
Questions?