Regulatory challenges of prequalified vaccines supplied through the UN system
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Safety monitoring challenges with prequalified vaccines
What we worry about?

Unexpected events at time of licensure:

- Polio following IPV
- Intussusception following rotavirus vaccine
- Narcolepsy and H1N1 vaccination

Known vaccination problems and vaccine reactions:

- Immunization errors
- Anaphylaxis
- VAPP

Rumours, poor science and over-reaction:

- HPV vaccine coverage in Denmark
- Multiple sclerosis and hepatitis B vaccine in France
- OPV and chronic diseases in Nigeria
- Thiomersal and neuro-developmental disorders
- Pentavalent vaccine in Asian countries
Pentavalent vaccines in Asian countries

- Pentavalent DTwP-HepB-Hib vaccine introduced in >170 countries to date
- In three Asian countries, serious AEFI in the first week after introduction raised concerns and in 2 countries led to a suspension of vaccine use for more than one year
- Investigations did not identify any causal relationship between vaccine use and serious AEFI
## Pentavalent vaccine in Asian countries

<table>
<thead>
<tr>
<th>Country</th>
<th>AEFI</th>
<th>Action from authorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5 deaths in temporal association with vaccine (Manufacturer X) over first four months of introduction. Assessment suggest SIDS.</td>
<td>Suspend vaccine and reintroduce after 21 months.</td>
</tr>
<tr>
<td>B</td>
<td>5 cases with a history of fever and central nervous system symptoms starting 1 to 4 days after vaccine (Manufacturer Y) administration during first two months of introduction, including four deaths.</td>
<td>Suspend vaccine and reintroduce after 15 months.</td>
</tr>
<tr>
<td>C</td>
<td>3 deaths in temporal association with vaccine (Manufacturer X) over first two months of introduction. Provincial suspension as precautionary measure. WHO investigation within one month of suspension does not identify causal relationship.</td>
<td>Resumption of vaccination activities and extension to whole country.</td>
</tr>
<tr>
<td>Country</td>
<td>Infant mortality rate per 1000 live births (IMR)</td>
<td>Number of births per year (N)</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bhutan</td>
<td>42</td>
<td>15 000</td>
</tr>
<tr>
<td>Canada</td>
<td>5</td>
<td>388 000</td>
</tr>
<tr>
<td>China</td>
<td>13</td>
<td>16 364 000</td>
</tr>
<tr>
<td>Indonesia</td>
<td>25</td>
<td>4 331 000</td>
</tr>
<tr>
<td>Iran</td>
<td>21</td>
<td>1 255 000</td>
</tr>
<tr>
<td>Mexico</td>
<td>13</td>
<td>2 195 000</td>
</tr>
<tr>
<td>Sudan</td>
<td>57</td>
<td>1 477 000</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>4</td>
<td>761 000</td>
</tr>
</tbody>
</table>

Note: Assumes uniform distribution of deaths and immunization over the time period.
*The assumption here is a three-dose schedule for either DTP or PVV, with 90% coverage for each dose.
GACVS meetings related to HPV vaccines

Since licensure in 2006, over 270 million doses of HPV vaccines have been distributed. GACVS first reviewed the safety data in 2007,12 and subsequently in 2008,13 2009,14 2013,15 201416 and 2015.17 Early on, the Committee was presented signals related to anaphylaxis and syncope. The risk of anaphylaxis has been characterized as approximately 1.7 cases per million doses, and syncope was established as a common anxiety or stress-related reaction to the injection. No other adverse reactions have been identified and GACVS considers HPV vaccines to be extremely safe.

There are now accumulated safety studies that include several million persons25 and which compare the risks for a wide range of health outcomes in vaccinated and unvaccinated subjects. However, despite the extensive safety data available for this vaccine, attention has continued to focus on spurious case reports and unsubstantiated allegations. The Committee continues to express concern that the ongoing unsubstantiated allegations have a demonstrable negative impact on vaccine coverage in a growing number of countries, and that this will result in real harm.26 While ongoing monitoring
HPV vaccine – Cohort studies

Original Investigation

Quadrivalent HPV Vaccination and Risk of Multiple Sclerosis and Other Demyelinating Diseases of the Central Nervous System

Nikolai Madrid Scheller, MB; Henrik Svanström, MSc; Björn Pasternak, MD, PhD; Lisen Arnheim-Dahlström, PhD; Karin Sundström, MD, PhD; Katharina Fink, MD, DrMed; Anders Hviid, DrMedSci

CONCLUSIONS AND RELEVANCE  In this study with nationwide coverage of 2 Scandinavian countries, qHPV vaccination was not associated with the development of multiple sclerosis or other demyelinating diseases. These findings do not support concerns about a causal relationship between qHPV vaccination and demyelinating diseases.

New vaccine products for geographical indications

Ebola vaccine image from
http://www.huffingtonpost.com/2014/12/23/ebola-vaccine-development-funding_n_6375006.html

Malaria image from
http://navymedicine.navylive.dodlive.mil/archives/5689
Way forward

Strong methodologies to address concerns:

- Harmonized tools
- Methodological excellence
- Adjusted to local circumstances
- Information exchange (including industry)

International collaborations:

- Multicenter studies
- Training curriculums
- Laboratory access

Expert scientific advice:

- Local, regional and global committees
- Networks for technical support
Effective vaccine pharmacovigilance systems are established in all countries
Minimal capacity

- AEFI surveillance
- **Core variables**
- **Stimulated reporting**
- **National database**
- Independent experts
- Communication strategy

**PV resources**

**Managerial principles**

- Regulatory framework
- Lines of accountability
- Institutional development plan
- Commitment to share information
8 Implementation Objectives of the Global Vaccine Safety Blueprint 1.0

AEFI Detection: To strengthen vaccine safety monitoring in all countries

Investigation of Safety Signals: To strengthen the ability of countries to investigate vaccine safety signals

Vaccine Safety Communication: To develop vaccine safety communication plans at country level

Tools and Methods: To develop internationally harmonized tools and methods to support country vaccine safety activities

Regulatory Framework: To promote a legal, regulatory and administrative framework for the safety of vaccines at national, regional and international levels

Public-Private Information Exchange: To put in place systems for appropriate interaction between national governments, multilateral agencies, and manufacturers

Global Analysis and Response: To provide expert advice on vaccine safety issues at national, regional and international levels

Technical Support and Trainings: To strengthen regional and global technical-support platforms that meet countries’ expressed needs

Technical objectives

Enabling objectives

8 strategic objectives support the Blueprint main goals
AEFI reports 2010 & 2018

Countries meeting GVAP indicator, 2010

Cumulative AEFI reports from WHO/UNICEF joint reporting 2000-2017

Countries meeting GVAP indicator, 2018

Disclaimer:
The location and names chosen for the categories used in this map may not apply for expanded surveillance in other parts of the World Health Organization (WHO) region. This map is intended to provide a broad overview of the current status of reporting of adverse events following immunization (AEFI) in 2010 and 2018. The data presented in this map are based on information reported by countries to WHO/UNICEF. The data may not be representative of the actual situation in a country and should be used with caution. The map is not intended as a diagnostic tool for assessing the quality of AEFI reporting systems. It is not designed to evaluate the completeness, quality, or timeliness of reporting. The map is not intended to be used for reporting purposes or to assess compliance with the Global Vaccine Action Plan (GVAP) indicator. The map is not intended to be used for comparative purposes or to assess the extent to which countries are meeting the GVAP indicator. The map is not intended to be used for decision-making purposes or to assess the effectiveness of AEFI reporting systems.
Strategic areas for Blueprint 2.0

**Technical**
- Surveillance of adverse events following immunization (AEFI)
- Enhanced communication
- Fragile states and emergency situation (ex. Ebola)

**Enabling**
- Regulatory framework
- Governance and systems development
- Coordination of safety systems
WHO and partners technical resources

Vaccine safety: www.who.int/vaccine_safety/en/

Surveillance tools
Aide-memoires
Information sheets
Other technical docs
Links
Communicating about vaccines facing new challenges

• Decline of childhood infections
• Development of new communications technology
• Increasing volume of information from many sources, including the anti-vaccination lobby
• New vaccines target wider age-range
• Concern over new viruses
Vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence.

N. McDonald et al. Vaccine 2015

A clear lesson from the examples in this Special Issue is that immunization programs must systematically and comprehensively address not only supply-side but also demand-side strategies, and do so from inception through implementation.
Vaccine Safety Net

- Linking websites and web analytics for data driven vaccine safety information and communication
- Referencing from the global digital platforms

- Social media catalyzer (Twitter, Fb, blogs)
- International research in communication for vaccines