

Module 3: Introduction to Vaccine Pharmacovigilance

Vaccine PV Fellowship
WHO Collaborating Centre for Advocacy and
Training in Pharmacovigilance
Accra, Ghana
7th – 18th September 2015

Learning Outcomes

- At the end of this module, participants are expected to:
 - Know the definition of “vaccine pharmacovigilance”
 - Know the important differences between “pharmacovigilance” and “vaccine pharmacovigilance”
 - Appreciate the need for specialized monitoring of adverse events following immunization especially the public health imperatives

Food for thought

Vaccination programmes suffer from their own successes..... Because serious vaccine-induced injury is rare, there are significant challenges in getting good evidence on case causality studies and the success of mass vaccination makes it difficult to do epidemiological studies with satisfactory controls

– Edwards, I.R. (2009). *A risk worth taking?*. *Drug Saf* 32(10):1-4

What is pharmacovigilance?

- Pharmacovigilance is the science and activities relating to the **detection, assessment, understanding and prevention** of adverse effects or any other drug-related problem
 - *The importance of pharmacovigilance, WHO, 2002; EU GvP Definition (in line with WHO's definition)*

What is vaccine pharmacovigilance?

- Vaccine pharmacovigilance is defined as the science and activities relating to the **detection, assessment, understanding, prevention, and communication** of *adverse events following immunization, or of any other vaccine- or immunization-related issues*
 - *Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012.*

Goal of Vaccine Pharmacovigilance

Early detection of and appropriate and timely response to AEFIs in order to minimize negative effects to the health of individuals and lessen the potential negative impact on immunization of the population

Elements to consider in vaccine PV- I

- Vaccines are usually administered to healthy people, including infants
- Vaccines may be administered to the vast majority of the population or of a birth cohort or to groups at high risk for disease complications
- Subpopulations may be more susceptible to experience certain AEFIs

Elements to consider in vaccine PV- II

- The age at the time of immunization may coincide with the emergence of certain age-related diseases (e.g. neurodevelopmental disorders)
- Immunization with certain vaccines is mandated in some countries
- The benefits of immunization may not be immediately visible, particularly if the target disease incidence is low

Elements to consider in vaccine PV- III

- Due to the low acceptance of risks, intensive investigation of serious AEFIs, even if rare, is necessary
- Non-serious AEFIs may signal a potentially larger problem with the vaccine or immunization, or have an impact on the acceptability of immunization in general
 - They should therefore also be monitored and reported!

Elements to consider in vaccine PV- IV

- Appropriate methods are needed to detect and assess potential causal association of serious, rare, and/or delayed adverse events
- Consideration of dechallenge and rechallenge differs for vaccines compared with other medicinal products
 - Vaccines usually administered only once or with long intervals, and serious AEFIs often prevent further vaccine administration
 - Dechallenge not applicable to vaccines, given their long-term immunological effects

Elements to consider in vaccine PV- V

- Vaccines are often administered concomitantly with other vaccines, making causal attribution to a specific vaccine difficult
- The administration of live vaccines can lead to disease caused by the attenuated organisms in vaccinees or their contacts
 - Should be differentiated from coinciding natural infection



Elements to consider in vaccine PV- VI

- Vaccines are complex biological products, which may include multiple antigens, live organisms, adjuvants, and preservatives
 - Batch information critical for vaccines
 - Each component may have unique safety implications
- New vaccines are increasingly based on new production and administration technologies, with new adjuvants and alternative routes of administration, necessitating adapted safety monitoring systems



Elements to consider in vaccine PV- VII

- Vaccines may elicit herd immunity
 - Critically important when undertaking benefit/risk assessment
- Effective communication regarding safety of vaccines and immunization is challenging
 - Despite strong evidence that a serious adverse event is not related to immunization, perceptions of harm can have a negative impact on immunization

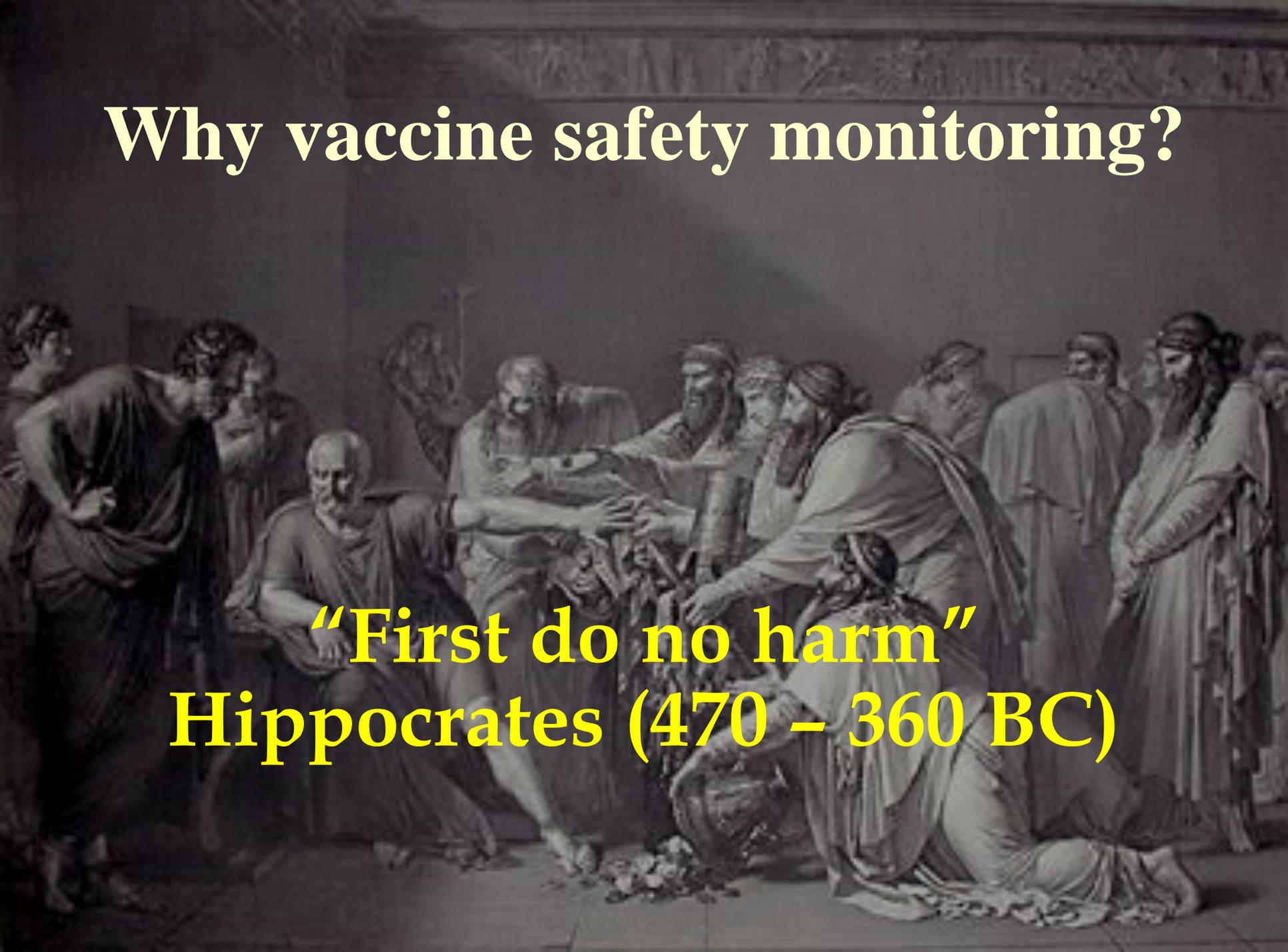
Vaccine PV and Vaccine Regulation

- Vaccine PV is an essential component of vaccine regulation which involves
 - Marketing authorization and licensing
 - Post marketing surveillance (including safety monitoring)
 - System of lot release
 - Laboratory access
 - Regulatory inspections
 - Oversight of clinical trials

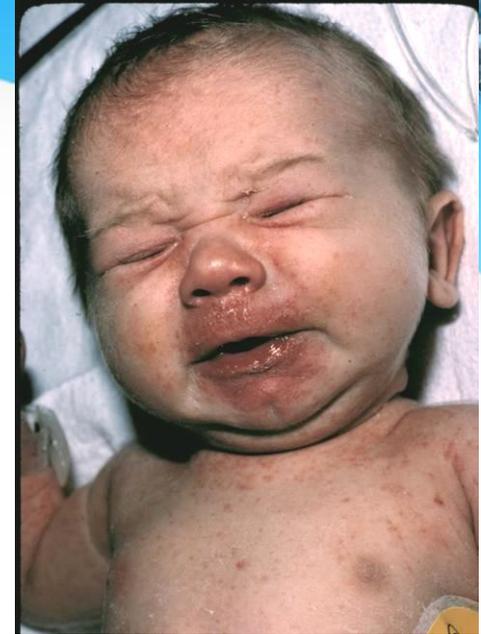
Why is vaccine pharmacovigilance necessary?

11 March 2011

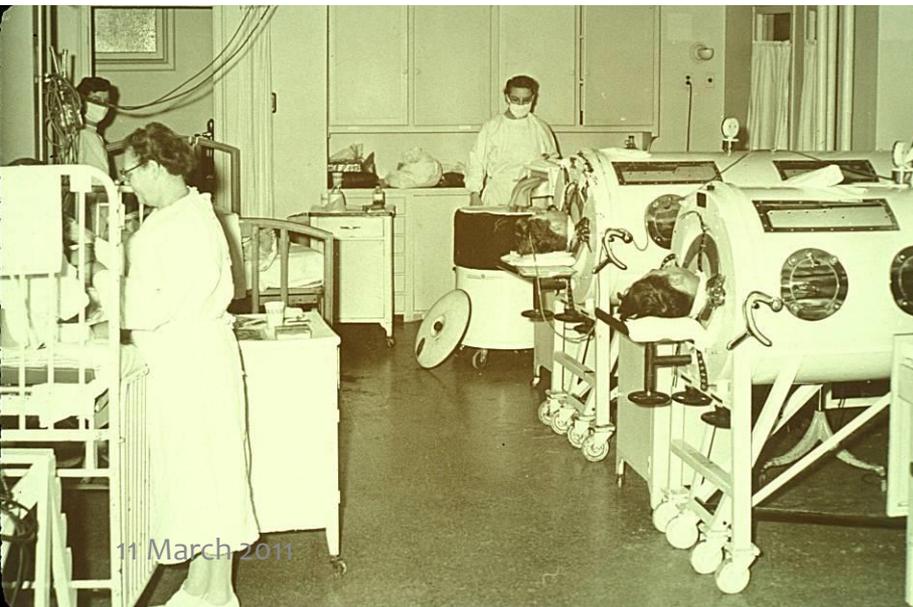
Why vaccine safety monitoring?



“First do no harm”
Hippocrates (470 – 360 BC)



Today, many parents and providers have not been exposed to the gruesome impact of **Vaccine preventable diseases**



Slide courtesy of Dr. Walt Orenstein



Vaccines used in NIPs are considered safe and effective.



Adverse events may still occur following vaccination.

- Most adverse events are minor e.g., redness at injection site, fever
- More serious events can occur, although infrequent e.g., seizures, anaphylaxis



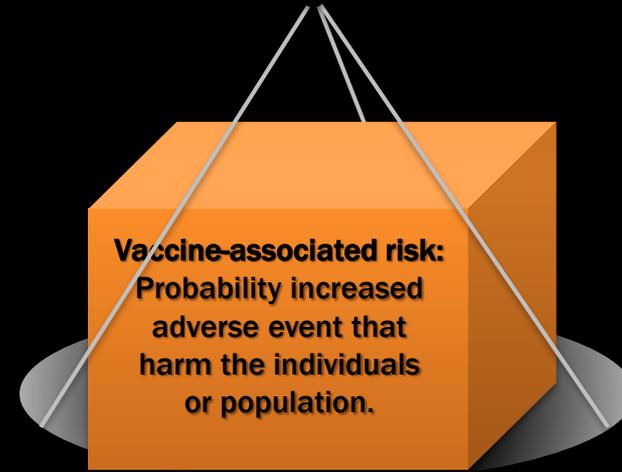
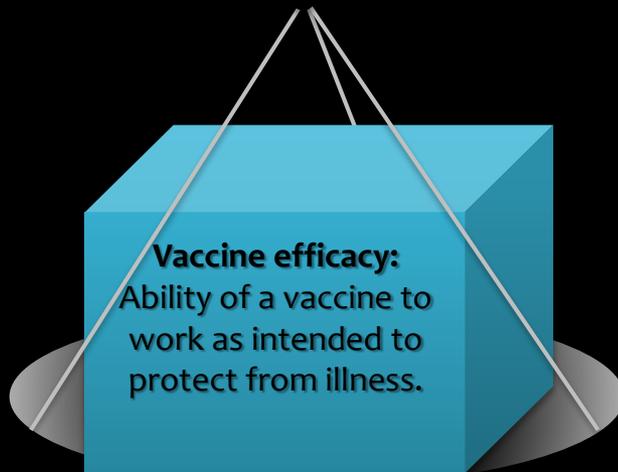
Public trust is key to the success of vaccination programmes.





Balancing efficacy and safety of a vaccine

Potential benefits of an effective vaccine must be weighed against potential risk of an AEFI.



Regulatory authorities must establish risk/benefit assessment of the immunization with a vaccine.

Why Vaccine PV?

- Clinical trials of vaccine often involve a limited number of participants
 - The numbers in vaccine clinical trials are typically much higher than in drug clinical trials
- Clinical trial typically (not always) excludes special groups and vulnerable populations
 - Vaccine trial often involves children but excludes pregnant women, the immuno-compromised, those with co-morbid conditions etc
- In real life use, some vaccines may need to be withdrawn due to safety and/or quality concerns or when the benefits/risk ratio is unfavourable (or appears so)

Keywords: wyeth-lederle, withdraws, rotashield, vaccine, updated, story, cases

Wyeth-Lederle withdraws RotaShield vaccine - updated story

Article | 21 October 1999

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Wyeth-Lederle says it has voluntarily withdrawn its rotavirusgastroenteritis vaccine RotaShield (live oral tetravalent rotavirus) from the market and requested the immediate return of all doses of the product following reports of intussusception in infants.

Earlier this year, Wyeth-Lederle suspended distribution and administration of the vaccine after the Vaccine Adverse Events Reporting System received 15 reports of intussusception (Marketletter July 26). An additional five cases had also been documented by the Minnesota Department of Health.

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Aquila victorious in Stimulon patent dispute
18 October 1999

Wyeth-Lederle withdraws RotaShield

Global Vaccine Safety

Global Advisory Committee on Vaccine Safety, 9-10 June 2005

Published in the WER 15 July 2005

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body reporting to WHO, was established to deal with vaccine safety issues of potential global importance independently and with scientific rigour.¹ GACVS held its twelfth meeting in Geneva, Switzerland, on 9–10 June 2005.² The following issues, inter alia, were considered.

Mouse brain-derived Japanese encephalitis vaccine

The Committee considered the decision taken by the Government of Japan on 30 May 2005 to suspend routine vaccination with the mouse brain-derived Japanese encephalitis (JE) vaccine currently used in Japan.³ This decision followed a review by the Japanese national advisory committee on vaccine adverse events of a single case of acute disseminated encephalomyelitis following JE vaccination and the national committee's conclusion that it could not rule out a causal link with the vaccine. GACVS was advised that there is no definite evidence of an increased risk of acute disseminated encephalomyelitis temporally associated with JE vaccine and a causal link has not been demonstrated. The national authority recommends vaccination in high-risk areas only and for travel to endemic regions. The Japanese Government expects that the national recommendation for vaccination will be reconsidered when newer, possibly safer, inactivated JE vaccines become available. GACVS concluded on the information presently available, that there is

Why Vaccine PV?

- Vaccines are **special** and **complex**
- Vaccines are complex
 - In their composition
 - In their usage or schedule for use
- Vaccines are special
 - Vaccination represent one of the most remarkable public health interventions, helping in disease reduction, elimination or eradication
 - Victim of its own success?

Unsafe vaccines can have serious consequences

Safety crises derail immunization programs

- **Real incidents**
 - Tuberculosis following oral BCG
 - Polio following IPV
 - H1N1 immunization and GBS, Narcolepsy
- **Real safety issues**
 - Programme errors.
 - Anaphylaxis.
 - VAPP.
 - Disseminated BCG disease
- **Rumours, poor science and over-reaction**
 - Pertussis vaccine coverage in the UK
 - MS and hepatitis B vaccine in France
 - OPV and chronic diseases in Nigeria
 - Thiomersal and neuro-developmental disorders



Exercise

- What are the issues likely to be encountered following the approval for use of the malaria vaccine?
- What steps should be taken for effective PV of the malaria vaccine
- Do vaccines for pandemics e.g. Ebola vaccine require any special pharmacovigilance approach?

Facts, Scares and Rumours



CHILD FLU VACCINE CONTAINS MERCURY

Sunday January 9, 2011
By Lucy Johnson

UP to a million children have been given inoculations containing a controversial and poisonous preservative.

Flu jab: Up to a million children have been given vaccines containing mercury

Recommend Be the first of your friends to recommend this.

childhood vaccines in 2004 after fears about its safety.



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Flu vaccine: Do it for you, do it for your family — Washington State Department of Health

Occupy Wall Street Achieves Victory: Free Flu Shots for All — YouTube →

Government Inquiry Has Found That Polio Vaccines For Infants Funded By Gates' GAVI Are Causing Deaths And Disabilities — Express Tribune

Posted on November 18, 2011 by The Refusers

Bill Gates said in a CNN interview *'the people who go and engage in those anti-vaccine efforts — you know, they, they kill children.'* But according to the government report quoted in this article, it's actually Bill Gates' vaccine foundation that is killing children. Governments in developing nations are taking notice and withdrawing GAVI vaccines from their markets.

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'There have been reports of deaths of a number of children and occurrence of other side-effects soon after the vaccination is administered in Pakistan, India, Sri Lanka,

THE REFUSERS

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Recent Posts

- 90% of peer-reviewed clinical research is completely false — GreenMedInfo
- Bill Gates malaria vaccine flops in huge clinical trial — Reuters
- Chickenpox immunization leads to shingles — KTVU San Francisco
- Rhode Island's flu-shot mandate for health workers 1st of its kind in nation — AMA



The MMR-autism saga





New vaccines

Coming soon: malaria, dengue, Japanese encephalitis, typhoid conjugate, new TB vaccine, etc..

IT'S HERE!
AFRICA'S PROTECTION
FROM MENINGITIS

00 DAYS

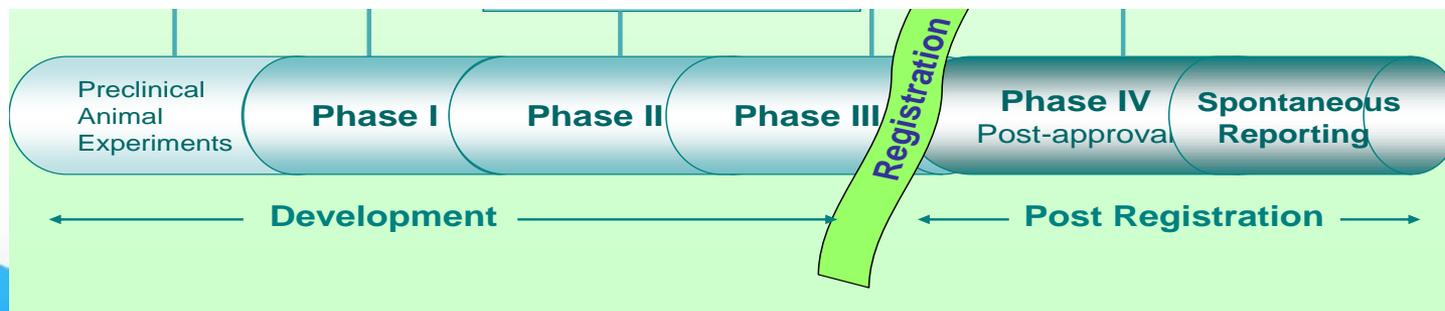
TO A NEW VACCINE



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When should we undertake vaccine PV?

- Safety should be built into vaccines right from the beginning and all through the life of the product
 - The so-called life cycle approach
 - Breckenridge A, Mello M, Psaty BM (2012) New horizons in pharmaceutical regulation. *Nature Reviews Drug Discovery* 11(7):501–502



Vaccine PV Issues

Some Pre-Registration (Pre-licensure) safety issues

- Risk of shedding the vaccine active ingredient, e.g. an attenuated live virus, during the trial
- Reversion to virulence
- Potential for transmission of the vaccine product to close contacts including pregnant women
- Concomitant drugs and vaccines
- Possibility of interference in response by other infectious agents

Some Post-Registration safety considerations

- Reactogenicity of the vaccine
- Adverse events of special interest e.g. Intussusception (Rotavirus), Narcolepsy (H1N1 vaccine)
- Effect of virus strains on reactogenicity
- Adjuvants, preservatives etc and reactogenicity, immunogenicity etc
- EPI schedule and impact on vaccine effectiveness e.g. waning immunity, booster doses etc

Vaccine PV – the next decade

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Decade of Vaccines Collaboration

<http://www.dovcollaboration.org/>

- Vision

- The vision for the DoV is a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases. Its mission is to extend, by 2020 and beyond, the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live

DoVC and Vaccine Safety

- To support low- and middle-income countries in managing such important issues, WHO and its partners have developed the **Global Vaccine Safety Blueprint**
- Implementing the Global Vaccine Safety Blueprint strategies to build capacity for safety surveillance during the Decade of Vaccines (2011–2020) will ensure that **everyone everywhere receives the safest vaccines possible and that safety concerns are not a cause of hesitancy in using vaccines**

Vision for the Global Vaccine Safety Blueprint

**Effective vaccine
pharmacovigilance systems are
established in all countries**

http://www.who.int/vaccine_safety/en/

Goals of the GVSI for Vaccine Safety

Minimal Capacity

To assist low and middle income countries to have at least minimal capacity for vaccine safety activities.

Enhanced Capacity

To enhance capacity for vaccine safety assessment in countries that introduce newly developed vaccines, that introduce vaccines in settings with novel characteristics or that both manufacture and use prequalified vaccines.

International Collaboration

To establish a global vaccine safety support structure

Conclusions

- Vaccine PV is an important part of vaccine regulation
- The vaccine product and the process of vaccination must all be considered in vaccine PV
- Methods for PV need to evolve in line with technological advancements and the production of new vaccines

Questions, Comments etc.



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