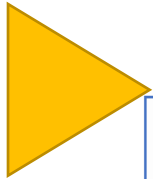


# MONITORING VACCINE SAFETY

Suzette H. Lazo, MD

Pediatric Infectious  
Disease Society of the  
Philippines 24<sup>th</sup> Annual  
Convention  
February 16, 2017  
3:45-4:30 PM  
Crowne Plaza Hotel, Ortigas

# OBJECTIVES

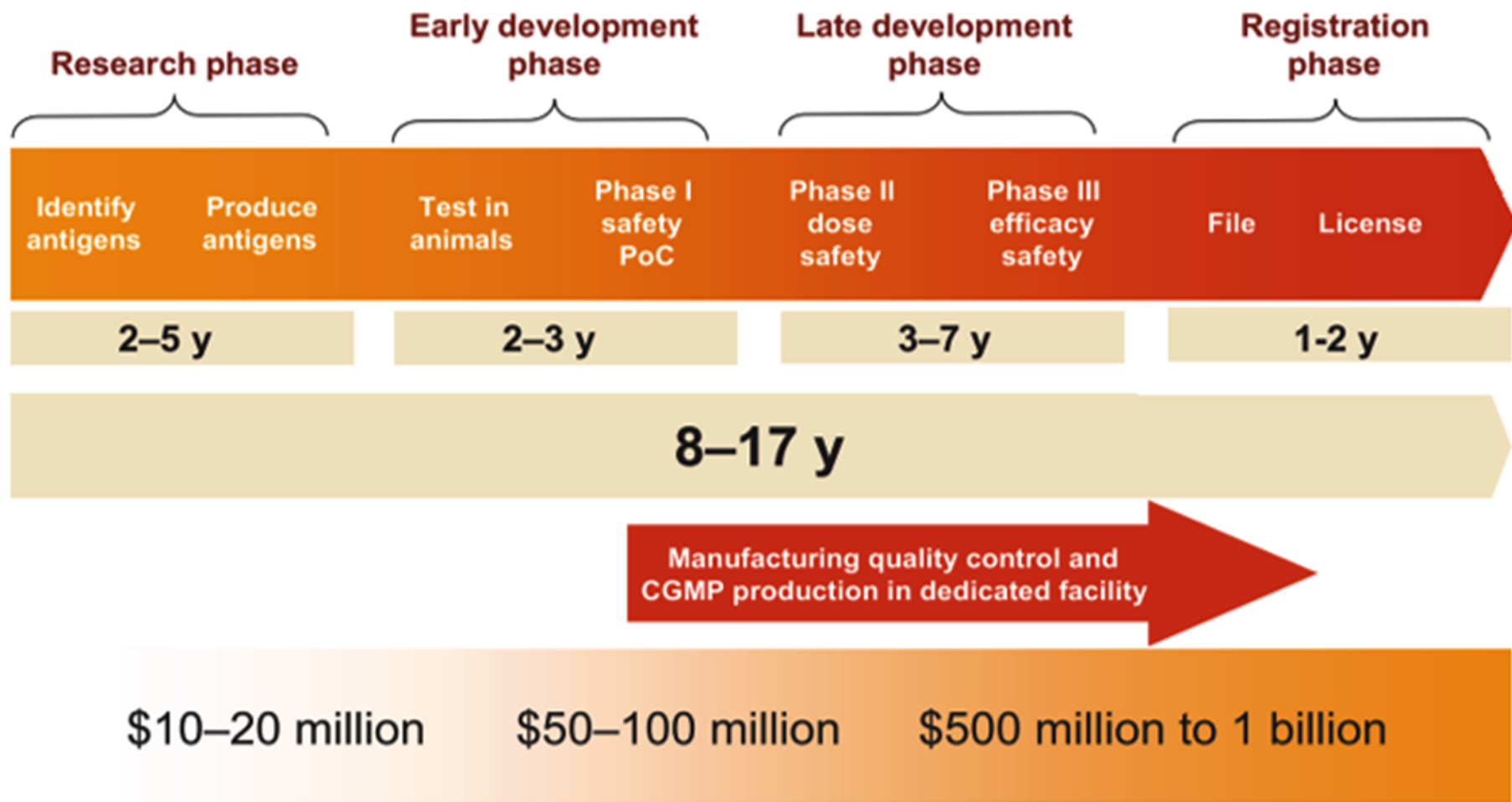


1. To describe the steps in the licensing of vaccines.

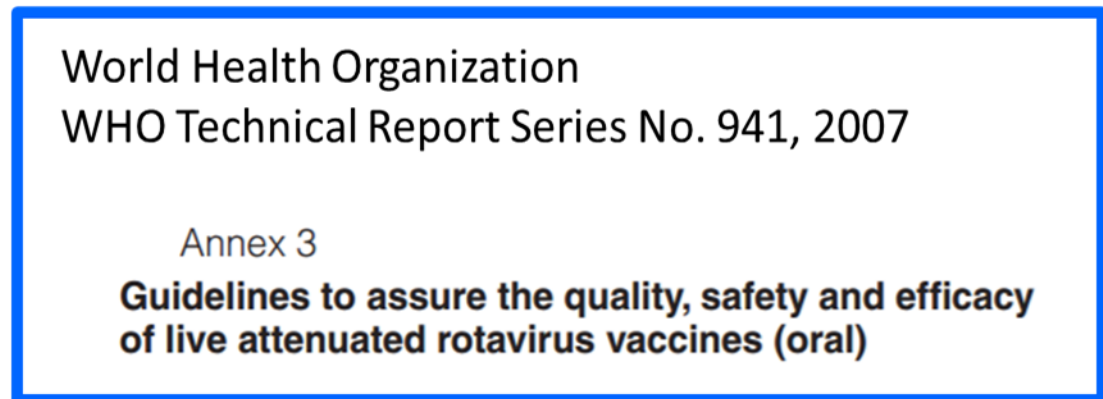
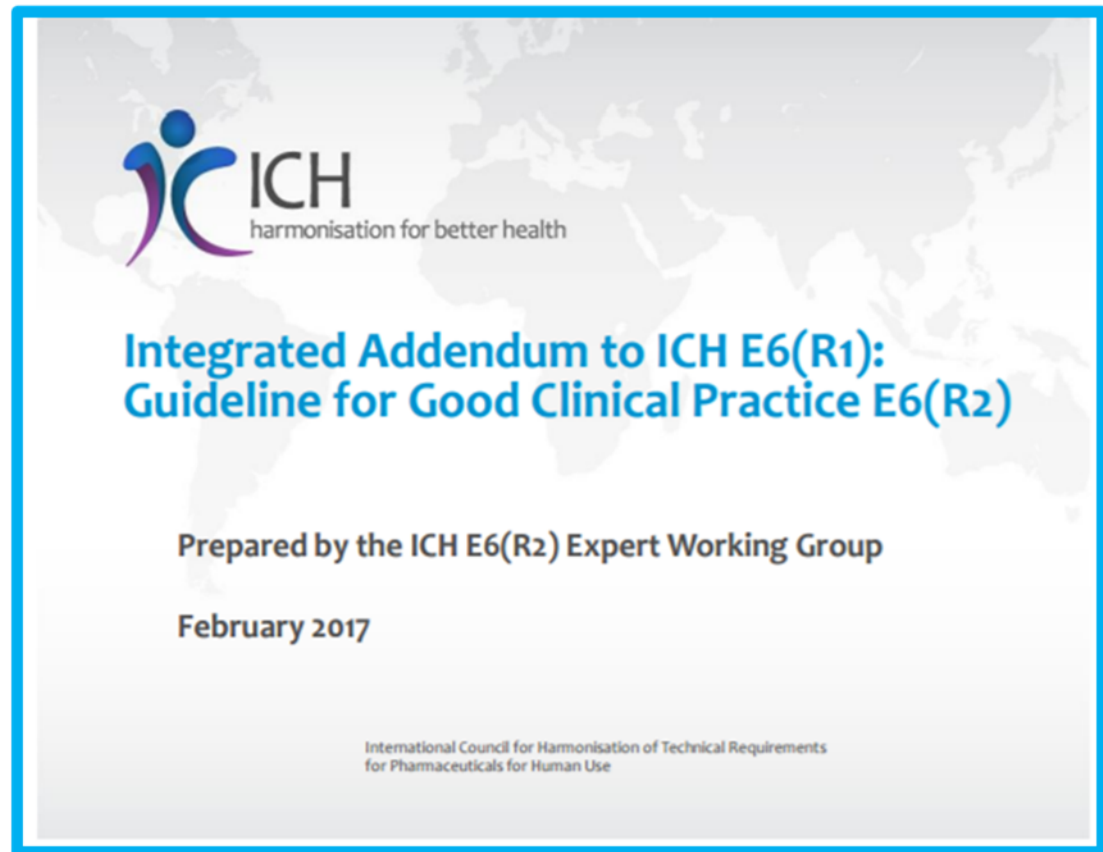
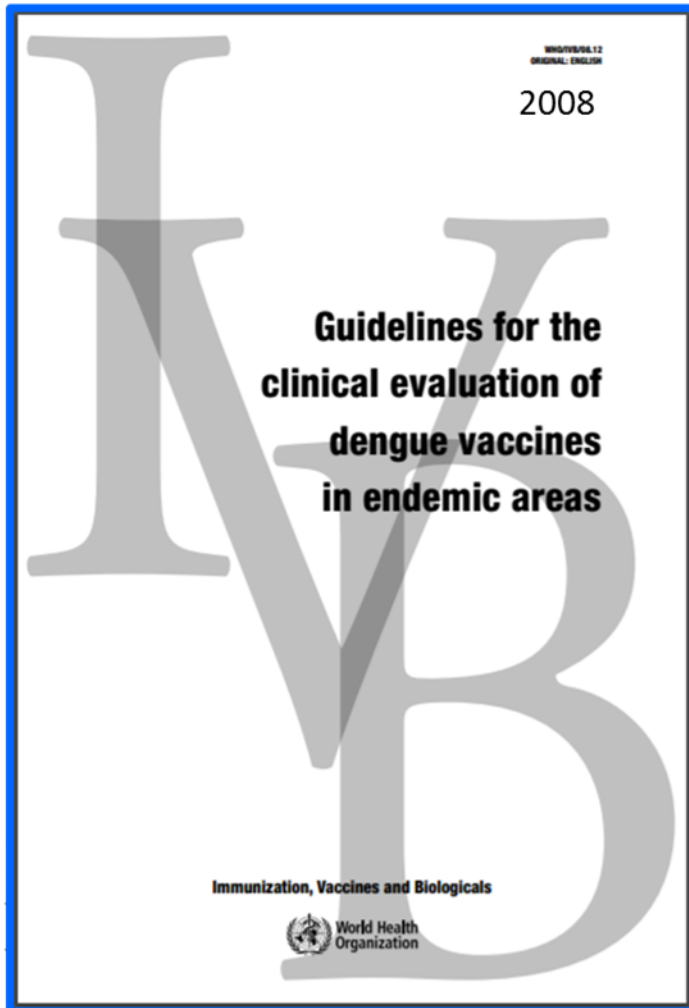
2. To discuss the importance of monitoring vaccine safety, pre-and post-licensure.

3. To discuss the safety of mass vaccination programmes.

# Vaccine research, development and manufacturing: ENSURING SAFETY FROM INCEPTION TO PRODUCTION

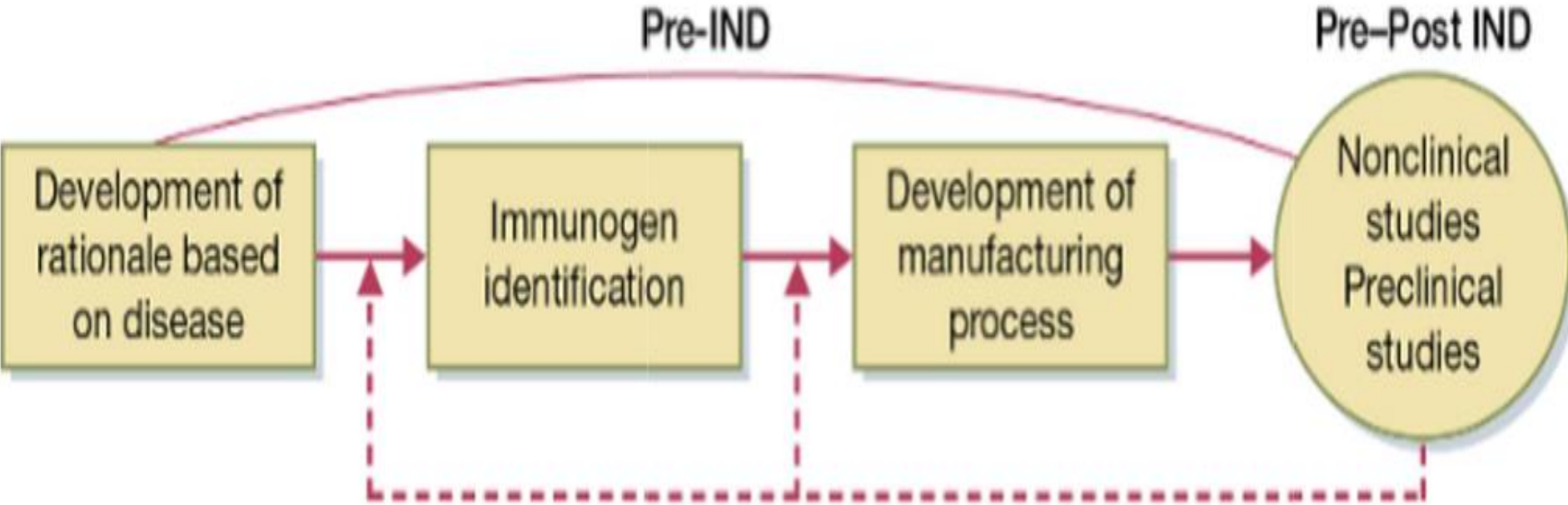


# GUIDELINES ON VACCINE CLINICAL TRIALS



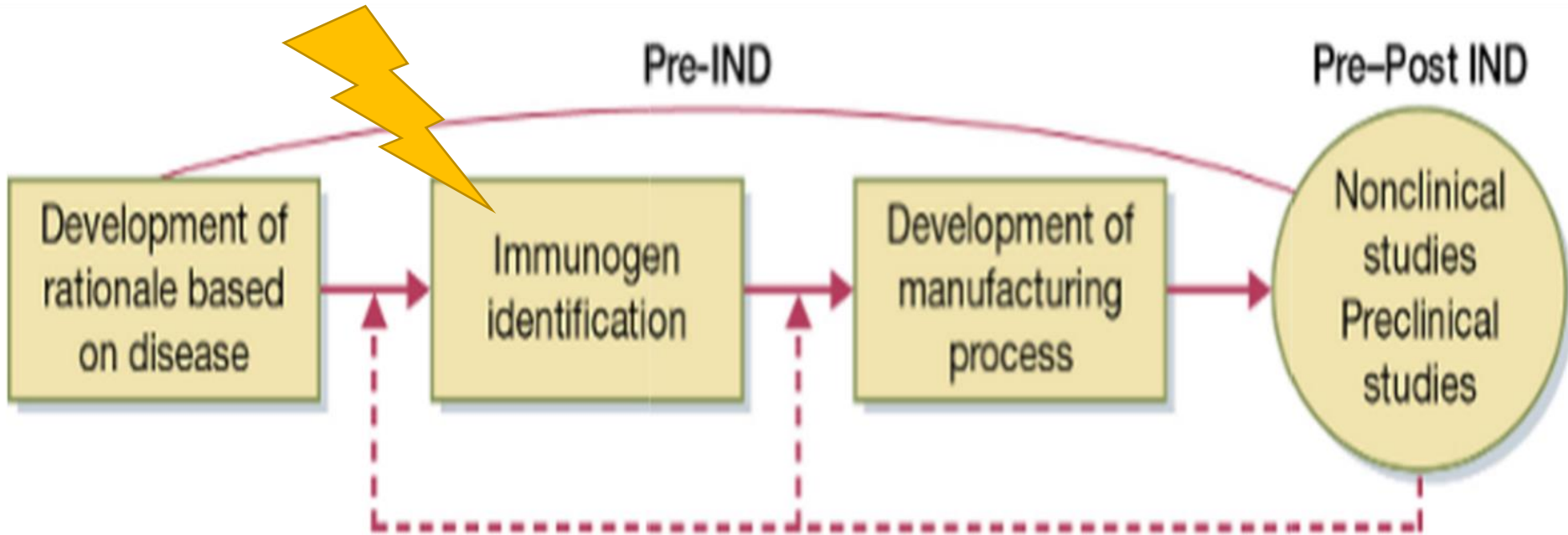
# Scientific Framework of Vaccine Safety (1/2)

## THE PRE-CLINICAL DEVELOPMENT PHASE



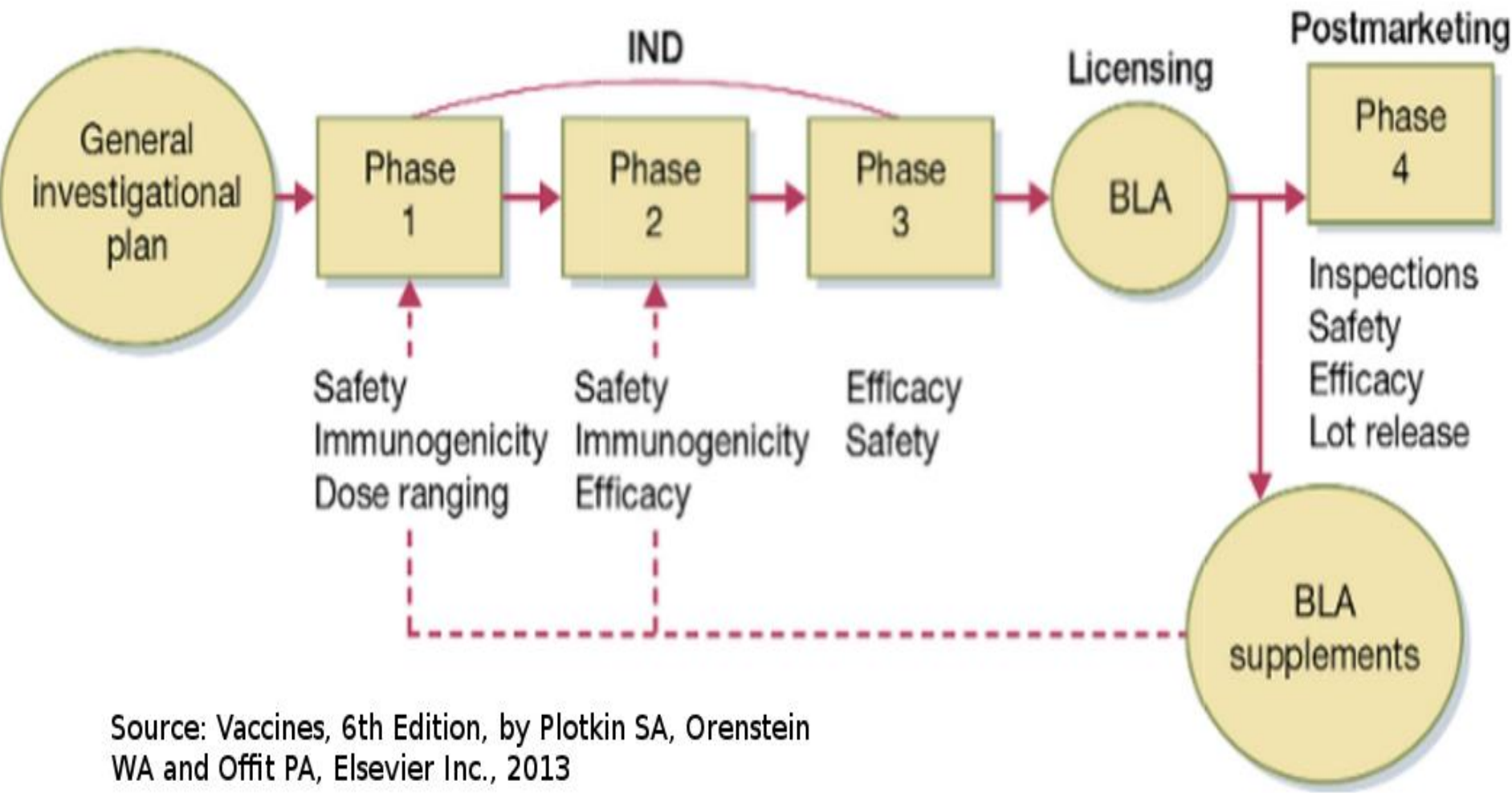
# Scientific Framework of Vaccine Safety (1/2)

## THE PRE-CLINICAL DEVELOPMENT PHASE



# Scientific Framework of Vaccine Safety (2/2)

## THE CLINICAL DEVELOPMENT PHASE



Source: Vaccines, 6th Edition, by Plotkin SA, Orenstein WA and Offit PA, Elsevier Inc., 2013

License  
Approval



Phase 4

Inspections  
Safety  
Efficacy  
Lot Release

## Lot Release Testing

---

Sterility, purity: detects the presence of bacterial or fungal contaminants

General safety test: detects toxicity (conducted in small animal models)

Identity test: verifies that a product induces specific antibodies after vaccination (conducted in small animal models)

Potency: verifies immunogenicity, antigen content, or chemical composition (in vivo or in vitro)

Purity: verifies freedom from extraneous materials

Tests for removal of process contaminants

Pyrogenicity: detects the presence of fever-inducing substances

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# The regulatory agency must ensure the availability of safe and effective vaccines.

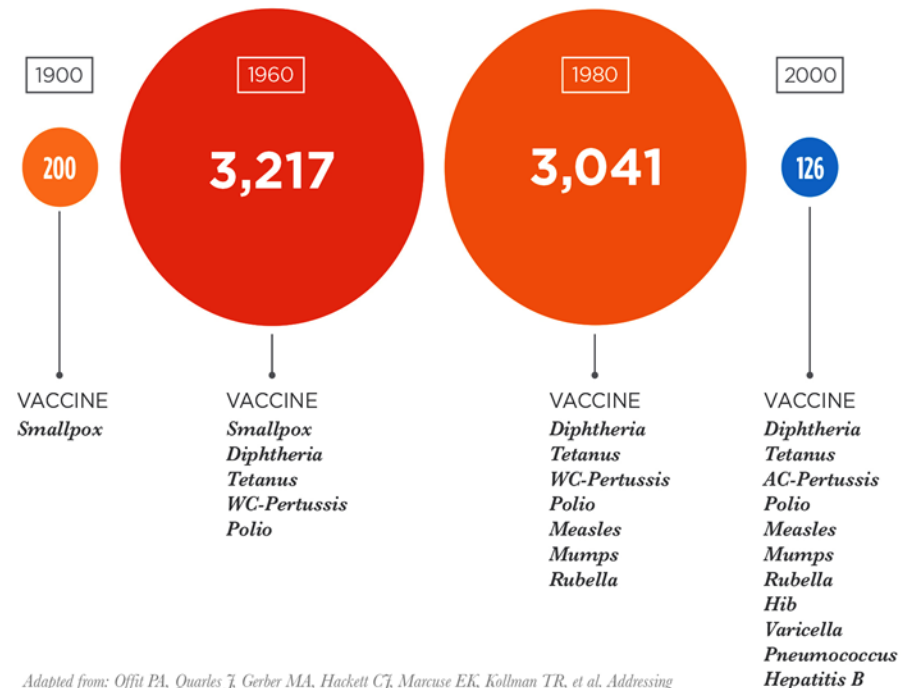
Guidelines on  
Clinical Evaluation  
of Vaccines:  
Regulatory  
Expectations.  
Proposed revision of  
WHO TRS 924,  
Annex 1 (2015 )

FDA Circular 2013-026  
Adoption of ICH  
Guideline on Quality of  
Biotechnological  
Products: Stability  
Testing of  
Biotechnological/  
Biological Products Q5C

# Vaccines today are much safer than ever

1. Better quality & safer vaccines
2. Better manufacturing process, transport & storage, equipment
3. Better formats & posology
4. Better aseptic practices (e.g., infection control)
5. More advanced diagnostics & therapeutics
6. Pharmacovigilance monitoring
7. Standardization & harmonization

## NUMBER OF IMMUNOGENIC PROTEINS AND POLYSACCHARIDES CONTAINED IN VACCINES OVER THE PAST 100 YEARS



# Need for vaccine safety has become more urgent

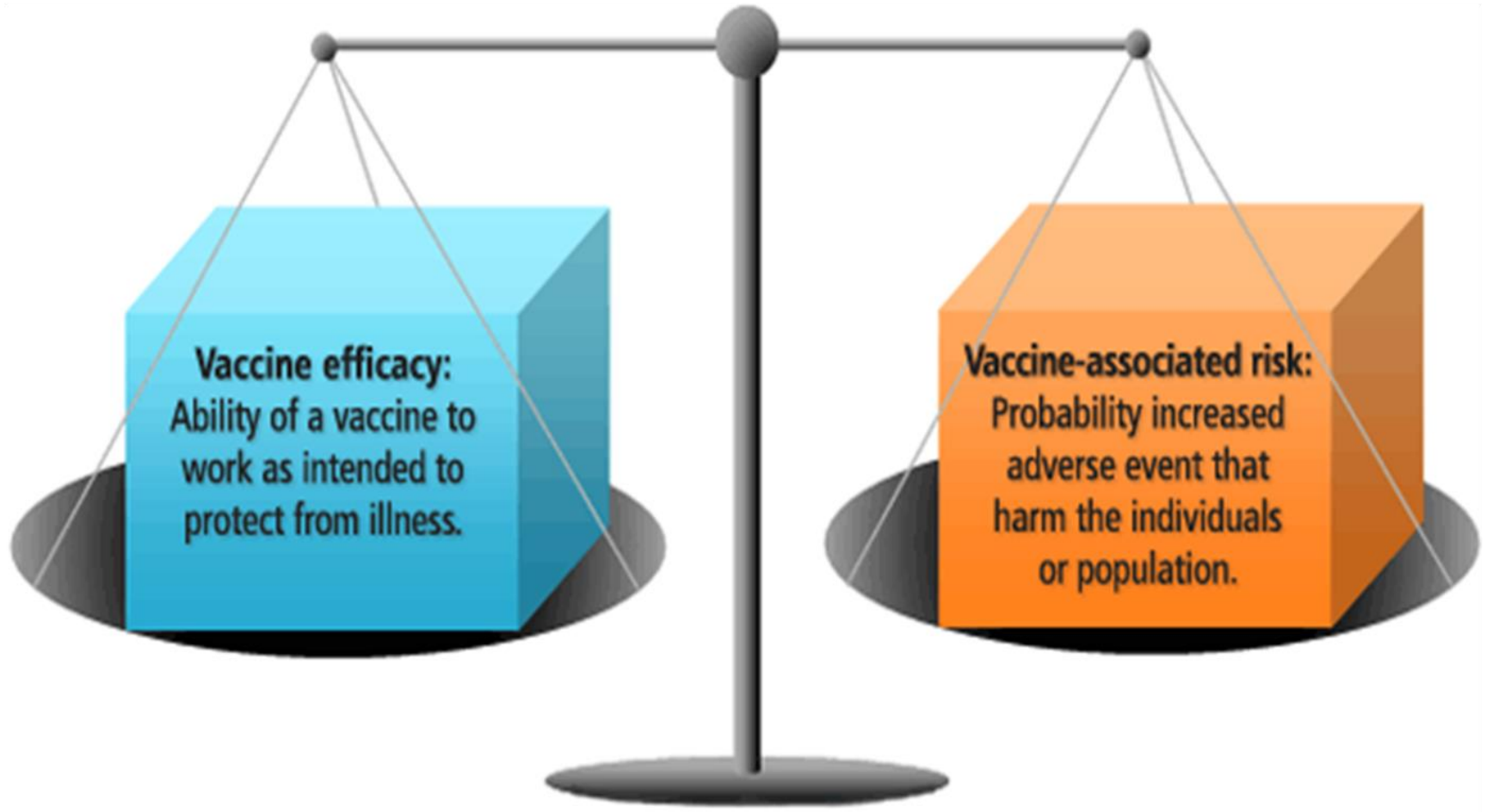


**Low tolerance  
requires safe  
vaccination**

Expectations to safety standard is higher with vaccines compared to medicines for sick people.

Public has low tolerance to adverse events as vaccines are usually given to healthy persons.

# POTENTIAL BENEFIT MUST OUTWEIGH POTENTIAL RISK



*The determination of safety does not suggest an absence of risk.*

# *Trending: a qualitative approach to BRA*

## US FDA Structured Benefit-Risk Assessment in Drug Regulatory Decision-Making

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
<b>Benefit-Risk Summary Assessment</b>		

*Similar approaches adopted by WHO, ICH, EMA .....& Philippines*

# OBJECTIVES

1. To describe the steps in the licensing of vaccines.



2. To discuss the importance of monitoring vaccine safety, pre-and post-licensure.

3. To discuss the safety of mass vaccination programmes.

# Vaccine adverse events due to production errors

## **1955 Cutter Laboratories incident**

→ One of five companies first contracted to produce Salk vaccine; failed to inactivate vaccine preparation (insufficient formalin duration); 120,000 infected; 40,000 mild polio; 200 paralyzed; 10 deaths

**1906 Richard Pearson Strong and the iatrogenic plague disaster in Bilibid Prison, Manila. 24 inmates given cholera vaccine contaminated with plague organisms; 13 men died.**

## **1930 Lubeck Disaster**

→ 251 of 452 infants received 3 doses of BCG vaccine by the mouth during the first 10 days of life. Of 251, 72 died of tuberculosis, 135 suffered from clinical tuberculosis but eventually recovered.

# Vaccine adverse events due to rare biological events

Acute encephalopathy after whole-cell pertussis vaccine

Guillain–Barré syndrome (GBS) after swine flu vaccine

Acute arthropathy following rubella vaccine

Paralytic polio following live, attenuated oral polio vaccine (OPV)

Thrombocytopenia following measles virus-containing vaccine

Anaphylaxis following receipt of vaccines containing egg proteins or gelatin



## *Clinical trials and assessment of vaccine safety*

	Activity	Sample size (estimates)	Detection of Adverse events	
			Common	Rare
<b>Clinical Trial Phase I</b> ↓	Test the safety and immunogenicity of a vaccine candidate in a few low-risk individuals (usually healthy adults) to determine tolerability.	10 – 100	+/-	–
<b>Clinical Trial Phase II</b> ↓	Monitor safety, potential side effects, immune response, and determine optimum dosage and schedule.	100 – 1,000	+	–
<b>Clinical Trial Phase III</b> ↓	Address clinical efficacy in disease prevention and provide further safety information from more heterogeneous populations and longer times of observation.	1,000 – 10,000	+	–
<b>Submission</b> ↓	The vaccine application is submitted to regulatory authorities for approval to market.			
<b>Introduction</b>	Involves making the vaccine available for use.			

# Post-licensure Surveillance is necessary!

To protect the health of the public  
& preserve vaccine confidence

- Pre-licensure studies are not powered enough to detect common and rare vaccine reactions; also those with delayed onset.
- Identify subpopulations at high risk for undesirable effects (e.g. with underlying medical conditions, preterm infants).
- Identify factors leading to AEFIs, such as incorrect administration practices, vaccine lots with unusual rates or types of AEs

# Monitoring/Surveillance

“Surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health.”

- U.S. Centers for Disease Control and Prevention

# The Vaccine Safety Landscape



Lot-release



Pharmacovigilance:  
passive, active,  
sentinel surveillance



Best practices in  
clinics providing  
vaccines

Best practices in  
storage, prescribing,  
dispensing, & disposal

Best practices in  
NIPs

Safe Injection  
Practice

Record-keeping,  
Risk -Communication

# Counterfeit Drugs & Vaccines

## China Arrests 37 For Selling Fake Vaccines

23 March 2016, 9:54 am EDT By Catherine Cabral-Isabedra Tech Times



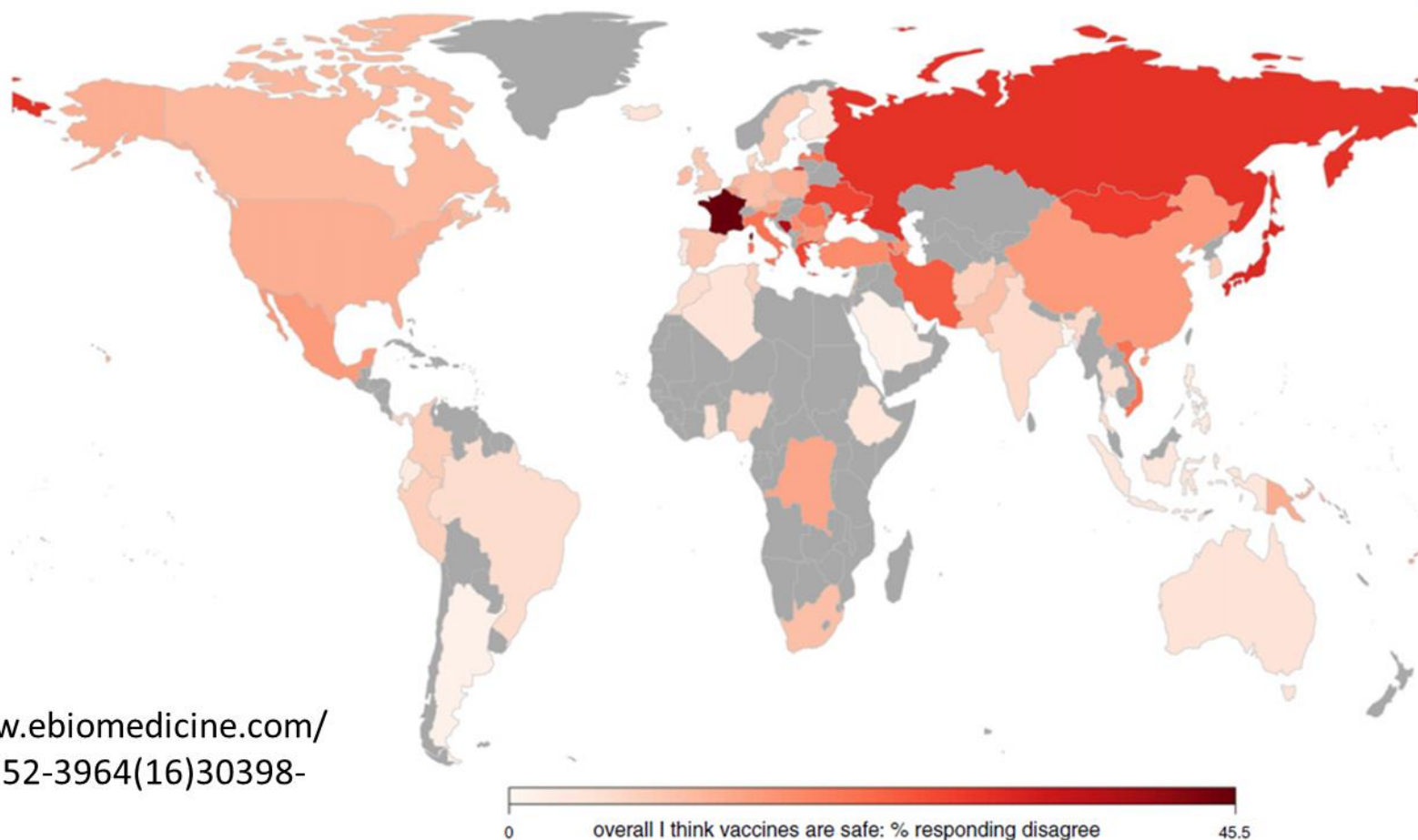
Counterfeit vaccine medication confiscated by the Criminal Investigation Agency of the National Police at the National Police headquarters in Jakarta. Indonesian parents were on June 29 being advised to consult their doctors and consider re-inoculating their children as a massive counterfeit vaccine scandal sweeps the country. AFP / Handout from Bareskrim

### Counterfeit vaccines draw condemnation in Indonesia

# VACCINE SAFETY SURVEILLANCE

## IS CRUCIAL IN DEVELOPING CONFIDENCE IN THE SAFETY OF VACCINES

The State of Vaccine Confidence 2016: Global Insights Through a 67-Country Survey <sup>B</sup>

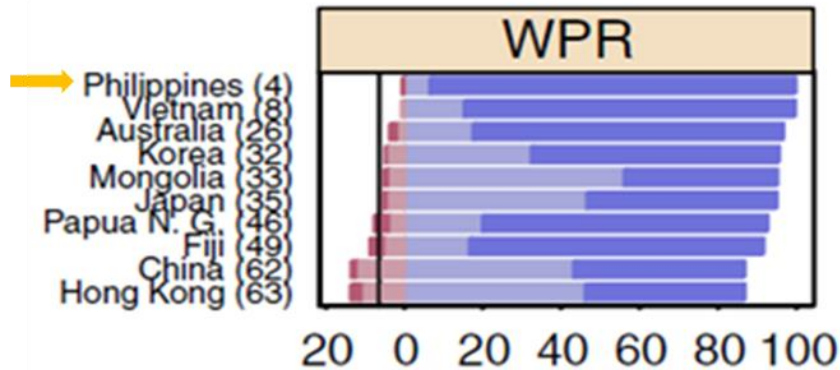


[http://www.ebiomedicine.com/  
article/S2352-3964\(16\)30398-  
X/pdf](http://www.ebiomedicine.com/article/S2352-3964(16)30398-X/pdf)

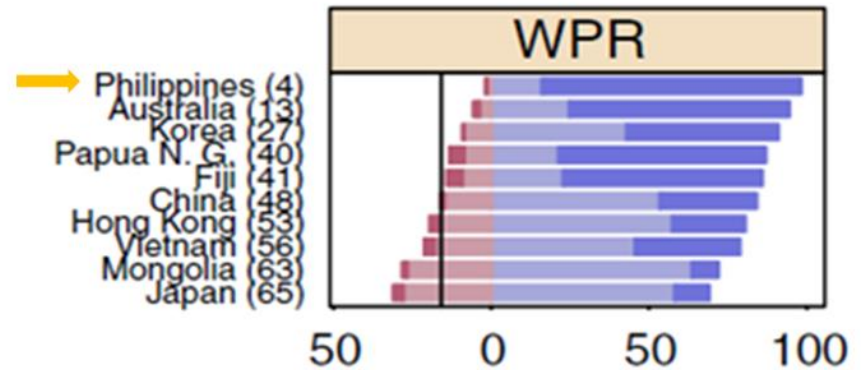
# What is the state of vaccine confidence in the Philippines?

## The State of Vaccine Confidence 2016

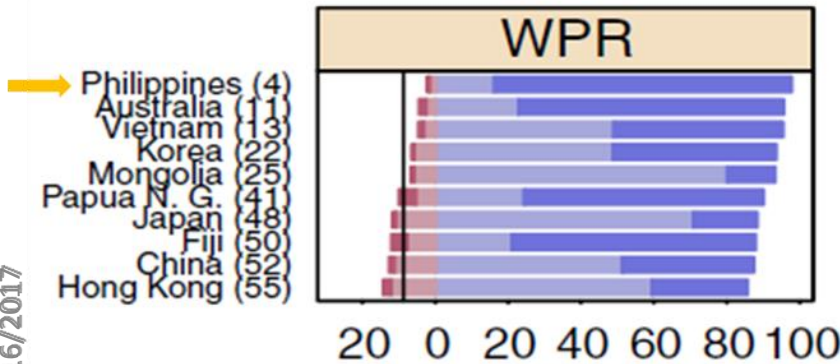
Vaccines are important for children to have



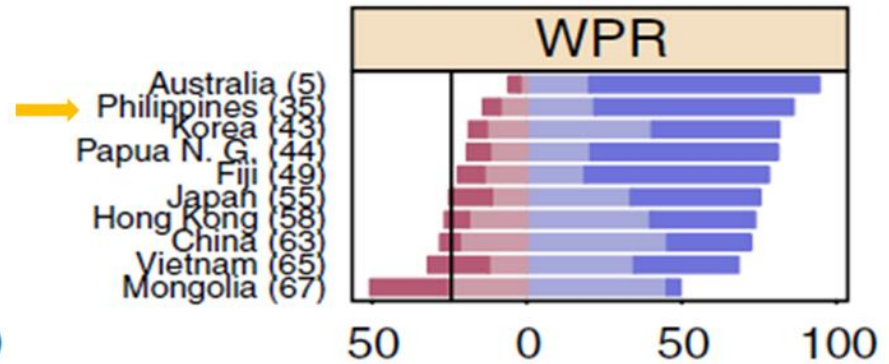
Overall I think vaccines are safe



Overall I think vaccines are effective



Vaccines are compatible with my religious beliefs



Strongly disagree

Tend to disagree

Tend to agree

Strongly agree

# Vaccine Safety Monitoring Objectives

- Measure AEFI
- Monitor trends
- Guide program planning and implementation
- Evaluate public policy/public immunization programs
- Prioritize health care resources



# Main Types of Monitoring for AEFI

1/4

- Passive Surveillance
- Active Surveillance
- Sentinel Surveillance

# Main Types of Monitoring for AEFI

2/4

- Passive Surveillance
  - Reported to health authorities by health care provider when case occurs
  - Least expensive method
  - Limitations: non-reporting, under-reporting, unrepresentative, limited clinical detail; fear of litigation
- Active Surveillance
- Sentinel Surveillance

# Main Types of Monitoring for AEFI

3/4

- Passive Surveillance
- Active Surveillance
  - Outreach to detect cases or stimulate case reporting
  - Active case searching of hospital records, laboratory reports, discharge summaries, etc.
  - More resource intensive than passive
  - More representative than passive
  - More timely results
- Sentinel Surveillance

# Main Types of Monitoring for AEFI

4/4

- Passive Surveillance
- Active Surveillance
- Sentinel Surveillance
  - Monitoring in selected groups/populations
  - Population represents entire group
  - Standard case definitions and protocols

# What should be reported

AEFIs should be reported when the event:

- **Has a temporal association with a vaccine**
- **Has no other clear cause at the time of reporting:**

A causal relationship between immunization and the event that follows does not need to be proven and submitting a report does not imply or establish causality. Sometimes the vaccinee's medical history, recent disease, concurrent illness/ condition and/or concomitant medication(s) can explain the event(s).

# Be alert for known AEFIs

**VAERS Table of Reportable Events Following Vaccination\***

Vaccine/Toxoid	Event and interval from vaccination
Tetanus in any combination; DTaP, DTP, DTP-Hib, DT, Td, TT, Tdap, DTaP-IPV, DTaP-IPV/Hib, DTaP-HepB-IPV	<ul style="list-style-type: none"> <li>A. Anaphylaxis or anaphylactic shock (7 days)</li> <li>B. Brachial neuritis (28 days)</li> <li>C. Any acute complications or sequelae (including death) of above events (interval - not applicable)</li> <li>D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)</li> </ul>
Measles in any combination; MMR, MMRV, MR, M	<ul style="list-style-type: none"> <li>A. Thrombocytopenic purpura (7-30 days)</li> <li>B. Vaccine-strain measles viral infection in an immunodeficient recipient (6 months)</li> <li>C. Any acute complications or sequelae (including death) of above events (interval - not applicable)</li> <li>D. Events described in manufacturer's package insert as contraindications to additional doses of vaccine (interval - see package insert)</li> </ul>
Oral Polio (OPV)	<ul style="list-style-type: none"> <li>A. Paralytic polio               <ul style="list-style-type: none"> <li>o In a non-immunodeficient recipient (30 days)</li> <li>o In an immunodeficient recipient (6 months)</li> <li>o In a vaccine-associated community case (interval - not applicable)</li> </ul> </li> <li>B. Vaccine-strain polio viral infection               <ul style="list-style-type: none"> <li>o In a non-immunodeficient recipient (30 days)</li> <li>o In an immunodeficient recipient (6 months)</li> </ul> </li> </ul>

# Vaccine components that can cause reactions

- Antigen (active component of the vaccine)
- Adjuvant –Aluminum salts, AS03, AS04, MF59)
- Preservative –thimerosal
- Stabilizer – gelatin
- Antibiotics – neomycin
- Others – pH, osmolarity

# Adverse Events Following Immunization (AEFI) Surveillance

AO2010-0017 Guidelines in Surveillance and Response to Adverse Events Following Immunization



- Detect, correct, and prevent programme errors
- Identify problems with vaccine lots or brand
- Maintain confidence by properly responding to parent/community concerns while increasing awareness (public and professional) about vaccine risks
- Estimate rates of occurrence on AEFI in the local population, compared with trial and international data; identify increases in known reactions



# Causality Assessment of an Adverse Event Following Immunization (AEFI), WHO 2013

**Adequate  
information  
available**

## A. Consistent causal association to immunization

A1. Vaccine product-related reaction (As per published literature)

A2. Vaccine quality defect-related reaction

A3. Immunization error-related reaction

A4. Immunization anxiety-related reaction

## B. Indeterminate

B1. \*Temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event)

B2. Qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization

## C. Inconsistent causal association to immunization

C. Coincidental  
Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine

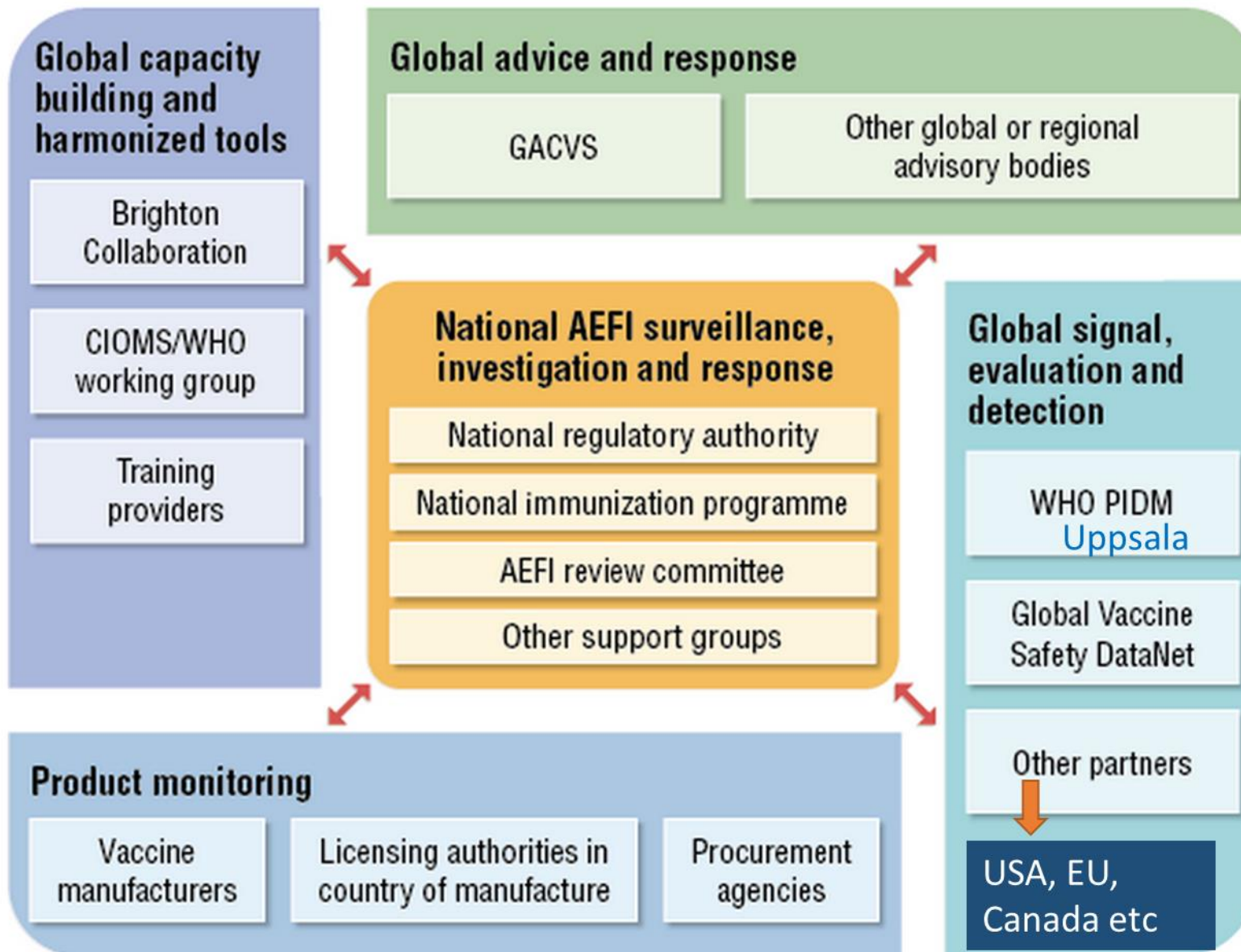
## Unclassifiable

**Adequate  
information  
not available**

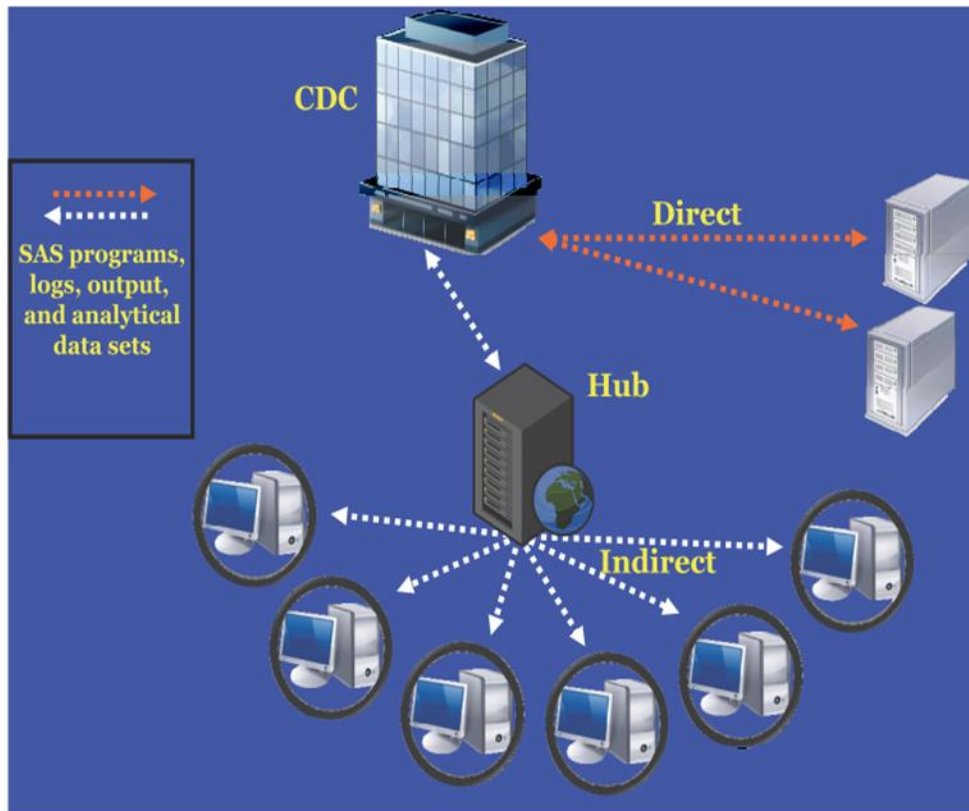
Specify the additional information required for classification

\*B1 : Potential signal and maybe considered for investigation

# Global Vaccine Safety Monitoring



# VACCINE SAFETY DATALINK (VSD)




## Strategic Priorities

- Evaluate the safety of newly licensed vaccines
- Evaluate the safety of new vaccine recommendations for existing vaccines
- Evaluate clinical disorders after immunizations
- Assess vaccine safety in special populations at high risk
- Develop and evaluate methodologies for vaccine-safety assessment

# OBJECTIVES

1. To describe the steps in the licensing of vaccines.

2. To discuss the importance of monitoring vaccine safety, pre-and post-licensure.

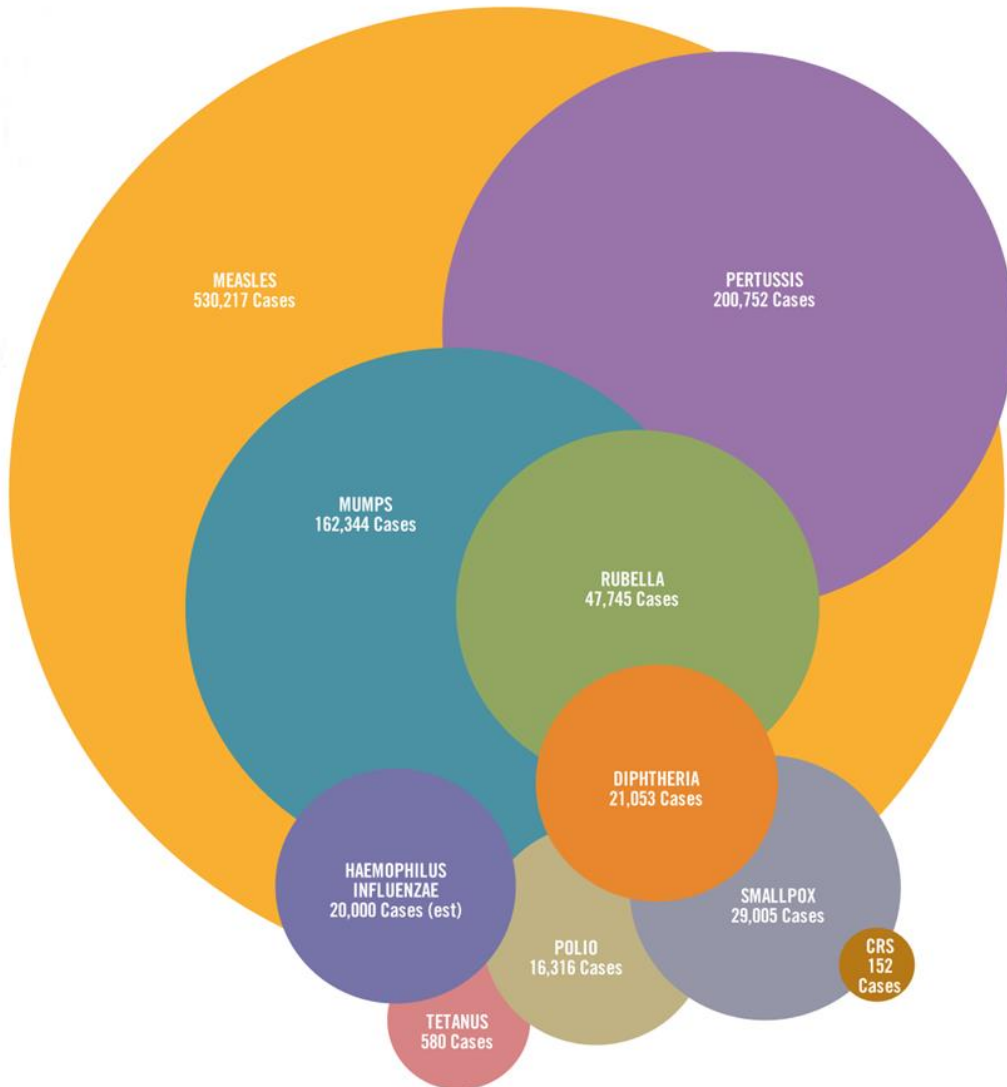


3. To discuss the safety of mass vaccination programmes.

# VACCINES WORK!

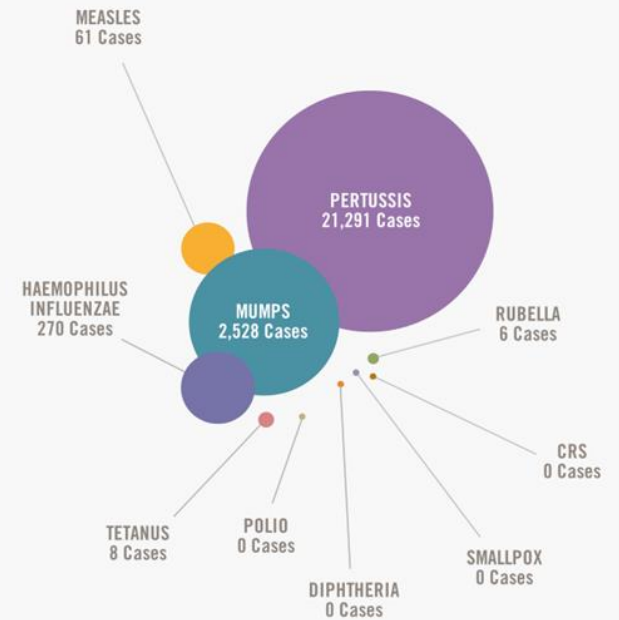
## THEN

Annual US disease cases in the 1900s



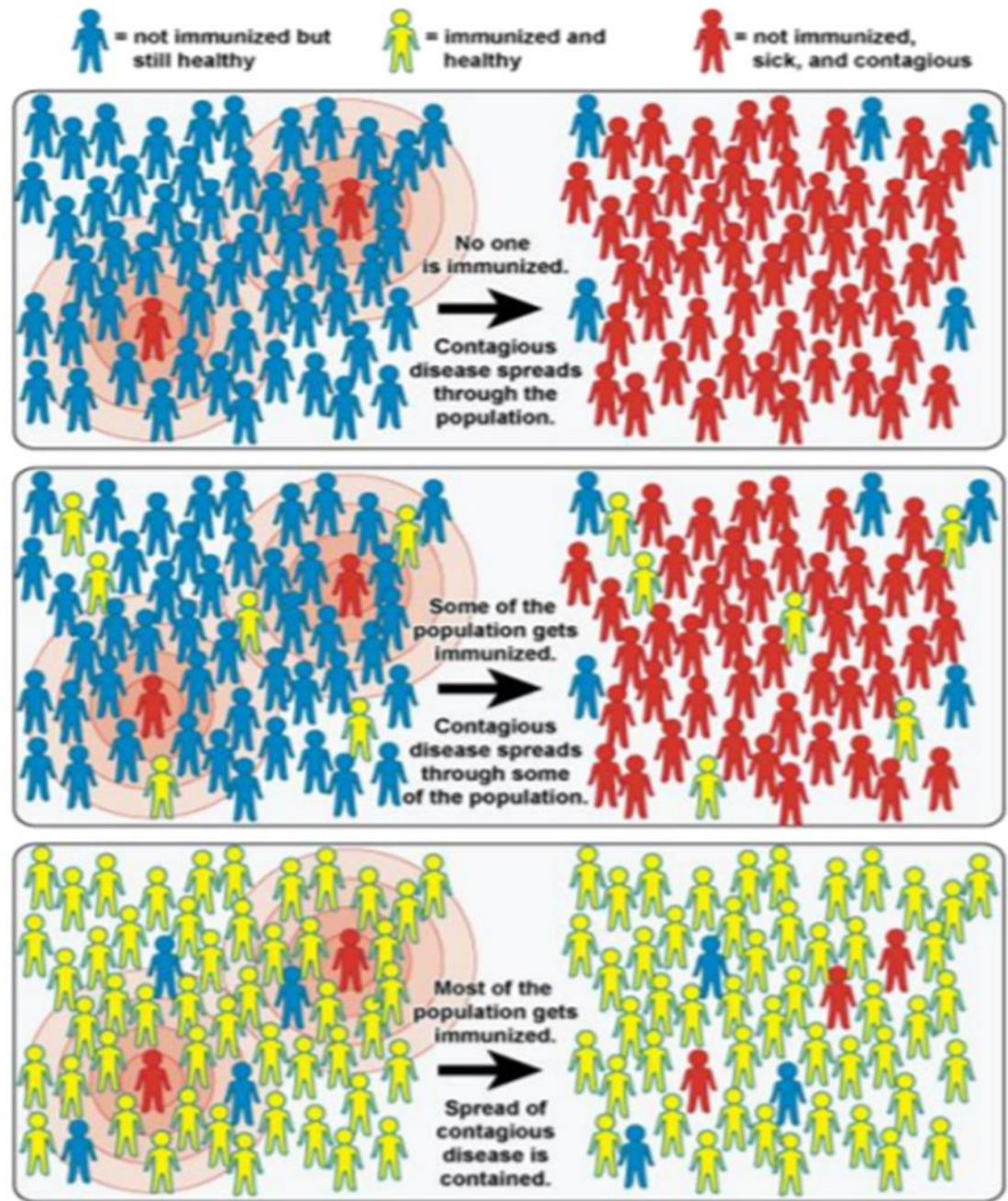
## NOW

US disease cases in 2010



[http://www.vaccines.com/\\_downloads/PDF/infographic\\_vacforgranted.pdf](http://www.vaccines.com/_downloads/PDF/infographic_vacforgranted.pdf)

Maximizing the public health benefits of vaccines requires relatively high and sustained vaccine coverage.



Credit: NIAID

# IMMUNIZATION IN THE PHILIPPINES

## VARIABLES

PUBLIC SECTOR

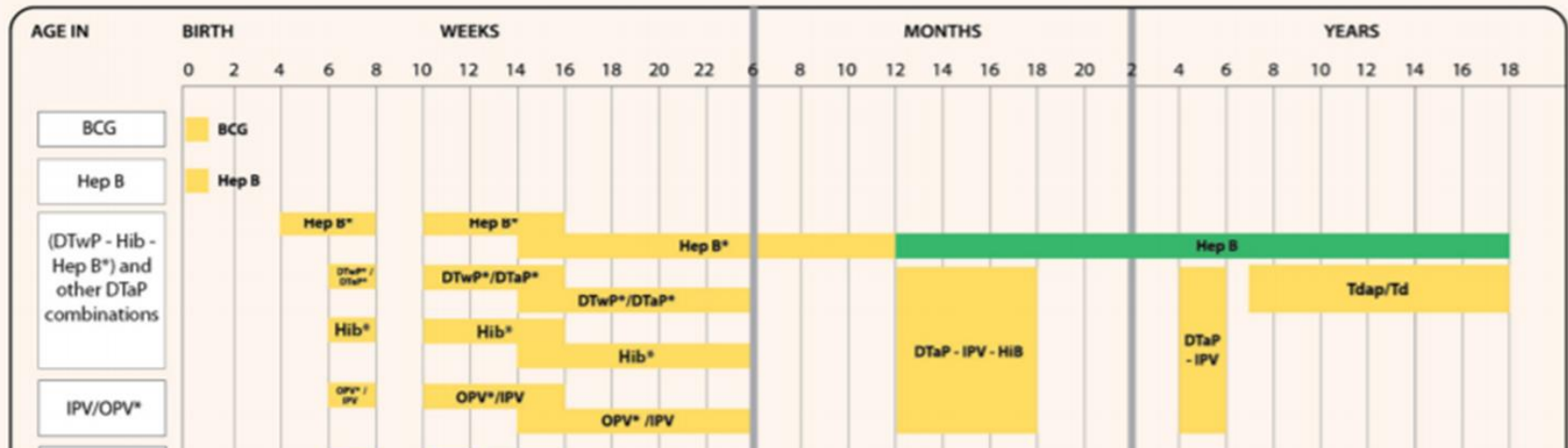
PROVIDER: DOH &  
LOCAL  
GOVERNMENT  
SOURCE: WHO  
PREQUALIFICATION,  
UNICEF, PHARMA  
COMPANIES

PROVIDER  
SOURCE  
COLD-CHAIN  
COST (PROVIDER/PATIENT)  
SCREENING PROCESS  
POST-VACCINE CARE  
AEFI INCIDENCE  
(serious/non-serious)  
OTHERS

PRIVATE SECTOR

PROVIDER: PRIVATE  
PRACTITIONERS &  
CLINICS &  
HOSPITALS  
SOURCE: PHARMA  
COMPANIES

## Childhood Immunization Schedule 2016



# SAFETY OF VACCINES FOR ROUTINE IMMUNIZATION

## The Childhood **IMMUNIZATION SCHEDULE** and Safety

STAKEHOLDER CONCERNS, SCIENTIFIC  
EVIDENCE, AND FUTURE STUDIES

Institute of Medicine, National  
Academies Press, 2013

“...no significant  
evidence to imply that  
the recommended  
immunization schedule  
is not safe.”

## Safety of Vaccines Used for Routine Immunization of U.S. Children: A Systematic Review

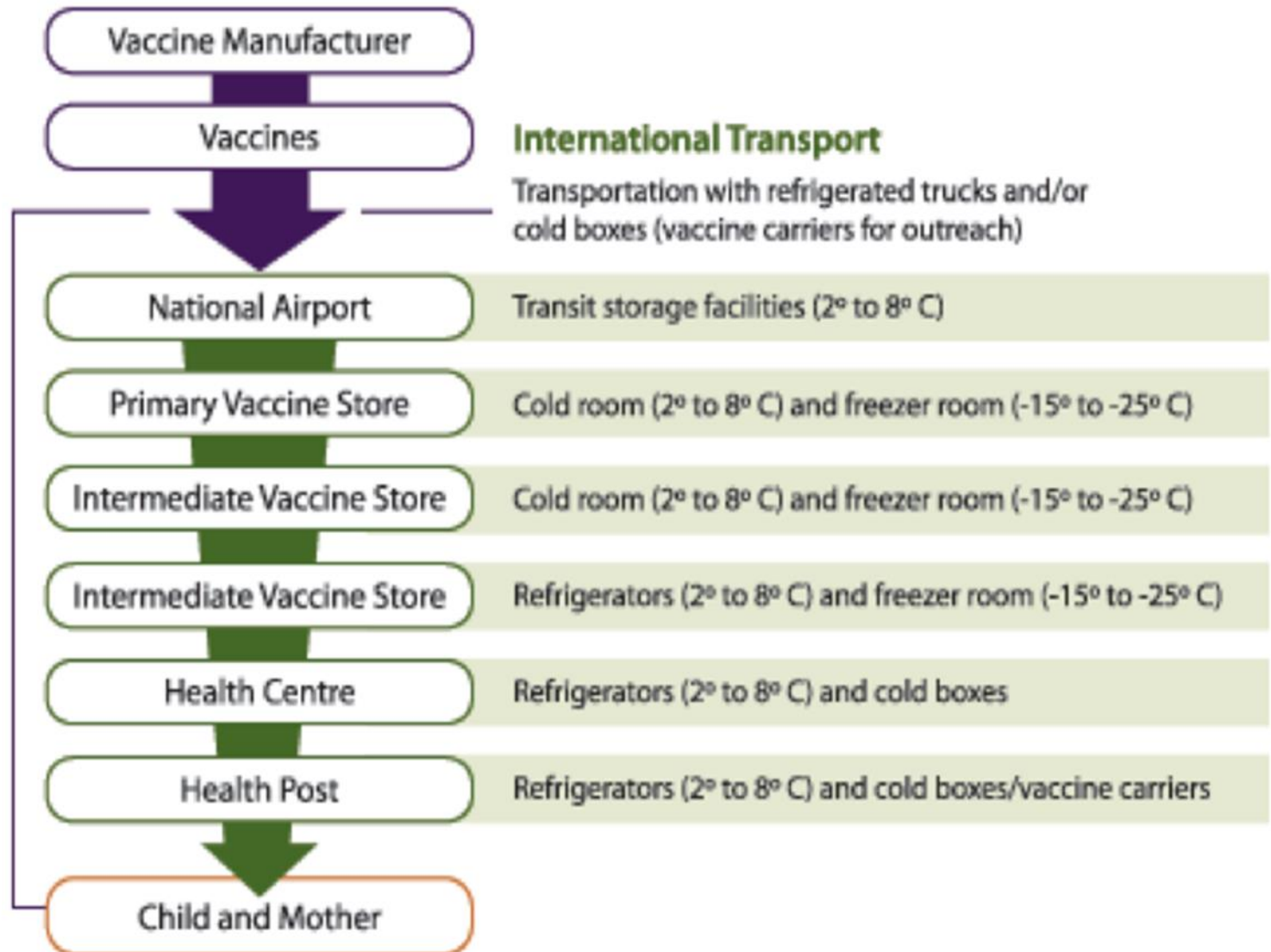
**CONCLUSIONS:** We found evidence  
that some vaccines are associated  
with serious AEs; however, these  
events are extremely rare and must  
be weighed against the protective  
benefits that vaccines provide.

PEDIATRICS Volume 134,  
Number 2, August 2014



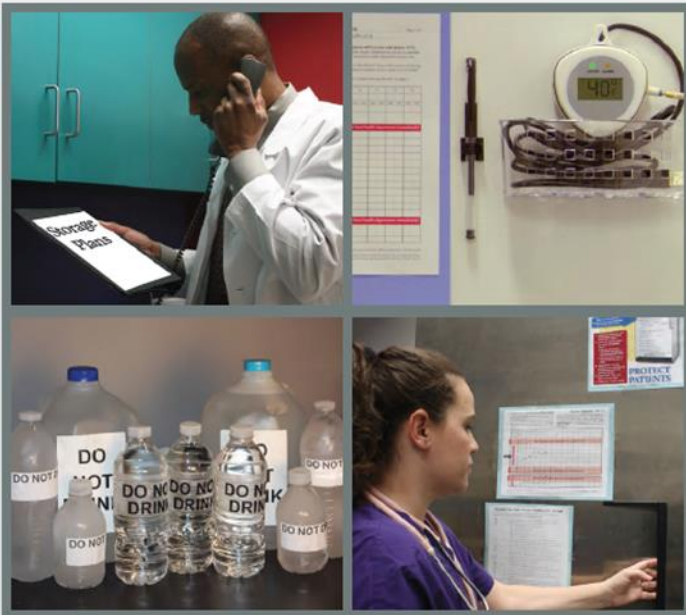
# Keeping the Cold-Chain for Vaccines — a Major Challenge!

Most heat-sensitive vaccines must be kept between a range of 2 - 8 degrees Celsius at any and every given point throughout the links of the cold chain.



# Vaccine Storage & Handling Toolkit

June 2016



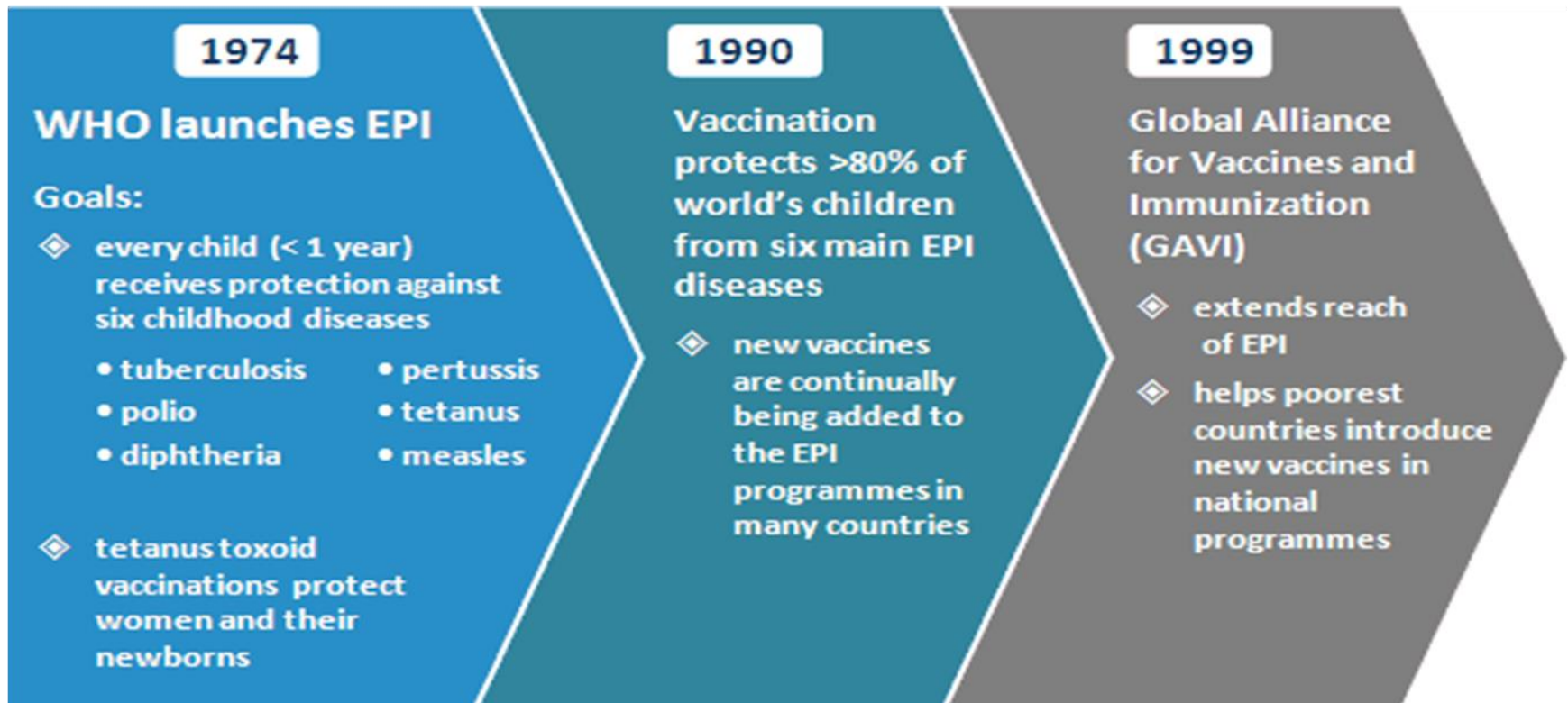
U.S. Department of Health and Human Services  
Centers for Disease Control and Prevention

<https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf>



Do not store any vaccine in a dormitory-style or bar-style combined refrigerator/freezer unit under any circumstances.

# EXPANDED PROGRAM ON IMMUNIZATION



“Vaccines used in national immunization programmes (NIPs) are considered safe and effective when used correctly. Vaccines are, however, not risk-free and adverse events will occasionally occur following vaccination...”

-WHO

# PHILIPPINES DOH EPI

1976	EPI launched
1979	OPV, BCG, DPT & TT
1982	Anti-measles Vaccine
1992	Hepatitis B vaccine
2010	MMR, Pentavalent (DPT, HepB, HiB) vaccines

2012	Rotavirus, Flu & PPV Sr Citizens
2013	PCV, MR & Td
2014	IPV
2015	HPV
2016 & beyond	Dengue, JE & Cholera vaccines

# MASS IMMUNIZATIONS

A challenge for any country.

- Know the target disease
- Know the vaccine & expected AEFIs
- Know vaccinees
- Know the site
- Communicate!

# Future Possibilities

- Strengthening of AEFI Surveillance, Reporting & Assessment
- Consortium of private and DOH hospitals to link as Sentinel Surveillance Centers and serves as large database to detect rare AEFIs
- Strengthen NAIEFIC Committee (AO 2010-0017)
- Masters and advanced courses in vaccinology offering —by academic institutions
- Philippine version of U.S. National Compensation for Vaccine Injury Act?