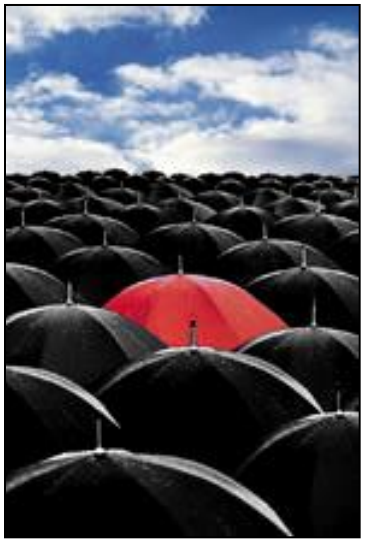
How do we know vaccines are safe ?



A/Professor Michael Gold

Head Allergy and Immunology

Women's and Children's Health Network and
Discipline of Paediatrics University of Adelaide


MILLENNIUM
Sea Breeze Resort Bagamoyo
The Only Place Where Dreams Come True


World Health Organization
Western Pacific Region
TRAINING WORKSHOP ON ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)
CAUSALITY ASSESSMENT AND COMMUNICATION CAPACITY - BUILDING FOR IMMUNIZATION
12 to 16 May 2014, Manila, Philippines

Outline

- **Context of vaccine safety**
  - General
  - In LMIC
- **Concepts and terminology**
  - Adverse Events Following Immunisation (AEFI)
  - Serious or Severe AEFI
- **Cause specific definitions** of AEFI
- **AEFI Surveillance systems**

Historical context

The cow pock or wonderful effects of the new inoculation
Publications of ye Anti-Vaccine Society circa 1800 (Jenner's vaccination 1796)

OUR GIRLS ARE NOT GUINEA PIGS

Is an upcoming mass inoculation of a generation unnecessary and potentially dangerous?

Ingredients: Mercury, Formaldehyde, Aluminum Phosphate, Aspartame, Human Fetal Tissue, Monkey Kidney & Lung Cells, MSG, Bovine Fetal Serum

There will always be concerns about vaccine safety

Perception of Risk from Adverse reactions

- Low threshold for reactions
  - Healthy
  - Vulnerable – neonates, pregnancy, adolescent girls
- Reporting of Adverse Events Following Immunisation (AEFI)
- Globalisation of Information and misinformation
  - WWW, social media, secondary gain

Globalisation of vaccine safety issues

The global perception

Research

Improving global media monitoring - Pentavalent vaccine (DTP-HBV-Hib) and Sudden Infant Death Syndrome (SIDS) in India

Heidi Larson[1], David Smith[1], Benedikt Becker[2], Jan Kors[2], Daniel Weibel[2], Yolanda Brauchli Pernus[3], Miriam Sturkenboom[2] and Jan Bonhoeffer[3]

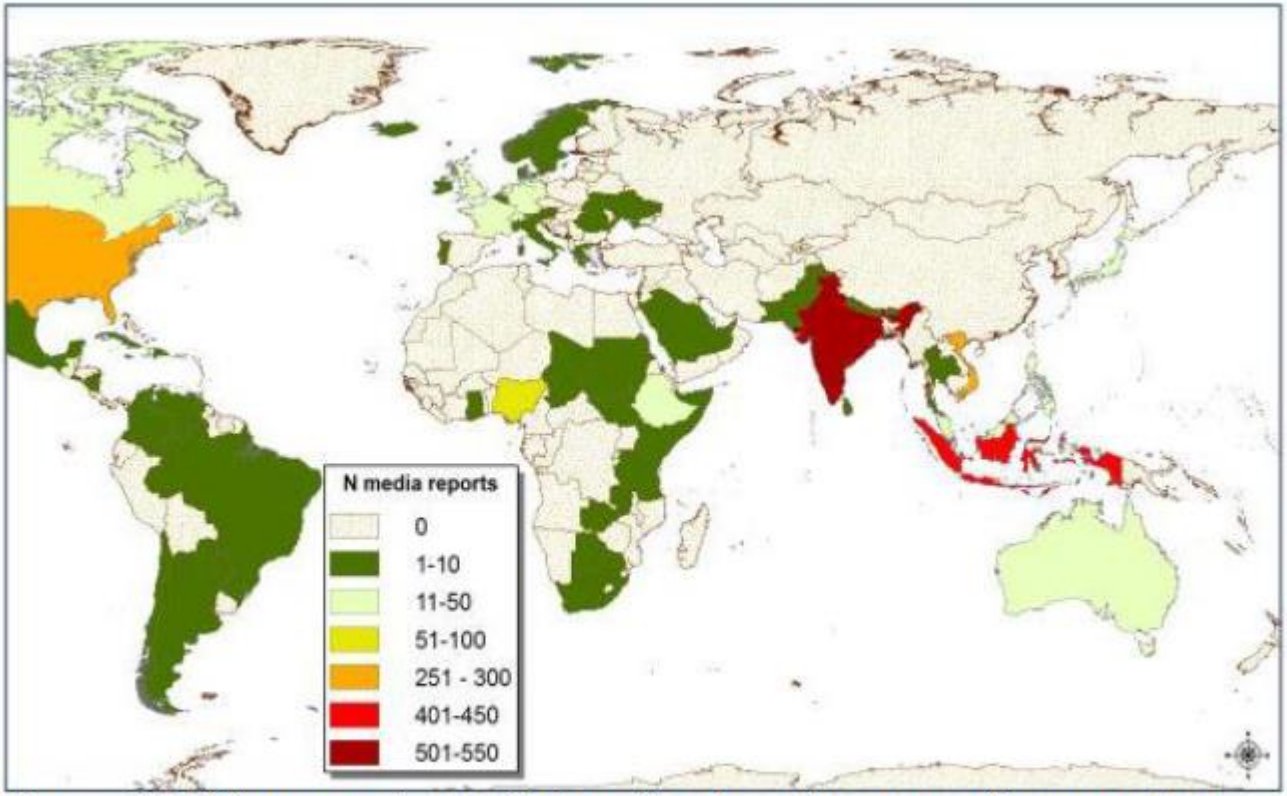


Figure 3: GIS processing and visualization of reports of pentavalent vaccine discussion

Perception of Risk from Vaccine Preventable Disease

"Hidden" Vaccine preventable disease

- Eliminated
  - Polio, Measles
- Reduced prevalence
  - HiB, Hepatitis B, Pneumococcal
- Consequence of infection – delayed/cancer
  - Hepatitis B, HPV

Context in LMIC

Increase in **number and types** of vaccines

Vaccine **manufacture**

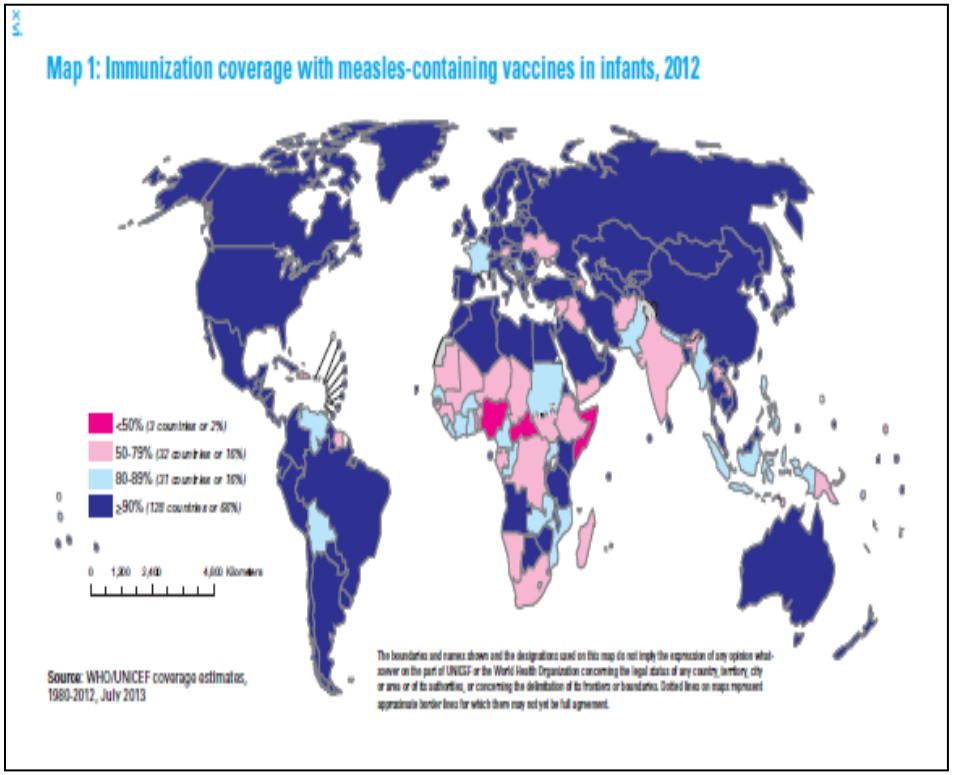
Strengthening of AEFI surveillance systems

Increase in **number and types** of vaccines

- **EPI vaccines**
- **Underused and new vaccines**
  - Hib, Hepatitis B (Pentavalent vaccine), Rotavirus and PNC
  - HPV – Expanded age
- **Polio End game**
  - Pentavalent vaccine (IPV)
- **Novel** vaccines to be used in LMIC

Expanded Programme on Immunisation (EPI)

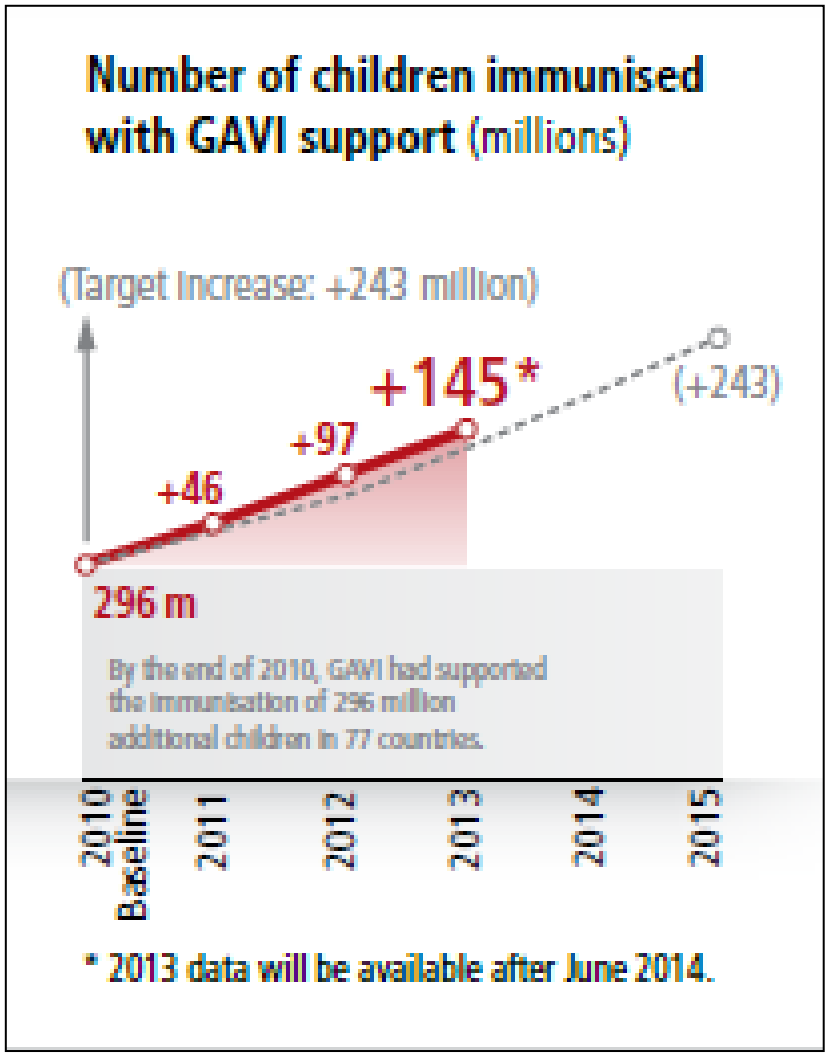
- Established 1974
- 5% of worlds children protected
  - Polio, diphtheria, TB, pertussis, measles and tetanus
- Today, 83% protected
- 22 million children incompletely immunised
  - In approximately 10 countries
- 2 million deaths could be prevented per year by existing vaccines



Beyond expectations: 40 years of EPI Margaret Chan www.thelancet.com Vol 383 May 17 2014

GAVI ALLIANCE

Saving children's lives and protecting people's health by increasing access to immunisation in poor countries



Global Alliance for Vaccines and Immunisation (2000)

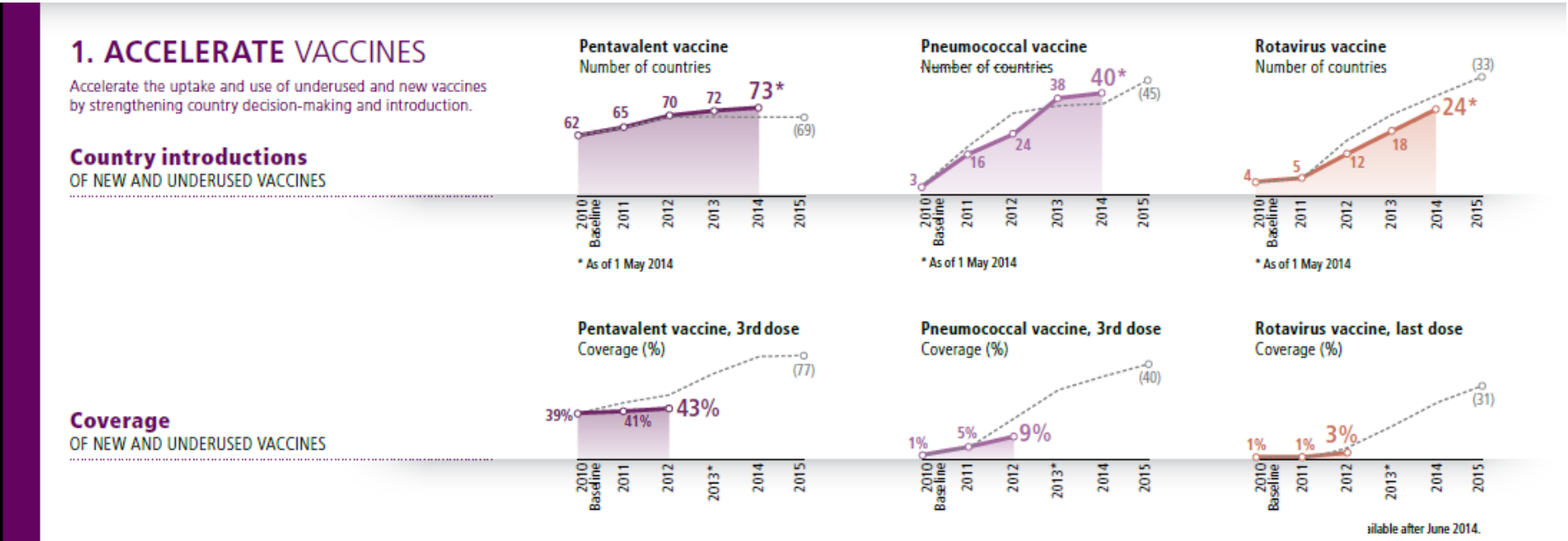
Supported immunisation of 296 million additional children in 77 countries. Target by end 2015. 500 million (1/2 billion)

Estimated global population
< 19 years = 2.3 billion

GAVI Goal Level Indicator (1)

*Accelerate the uptake of **underused and new** vaccines*

- Hib and Hepatitis B (Pentavalent - DTP-Hib-HepB)
- Pneumococcal Conjugate, Rotavirus, (HPV)



GAVI ALLIANCE

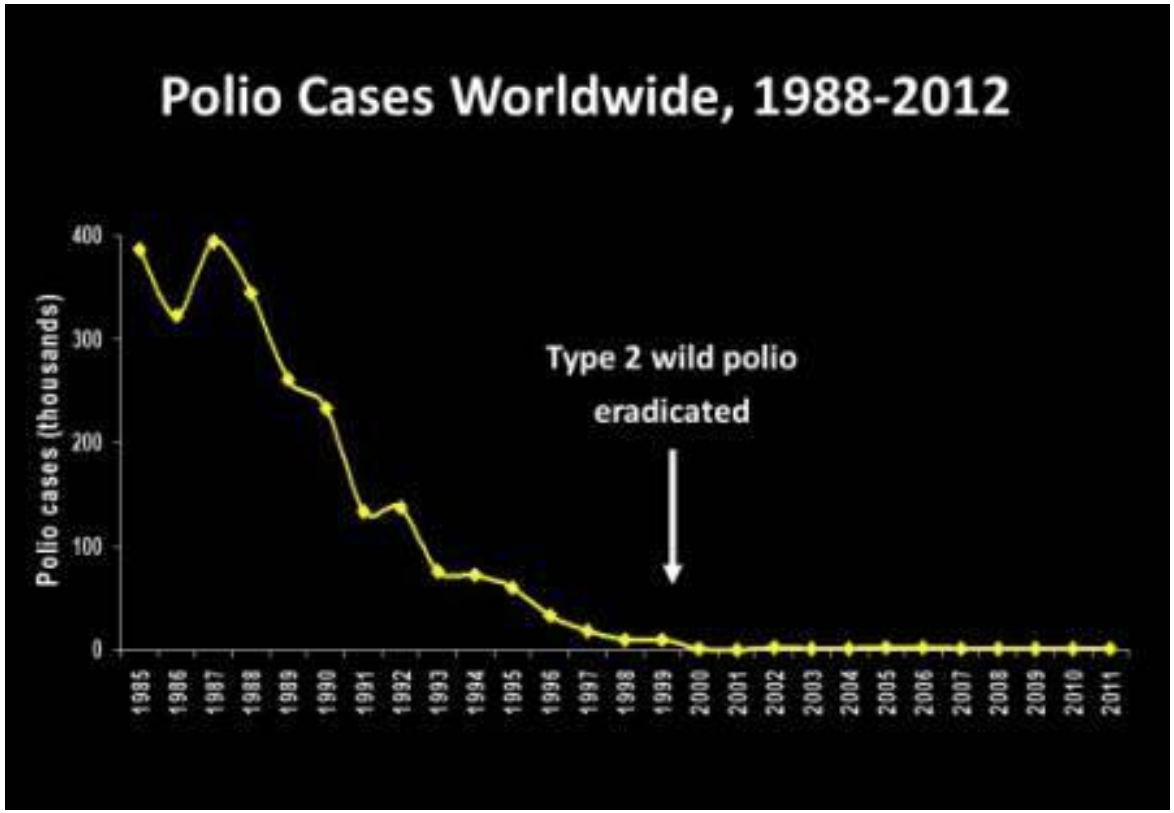
Goal-level indicators

Updated: May 2014

For detailed descriptions of indicators and data sources, please see:
www.gavialliance.org/results/goal-level-indicators

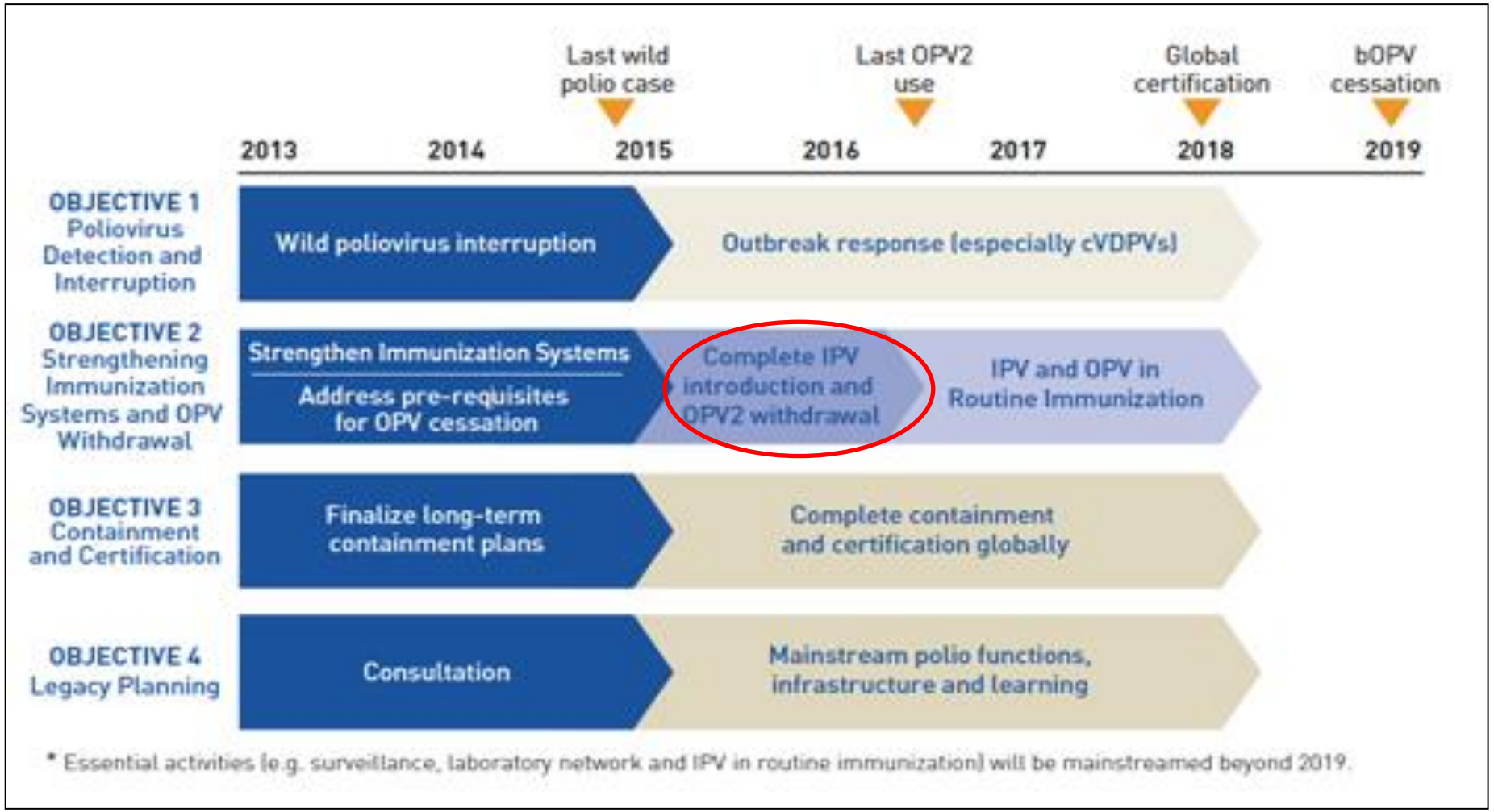
Polio End Game

Replacement of ***OPV with IPV***



Polio End Game

+ IPV = Pentavalent or Hexavalent vaccines



Pentavalent vaccine (DTwP-HepB-HiB)

- Sept 2006 — PV vaccine pre-qualified by WHO
- Jan-April 2008 — Introduced **Sri Lanka**
  5 reported deaths
  Vaccination suspended
  Investigated by WHO - Re-introduction
- Sept 2009 — Introduced into **Bhutan**
  9 cases seizures, sudden death, encephalitis
  Vaccination suspended
  Investigated by WHO - Re-introduction
- April 2010 introduction — High court action in **India** to prevent PV
- Dec 2012/13 — Introduced into **Vietnam**
  9 deaths
  Vaccination suspended
  Investigated by WHO - Re-introduction

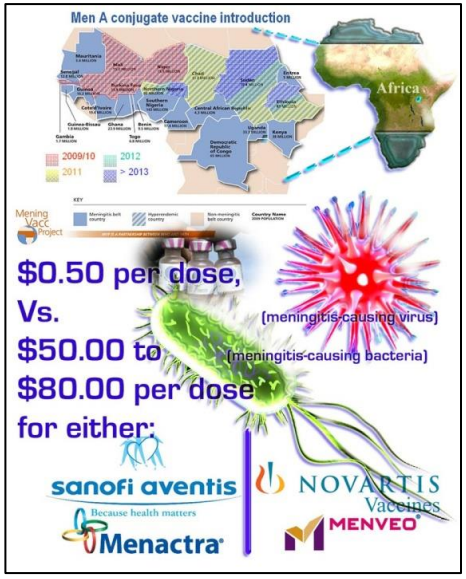
Novel vaccines

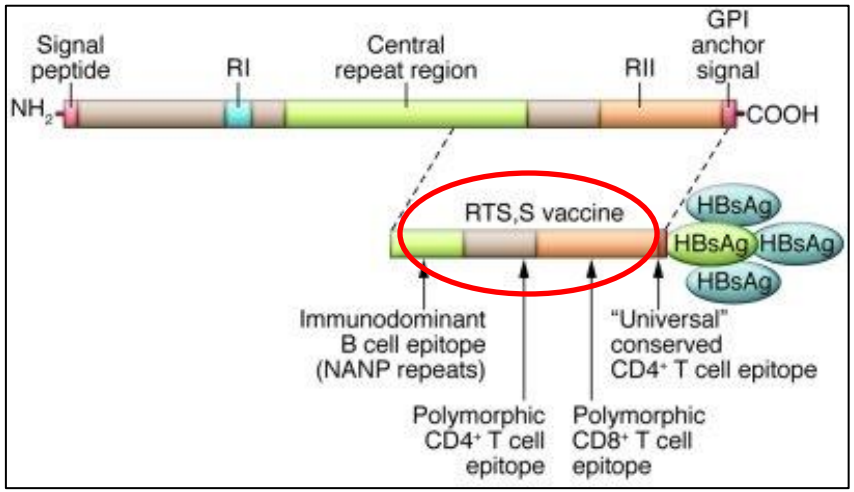
No prior or planned use in HIC

MenAfriVac (Meningococccal A conjugate vaccine)

+100 million (End 2012), Serum Institute India (WHO/PATH)

Malaria, TB, HIV, Dengue, Hepatitis E



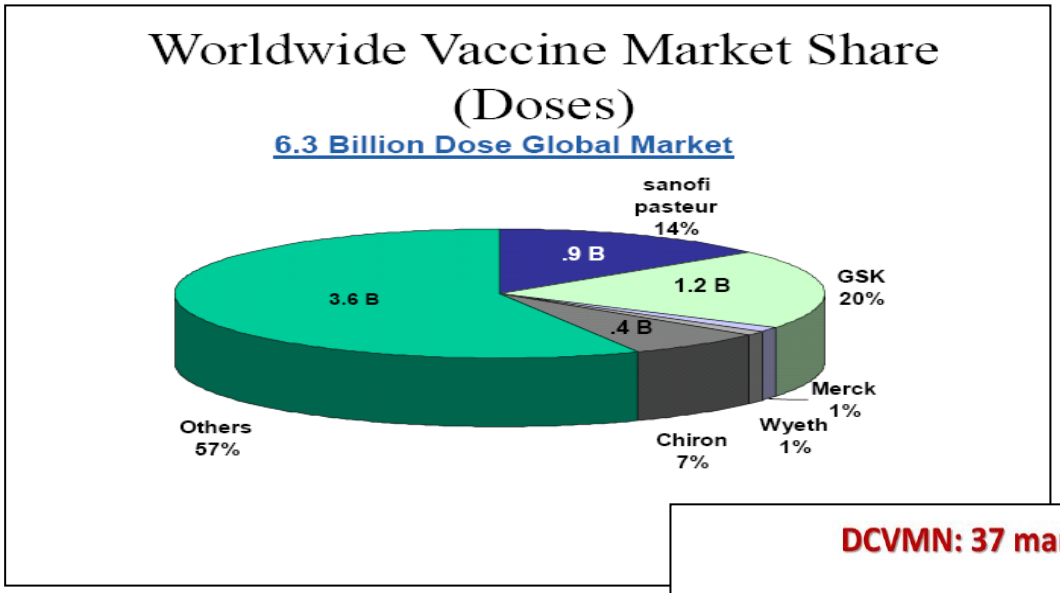


RTS,S Malaria Vaccine

Increased **use** of vaccines
Implications for safety

- **EPI vaccines**
  - Increased vaccine use
- **Underused and new vaccines**
  - Pentavalent vaccine — Coincidental death
  - Rotavirus — Intussception
  - HPV — Somatic conversion/Psychogenic
- **Polio End game**
  - Pentavalent vaccine (IPV)
- **Novel** vaccines to be used in LMIC
  - ? Novel reactions in sub-populations need for PMS

Increase in **vaccine manufacture and supply from LMIC**



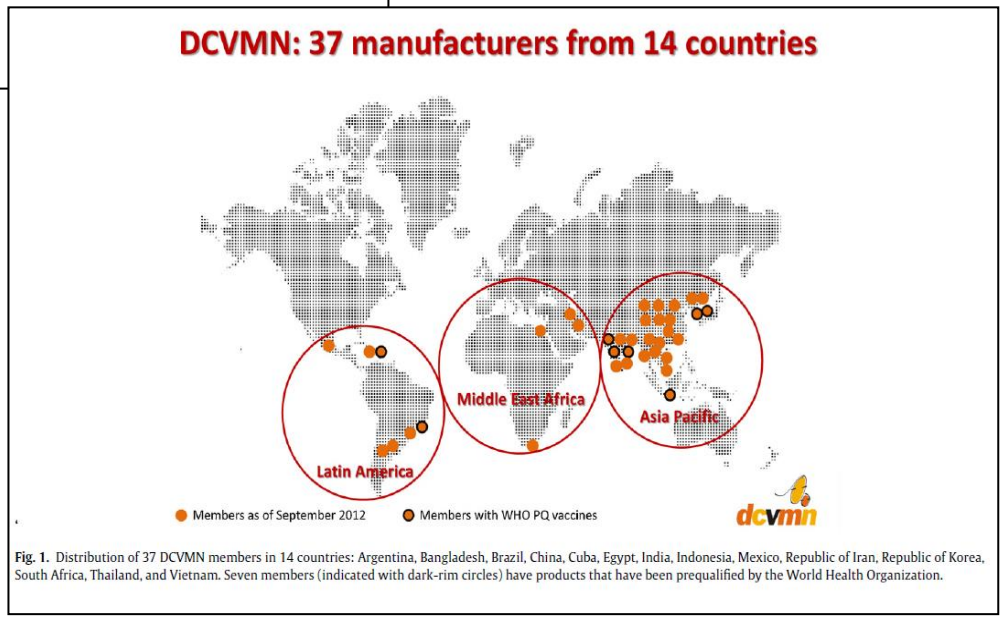
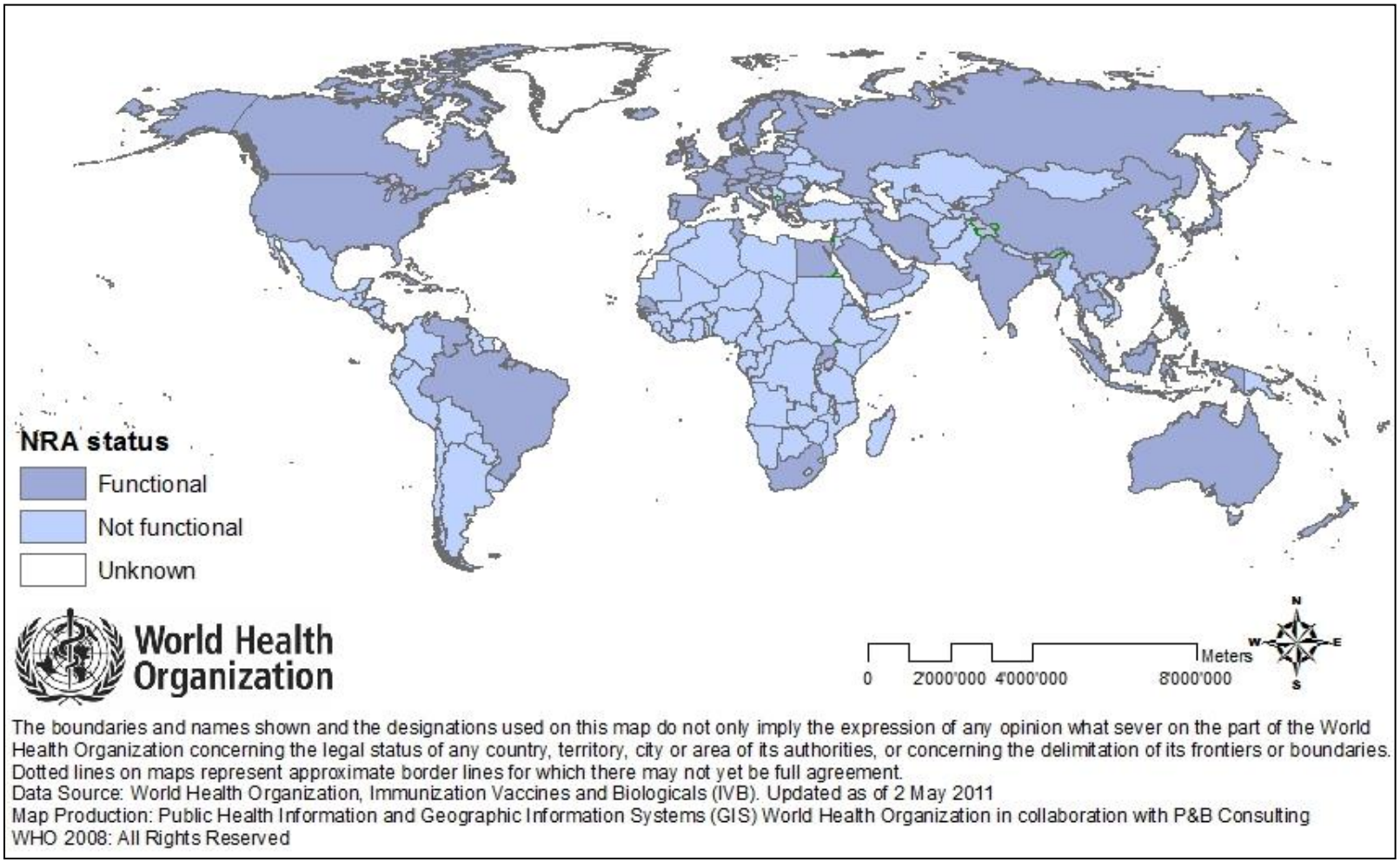


Fig. 1. Distribution of 37 DCVMN members in 14 countries: Argentina, Bangladesh, Brazil, China, Cuba, Egypt, India, Indonesia, Mexico, Republic of Iran, Republic of Korea, South Africa, Thailand, and Vietnam. Seven members (indicated with dark-rim circles) have products that have been prequalified by the World Health Organization.

Strengthening of AEFI systems

Status as of October 2011:

60 countries have a functional NRA to regulate vaccines

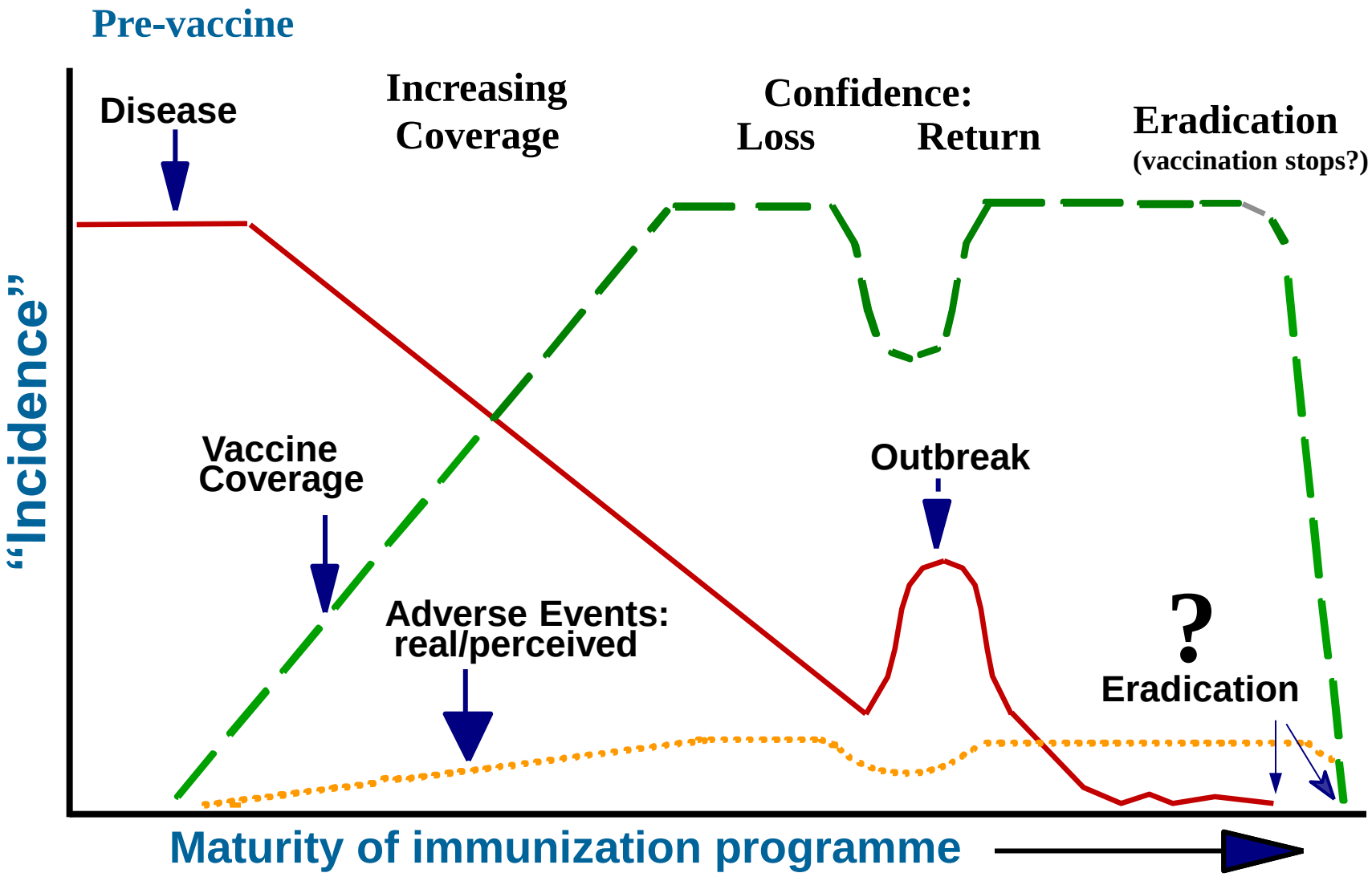


World Health Organization

Global Manual on Surveillance of Adverse Events Following Immunization

DoV	Decade of Vaccines
	http://www.dovcollaboration.org/
GVAP	Global Vaccine Action Plan
	http://www.who.int/immunization/global_vaccine_action_plan/en/
GIVS	Global Immunisation Vision and Strategy
	http://www.who.int/immunization/givs/en/
GAVI	Global Alliance for Vaccines and Immunisation
	http://www.gavialliance.org/
GACVS	Global Advisory Committee on Vaccine Safety
	http://www.who.int/vaccine_safety/en/
GVSB	Global Vaccine Safety Blueprint
	http://www.who.int/vaccine_safety/en/
GVSI	Global Vaccine Safety Initiative
	http://www.who.int/vaccine_safety/en/
PEEGSP	Polio Eradication and Endgame Strategic Plan
	http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx

Impact of AEFI on immunization programmes



Adapted from: Chen RT et al, Vaccine 1994; 12:542-50

Increase in **vaccine manufacture and supply from LMIC**

Implications for safety

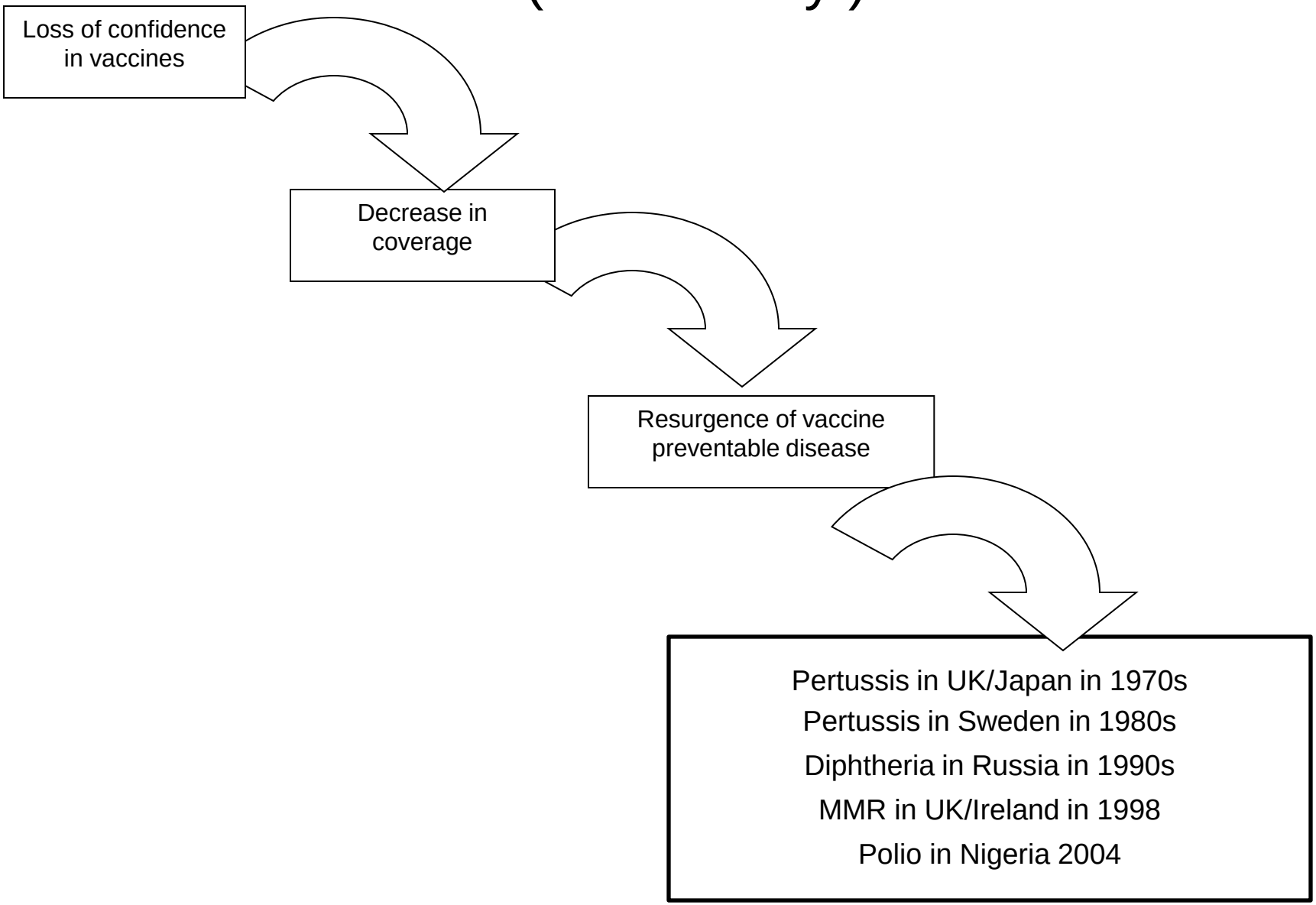
- Regulation via NRA
- GMP monitoring - ? *Particular issues with Influenza vaccines*

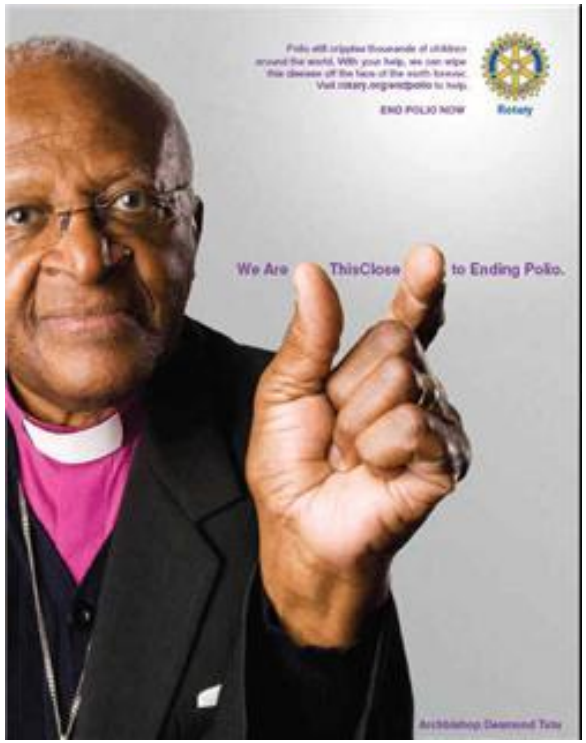
Strengthening of AEFI systems

Implications for safety

- Increased AEFI reports
- Must have a system to analyses, investigate and communicate

Concerns about vaccine safety affect coverage (not efficacy)





Current Drug Safety, 2006, *1*, 117-119

How Vaccine Safety can Become Political – The Example of Polio in Nigeria

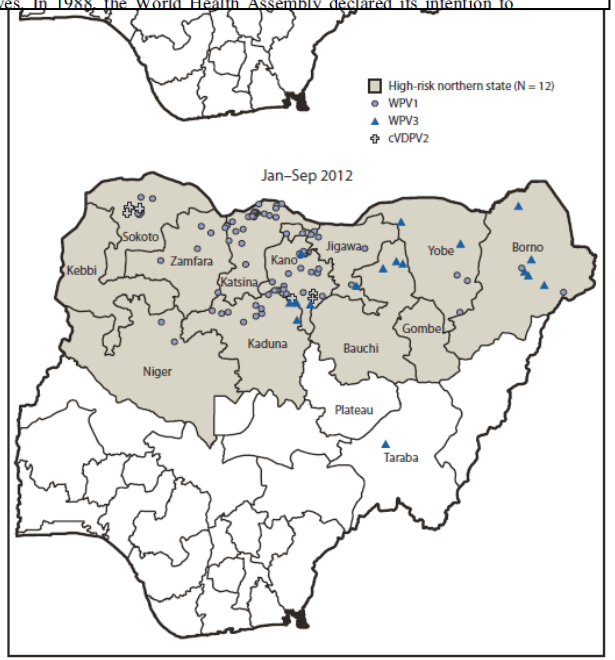
Christopher J. Clements[*,1], Paul Greenough[2] and Diana Shull[3]

[1]*Centre for International Health, The Macfarlane Burnet Institute for Medical Research and Public Health Ltd., Melbourne, Australia*

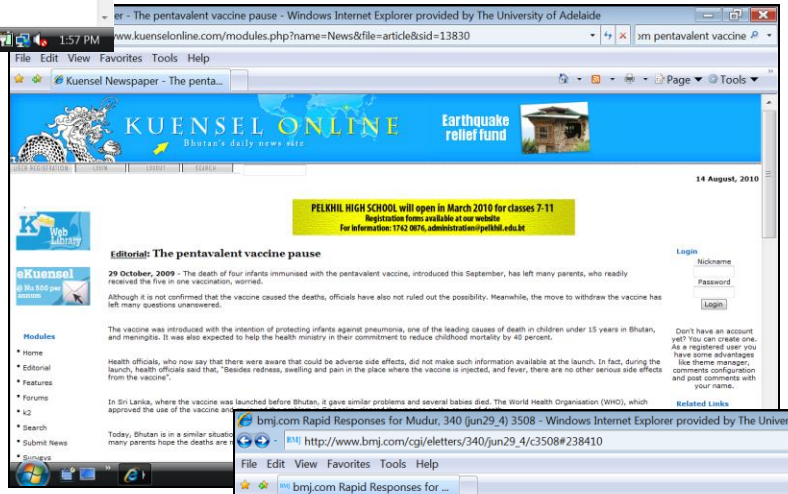
[2]*Departments of History and Community and Behavioral Health, University of Iowa, Iowa City, Iowa, USA*

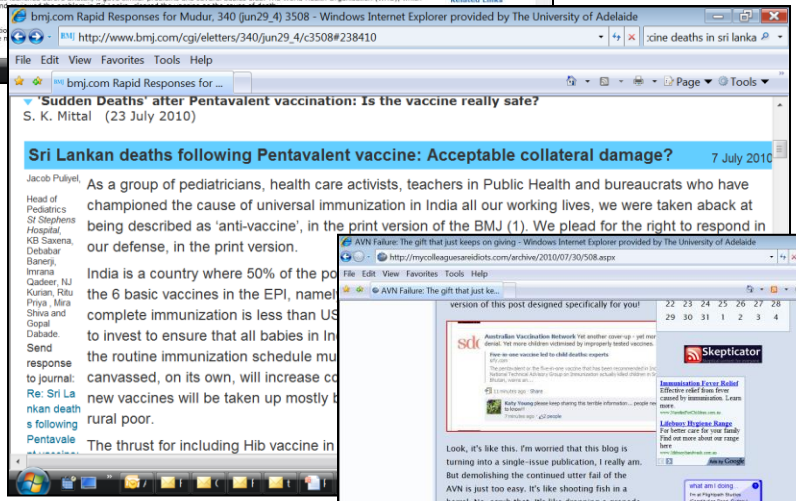
[3]*History Department, University of Colorado at Boulder, Boulder, Colorado 80309, USA*

Abstract: Vaccine safety is increasingly a major aspect of immunization programmes. Parents are becoming more aware of safety issues relating to vaccines their babies might receive. As a consequence, public health initiatives have had to take note of pressures brought to bear by individual parents and groups. Now we document a new phase in vaccine safety where it has been used to achieve political objectives. In 1988, the World Health Assembly declared its intention to



"*Many Muslims in the north believe that polio vaccination is being used as a ploy by Western countries to inject people with certain chemicals to reduce their fertility or infect them with HIV/AIDS in order to reduce the population of Muslims*. *(2004)*





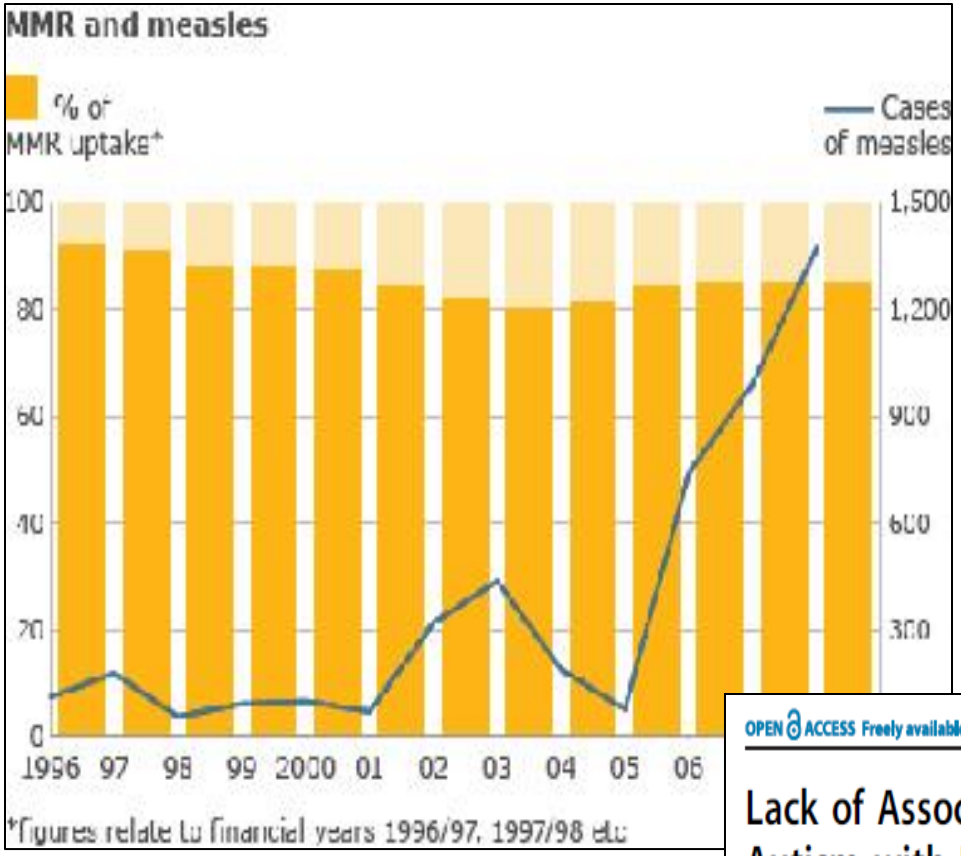
<u>September 2006</u>
PQ Pentavalent (PV) vaccine WHO

<u>Jan-April 08</u>
- PV introduced Sri Lanka, 5 deaths
- Vaccination suspended
- Investigated by WHO recommenced
- Re-introduction

<u>Sept 09</u>
- PV introduced into Bhutan
- 9 cases seizures, sudden death, encephalitis
- Vaccination suspended
- WHO report

<u>April 2010</u>
- High court action in India to prevent introduction of PV

<u>July 2010</u>
- BMJ letters
- AVN website/blog



OPEN ACCESS Freely available online

PLoS one

Lack of Association between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study

Mady Hornig[1]*, Thomas Briese[1], Timothy Buie[2], Margaret L. Bauman[3], Gregory Lauwers[4], Ulrike Siemetzki[1], Kimberly Hummel[5], Paul A. Rota[5], William J. Bellini[5], John J. O'Leary[6], Orla Sheils[6], Errol Alden[7], Larry Pickering[8], W. Ian Lipkin[1]*

Retraction--Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet retraction. Lancet 2010 Feb 6;375(9713):445.

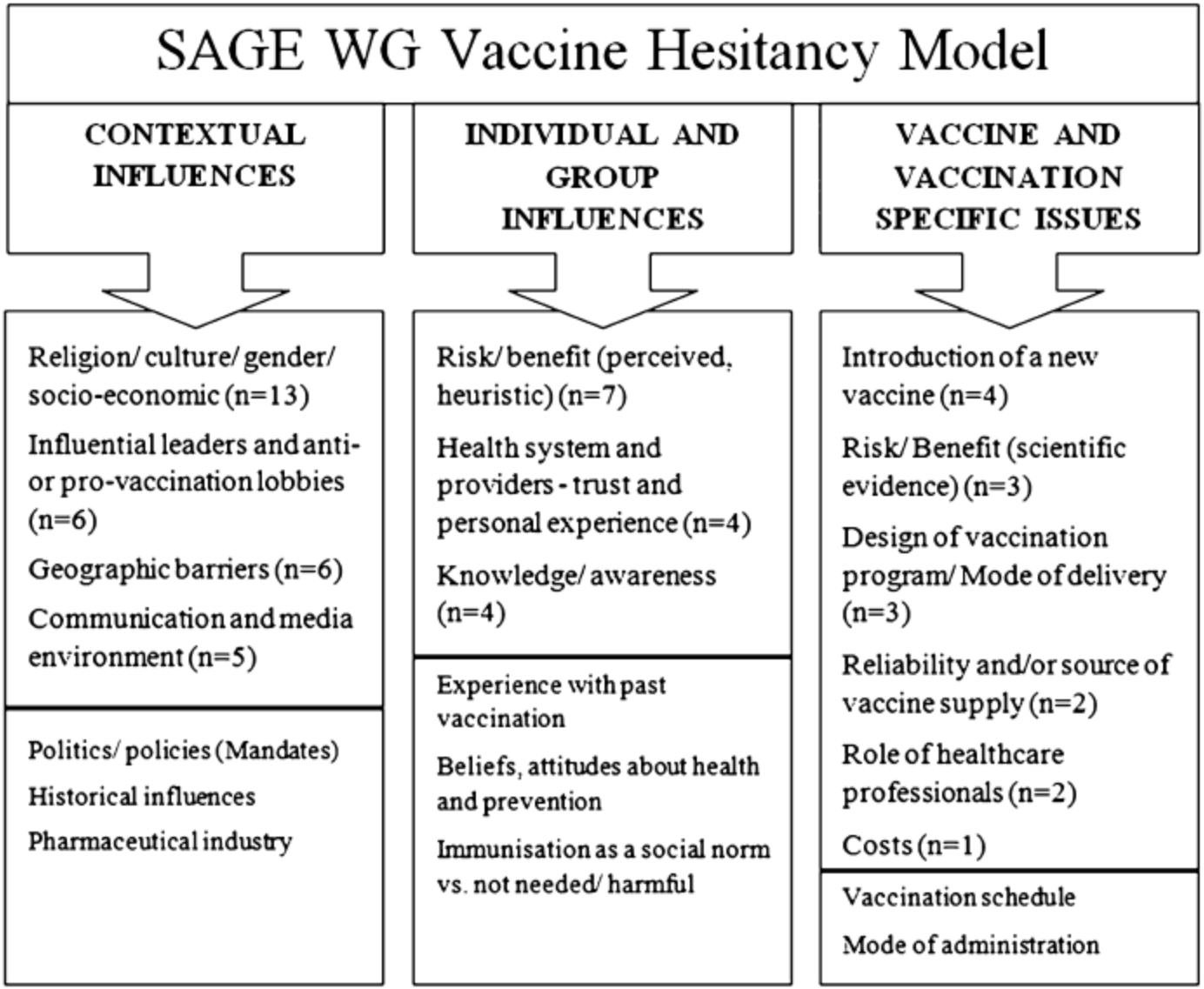


Fig. 1. Immunization manager's opinions regarding determinants of vaccine hesitancy*.

How do we know ..... is safe ?

Safety inferred because of an absence of adverse reactions

How do we detect **adverse vaccine reactions** ?

Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.

Pharmacovigilance

Vaccine Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization.

** Source: Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012*

McBride WG (1962). *Thalidomide and congenital abnormalities. Lancet 2:1358.*

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (' Distaval ') during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to " reports from two overseas sources possibly associating thalidomide (' Distaval ') with harmful effects on the fœtus in early pregnancy ". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

Developed in 1950's, used in '57 withdrawn '61
Used as an anti-emetic in pregnancy
No safety studies in pregnancy – animal or human
Phocomelia and organogenesis, 12,000 infants affected
Subsequently shown to be teratogenic in multiple animal studies

Vaccines

- Prevention in healthy, larger population
  - Lower risk tolerance
- Limited number of products
- With single dose, greater potential for temporal “coincidence”

Other Drugs

- Treatment in ill, smaller population
  - More tolerant of risk
- Large number of products, many classes
- Treatment over time: less “coincidence” after a single dose

Vaccines vs drugs continued

Vaccines

- Cold chain often critical
- Biological product – more prone to lot variation and instability
- Mass campaigns: many doses in short time, defined population
- Politics of access/safety
  - Collaboration between public health/NIP, NRA and manufacturers

Other Drugs

- Storage/handling less critical
- Chemical product
- No mass campaigns – “private” prescribing to less defined population
- Politics of access/safety
  - Less relationship between health system/govt/NRA and manufacturers

Vaccines demand higher safety and more careful quality standards and monitoring.

How do we assess adverse vaccine reactions ?

Pre-Licensure trials

↓

Licensure

↓

Post- Licensure Surveillance

Pre-licensure

On April 12, 1955 the Poliomyelitis Vaccine Evaluation Center announced that the polio vaccine was "safe, potent, and effective."[3] The largest clinical trial in U.S. history, involving 1.8 million schoolchildren, had shown the vaccine to be 80 to 90 percent effective.

Pre-licensure assessment of vaccine safety

	Sample size	Adverse Reactions	
		Common	Rare
Animal trials		+/−	−
Clinical trials			
Phase I	10-100	+/−	−
Phase II	100-1,000	+	−
Phase III	1,000-10,000	+	−

– **Does not detect adverse reactions which are**:
  - rare, delayed, unexpected
  - occur in sub-populations
  - with vaccine combinations

HPV Clinical Studies III – Safety

Unable to detect an adverse reaction that may occur less commonly than 1 in 1,000 vaccinations

GARDASIL®
[Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] 9682305

Table 6
Vaccine-related Injection-site and Systemic Adverse Experiences*

Adverse Experience (1 to 5 Days Postvaccination)	GARDASIL (N = 5088) %	Aluminum-Containing Placebo (N = 3470) %	Saline Placebo (N = 320) %
Injection Site			
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.6	18.4	12.1
Pruritus	3.1	2.8	0.6

Adverse Experience (1 to 15 Days Postvaccination)	GARDASIL (N = 5088) %	Placebo (N = 3790) %
Systemic		
Fever	10.3	8.6
Nausea	4.2	4.1
Dizziness	2.8	2.6

*The vaccine-related adverse experiences that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.

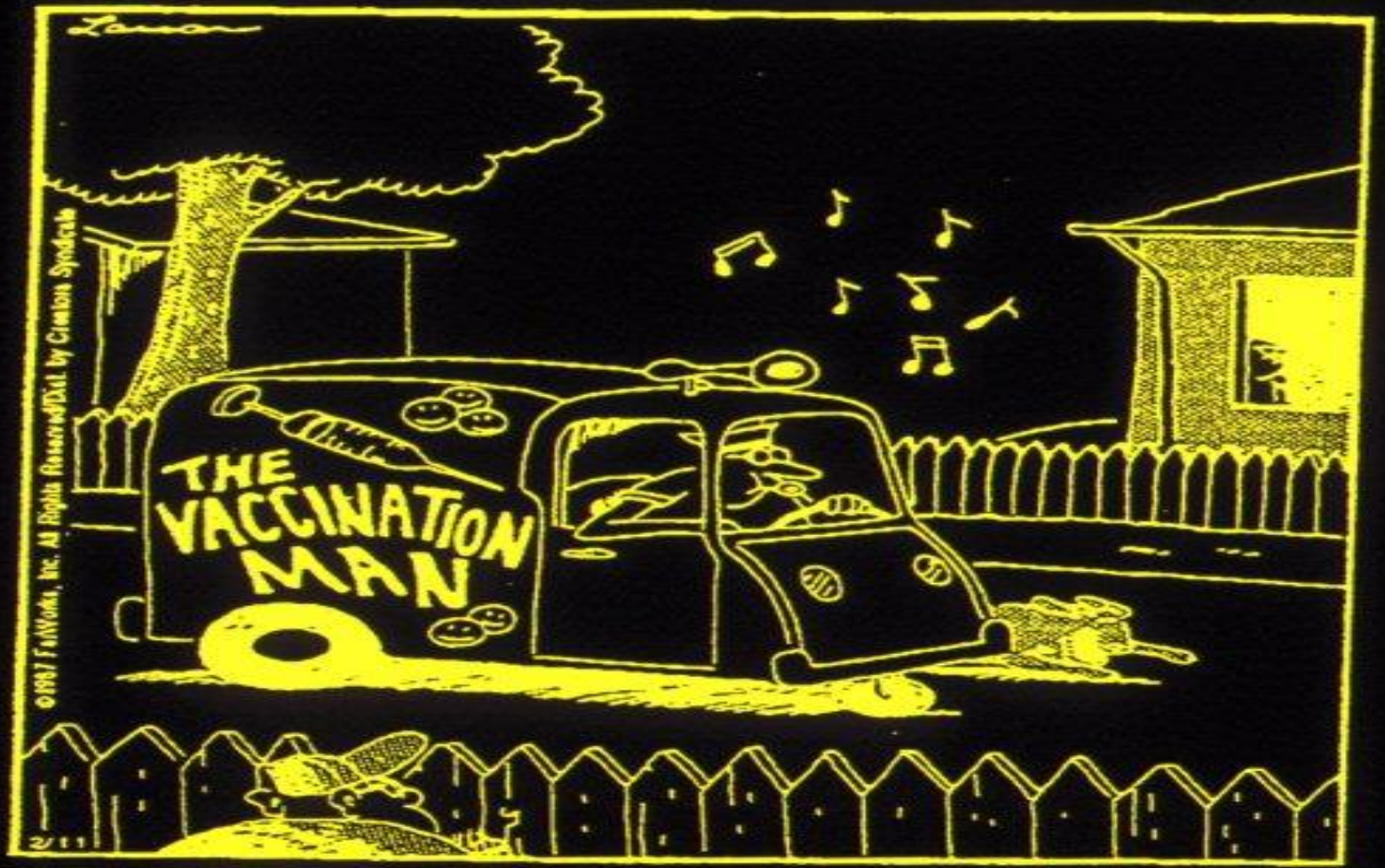
Serious Adverse Experiences

A total of 102 subjects out of 21,464 total subjects (9- to 26-year-old girls and women and 9- to 15-year-old boys) who received both GARDASIL and placebo reported a serious adverse experience on Day 1-15 following any vaccination visit during the clinical trials for GARDASIL. The most frequently reported serious adverse experiences for GARDASIL compared to placebo and regardless of causality were:

headache	(0.03% GARDASIL vs. 0.02% Placebo),
gastroenteritis	(0.03% GARDASIL vs. 0.01% Placebo),
appendicitis	(0.02% GARDASIL vs. 0.01% Placebo),
pelvic inflammatory disease	(0.02% GARDASIL vs. 0.01% Placebo).

One case of bronchospasm and 2 cases of asthma were reported as serious adverse experiences that occurred during Day 1-15 of any vaccination visit.

THE FAR SIDE



Slowly, he would cruise the neighborhood, waiting for that occasional careless child who confused him with another vendor.

Post-licensure (marketing) surveillance

Primary mechanism of surveillance is **passive (spontaneous)** reporting by health providers, consumers, manufacturers of an;

Adverse Events Following Immunization (AEFI):

Definition of AEFI

An AEFI is any untoward medical occurrence which follows immunization and which ***does not necessarily have a causal relationship*** with the usage of the vaccine.

The adverse event may be any *unfavorable or unintended sign, abnormal laboratory finding, symptom or disease*.

Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance, 2012

Difference between serious and severe reactions

Severe reactions
(Not regulatory term)

- Open to interpretation
- Severe reactions include serious reactions but also include other severe reactions.

Serious reactions (Regulatory term)

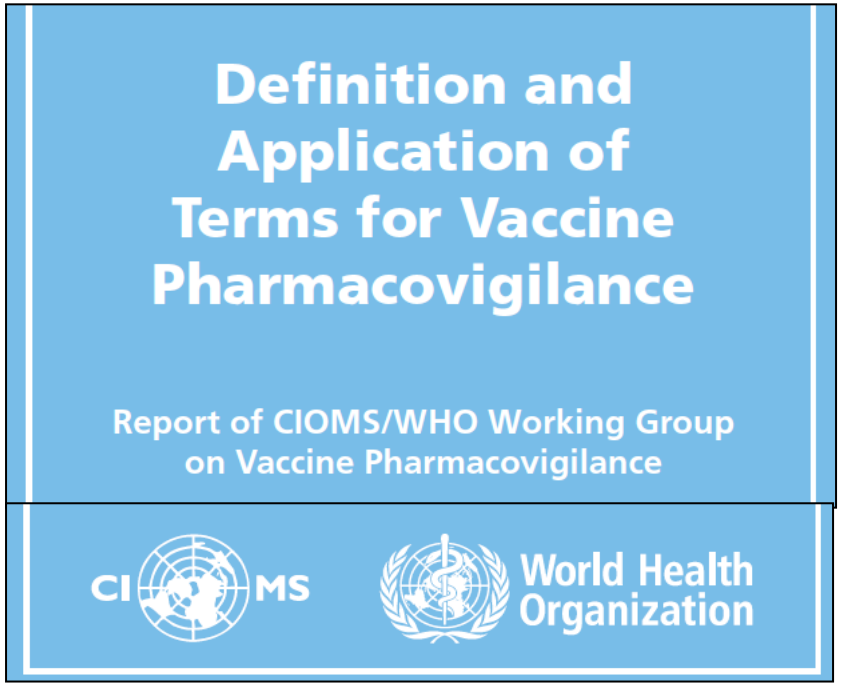
Results in death.

Requires inpatient hospitalization.

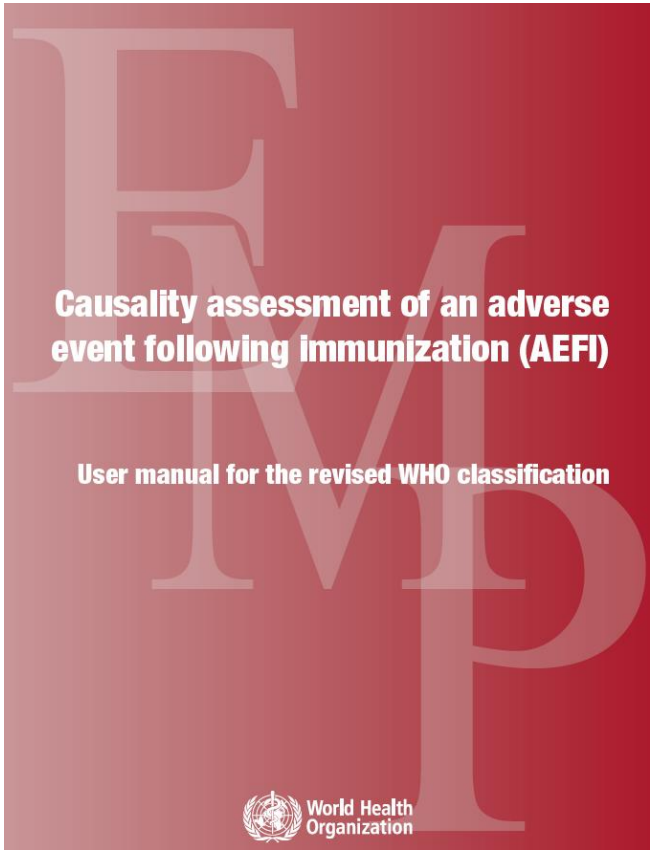
Results in persistent or significant disability.

Is life-threatening.

Congenital Anomaly



http://www.cioms.ch/index.html



CIOMS/ WHO cause specific definition of AEFIs

1
Vaccine product-related reaction

An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.

2
Vaccine quality defect-related reaction

An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.

3
Immunization error-related reaction

An AEFI that is caused by Inappropriate vaccine handling, prescribing or administration.

4
Immunization anxiety-related reaction

An AEFI arising from anxiety about the immunization.

5
Coincidental event

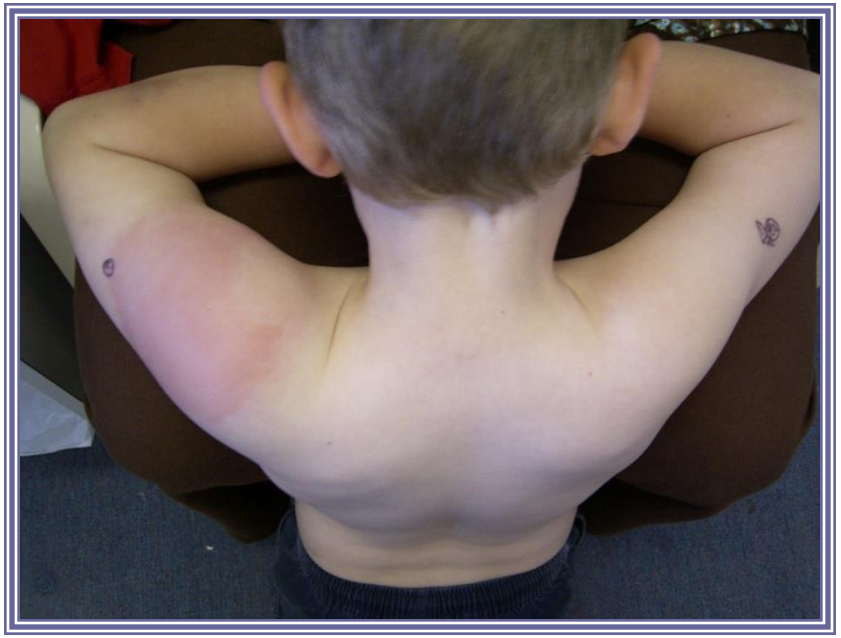
An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety

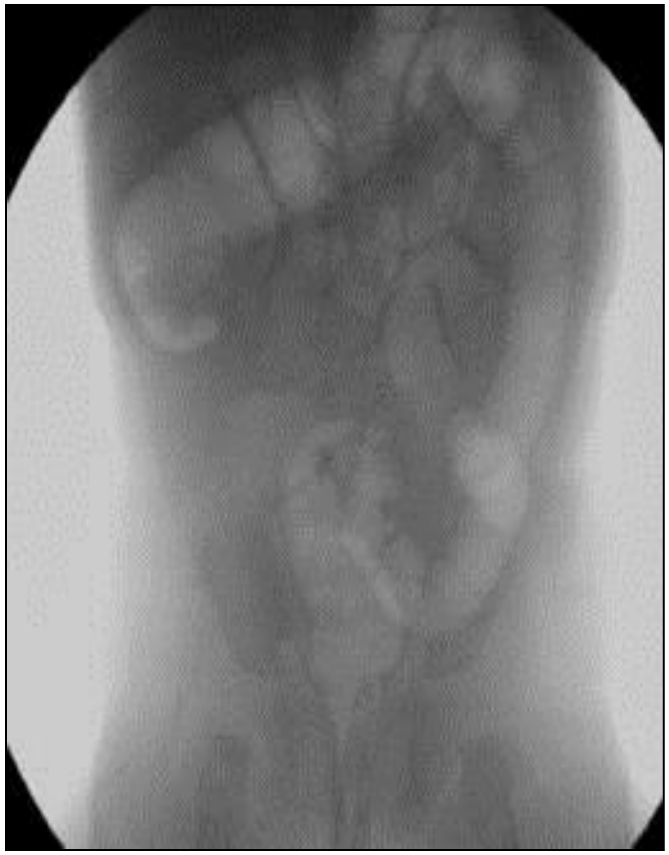
Vaccine Product Related Reaction

An AEFI that is caused or precipitated by a vaccine due to one or more of the **inherent properties** of the vaccine product.

- Known reaction
- Vaccine antigen (s) or excipient (s)
- Examples;

Vaccine Product Related Reaction





Event – Vaccine

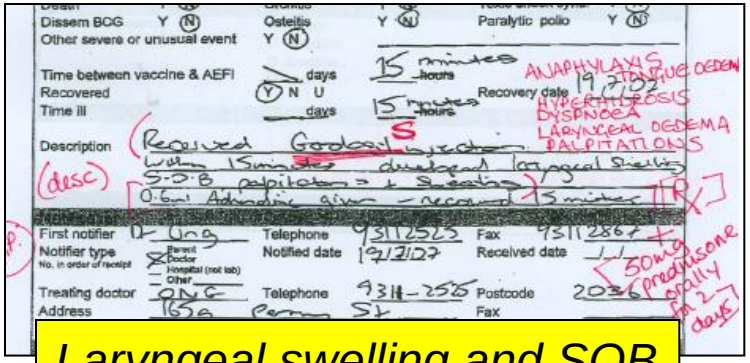
Early release, published at www.cmaj.ca on September 1, 2008. Subject to revision.

CMAJ RESEARCH

Anaphylaxis following quadrivalent human papillomavirus vaccination

Julia M.L. Brotherton MD MPH, Mike S. Gold MD, Andrew S. Kemp MD PhD, Peter B. McIntyre MD PhD, Margaret A. Burgess MD, Sue Campbell-Lloyd RN, on behalf of the New South Wales Health HPV Adverse Events Panel

Early release, published at www.cmaj.ca on Sept. 1, 2008.

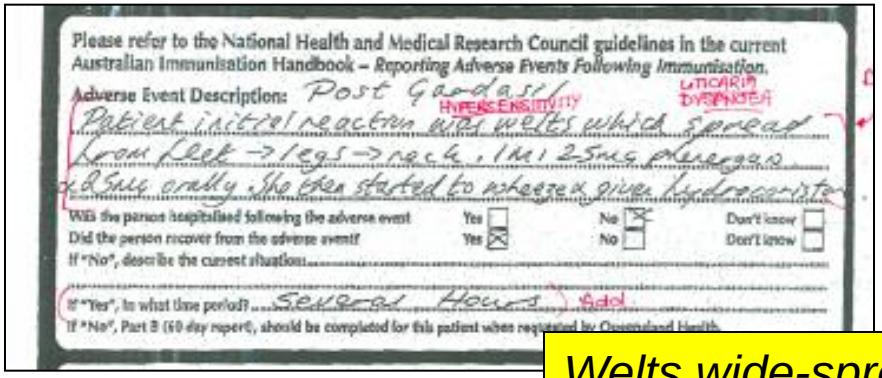


Laryngeal swelling and SOB

BMJ RESEARCH

Hypersensitivity reactions to human papillomavirus vaccine in Australian schoolgirls: retrospective cohort study

Liew Woei Kang, clinical fellow and associate consultant,[1,2] Nigel Crawford, consultant paediatrician,[3,4] Mimi L K Tang, associate professor and director,[1,5] Jim Buttery, infectious disease physician,[3,4] Jenny Royle, consultant paediatrician,[3] Michael Gold, senior lecturer and head,[6] Christine Ziegler, consultant allergist and immunologist,[6] Patrick Quinn, consultant allergist and immunologist,[6] Sonja Elia, immunisation nurse consultant,[3] Sharon Choo, consultant allergist and immunologist[1]

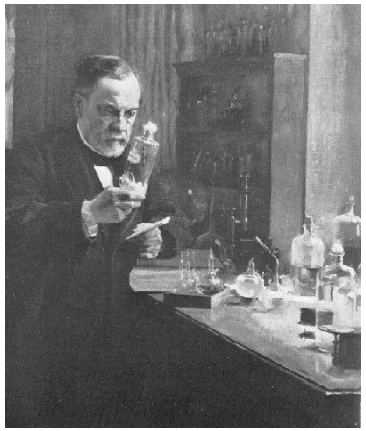


Welts wide-spread and wheeze

Vaccine Quality Defect-related Reaction

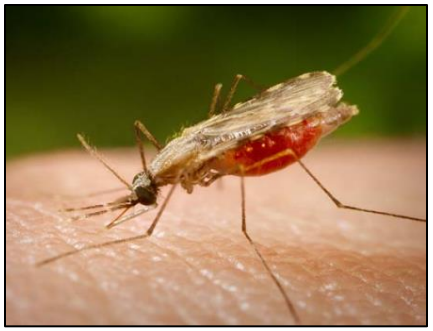
- An AEFI that is caused or precipitated by a vaccine that is due to one or more **quality defects** of the **vaccine** product including its **administration device** as provided by the manufacturer.

Vaccine quality defect-related reaction

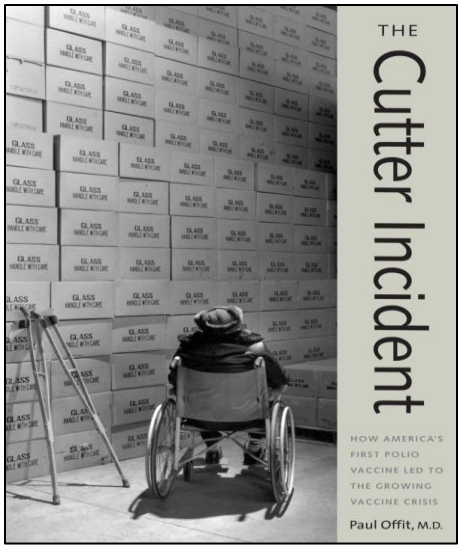


1800-Rabies
1 in 230
seizures,
paralysis
coma

1930 –TB-Lubeck
252 vaccinated
72 died



1942-YF, HepB,
330,000 infected,
50,000 hepatitis,
62 died



1955- IPV-
120,000 injected
40,000 mild polio
200 paralysed
10 died

Seasonal Influenza Vaccine
Febrile reactions including Seizures

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http://www.mediastatements.wa.gov.au/Pages/Results.aspx?ItemID=133378

vaccine suspension wa

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From To Go

Kim Hames
Deputy Premier; Health; Indigenous Affairs

Thu 22 April, 2010

Influenza vaccine program for young children suspended

Portfolio: Health

Health Minister Kim Hames tonight advised the State Government had, as a precautionary measure, temporarily suspended its free influenza vaccination program for children aged under five.

Dr Hames said the suspension came after a significant spike in the number of children who

Actions

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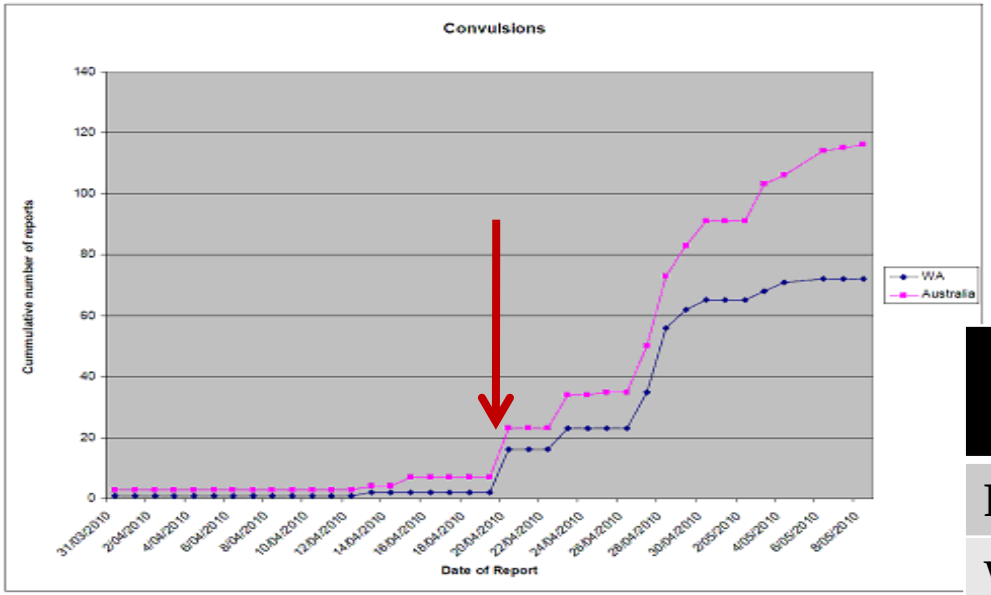
Vaccine Product Related Reaction

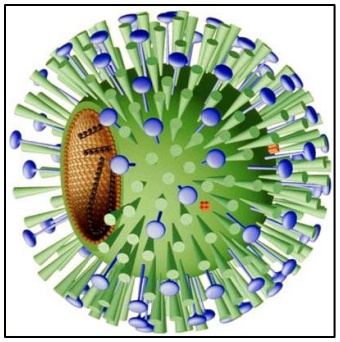
Limitations of passive surveillance



	Febrile seizures per 1,000 vaccines
Fluvax Jr	
Western Australia	9
Australia	5
Panvax	
Australia	0.08-0.17
USA	
CDC Vaccine Datalink	0.16

Vaccine manufacture and compliance with Good Manufacturing Practice

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm259888.htm



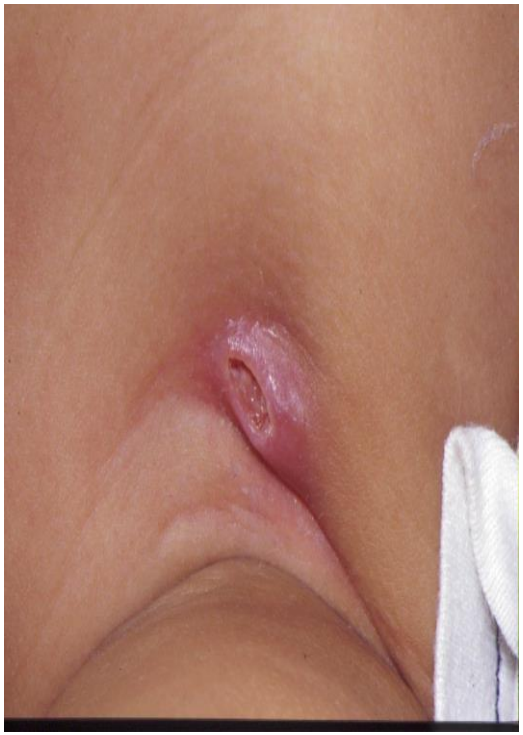
.....your Quality Control Unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of your monovalent influenza bulks and final drug products.

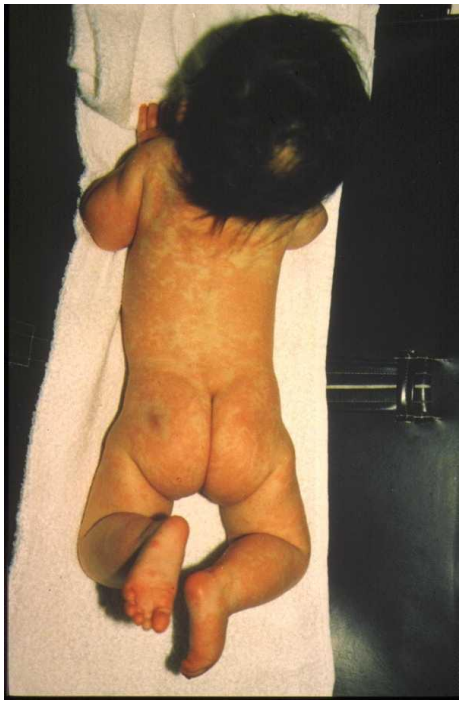
Immunization Error-Related Reaction

An AEFI that is caused by inappropriate vaccine **handling, prescribing or administration**.

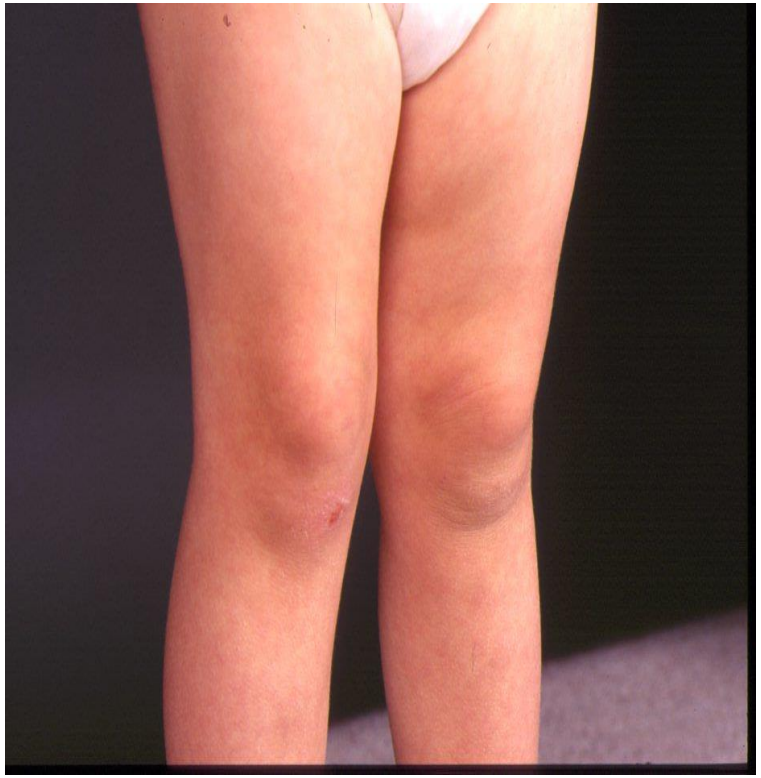
Immunization error Related reaction	
Error in vaccine handling:	Systemic or local reactions due to changes in the physical nature of the vaccine such as agglutination of aluminium-based excipients in freeze-sensitive vaccines. Failure to protect as a result of loss of potency or non-viability of an attenuated product**.**
Error in vaccine prescribing or non-adherence to recommendations for use	Anaphylaxis, Disseminated infection with an attenuated live, VAPP Systemic and/or local reactions, Neurologic, muscular, vascular or bony injury due to incorrect injection site, equipment or technique
Error in administration	Failure to vaccinate due to incorrect diluent , Reaction due to the inherent properties of whatever was administered other than the intended vaccine or diluent. Infection at the site of injection/ beyond the site of injection

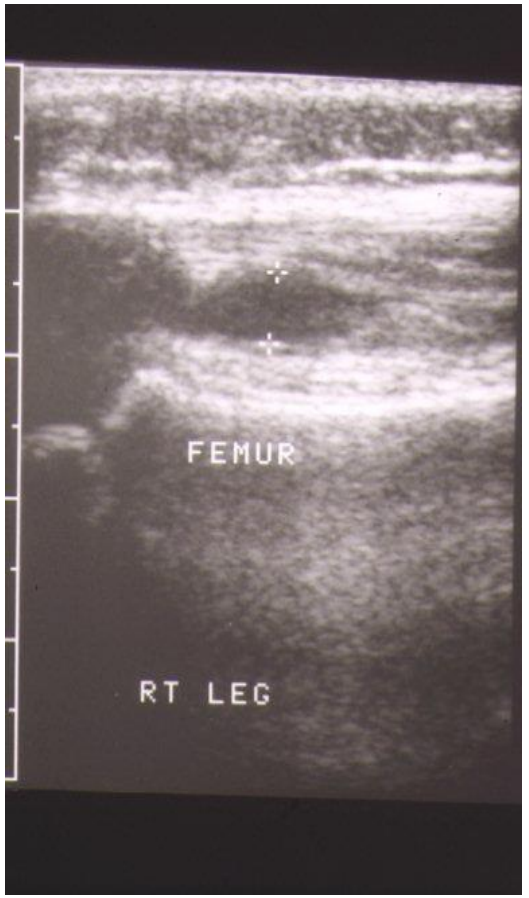
Immunization Error-Related Reaction





Immunization error-related reaction

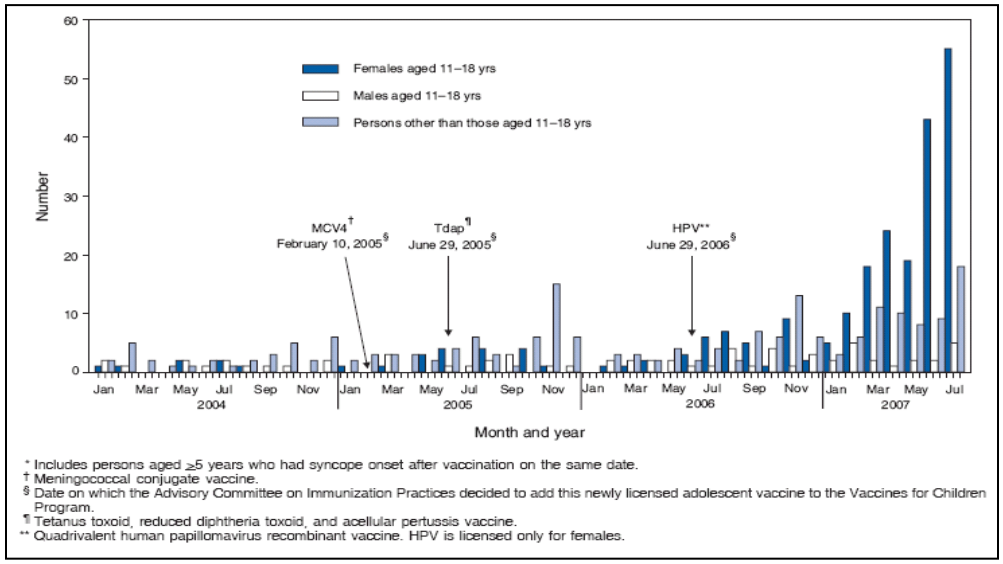




Immunization Anxiety-Related Reaction

AEFI arising from anxiety about the immunization

Immunization anxiety-related reaction



PUBLIC HEALTH

Mass psychogenic response to human papillomavirus vaccination

Jim P Buttery, Simon Madin, Nigel W Crawford, Sonja Elia, Sophie La Vincente, Sarah Hanieh, Lindsay Smith and Bruce Bolam

Policy and Practice

Mass psychogenic illness following tetanus-diphtheria toxoid vaccination in Jordan

Saad Kharabsheh,[1] Haidar Al-Otoum,[2] John Clements,[3] Adnan Abbas,[4] Najwa Khuri-Bulos,[5] Adel Belbesi,[6] Taky Gaafar,[7] & Nora Dellepiane[8]

Zade received her 1st HPV vaccine at school on 10-05-07, between 1130 and noon. Apparently she ha d sore eyes following, and ?visual disturbances – before lunch at 1230. She ate a meat pie for lunch at the hostel. Around 1300 hrs. she arrived at the Health Centre at the High School – having difficulty holding her eyes open. She laid down to rest, appearing very tired. After having a cold wet towel on her eyes, and a rest, she recovered somewhat, and said she would go to her period 5 class. Not long after, she returned with two concerned friends holding her, saying that she was having difficulty holding herself up, and her eyes were "going funny". She felt cold and clammy. She laid down on the bed and was covered with blankets. Her BP at 1430 was 90/50, pulse – 84. At 1505 her BP was 104/64, pulse – 84. By 1545 Zade's colour had improved a great deal, and she had drunk half a mug of tea.

Onset Date:	12/06/2007	
Reaction Outcome: ★	Recovered	A
Outcome Date:	12/06/2007	12/06/2007
Severity Details:		
Adverse Reaction Description:	A patient received 2nd dose of Gardasil and developed blurred vision 4 hours post vaccination which lasted until the following evening. The patient's mother reports that after the first dose of Gardasil the patient developed blurred vision which lasted a couple of days.	
Treatment:		

Co-incidental event

An AEFI that is caused by something other than the vaccine product, programme error or injection reaction

TABLE 5. ESTIMATED NUMBER OF COINCIDENTAL INFANT DEATHS THAT COULD BE TEMPORALLY LINKED TO IMMUNIZATION (E.G. WITH DPT/PVV) IN THE MONTH, WEEK AND DAY AFTER IMMUNIZATION IN SELECTED COUNTRIES

Country	Infant mortality rate per 1000 live births (IMR)	Number of births per year (N)	Estimated number of infant deaths in			Estimated number of PVV/DTP immunizations* in		
			a month	a week	a day	a month	a week	a day
Bhutan	42	15 000	53	12	2	3233	746	106
Canada	5	388 000	162	37	5	86 864	20 045	2856
China	13	16 364 000	17 728	4091	583	3 634 035	838 624	119 475
Indonesia	25	4 331 000	9023	2082	297	950 113	219 257	31 237
Iran	21	1 255 000	2196	507	72	276 445	63 795	9089
Mexico	13	2 195 000	2378	549	78	487 455	112 490	16 026
Sudan	57	1 477 000	7016	1619	231	313 382	72 319	10 303
United Kingdom	4	761 000	254	59	8	170 540	39 355	5607

Co-incidental or causal event ?

SIGNAL

SHORT REPORT

Multiple Sclerosis 2008; **00:** 1–4

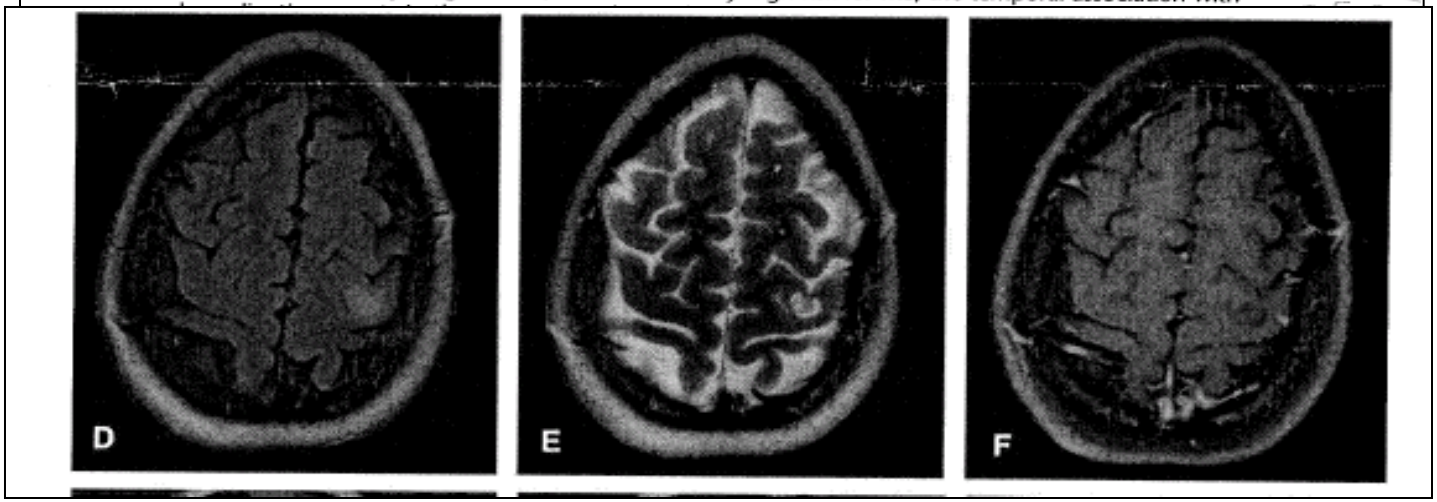
242795

236306

CNS demyelination and quadrivalent HPV vaccination

I Sutton[1,2], R Lahoria[3], IL Tan[1], P Clouston[4] and MH Barnett[2,3]

Vaccination is generally considered safe in patients with multiple sclerosis (MS). We report five patients who presented with multifocal or atypical demyelinating syndromes within 21 days of immunization with the quadrivalent human papilloma virus (HPV) vaccine, Gardasil®. Although the target population for vaccination, young females, has an inherently high risk for MS, the temporal association with



Serious AEFI post HPV

- AEFI reports
  - Pancreatitis (2)
  - Multiple sclerosis (2)
  - Acute Disseminated Encephalomyelitis (1)
  - Ascending neuropathy (1)
  - Nephrotic syndrome (1)
  - Vaginal blistering (6)
  - Macularetinopathy (1)
  - ITP (1), Hemolytic aneamia (1), Pancytopenia (1)
  - Deep Vein Thrombosis (2)
  - Brachial neuritis (1)

How do we know vaccines are safe ?

- We detect Adverse Events Following Immunisation

- Then perform cause specific classification to differentiate an event which is a reaction (consistent) from a co-incidental event (inconsistent)

Safety inferred because of an absence of adverse reactions

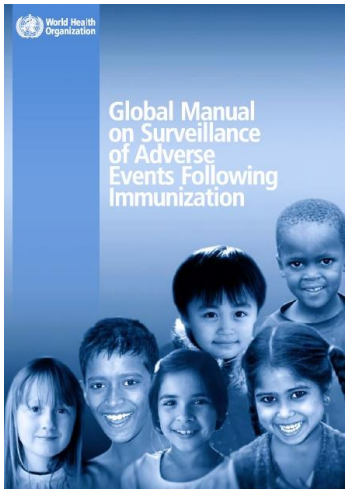
Vaccine safety surveillance systems

- **Reporting of AEFI's**
  - Passive
  - Active

- **Analysis**
  - Recording (data base), analysis, signal detection, hypothesis generation

- **Investigation**
  - Hypothesis testing

- **Communication**



Specific objectives of immunization safety surveillance

The specific objectives of immunization safety surveillance are:

- to detect and identify problems with vaccines which could be due to the inherent properties of a vaccine or to defects in quality, and to detect, correct and prevent immunization error-related reactions;
- to determine the observed vaccine reaction rate and relate this to the expected vaccine reaction rates in the population by country, by region and globally;
- to ensure that coincidental events are not mistaken for vaccine reactions and thus negatively affect the immunization programme;
- to ensure and facilitate causality assessment of individual AEFI reports (cases);
- to identify clustering or unusually high rates of AEFI, even if they are considered mild;
- to identify events which may indicate a previously unknown and potential vaccine reaction (i.e. a signal) and to generate new hypotheses about the causal relationship between the event and the vaccine (this will then require further investigations to support or refute the hypothesis);
- to maintain the confidence of the community and health staff in the immunization programme by appropriate and timely responses to their concerns about immunization safety;
- to create awareness on immunization safety among parents, community, the media and other stakeholders without jeopardizing the immunization programme;
- to collaborate and share information with the regulatory authorities in order to ensure vaccine safety;
- to ensure that channels of communication on AEFI between the NRA and the immunization programme are clear and that information is provided regularly by the unit responsible for immunization safety surveillance;
- to collaborate and share information with the WHO regional offices and globally in order to generate additional information on vaccine safety.

Why should we have a **country specific or regional** vaccine safety surveillance systems ?

- **Incomplete safety information because**
  - Country specific – schedules
  - Background disease
  - Genetic predisposition
  - Novel vaccines
- **Vaccine quality defects**
  - Vaccine manufacture
- **Immunisation error** (Programme error)
- **Differentiate local co-incidental events from reactions**
- **Responding to local community concern**

Conclusion

- Context of vaccine safety
  - General
  - In LMIC
- Concepts and terminology
  - Adverse Events Following Immunisation (AEFI)
  - Serious or Severe
  - Cluster Signal
- Cause specific definitions of AEFI
- AEFI Surveillance

michael.gold@adelaide.edu.au