VACCINE SAFETY

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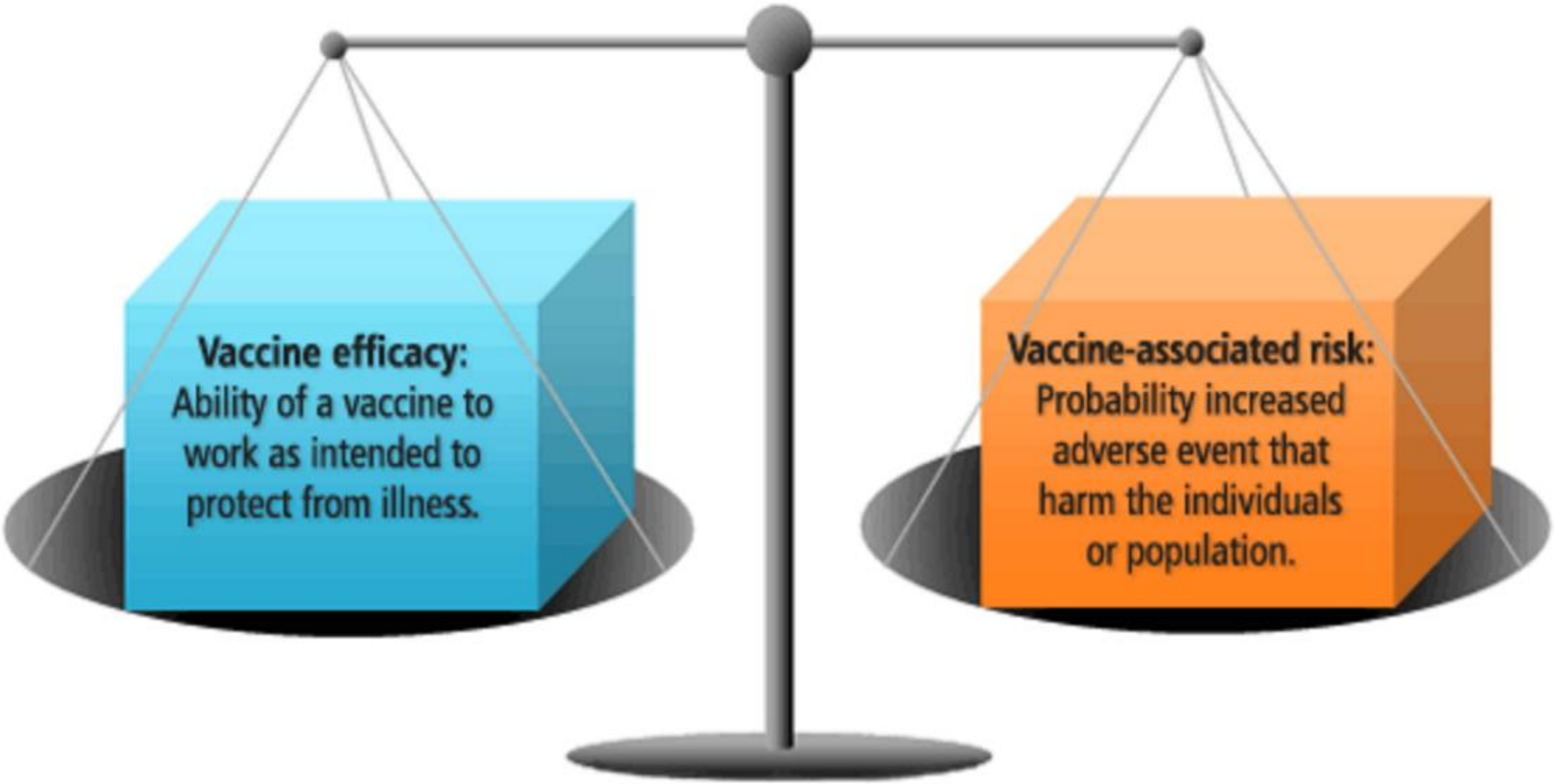
Asian Pacific Vaccinology Meeting

Bangkok, Thailand

Nov.30-Dec.3, 2015

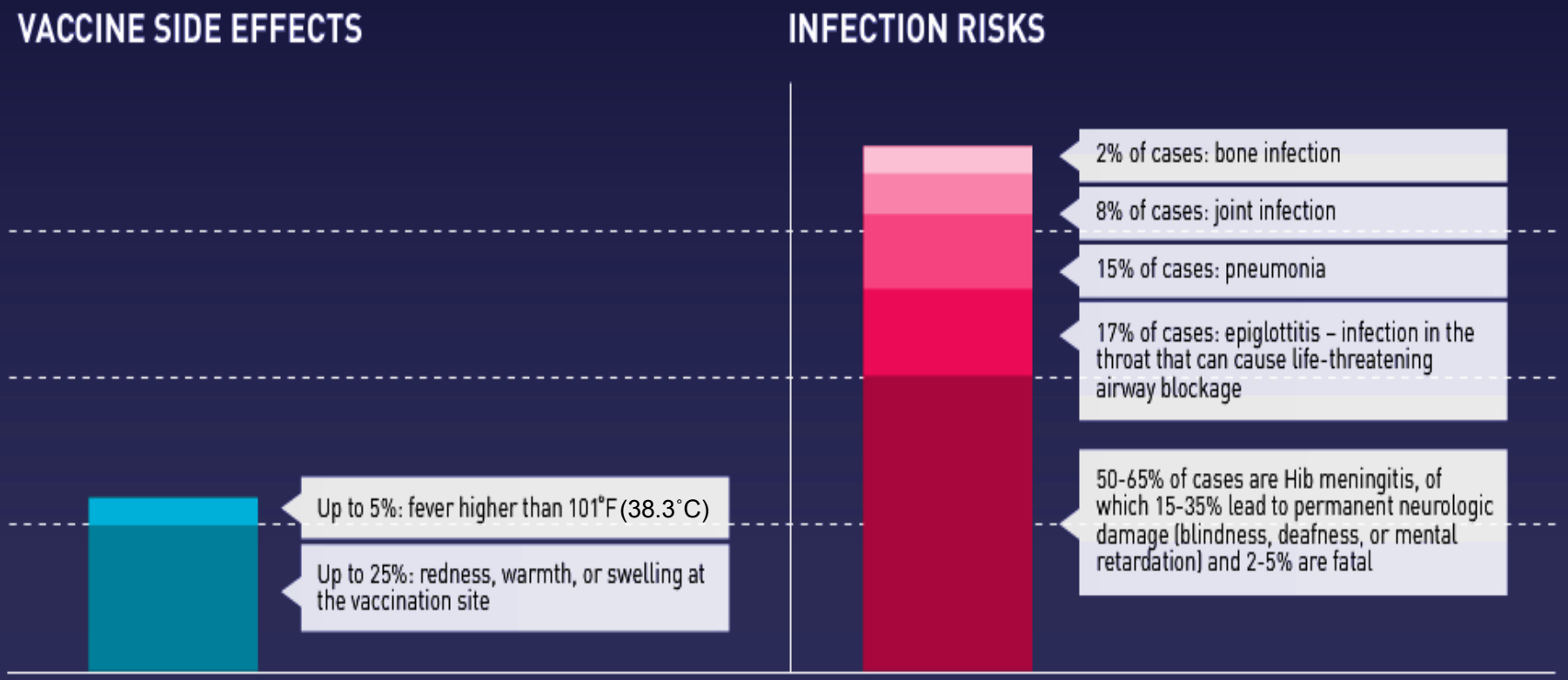
Weighing Vaccine's Benefits versus Risks



UNDERSTANDING RISKS

RISK COMPARISON | VACCINE VS. INFECTION | VACCINE VS. PLACEBO

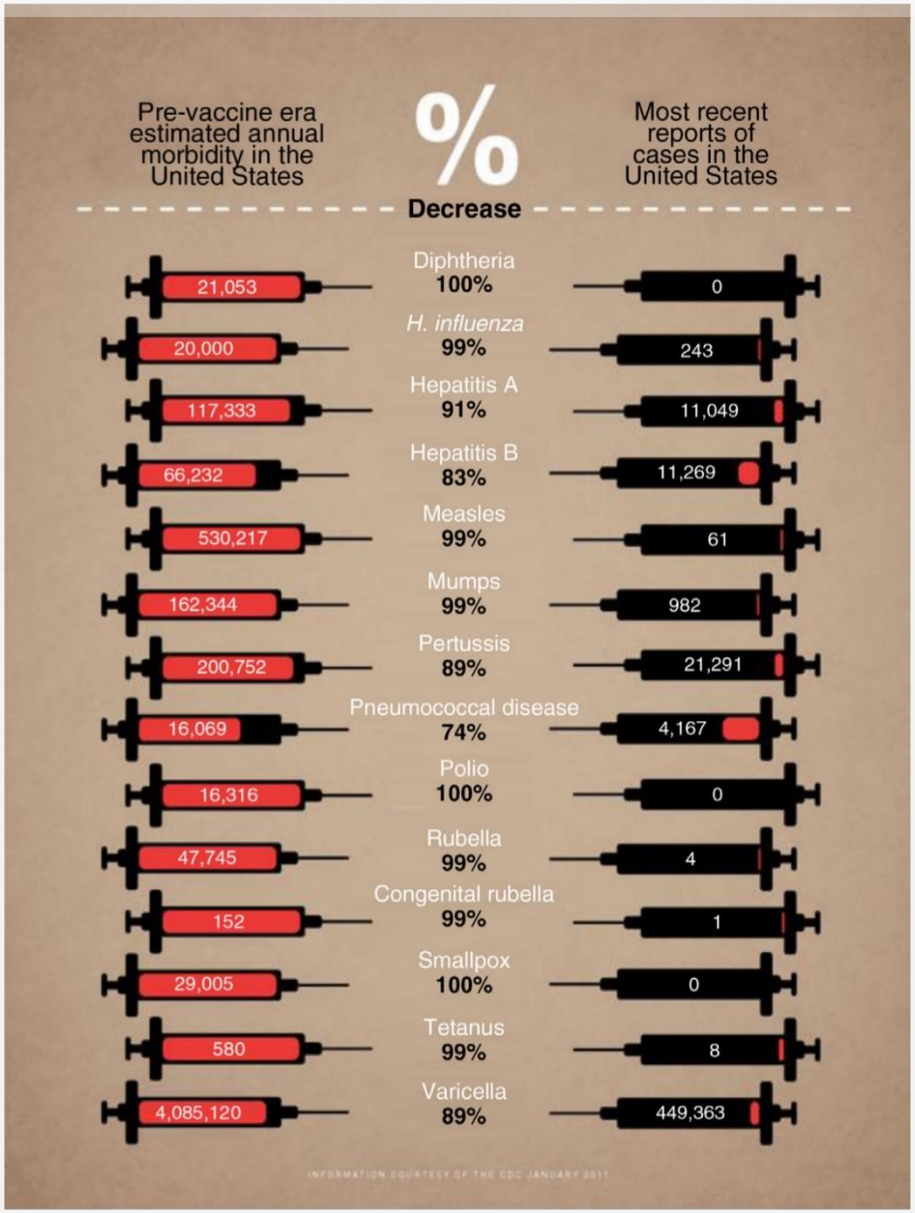
Most vaccines have a range of side effects, from mild to serious. Compare the risks of *Haemophilus influenzae* type b (Hib) vaccination with the risks associated with Hib disease.



Centers for Disease Control and Prevention. Possible Side Effects from Vaccines. http://www.cdc.gov/vaccines/vac-gen/side-effects.htm#hib

Immunization Action Coalition Vaccine Information. Hib Disease Questions and Answers. http://www.vaccineinformation.org/hib/qandadis.asp

VACCINES



ONE OF THE GREATEST PUBLIC HEALTH ACHIEVEMENTS OF ALL TIME!

Now universally mandated

Source: Farrant L. Vaccine infographic 2012. Available from: https://www.behance.net/gallery/2878481/Vaccine-Infographic [accessed 28 November 2015].

REVISITING VACCINE'S HISTORY

1800–1899	1900–1949	1950–1979	1980–1999	2000
1798 Smallpox	1923 Diphtheria	1955 Polio (IPV)	1981 Hepatitis B	2000 Pneumococcal conjugate
1885 Cholera	1923 Tuberculosis	1962 Polio (OPV)	1986 Meningitis B	2006 Human papilloma virus
1885 Rabies	1924 Tetanus	1963 Measles	1989 Hepatitis A	
1891 Anthrax	1926 Pertussis	1967 Mumps	1995 Varicella zoster	
1896 Typhoid	1927 Tetanus	1969 Meningitis A	1998 Rotavirus	
1897 Plague	1935 Yellow fever	1970 Rubella	1999 Meningitis C (conjugate)	
	1943 Typhus	1972 *Haemophilus influenzae*		
		1976 Viral influenza		
		1976 Pneumococcal polysaccharide		
		1977 Meningitis C (polysaccharide)		

WHO Vaccine Safety Basic Manual 2013

VACCINE ADVERSE EVENTS DUE TO PRODUCTION ERRORS

1880s Pasteur rabies vaccine
→ Seizure, paralysis, coma in 1/230 immunized

1942 US military yellow fever vaccine;
→ Formulated with human serum; contaminated with infectious hepatitis B virus; 330,000+ infected; 50,000+ with disease; 62 deaths

1902 Plague Vaccine: The Mulkowal Incident
→ 19 persons injected with plague vaccine contaminated with tetanus and all died within 7-10 days.

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

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

HOW VACCINES DIFFER FROM OTHER DRUGS

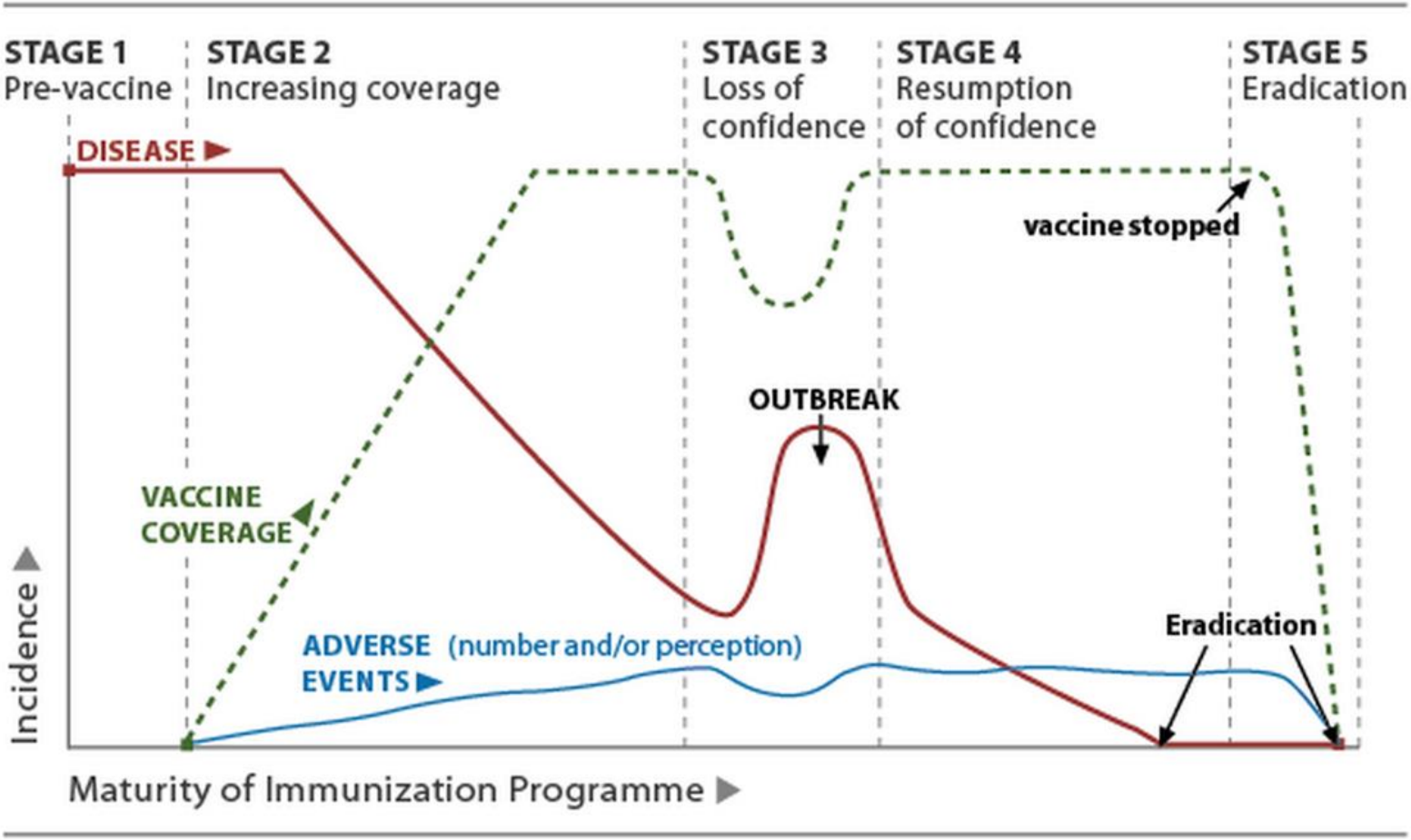
- Complex protein molecules; more stringent regulations
  - More complicated protein molecular structures
  - Immunogenic
  - Production more complicated; unstable-distribution and storage requires controls
  - Subject to lot release program
- Target high population (e.g., birth cohorts); universal global mandate
- Schedule protects before age of greatest risk; period of life coincides with emergence of underlying disease (e.g., neurodevelopmental disorders)
- AEFIs; causality assessment complicated by inability to readily “dechallenge” and reluctance to “rechallenge”

VACCINE COMPONENTS
THAT CAN CAUSE REACTIONS:

- Antigen (active component of the vaccine)
- Adjuvant –Aluminum salts, AS03, AS)4, MF59)
- Preservative –thimerosal
- Stabilizer – gelatin
- Antibiotics – neomycin
- Others – pH, osmolarity

Vaccines:
Success into weakness

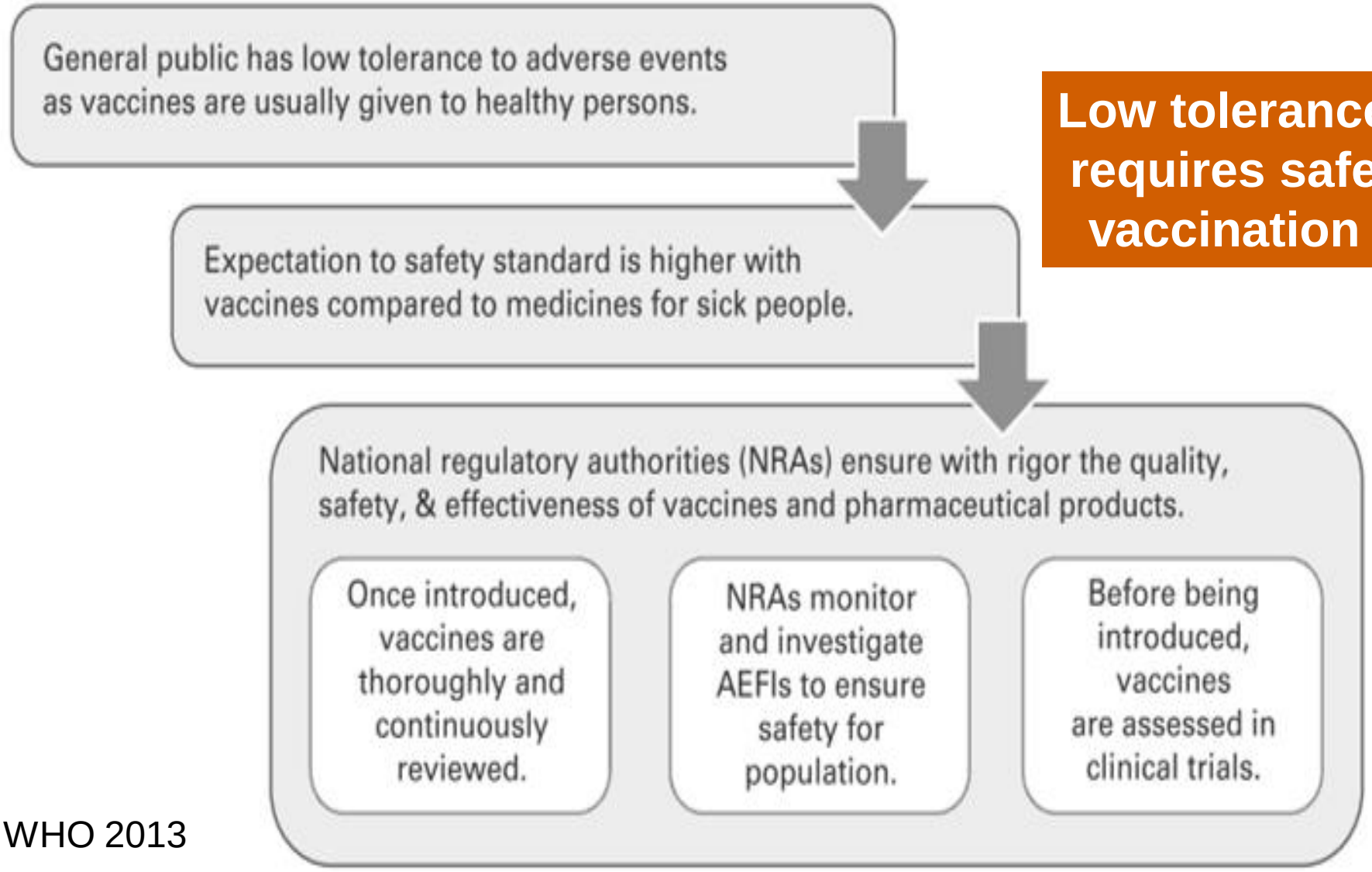
Effect of Vaccination on Disease Incidence



Potential stages in the evolution of an immunisation programme.

Diagram adapted from Chen RT et al. The Vaccine Adverse Event Reporting System (VAERS). Vaccine, 1994: 12(6):542–550.

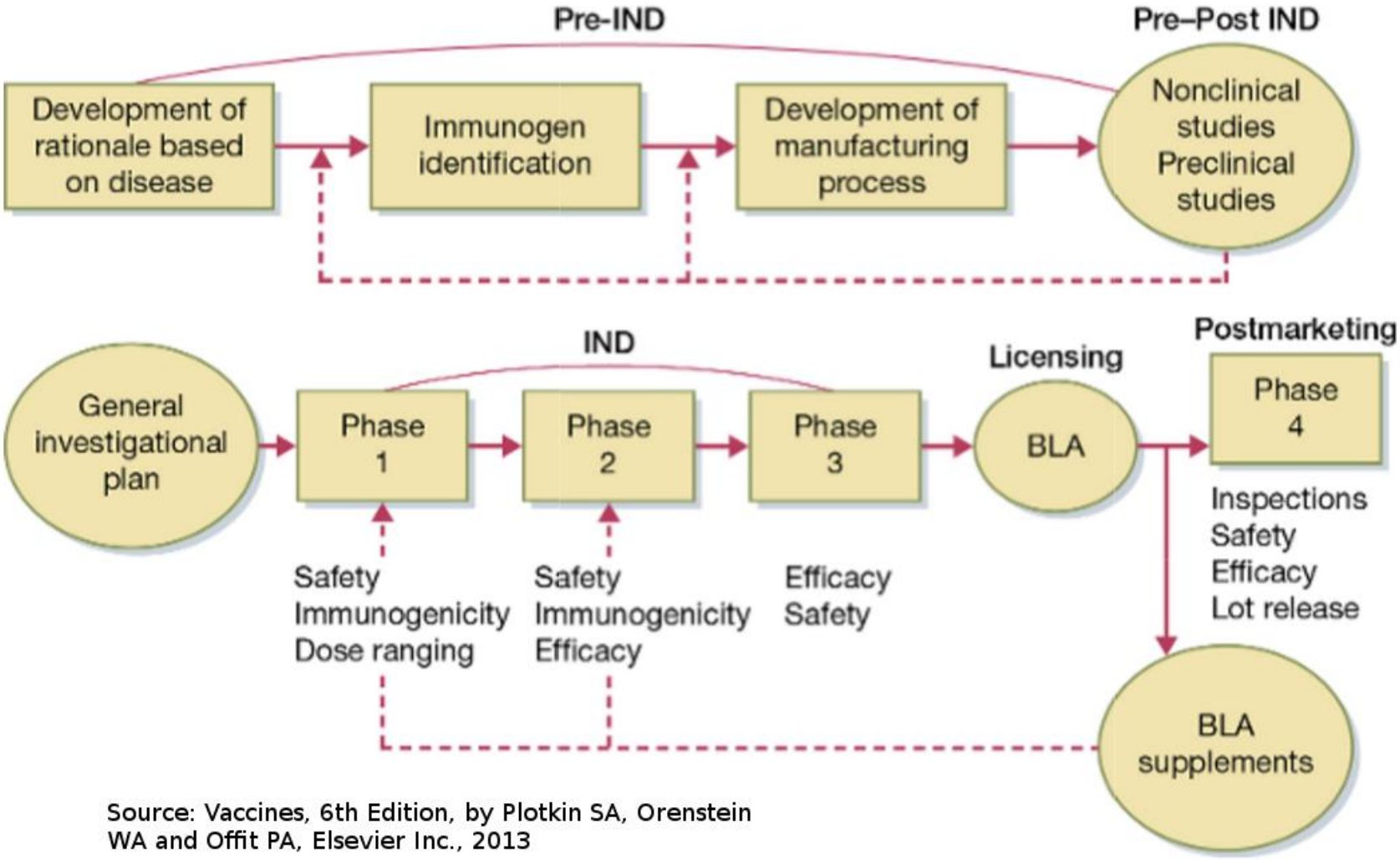
NEED FOR VACCINE SAFETY HAS BECOME MORE URGENT



Low tolerance requires safe vaccination

WHO 2013

VACCINE SAFETY
FROM INCEPTION TO PRODUCTION



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

Prelicensure Evaluations of Vaccine Safety

Phase I

involves, typically, 20-80 participants is used to evaluate safety and the most appropriate dose and dosage

Phase 2

further evaluates safety and efficacy and continues to determine vaccine dose in larger numbers of subjects (usually 100-300 participants)

Phase 3

involves much larger numbers of subjects (1000 to 3000) and is used to confirm efficacy, collect additional safety information and, if applicable compare with existing vaccines.

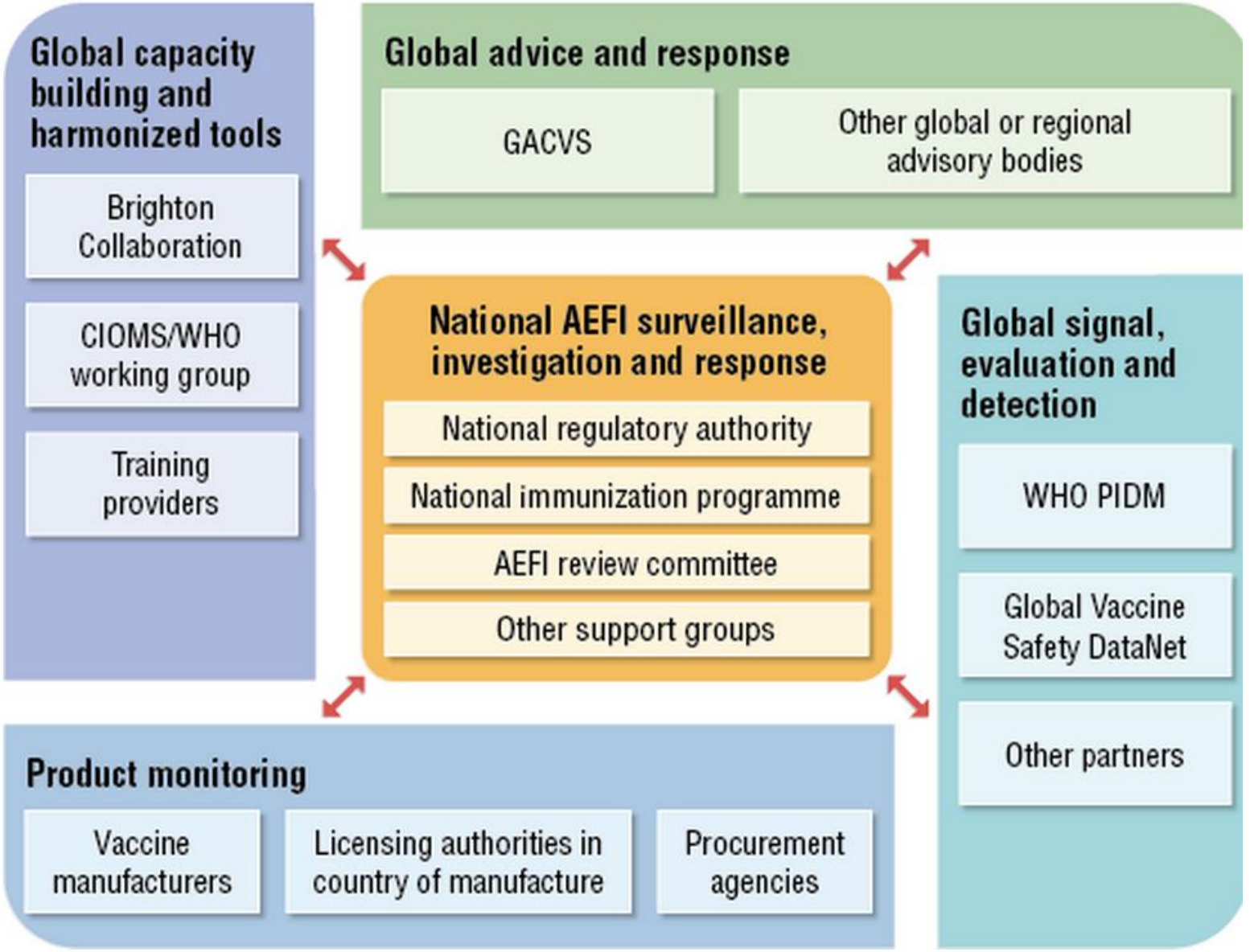
Post-licensure Surveillance *is necessary!*

- Pre-Licensure studies of new vaccines not large enough to detect all serious and rare AEs.
- Identify rare reactions/ monitor increases in known reactions
- Identify risk factors for AEs/higher risk groups
- Identify signals
- Identify vaccine lots with unusual rates or types of AEs
- Public confidence in vaccines

Adverse Events Following Immunization (AEFI) Surveilance

- 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

Global Vaccine Safety Monitoring



INSTITUTE OF MEDICINE
(NATIONAL ACADEMIES PRESS)

- **MMR and Autism (2001)**
- **Thimerosal and Neurodevelopmental Disorders (2001)**
- **Multiple Immunizations and Immune Dysfunction (2002)**
- **HepB Vaccine and Demyelinating Neurological Disorders (2002)**
- **SV40 Contamination of Polio Vaccine and Cancer (2002)**
- **Influenza vaccines and Neurological Complications (2003)**
- **Vaccines and Autism (2004)**
- **Adverse Effects of Vaccines: Evidence & Causality (2012)**

Safety of Vaccines Used for Routine Immunization of US Children: A Systematic Review

AUTHORS: Margaret A. Maglione, MPP,[a] Lopamudra Das, MPH,[a] Laura Raaen, MPH,[a] Alexandria Smith, MPH,[a] Ramya Chari, PhD,[a] Sydne Newberry, PhD,[a] Roberta Shanman, MLS,[a] Tanja Perry, BHM,[a] Matthew Bidwell Goetz, MD,[b] and Courtney Gidengil, MD, MPH[a,c]

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abstract

FREE

BACKGROUND: Concerns about vaccine safety have led some parents to decline recommended vaccination of their children, leading to the resurgence of diseases. Reassurance of vaccine safety remains critical for population health. This study systematically reviewed the literature on the safety of routine vaccines recommended for children in the United States.

RESULTS: Of 20 478 titles identified, 67 were included. Strength of evidence was high for measles/mumps/rubella (MMR) vaccine and febrile seizures; the varicella vaccine was associated with complications in immunodeficient individuals. There is strong evidence that MMR vaccine is not associated with autism. There is moderate evidence that rotavirus vaccines are associated with intussusception. Limitations of the study include that the majority of studies did not investigate or identify risk factors for AEs; and the severity of AEs was inconsistently reported.

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 2014;134:1–13

PEDIATRICS
Volume 134,
Number 2,
August 2014

THIMEROSAL AND THE DANISH STUDY

- Denmark has extensive medical records of its citizens
- Abandoned thimerosal in childhood vaccines in 1992
- Evaluated the incidence of autisms in children immunized with thimerosal-free and thimerosal-containing vaccines
- Results
  - 956 autistic children
  - 3.5:1 male: female ratio
  - From 1970 to 1990, no increased incidence of autisms was observed
- After removal of thimerosal, the incidence of autisms began to increase

Madsen et al. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. Pediatrics. 2003. 12:604-6.

VACCINE SAFETY DATALINK (VSD)

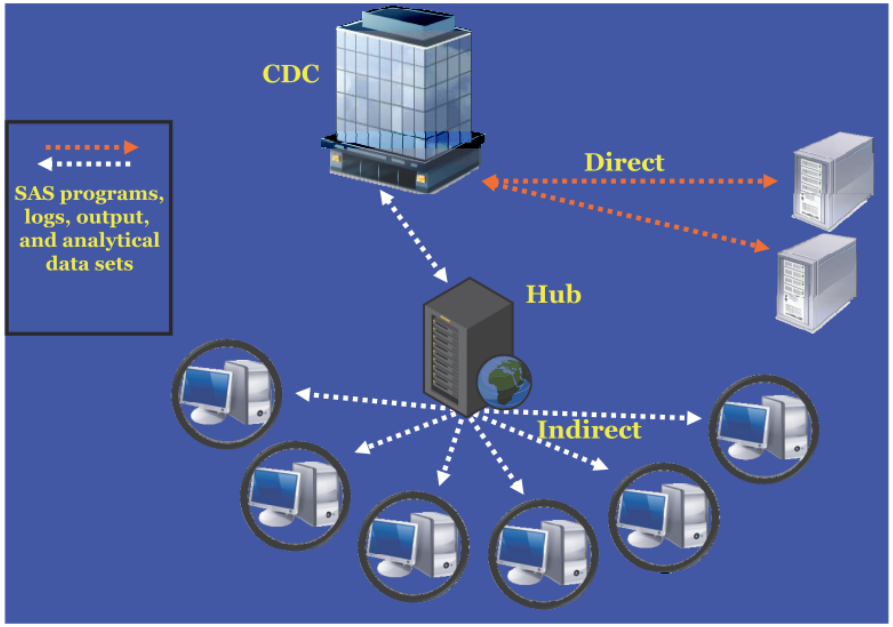


TABLE 1 VSD Strategic Priorities

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

PEDIATRICS Volume 127, Supplement 1, May 2011

Clinical Immunization Safety Assessment (CISA) Project

- Improve understanding of vaccine safety issues at individual level
- Review individual cases
- Develop strategies to assess individuals
- Conduct studies to identify risk factors

The Pink Book

THE PROVIDER'S ROLE

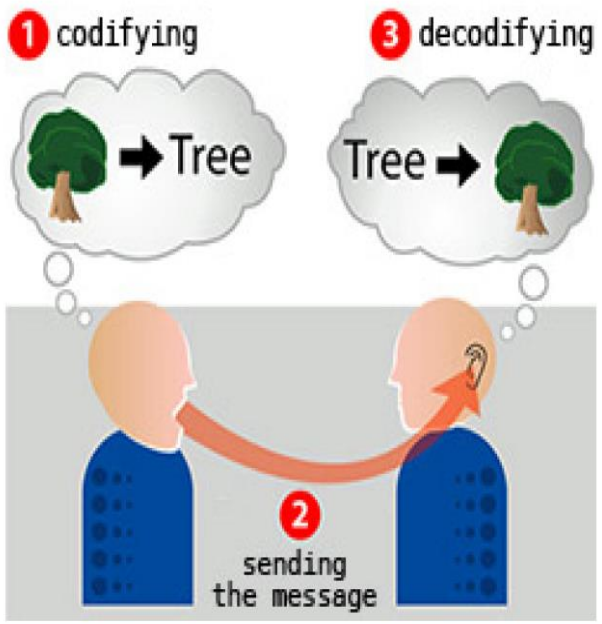
Immunization providers can help ensure the safety and efficacy of vaccines through :

- Study of products (labels & publications) and observing contraindications & precautions
- Implementing proper timing and spacing of vaccine doses
- Management of vaccine side effects
- Reporting of suspected side effects
- Communicating vaccine benefits versus risk considerations
- Adherence to proper storage, dispensing and administration practices.

NEED FOR IMPROVED COMMUNICATION

Communicate only reliable information

Simplify Key Messages



Risk Perception

The public sees risk in terms of:

- Voluntariness of exposure,
- Familiarity of risk,
- Control over risk,
- Catastrophic potential,
- Fatal outcomes,
- Unequal balance between risk & benefit,
- Unequal distribution of risk.

Experts see risk in terms of:

- Morbidity and mortality levels

IMMUNIZATION SAFETY IN US PRINT MEDIA 1995-2005

RESULTS: The mean number of vaccine-safety articles per state was 26. Six (not mutually exclusive) topics were identified: vaccine-safety concerns (46%); vaccine policy (44%); vaccines are safe (20%); immunizations are required (10%); immunizations are not required (8%); and state/school exemption (8%). Three spikes in the number of newspaper articles about vaccine-safety issues were observed: in 1999 regarding rotavirus vaccine and in 2002 and 2003 regarding smallpox vaccine. Excluding articles that referred to rotavirus and smallpox vaccines, 37% of the articles had a negative take-home message.

CONCLUSION: Ongoing monitoring of news on vaccine safety may help the content and framing of vaccine-safety messages. *Pediatrics* 2011; 127:S100–S106

Vaccinomics

Published in final edited form as:
Pharmacogenomics. 2009 May ; 10(5): 837–852. doi:10.2217/PGS.09.25.

Application of pharmacogenomics to vaccines

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Abstract

The field of pharmacogenomics and pharmacogenetics provides a promising science base for vaccine research and development. A broad range of phenotype/genotype data combined with high-throughput genetic sequencing and bioinformatics are increasingly being integrated into this emerging field of vaccinomics. This paper discusses the hypothesis of the 'immune response gene network' and genetic (and bioinformatic) strategies to study associations between immune response gene polymorphisms and variations in humoral and cellular immune responses to prophylactic viral vaccines, such as measles–mumps–rubella, influenza, HIV, hepatitis B and smallpox. Immunogenetic studies reveal promising new vaccine targets by providing a better understanding of the mechanisms by which gene polymorphisms may influence innate and adaptive immune responses to vaccines, including vaccine failure and vaccine-associated adverse events. Additional benefits from vaccinomic studies include the development of personalized vaccines, the development of novel vaccines and the development of novel vaccine adjuvants.

Towards designing safer & more effective vaccines