DCVMN Pharmacovigilance Training
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dcvmn
Developing Countries Vaccine Manufacturers Network

Specificities of Vaccine Pharmacovigilance

Katharina Hartmann, PharmD
Senior Vaccine Safety Expert

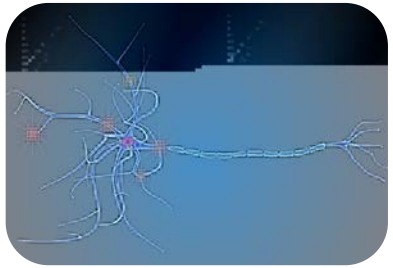
Lessens learned from vaccine safety issues

1926: Diphtheria toxin incomplete inactivation

1929: BCG contaminated strain leading death of 72 infants

1942: YF vaccine - stabilizer (human albumin) contaminated with Hep B

1955: Cutter incident (incomplete inactivation of polo vaccine)



1997: HepB vaccination and demyelinating disease

1999: RotaShield and intussusception

2010: Pandemrix and narcolepsy

Vaccine Pharmacovigilance Definition (WHO)

The science and activities relating to the detection, assessment, understanding, prevention and communication of adverse events following immunization (AEFIs) or any other possible vaccine or immunization-related problems.

Vaccine Pharmacovigilance also known as

Vaccine Safety

Vaccine Pharmacovigilance is a key global public health function

PV has a vital role in Public Health

- to ensure patient safety
- to prevent or reduce harm of medicines
- to improve the use and benefit of medicines

Public trust in vaccine safety
is key for successful
immunization programs

Vaccine Pharmacovigilance is a key global public health function

Specific aims of PV are

- to collect good quality data on medicines and their safety
- to improve public health by evaluating and monitoring safety
- to contribute to the assessment of the benefit, risk and effectiveness of medicines.

Vaccine Pharmacovigilance in Industry

Vaccine Pharmacovigilance is a key responsibility for all vaccine manufacturers

- **Legally responsible** for the vaccine quality, safety and efficacy
- **Shared responsibility**, not only a regulatory requirement
- **Proactive vaccine safety surveillance** during the whole life-cycle

Why Vaccine Pharmacovigilance?

- To protect the vaccinated individuals as well as the population from harm
- To ensure lot-related safety
- To ensure ongoing effectiveness
- To ensure continuous positive benefit risk ratio
- To clarify signals from individual AEFIs
- To be able to react to changes of the benefit risk balance
- To protect the vaccine from false positive signals
- To respond to safety crisis

Important specific - Vaccines versus Drugs

Vaccines: Higher safety standards expected

Vaccines

- given to healthy populations, all ages
- preventive aim
- biological products with complex compositions
- de- and re-challenge negligible for assessment
- mainly immunological considerations
- short duration of exposure with a long time for response
- minor adverse events are important (can jeopardize acceptance or indicate program error)
- may cause the illness they are meant to prevent (e.g., VAPP)

Drugs

- given to sick populations, manly adults
- therapeutic aim
- chemical products with many drug classes
- de- and re-challenge important for assessment
- mainly pharmacological considerations
- longer duration of exposure with shorter time for response
- minor adverse events rarely important

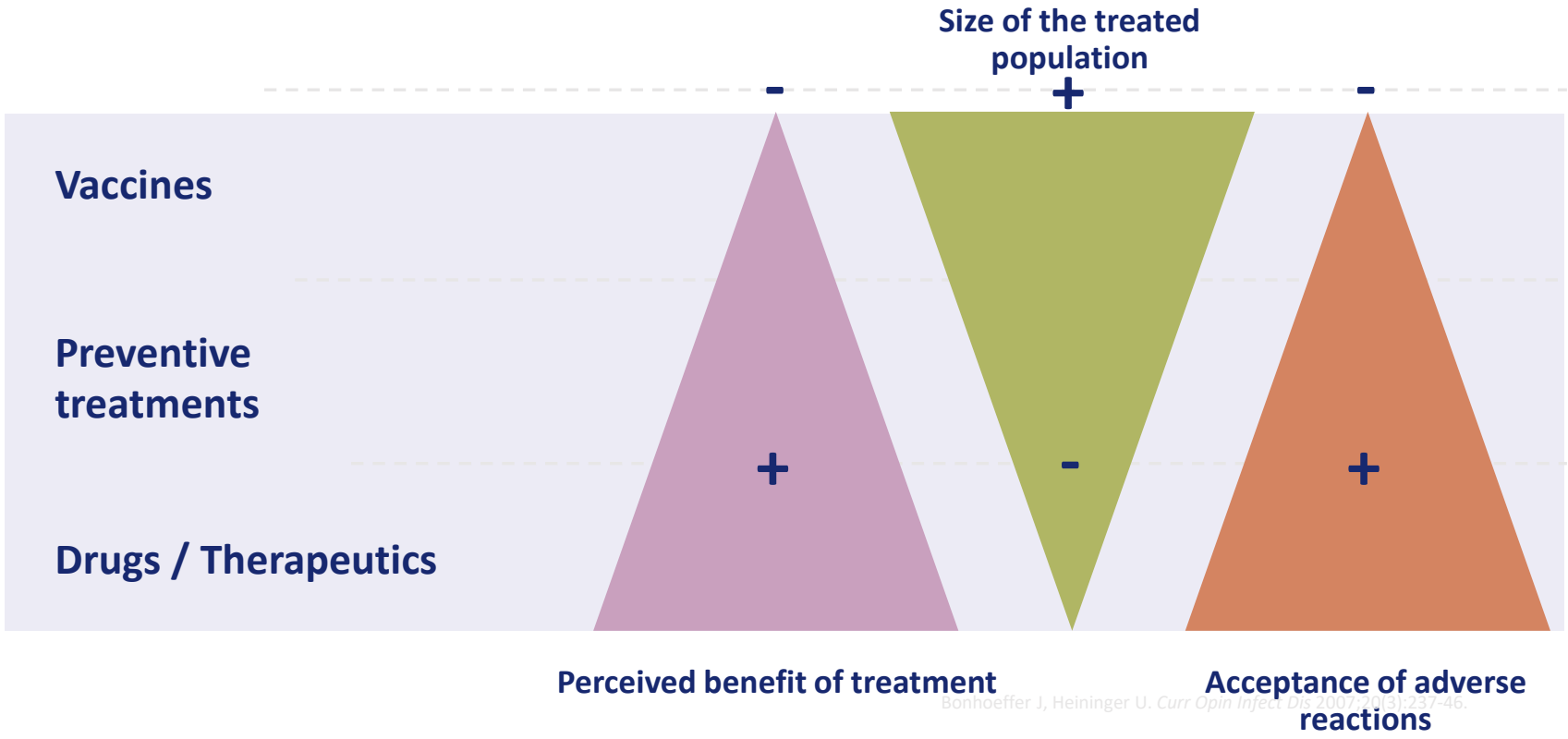
Main differences between Vaccines and Drugs

Characteristic	Small molecule drugs	Prophylactic vaccines	Implication for vaccine Pharmacovigilance
Composition	• Well defined products • Low batch variability	• Complex biologicals • Batch-related variability • Potential contamination witbh adventious agents (from cell banks, substrates etc.) • Can contain live attenuated organisms	• Batch-related safety surveillance • Monitoring for infections
Indication and administration	• Largely therapeutic • Administration triggered by disease or condition	• Prophylactic • Administration «imposed» by, recommended or mandatory vaccination schedules	• Usually co-suspect vaccines according to vaccination schedules • Timing of administration of childhood vaccines may coincide with peak period or onset of conditions (e.g., sudden infant death, autism) • Low risk tolerance
Population	• Patients, mainly adults	• Healthy subjects, largely children	• Low risk tolerance in healthy and vulnerable population

Main differences between Vaccines and Drugs

Characteristic	Small molecule drugs	Prophylactic vaccines	Implication for vaccine Pharmacovigilance
Exposure	• Often chronic • Dosage varies depending on disease severity	• Large segments of population are exposed • Exposure to very few single doses at fixed dosage in a given population	• Low case volume • High impact of safety issues • Concepts of dose-dependency, de-challenge, re-challenge usually not applicable
Benefit-risk perception	• Individual benefit easy to perceive • Risk acceptance depends on disease severity and expectation of benefit • Risk acceptance can be high for serious conditions	• Individula benefit (i.e., not contracting disease) usually not perceived • Population benefit (i.e., herd immunity/protection) rarely perceived • Low risk acceptanceby parents for their cildren • Lack of vaccine confidence problematic across various cultures	• Low risk tolerance • Challenge of appropriate safety communication • Impact of individual serious or fatal cases • Prepareness for vaccine confidence crisis
Lack of effect	• Affects individual patient	• Vaccination failure decreases herd protection / affects population	• Product-specific assessment of vaccination failure • Expedited reporting of cases

Perceived Benefit and Acceptance of Risks

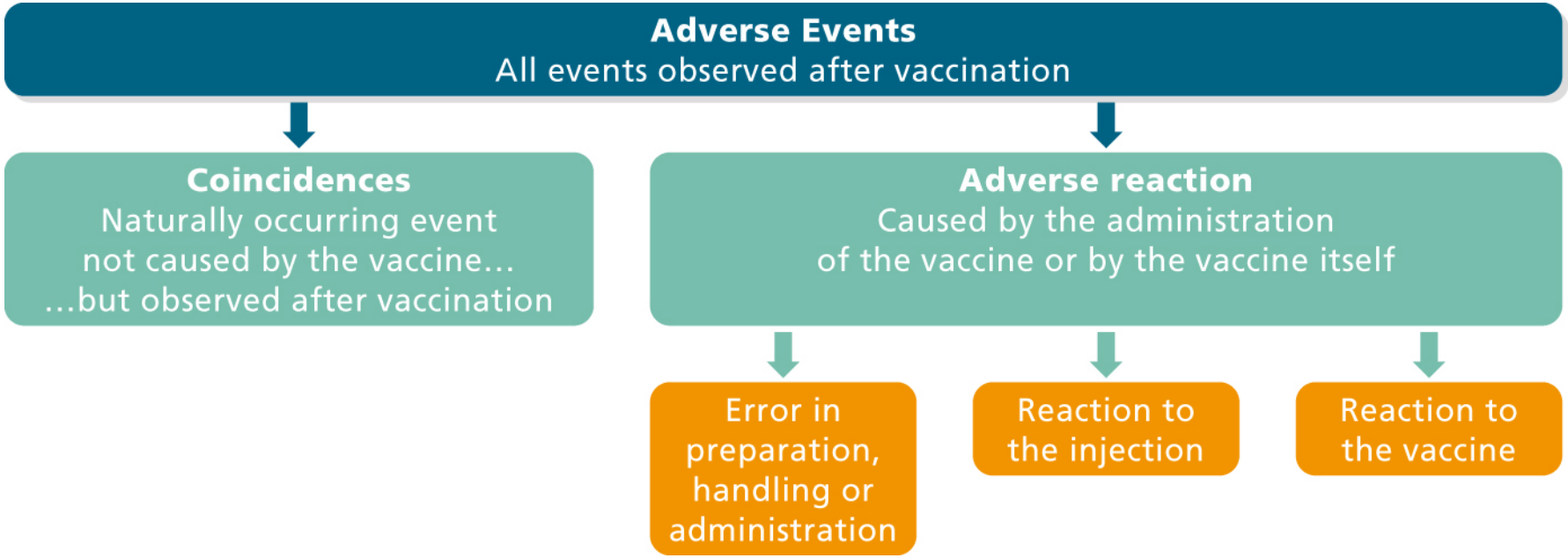


Bonhoeffer J, Heininger U. *Curr Opin Infect Dis* 2007;20(3):237-46.

Focus of Vaccine Safety Surveillance

- Intensive investigation of rare adverse events
- Case definitions for case ascertainment (i.e., Brighton Case Definitions)
- Long-term follow up in post-marketing setting
- Adverse events affecting acceptability of immunization
- Age-relatedness of AEs / safety in different target groups
- Methods of assessing causality of serious and rare adverse events
- Batch-relatedness of adverse events
- Safety surveillance in pre-licensure/ post-licensure
- Vaccine risk communication

Adverse Events following Immunization AEFI



AEFI: any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The AE may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

Adverse Events following immunization AEFI

Reaction to vaccine

Antigens

Different vaccines are prepared with different types of antigens, using different scientific methods:

- ✓ Attenuation
- ✓ Inactivation,
- ✓ Fragmentation
- ✓ Conjugation
- ✓ Recombination DNA technology

Adjuvants

Some vaccines include components to enhance immune response, such as adjuvants, e.g.

- ✓ Aluminum salts
- ✓ Monophosphoryl lipid A (MPL)
- ✓ AS01/AS02/AS03 /AS04
- ✓ MF59
- ✓ CpG 1018 Adjuvant

Adjuvants are part of the benefit –risk equation

Other

Added for stability of conservation:

- ✓ Preservatives
- ✓ Stabilizers

Cause-specific Definitions

Vaccine product-related reaction

AEFI caused or precipitated by the vaccine when given correctly, and due to one or more of the inherent properties or quality defects of the vaccine.

Vaccine quality defect-related reaction

AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects (defined as any deviation of the vaccine product as manufactured from its set quality specifications) of the vaccine product including its administration device as provided by the manufacturer.

Immunization error related reaction

AEFI caused by inappropriate vaccine handling, prescribing and administration, and thus by its nature is preventable.

Immunization anxiety-related reaction

AEFI arising from anxiety about immunization (may include anticipated pain or other fears related to the vaccine(s) or its administration).

Coincidental event

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

Vaccine reaction rate

Observed rate
Total number of
observed adverse events
in a cohort of e.g.,10,000:
observed AE rate is 6/10,000

Attributable rate
(Vaccine reaction rate)
Number of observed AEFIs
in a vaccinated cohort
related to vaccination
e.g., attributable rate 2/10,000

Background rate
Number of observed adverse events
in an unvaccinated cohort
(not related to vaccination)
e.g., background rate 4/10,000

Attributable rate (Vaccine reaction rate) **= Observed rate – Background rate**

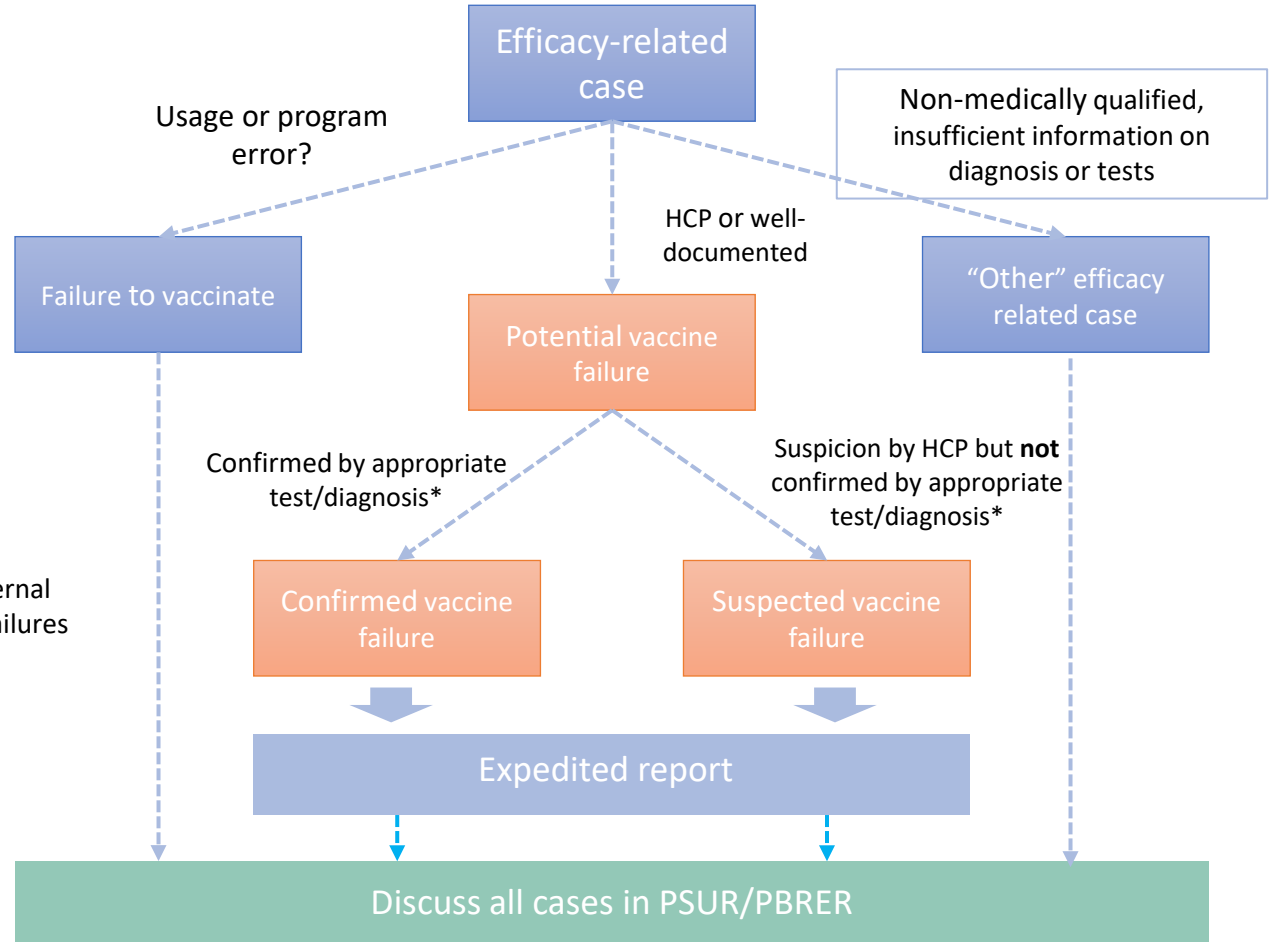
Vaccination Failure (Lack of Effect)
Causes of vaccination failures

Type of failure	Causes
Failure to vaccinate	
Usage-related	- Administration error (wrong route, dose, diluent) - Vaccination schedule not adhered to - Wrong storage (out of cold chain) - Expired vaccine used
Program-related	- Suboptimal recommendation (number and time points of doses - primary and booster) - Vaccine shortage
Vaccine failure	
Host-related	- Immunodeficiency, immunosuppressive therapy, health status - Waning immunity, age-related decrease in immune response - Low/Non-responders - Interference (antibodies or infection)
Vaccine-related	- Vaccine not 100% efficacious - Incomplete coverage of strains, variants, mutants - Vaccine-vaccine interactions (co-administered vaccines) - Manufacturing related (batch variation, quality defect)

Report of WHO/CIOMS WG on Vaccine PV (2013): Definitions and Application of Terms for Vaccine Pharmaco-vigilance.

Vaccination Failure (Lack of Effect)

Assessment of efficacy related cases



Vaccines are not 100% effective. Vaccination failure is not an event, but an assessment based on vaccine specific guidelines.

* Vaccine-specific, as per internal guideline on vaccination failures

Report of WHO/CIOMS WG on Vaccine PV (2013):Definitions and Application of Terms for Vaccine Pharmacovigilance.

Diseases attributed to vaccines - without attributed causality

Examples:

- Autoimmune disorders
- Diabetes mellitus type I
- Graves' disease
- Multiple sclerosis / neuro-inflammatory diseases
- Neuro-developmental disorders (e.g., ADHD, autism, etc.)
- Rheumatoid arthritis
- Systemic lupus erythematosus

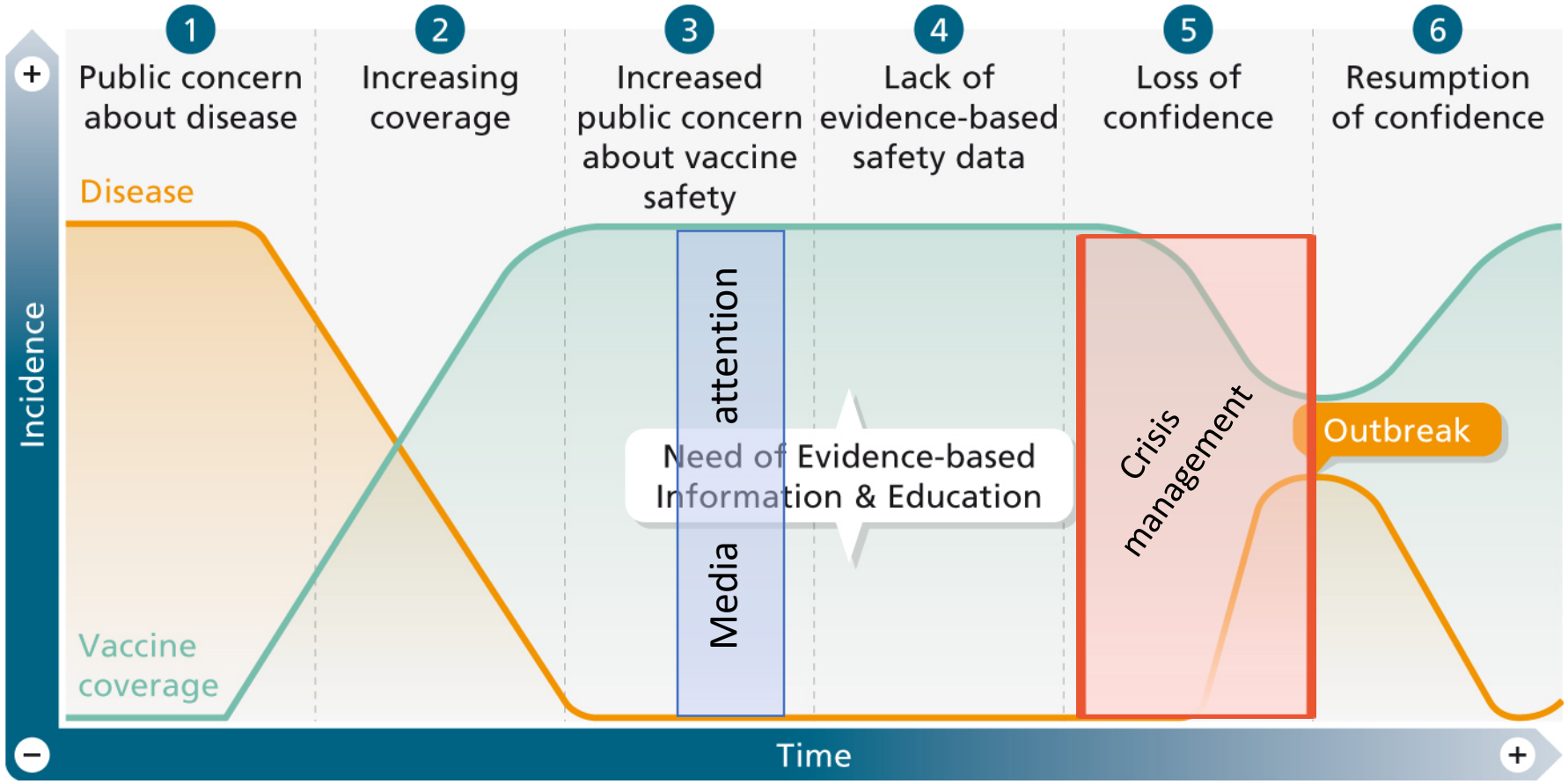
Adverse events of special interest (AESIs) in Vaccine Pharmacovigilance

A pre-identified and pre-defined medically significant event that has the potential to be causally related with a vaccine product that needs to be carefully monitored and confirmed by further specific studies.

Adverse events of special interest AESIs

- **Examples:**
- Anaphylaxis
- Encephalopathy / encephalitis
- Neurological disorders (e.g., Guillain Barré syndrome, Bell's palsy)
- Aseptic meningitis
- Vasculitis
- Thrombocytopenic purpura
- Vaccine-enhanced disease (e.g., COVID-19 vaccines, Dengue vaccines)

Immunization, Disease Rates and Public Concern



Chen, CDC 1996, adapted by Kohl / Loupi 2004

Thank You

Questions?