Monitoring Vaccines Introduction

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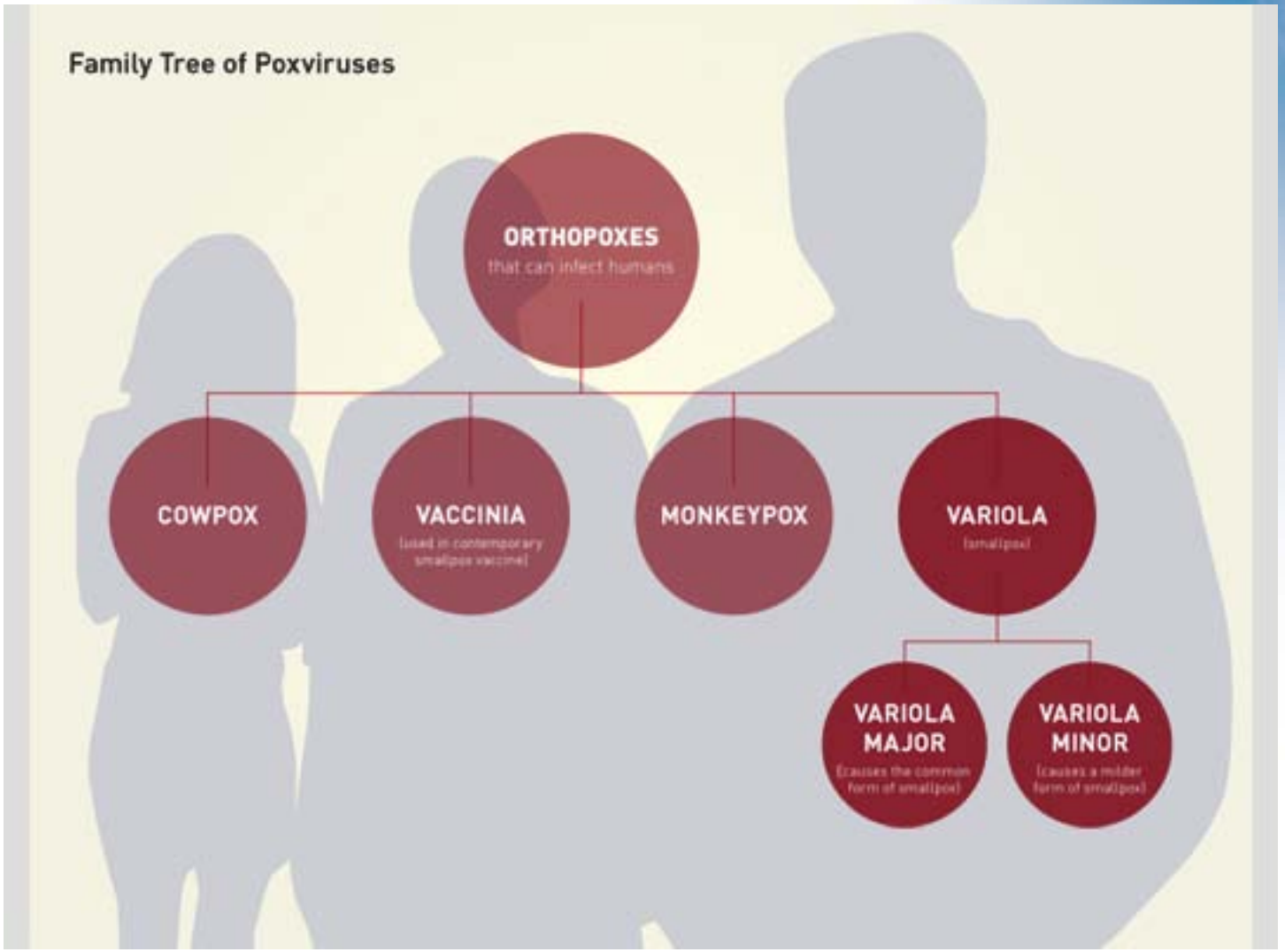
Outline

- Historical background
- Are vaccines different from other medicinal products?
- Different vaccines – different potential safety issues
- Immunization programmes
- AEFI or ADR?
- Basic concepts in causality assessment
- Communication

Smallpox – a long story

- Viral disease unique to humans
- Infection by variola virus (Orthopoxvirus)
- Highly contagious: contact, droplets, transplacentar infections – no animal vectors
- No asymptomatic carriers
- Mortality approx 30% (haemorrhagic variola 100%, variola minor <10%)
- Aquired immunity



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Variola

- Incubation 12 days
- Fever, muscle pain, fatigue, prostration, vomiting, enanthema

- 900 AD: first description by Rhazes (Persia)
- 1000: first inoculation in China
- 1684: Dr Sydenham (England) -> mortality rich>poor. Treatment harmful?
- 1706: variolation in use in Africa, India and Ottoman Empire (mortality 2-3%)
- 1721 first variolation in England
- 1770: Jenner-> protection by cowpox infection

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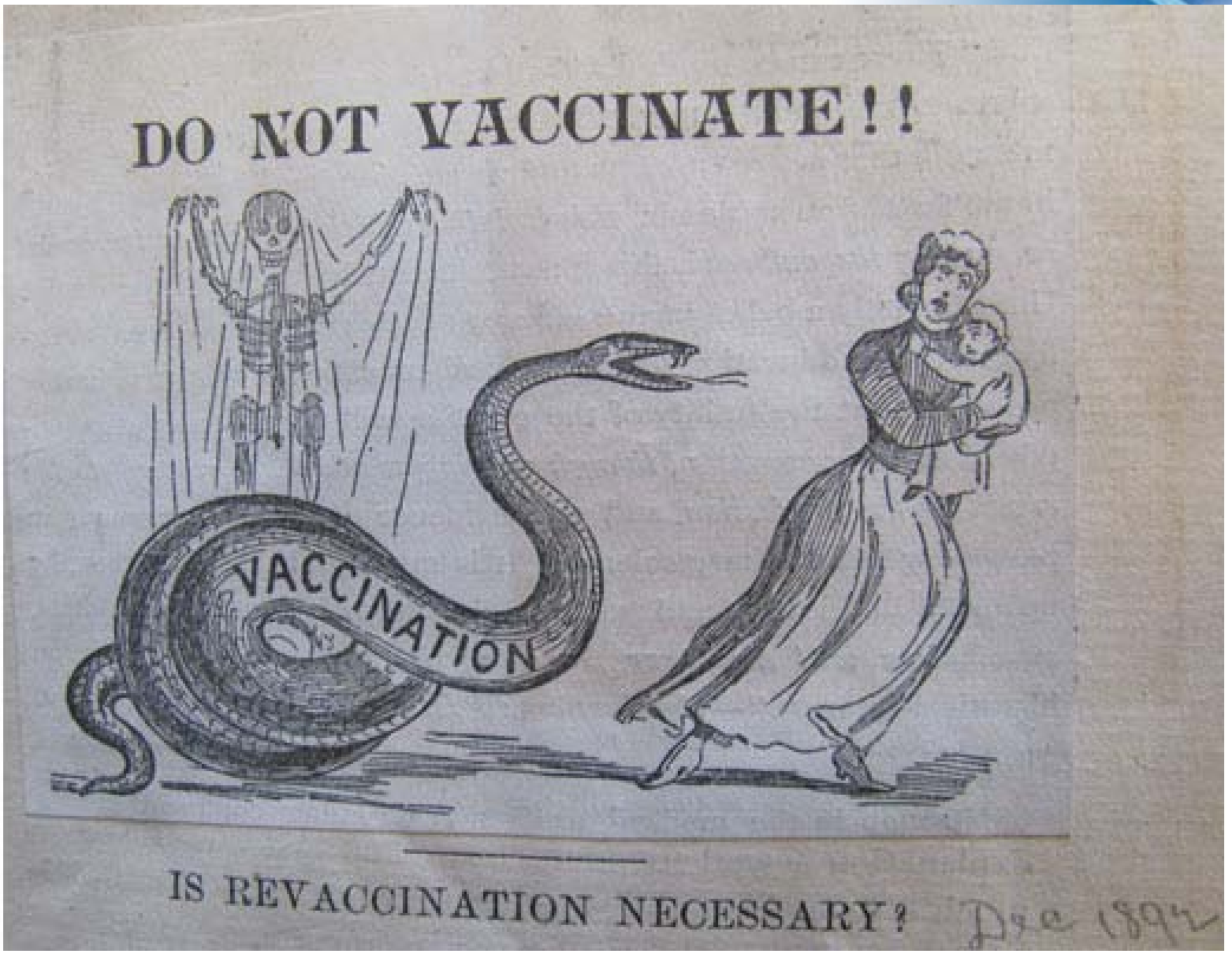
- 1796: James Phipps, first inoculated with cowpox and then variolated, survives
- 1853 United Kingdom Vaccination Act
- 1882: 1st meeting of the Antivaccination League of America
- 1922 smallpox vaccination as school requirement in the USA
- 1980: WHO declares smallpox eradicated


DO NOT VACCINATE!!
VACCINATION
IS REVACCINATION NECESSARY?
Dec 1892

Sources

- US National Library of Medicine
  - www.nlm.nih.gov
- College of Physicians of Philadelphia
  - www.history of vaccines.org

Concerns

- Parents –> fear
- Clergy –> animal into human
- General public –> distrust in medicine

  -> violation of personal freedom

Vaccines

- Given to healthy population (young children)
- No immediate visible benefit for the individual
- Great exposure
- Herd immunity
- Simultaneous administration of several vaccines
- Authorization and surveillance by lot
- Immunization programmes (mandatory)

Medicinal Products

- Prescribed to single person for specific health complaints
- Immediate benefit to the individual patient
- No specific vulnerable population
- Variable tolerance re safety issues dependent on individual benefit
- Authorization and surveillance by product

Safety issues

Vaccines

- Related to
  - Active agent
  - Adjuvant/ingredients
  - Programmatic errors
  - Procedure (injections)
  - Perception

Drugs

- Related to:
  - Active ingredient
  - Additives/formulation
  - Medication errors
  - (Procedure)
  - Perception

Are all vaccines the same?

- Bacterial or viral origin
- Live attenuated
- Inactivated
- Subunits (purified antigen)
- Toxoids

Live attenuated vaccines (LAV)

- Living organisms
- Tuberculosis (BCG), oral polio (OPV),measles, mumps, rubella,yellow fever, rotavirus
- Excellent immune response even after single dose
- Reversion to pathogenicity possible
- Contraindicated in pregnancy
- Caution with immunocompromized people

Inactivated vaccines

- Virulent strains inactivated by heat or chemical treatment
- Inactivated polio (IPV), whole cell pertussis (wP)
- No live component
- Stable and more predictable than LAV
- Immune response less strong -> > 1 dose

Subunit vaccines

- Purified antigen (AG) one or more (viral and bacterial proteins and bacterial capsular polysaccharides)
- Acellular Pertussis, Hepatitis B, pneumococcal and HiB vaccines
- Targeted, very stable
- Low immunogenicity, multiple dose immunization

Toxoids

- Based on toxins produced by bacteria, protein base
- Tetanus toxoid
- Very stable, cannot induce disease
- Anaphylactic reactions possible but rare

Ingredients and adjuvants

- Antigens
- Stabilizers
  - Magnesium, sorbitol-gelatine or lactose-sorbitol based
- Adjuvants
  - Several hundred types, ex aluminuim salts
- Antibiotics
  - Manufacturing, only traces in vaccines
- Preservatives
  - Thiomersal, formaldehyd

Route of administration

Examples

- Oral: OPV, Rotavirus vaccine
- Intramuscular: Di-Te-Pe, Hepatitis B, HiB
- Subcutaneous: measles, yellow fever
- Intradermal: BCG

Contraindications to immunization

- Previous severe allergic reaction of the immediate type
- Pregnancy: all LAV and Hepatitis B
- Immunocompromized patients: all LAV and inactivated vaccines
- Egg allergy: all vaccines with egg component

Immunization Programmes

- Many vaccinees at the same time
- Suboptimal infrastructure
- Multidose vials
- Cooling chain

Programmatic Errors

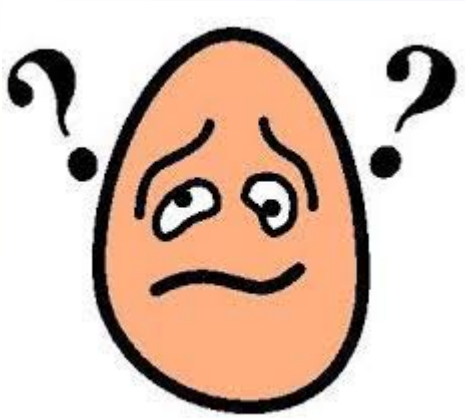
- Non sterile injections
- Injection at incorrect site
- Incorrect storage
- Reconstitution error
- Ignored contraindications

AEFI Surveillance System

- detect, correct, and prevent programme errors
- identify problems with vaccine lots or brand
- address false blame from coincidental events
- maintain confidence by properly responding to concerns while increasing awareness about vaccine risks
- estimate rates of occurrence on AEFI in the local population, compared with trial and international data

AEFI or ADR?

- Adverse Event Following Immunization
- Adverse Drug Reaction
- Adverse Event



Adverse Event

- Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse Drug Reaction

- A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. (WHO, 1972).
- An adverse drug reaction, contrary to an adverse event, is characterized by the **suspicion of a causal relationship** between the drug and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.

AEFI

- Adverse Event Following Immunization

Event even if spontaneously reported

→ CAUSALITY?

Vaccines

classification of AEFI

- **vaccine reaction**
  event caused or precipitated by the vaccine when given correctly; caused by inherent properties of the vaccine
- **programmatic error**
  caused by error in vaccine preparation, handling, or administration
- **coincidental event**
  happens *after* immunization but **not** caused by it – a chance association
- **injection reaction**
  event from anxiety about or pain from the injection itself rather than the vaccine
- **unknown**
  whose cause can not be determined

Causality Assessment

- Some concept from causality assessment for drugs cannot be applied
  - Dechallenge
  - (Rechallenge when only one dose must be administered)
- Dose - response

But...

- Time to onset
- Clinical picture (Brighton case definitions)
- Biological plausibility
- Knowledge about the vaccine
- Comorbidities/personal and family history
- Concomitant medication

http://www.who.int/vaccines-documents/DocsPDF05/815.pdf

WORLD HEALTH ORGANIZATION

ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI): CAUSALITY ASSESSMENT

AIDE MEMOIRE

Purpose: This *aide-mémoire* serves as a guide to a systematic, standardized causality assessment process for serious adverse events following immunization (including clusters). It is intended to be used by staff at the national (or first sub-national) level.

AEFI causality assessment overview

All reported AEFIs require verification of the diagnosis, coding, review, collation and storage; if an AEFI is serious, it requires triage for systematic, standardized causality assessment. Many AEFIs, including serious ones, may be coincidental while others are well known to be vaccine related (e.g., oral polio vaccine-associated paralytic polio [VAPP]).

Causality assessment is the systematic review of data about an AEFI case to determine the likelihood of a causal association between the event and the vaccine(s) received.

Causality assessment is a critical part of AEFI monitoring and enhances confidence in national immunization programmes.

Routine AEFI review and triage

All AEFIs need to be screened and triaged by trained immunization programme staff to determine the subsequent steps needed (follow up, action, addition to database, analysis, reference for systematic causality assessment, etc.).

AEFI must be reviewed to verify the diagnosis and the timing with respect to immunization, and to classify them on the basis of standardized national case definitions.[1]

[1] Standardized case definitions for some AEFIs are available from the Brighton Collaboration at (*http://www.brightoncollaboration.org*). Use of these definitions is encouraged, especially for serious cases where systematic standardized causality assessment is required.

Systematic causality assessment

All ***serious AEFIs*** and ***signals***, defined below, require systematic causality assessment *(see Checklist, Section C, page 2).*

Serious AEFI[1]:

1) WHO standard definition for drug and vaccine adverse events

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Brighton Collaboration

- https://brightoncollaboration.org/public
- Indipendent vaccine research network
- Case definitions
- Library

Case Definitions

- Ensure that the AEFI term used matches standard criteria
- 3 levels of diagnostic certainty
  - Level 1 highest

- What with reports ion reactions that do not match Brighton case definitions?

Background Rates

- Frequency of the natural occurrence of a clinical event that might be reported as AEFI
- Help assessing changes in observed frequency of AEFI in a study setting
- Limited use in spontaneous reporting

Estimated Rates of AEFI

- http://whqlibdoc.who.int/hq/2000/WHO_V&B_00.36.pdf

- Hepatitis B and Guillain Barré: 5/mio doses
- Yellow fever and anaphylaxis 5-20/mio doses
- Measles and fever 5%

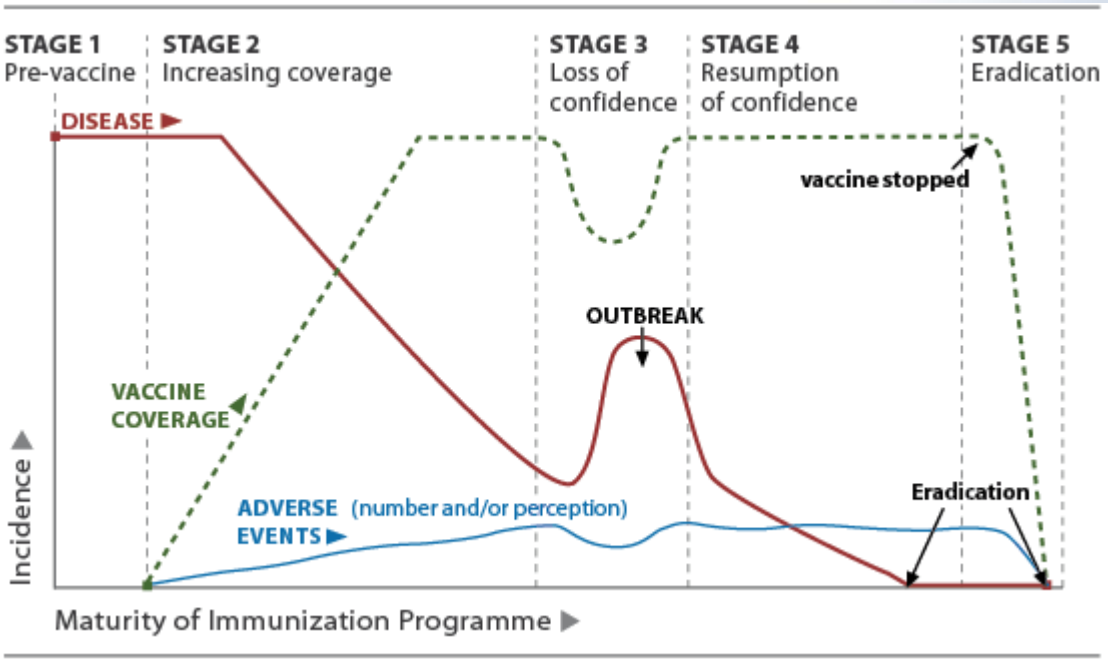
Benefit – Risk Assessment

- Targeted disesase
  - seriousness
  - severity
  - risk of complications
  - treatment options
  - effect on population
- Vaccine
  - as above
  - efficacy of vaccine

Communication

- Openness and transparency -> trust
- Address and explain coincidental events
- Loss of confidence in immunization programmes

Confidence in Immunization Programmes (RT Chen, CDC)



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Discussion

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