Adverse Events Following Immunisation

(common, uncommon, shockin' rare, and how do we know their likely cause?)

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Portiuncula Hospital, Sept. 18, 2017

Definitions

- **Adverse Event (AE)**

  .. untoward medical occurrence…during treatment with a pharmaceutical product but which **does not necessarily have a causal relationship** with this treatment

- **Adverse Reaction (ADR, AR)**

  Response to a drug which is noxious and unintended..

Definitions

Adverse Event Following Immunisation (AEFI)

Any untoward medical occurrence which follows immunisation and which *does not necessarily have a causal relationship with the usage of the vaccine*

Can be an unfavourable or unintended sign, abnormal laboratory finding, symptom or disease

Known Adverse Reactions

More Common (>1 in 100)	Less Common (<1/100)
• Redness • Swelling, nodule • Pain • Fever, irritability, loss of appetite •nausea, D+V	• Encephalitis • Paralysis • Arthritis • Allergic reaction • Thrombocytopoenia • Febrile seizure • Fainting • Narcolepsy • Death

Causes of AEFIs

Vaccine product-related reaction

very common (>10%): site pain, swelling

uncommon (1/100-1/1,000): headache, fever

rare (1/1,000-1/10,000): febrile seizure (MMR)

very rare (<1/10,000): anaphylaxis

Vaccine quality defect-related reaction: manufacture, storage

Immunisation error-related reaction: inappropriate usage, prescribing, administration, needle

Immunisation anxiety-related reaction: syncope, hyperventilation

Coincidental: AEFI caused by something other than above

Causes of Coincidental AEFI

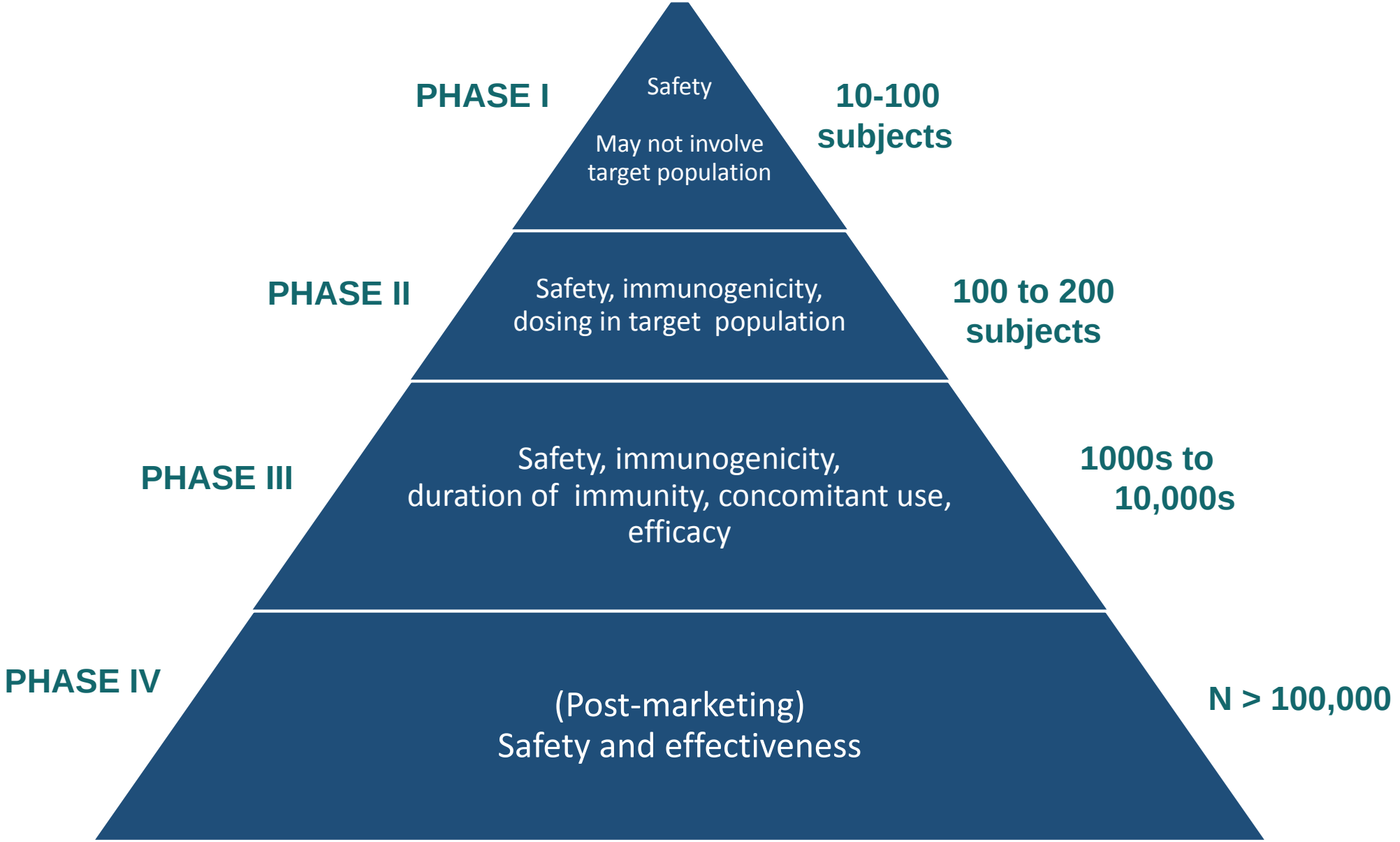
- Pre-existing or newly acquired illness
- Emergence of a genetically programmed disease
- Exposure to other drug or toxin prior to the event
- Surgical or other trauma that leads to a complication
- Coincidental infection present/incubating/not apparent at time of vaccination
- Spontaneous occurrence (event without known risk factors)

Your Role in Vaccine safety

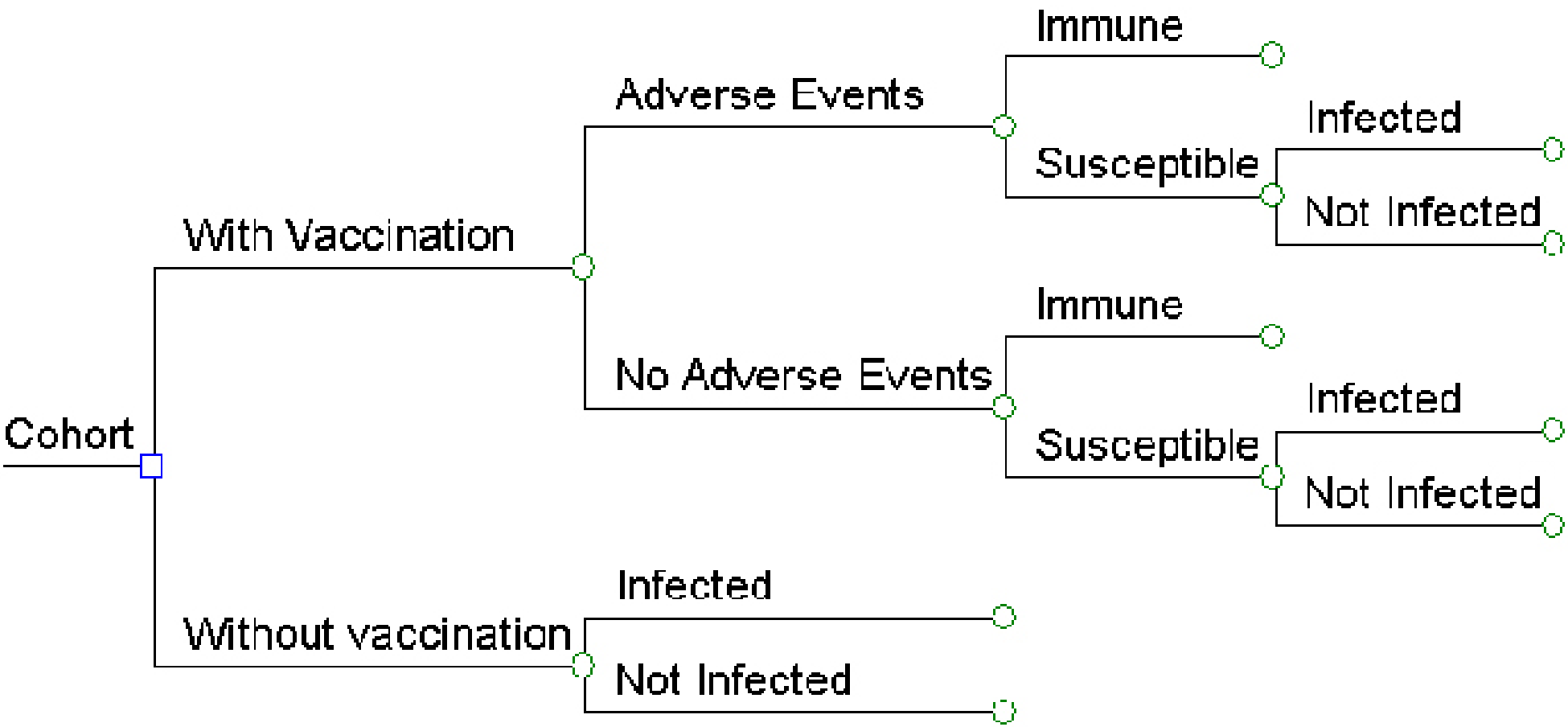
- Storage and Handling
- Timing and Spacing
- Administration Issues
  - Equipment
  - Injection site recommendations
  - Identify contraindications
- Education
- Report and treat AEFIs

Pre- and post-marketing Safety Assessment

Vaccine Safety Studies



Benefit-risk Balance



Numbers needed to test for increased relative risk of an adverse event

	Rate In Vaccinated Population		
Background rate in general population	**2-fold higher**	**10-fold higher**	**100-fold higher**
1 in 10,000	141,000	5,500	500
1 in 100,000	1,238,000	53,500	2,500
1 in 1,000,000	12,951,500	532,500	23,500

Evans D et al. J Infect Dis. 2009;200:321-8.

Hierarchy of Evidence

Pharmacovigilance (PhV)

Detection, assessment, understanding, prevention of ARs

Objectives : - prevent harm

- promote safe, effective use

Why Pharmacovigilance?

- No vaccine is 100% safe

  Rare events require huge numbers to detect

- Benefit/risk balance changes over time
  - as incidence falls - e.g. VAPP and oral polio vaccine
  - as society becomes more critical

Why Pharmacovigilance?

- Identify previously unrecognized ARs (new, frequent, severe)
- Identify subgroups of patients at particular risk of ARs
- Continue surveillance to ensure benefits/harms balance remains acceptable
- Confirm or refute false-positive signals that arise

MMR vaccine and Measles (1m children <5 yrs)

MMR vaccine	Measles infection
300 children have febrile fits	10,000 have febrile fits
25 have thrombocytopoenia	330 have thrombocytopoenia
1-3 have anaphylaxis	0 will have anaphylaxis
1 may have encephalitis	2,000 may have encephalitis
0 will have SSPE	10 will have SSPE

Pertussis Disease v. Pertussis Vaccine

Pertussis

Condition	%
• Pneumonia (12% in <6/12)	5
• Convulsions	1.4
• Encephalopathy	0.2
• Death (83% <3/12)	0.2

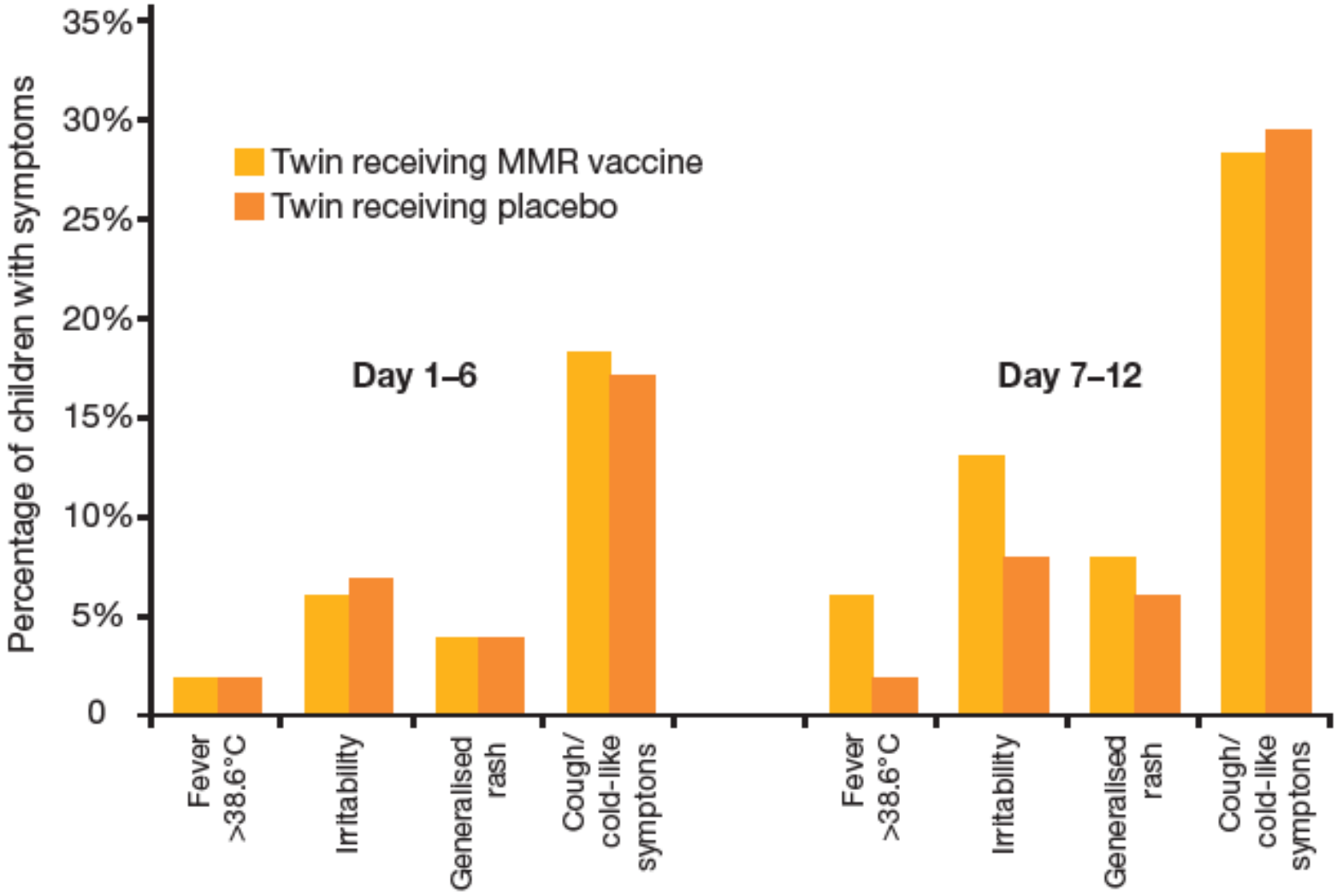
Pertussis Vaccine

Reaction	DTwP %	DTaP %
• Pain	25	9
• Cry>3 hrs	0.4	0.04
• High fever	0.24	0.04
• Convulsion	0.02	0.007
• Death	0	0

Outpatient Fever Visits Among 12-23 Month Olds after First Dose Vaccine: VSD Automated Data 2000-2008*

Vaccine	Days	RR	P Value
MMRV (N=83,107)	7-10	6.1	0.0001
MMR + V (N=376,354)	7-10	4.4	0.0001
MMR (N=145,302)	7-10	4.3	0.0001
Varicella (N=107,744)	9-14	1.2	0.06

Common symptoms in a paired twin study (MMR v. Placebo)

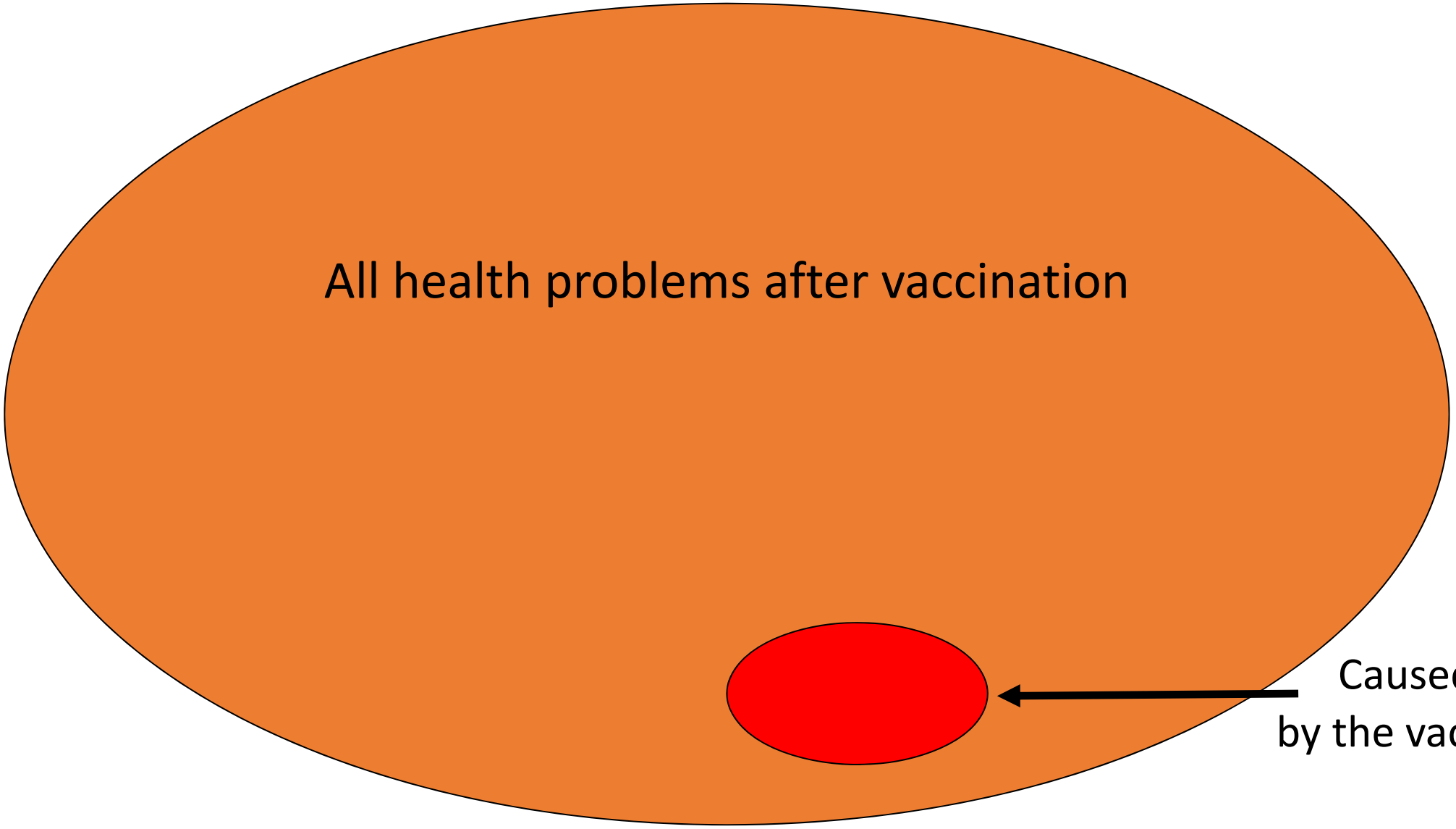


What do rare, very rare mean?

Frequency of known injury*	What else is this common?
1/1,000 to 1/100,000 – Fainting or collapse – Febrile seizure – Thrombocytopoenia	Having quadruplets
1/100,000 to 1/1,000,000 – Serious allergic reaction – Arthritis	Getting struck by lightning
> 1 in a million – Encephalitis – Paralysis – Death	Winning the lottery

*highest rate for any childhood vaccine

AEFI – Cause or Coincidence?



Correlation is not Causation

- **Correlation**: the extent to which two or more variables fluctuate together

- **Cause**: one event is the result of the occurrence of the other event

Criteria of Causality at Population level

- **Temporal**: exposure must precede AEFI
- **Strength of association**: statistically significant (not chance occurrence)
- **Dose-response relationship**: increasing exposure increases risk of AE
- **Consistency of evidence**: similar results in studies using different methods, settings
- **Specificity**: the vaccine is only known cause of the AEFI
- **Plausibility and coherence**: association between vaccine and AEFI plausible and consistent with current knowledge of biology of vaccine and AEFI

Criteria of Causality in an Individual

- Usually not possible to establish *definite* causal relationship between AEFI and vaccine based on single report
- Important to try (may identify product-related AEFI; false attribution may result in reduced vaccine uptake
- Seldom possible to get straightforward answer
- Systematic consideration of all possible causes of AEFI necessary to conclude that evidence is consistent

Possible Causes of Coincidental AEFI

- Pre-existing or newly acquired illness
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Benefit-risk Balance

Remember:

- Medicines tested in trials (selected, relatively few subjects)
- Then used in patients who differ from trial subjects

  (age, diseases, other medicines, genetic, nutrition,….)

Minimising Immunisation Errors

- Right patient
- Right vaccine and diluent
- Right time (age, interval, expiry)
- Right dose
- Right site
- Right route
- Right needle
- Right documentation