Vaccine pharmacoepidemiology

Prof Kristine Macartney

NCIRS Director

Learning objective: appreciate different types of vaccine safety investigations and studies

Australian Vaccinology Course 2026

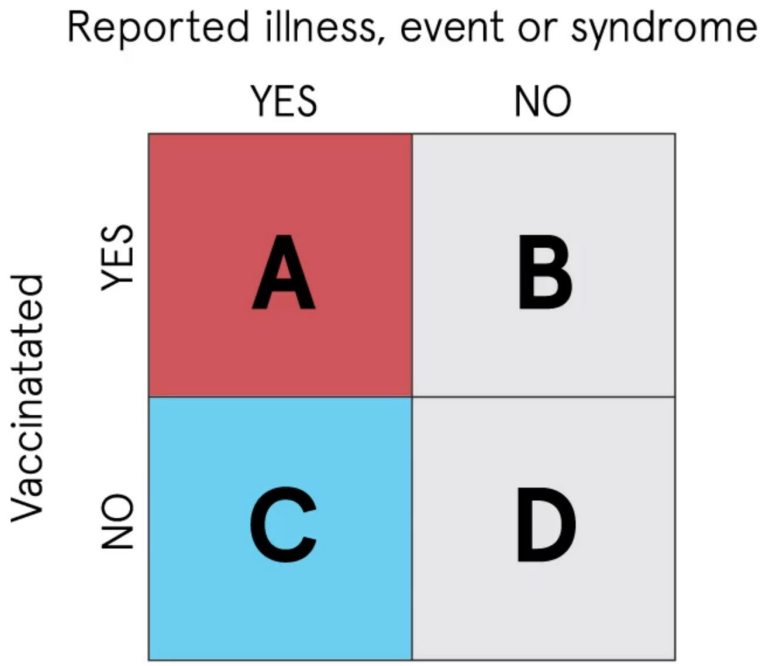
In partnership with

NCIRS National Centre for Immunisation Research and Surveillance Australia

THE UNIVERSITY OF SYDNEY
Sydney Infectious Diseases Institute

Passive or ‘spontaneous’ AEFI surveillance (= A)

- Relies on ‘spontaneous’ report
  - Anyone can submit – requirements for pharma
- Inherent data limitations
  - Incomplete, variable data quality (can be very limited)
  - Under and stimulated reporting
- Strengths
  - Whole population
  - Relatively simple and rapid
  - Signal detection – stimulates investigation
- Incidence rates hard to calculate
  - can’t be compared for unvaccinated
- Vaccine attributable risk cannot be calculated
- Causation <u>almost never</u> able to be inferred



% of adverse event in vaccinated = A/(A+B)

% of adverse event in unvaccinated = C/(C+D)

Active surveillance: cohort event monitoring

AusVaxSafety
An NCIRS led collaboration

Individual receives a vaccination

Individual receives a vaccination at a participating AusVaxSafety clinic.

AusVaxSafety send vaccine safety survey

AusVaxSafety sends a vaccine safety survey following vaccination giving participants the opportunity to report any adverse events they may have experienced and if they had to seek medical attention as a result.

Experts monitor data for safety issues

Epidemiologist and vaccine experts monitor and analyse de-identified survey responses to check for safety issues.

If the person reported going to the doctor or emergency department, this is flagged with the clinic. The clinic follows up with the vaccinated person and notifies the Therapeutic Goods Administration if

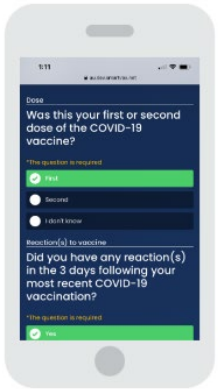
Safety data published weekly

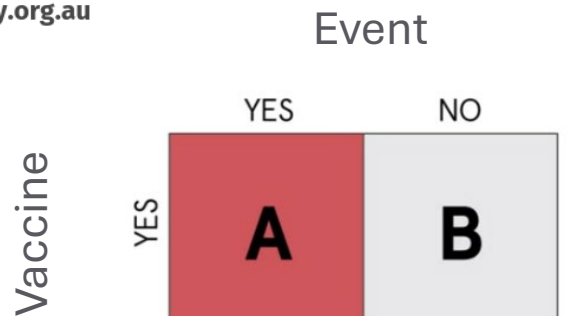
AusVaxSafety reports to the Department of Health and publishes safety data at:

www.ausvaxsafety.org.au



- Aboriginal medical servic
- General practice
- Pharmacies





World Health Organization accredited

Pfizer - all participants

Data as at 16 January

Safety surveys completed

2,050,089 Pfizer dose 1

1,863,825 Pfizer dose 2

399,713 Pfizer dose 3 / booster

Reported at least one adverse event





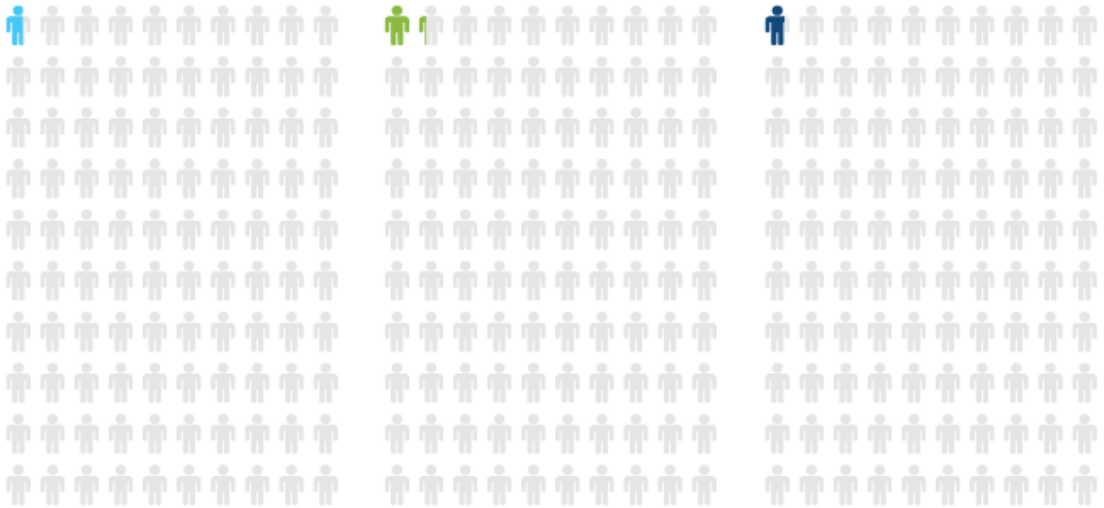


Medical attendance

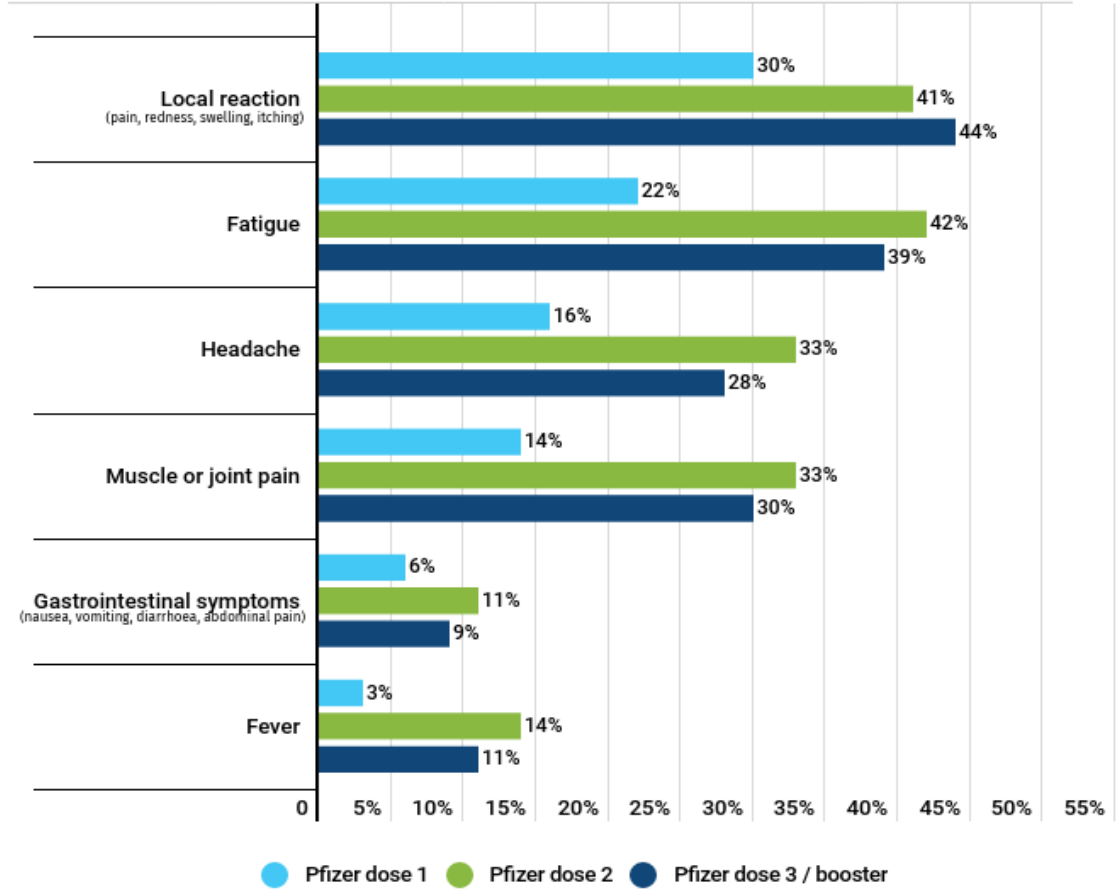
Less than 1 in 100 people reported seeing a doctor or going to the emergency department in the days after Pfizer dose 1

Just over 1 in 100 people reported seeing a doctor or going to the emergency department in the days after Pfizer dose 2

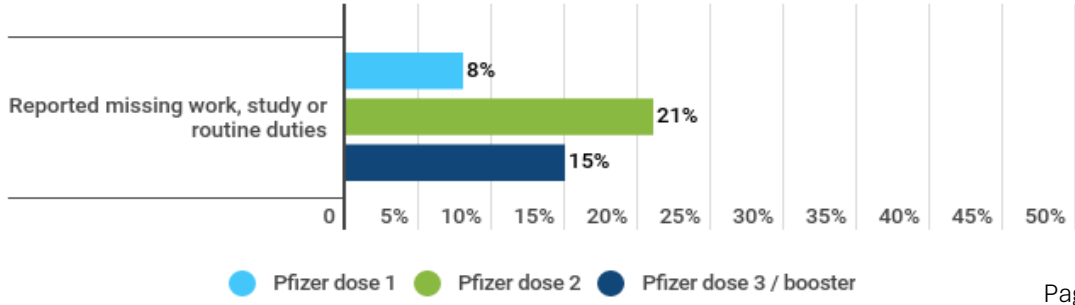
Less than 1 in 100 people reported seeing a doctor or going to the emergency department in the days after Pfizer dose 3 / booster

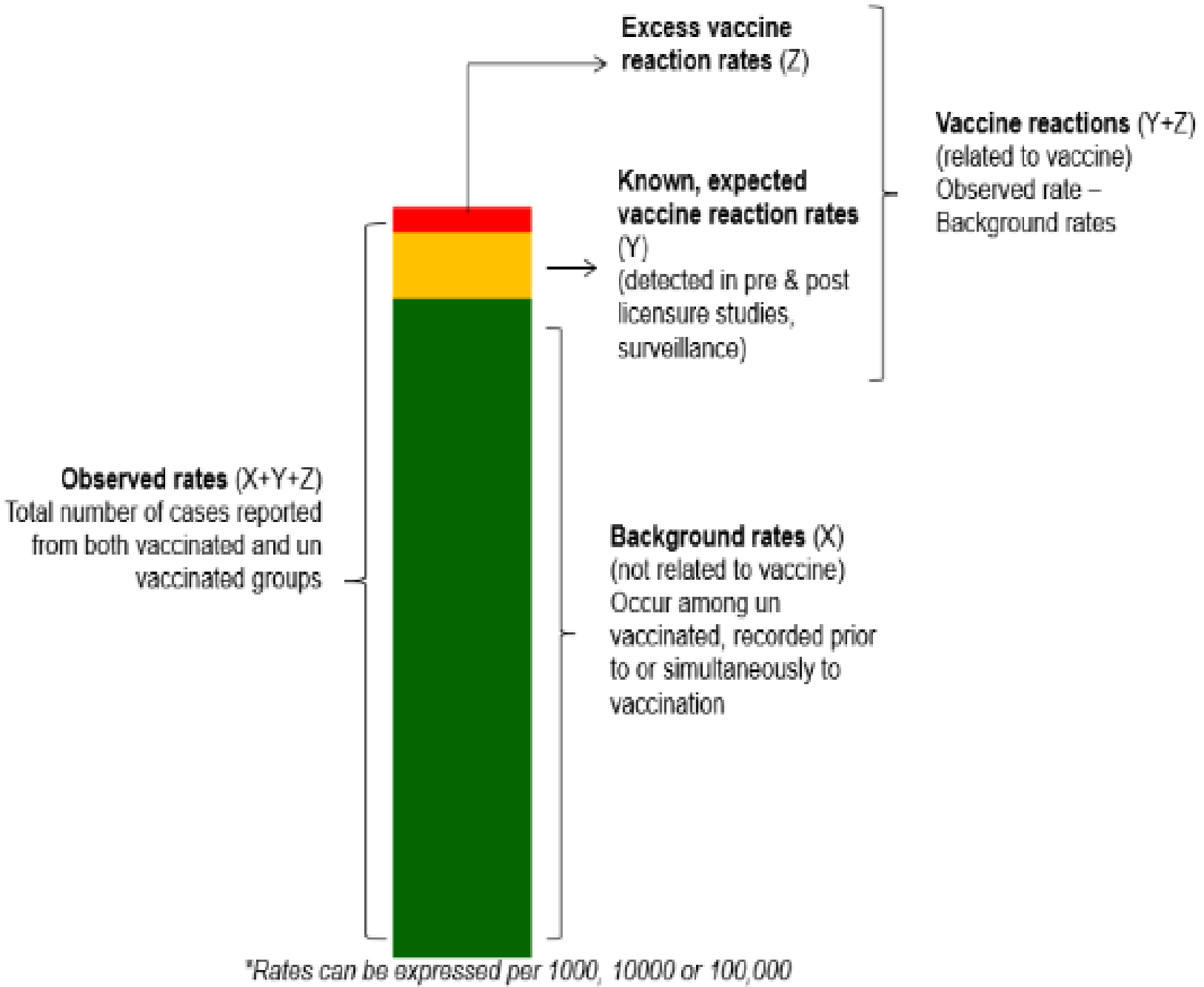


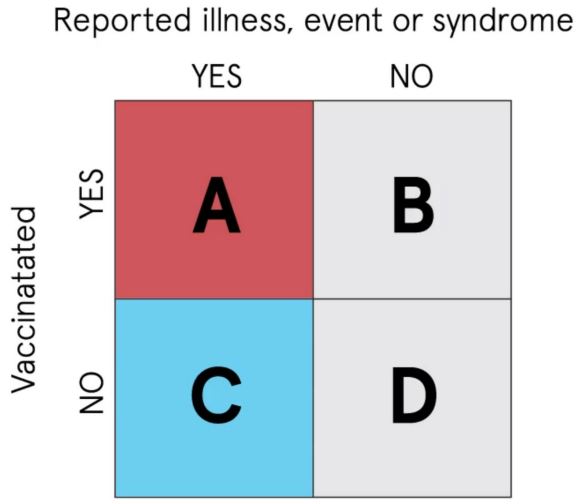
Commonly reported adverse events



Impact on routine activities



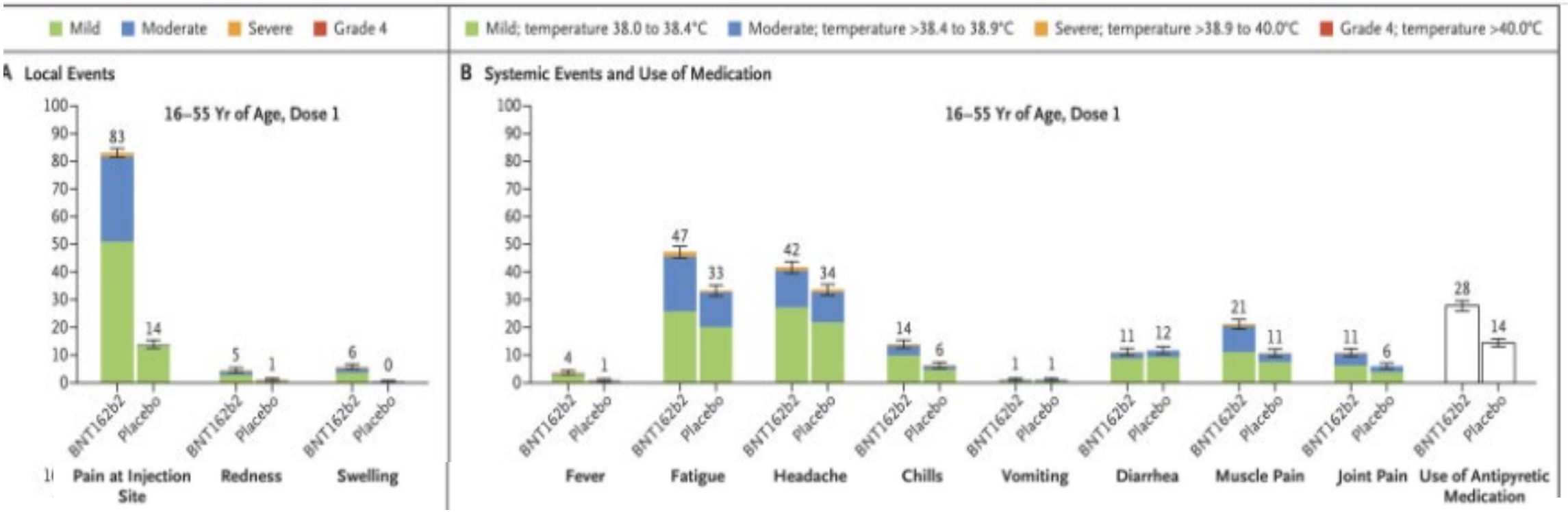




% of adverse event in vaccinated = A/(A+B)

% of adverse event in unvaccinated = C/(C+D)

https://vaccine-safety-training.org/classification-of-aefis.html



"Background rates" in clinical trials

Adverse events of any/unknown cause are common every day!

Timing, nature and clustering of expected adverse events can reasonably suggest they are vaccine related

Other than injection site reactions, proving 'causation' for most events is near

https://www.nejm.org/doi/full/10.1056/nejmoa2034577

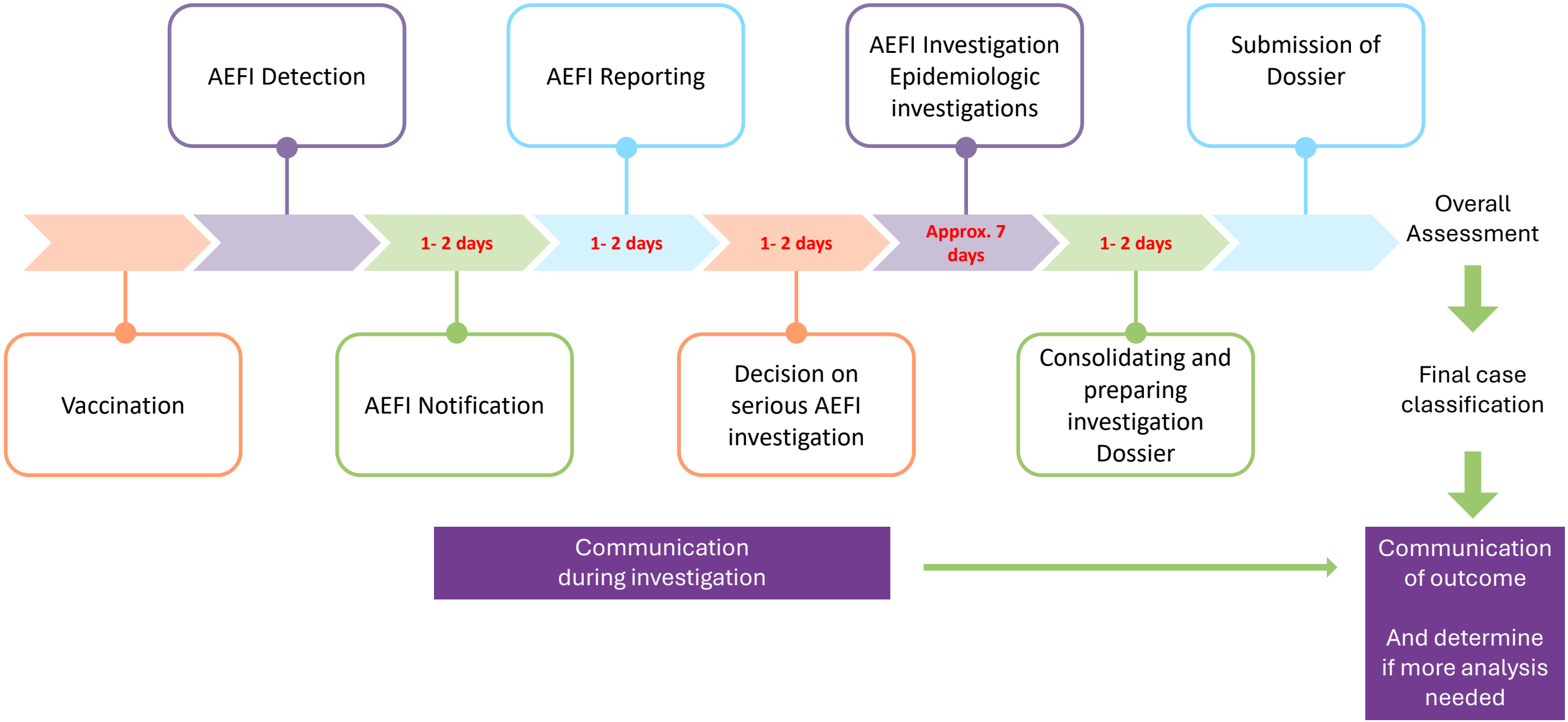
Message: Taking into account normal incidence of disease and death in the relevant age groups, coincidental events are inevitable when vaccinating

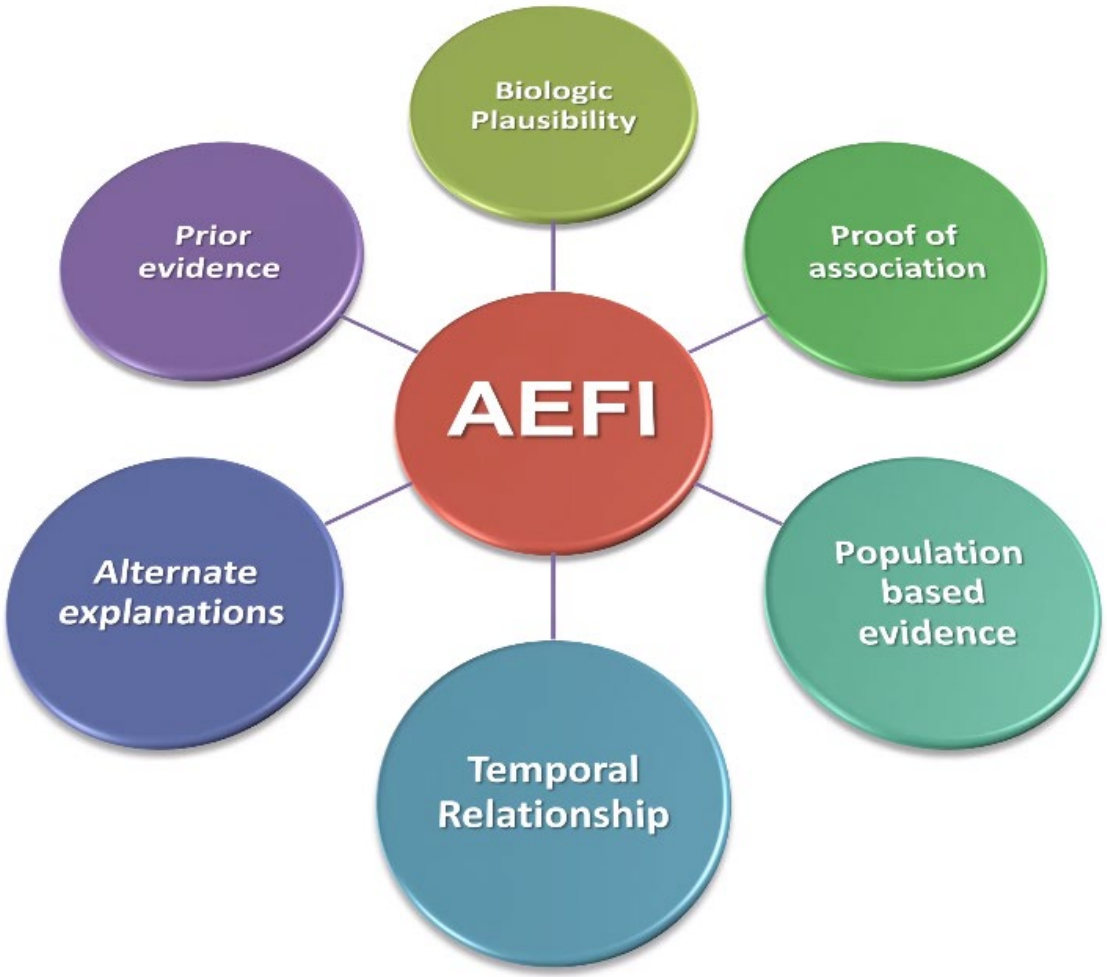
Table 6: Example of expected coincidental deaths following DTP vaccination (selected countries)

COUNTRY	INFANT MORTALITY RATE PER 1000 LIVE BIRTHS (IMR)	NUMBER OF BIRTHS PER YEAR (N)	NUMBER OF INFANT DEATH DURING YEAR IN		
			Month after immunization	Week after immunization	Day after immunization
			=(IMRxN/12)×nv×ppv	=(IMR×N/52)×nv×ppv	=(IMR×N/365)×nv×ppv
Australia	5	267 000	300	69	10
Cambodia	69	361 000	5605	1293	185
China	18	18 134 000	73 443	16 948	2421
Japan	3	1 034 000	698	161	23
Laos	48	170 000	1836	424	61
New Zealand	5	58 000	65	15	2
Philippines	26	2 236 000	13 081	3019	431

https://www.euro.who.int/__data/assets/pdf_file/0010/339625/Vaccine-safety-messages.pdf

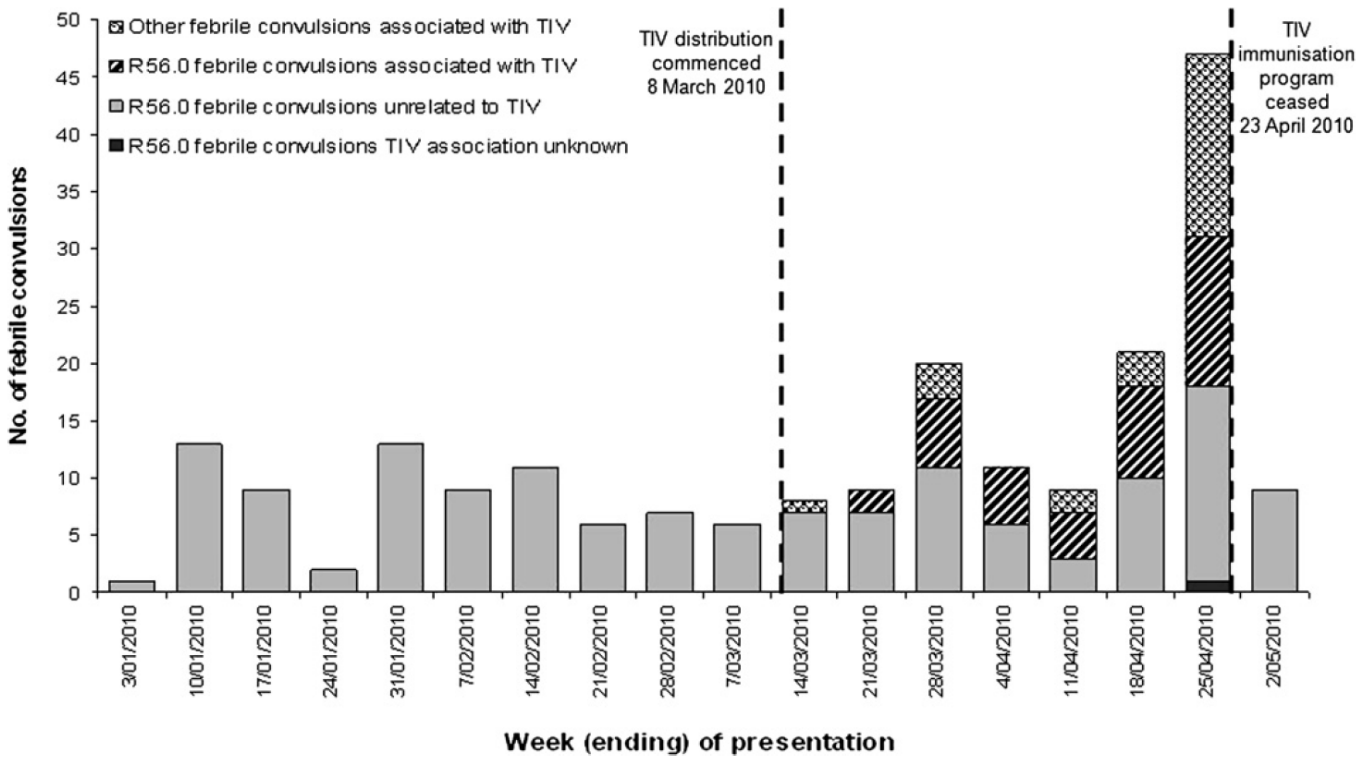
Approximate timelines for AEFI Investigation





2010 Australia:

- Fluvax brand of influenza vaccine in young children – was it causing excess rates of fever and febrile convulsions?
- Yes, epidemiologic evidence supported this, and mechanism - vaccine manufacturing issue - plausible (and later found)



Autoimmune diseases after adolescent or adult immunization: What should we expect?

Claire-Anne Siegrist MD

Tempting to consider that 2 events close in time have 'cause and effect'

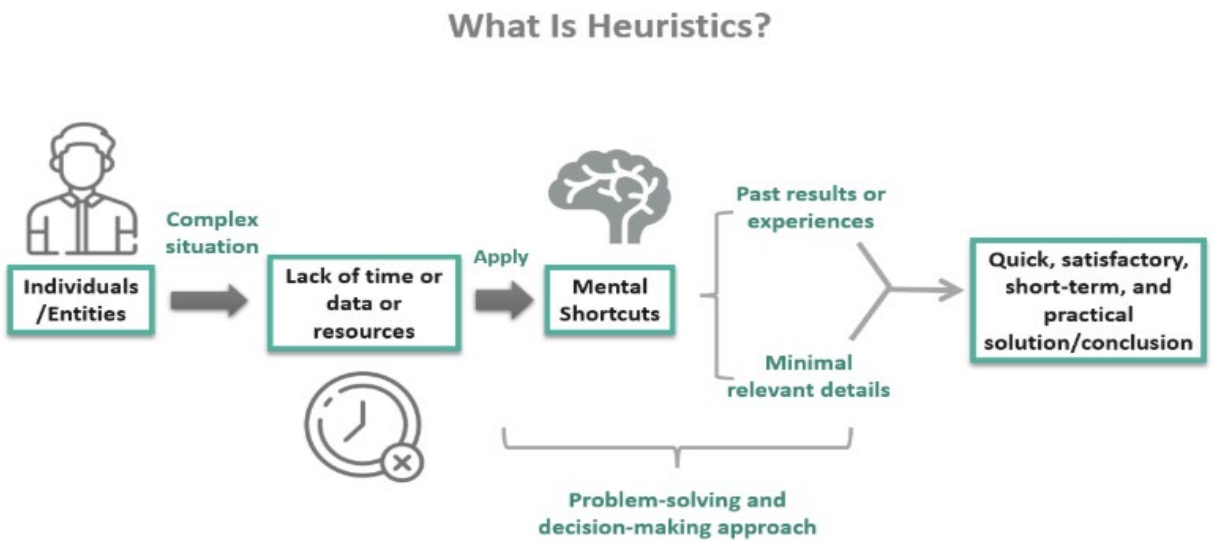
Especially if

- unexpected, severe or poorly understood adverse event in previously healthy person
- the first event (vaccine administration) is perceived to be complex, have long term effects, or is memorable

Likelihood of a temporal association is proportional to

- vaccine coverage, # doses given and disease prevalence
- Large scale programs will inevitably increase apparent number of cases

Coincident timing doesn't = causation
'Disproving' causation must be multi-faceted



https://www.cmaj.ca/content/cmaj/177/11/1352.full.pdf

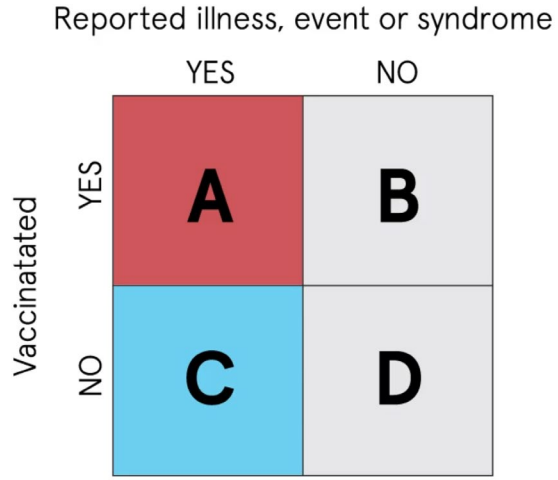
What is Vaccine Attributable Risk?

How much disease is actually due to to the exposure (vaccine, drug or other)

The risk difference is the extra risk caused by the vaccine

Risk Difference (or ratio or incidence rate ratio) =

Risk in vaccinated – Risk in unvaccinated



% of adverse event in vaccinated = A/(A+B)

% of adverse event in unvaccinated = C/(C+D)

Vaccine pharmacovigilance analysis methods

Generally retrospective analyses – but some can be quasi prospective or rapid cycle analysis

Observed versus expected

Studies comparing reported adverse event rate/s with 'expected' rates in similar population from recent historical period

Often in early vaccine safety signal investigation

Case control studies

Compare individuals with adverse event to those without it and their vaccination status

For rare events

Can control for (some) confounders

Case/control selection key

Cohort studies

Compare vaccinated and unvaccinated groups for rates of adverse events

For more common events

Challenge if very high coverage, characteristics of those vaccinated/not vaccinated differ, etc

'SCCS' design

Self controlled case series, comparing incidence rate of event in pre-specified risk period versus control periods

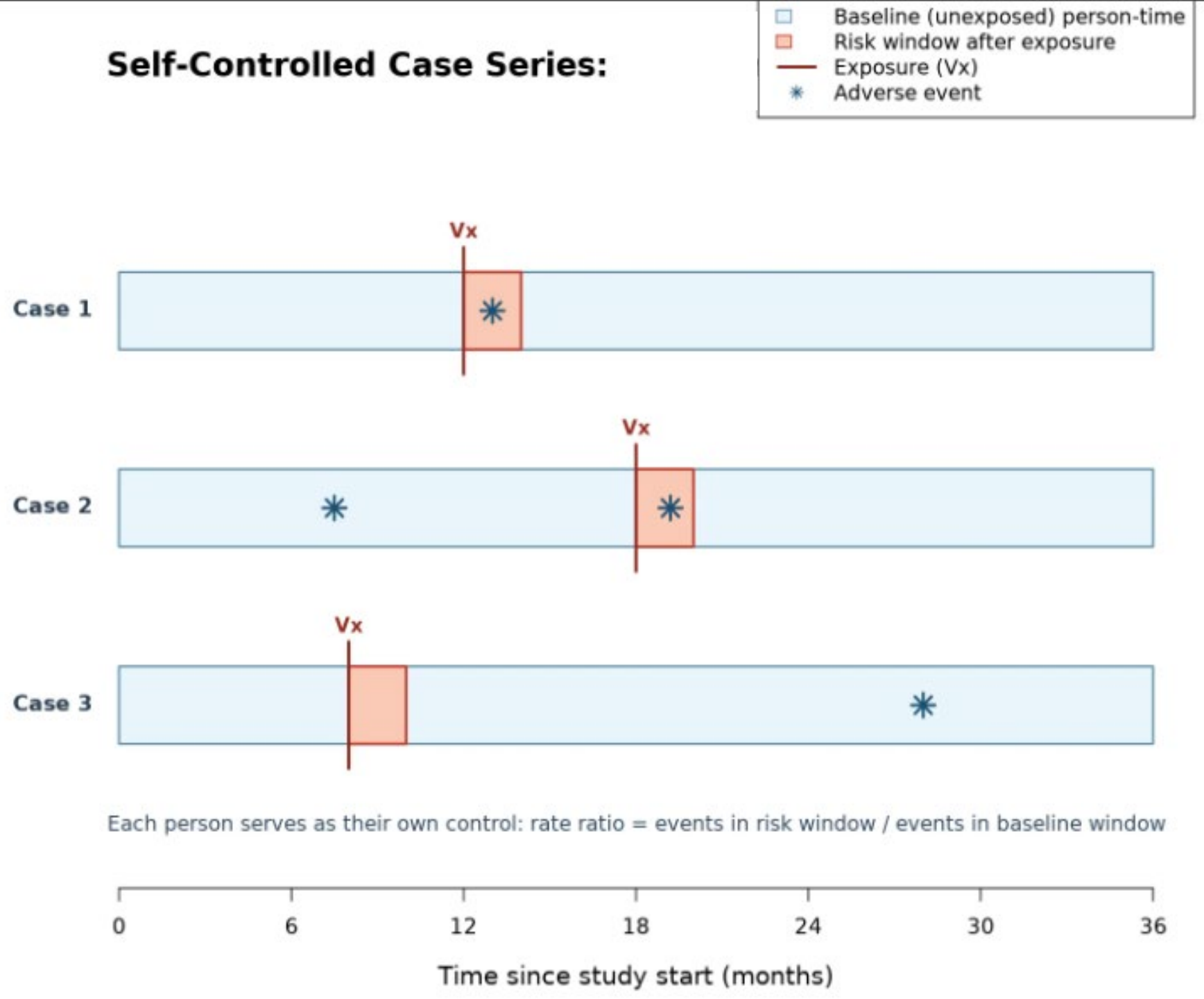
Useful for rare events, high vaccine coverage, multiple doses

Study cohort =

- All individuals in a population who had the condition in a defined calendar period of time
- Requires definition of plausible risk period
- Compare incidence rates in risk v. non risk periods
- Vx = vaccine date

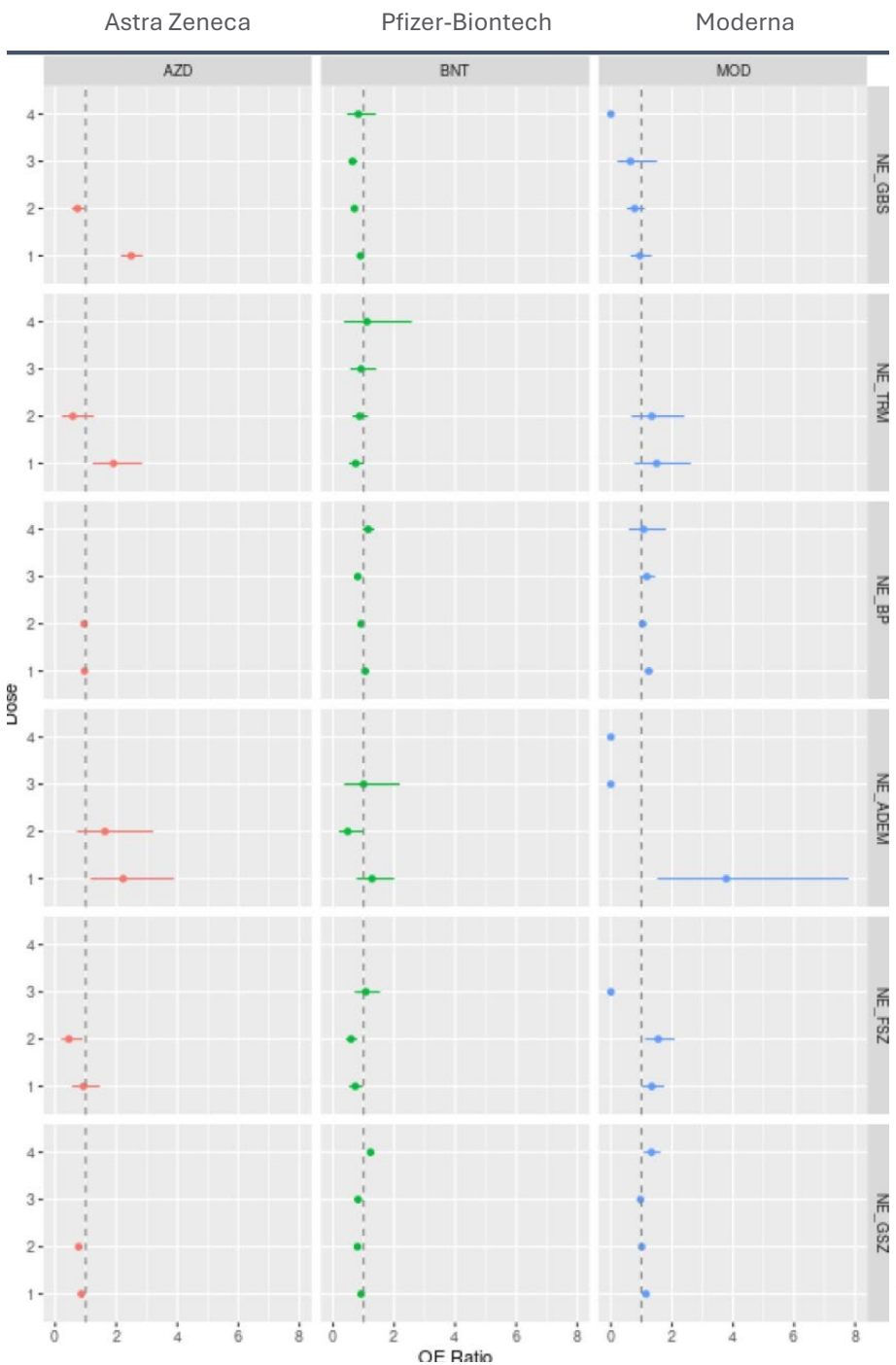
Risk periods = orange

Non risk periods = blue



COVID-19 vaccines and adverse events:

←Observed Expected analysis - multi-country



Guillain-Barré syndrome

Transverse myelitis

Facial (Bell's) palsy

Acute disseminated encephalomyelitis

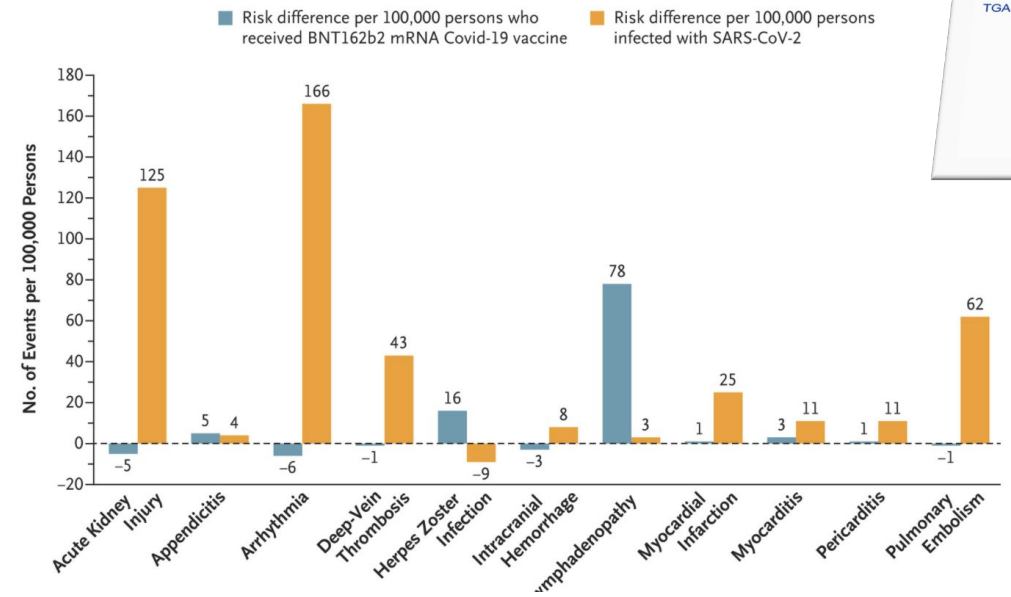
Febrile seizures

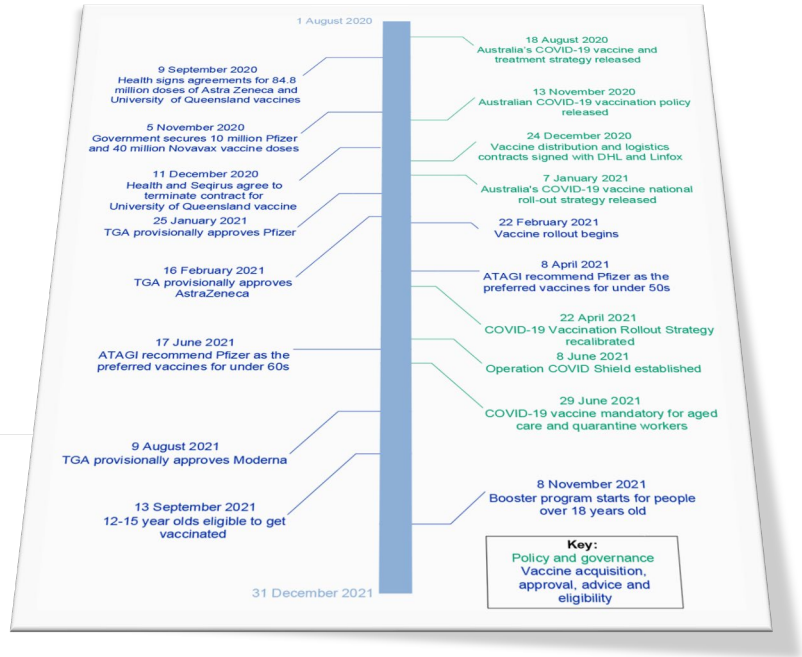
Generalised seizures

← COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals – PubMed



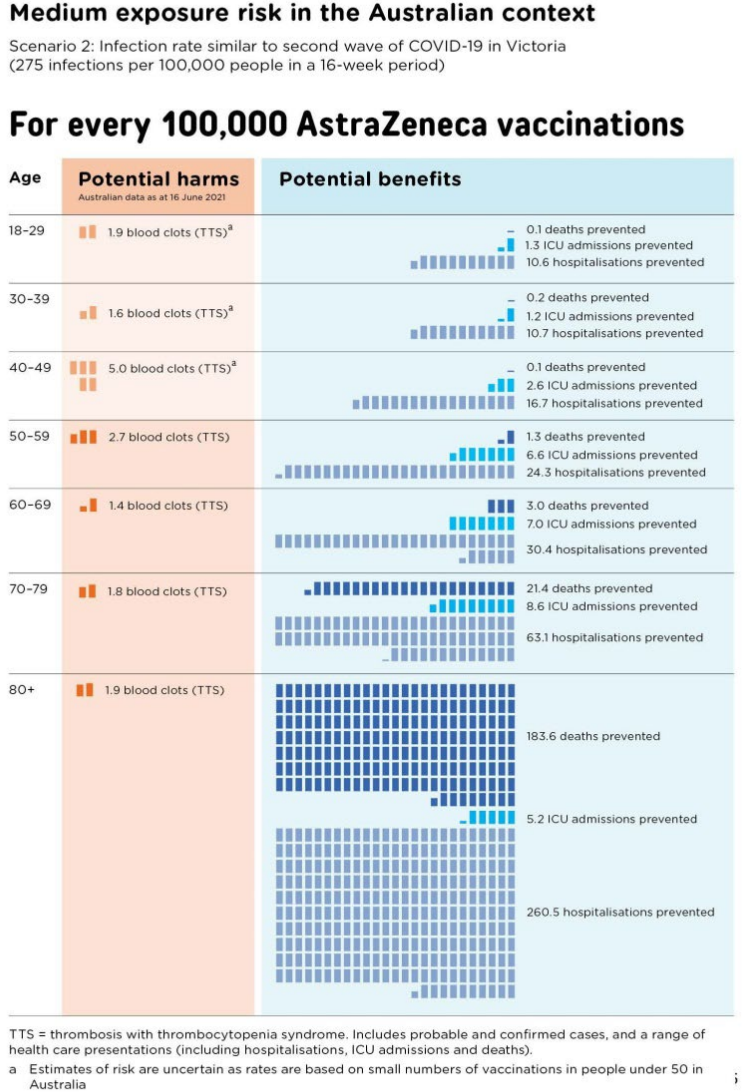
COVID-19 vaccines: Myocarditis and Pericarditis





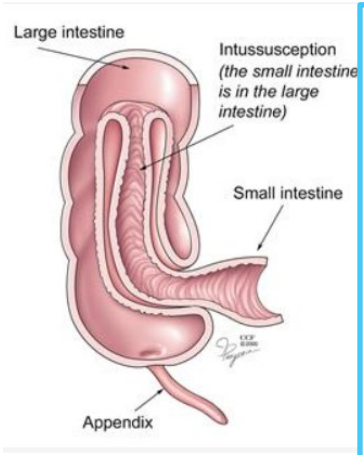
COVID-19 vaccines: Thrombosis Thrombocytopenia Syndrome (TTS)

But this was time and context specific....
No longer holds for all ages and vaccines



https://www.nejm.org/doi/full/10.1056/nejmoa2110475https://www.tga.gov.au/periodic/covid-19-vaccine-weekly-safety-report

Rotavirus vaccines and intussusception



Intussusception attributable to rotavirus vaccine now

- Very rare (or not increased overall) in high income countries
- Low income countries – studies overall show no increase
- Recommendations to remove upper age limits for vaccine dosing in LMICs to increase disease protection

Australia's trends in intussusception hospitalisations over 13 years, before and after Rotavirus vaccine introduction in 2007

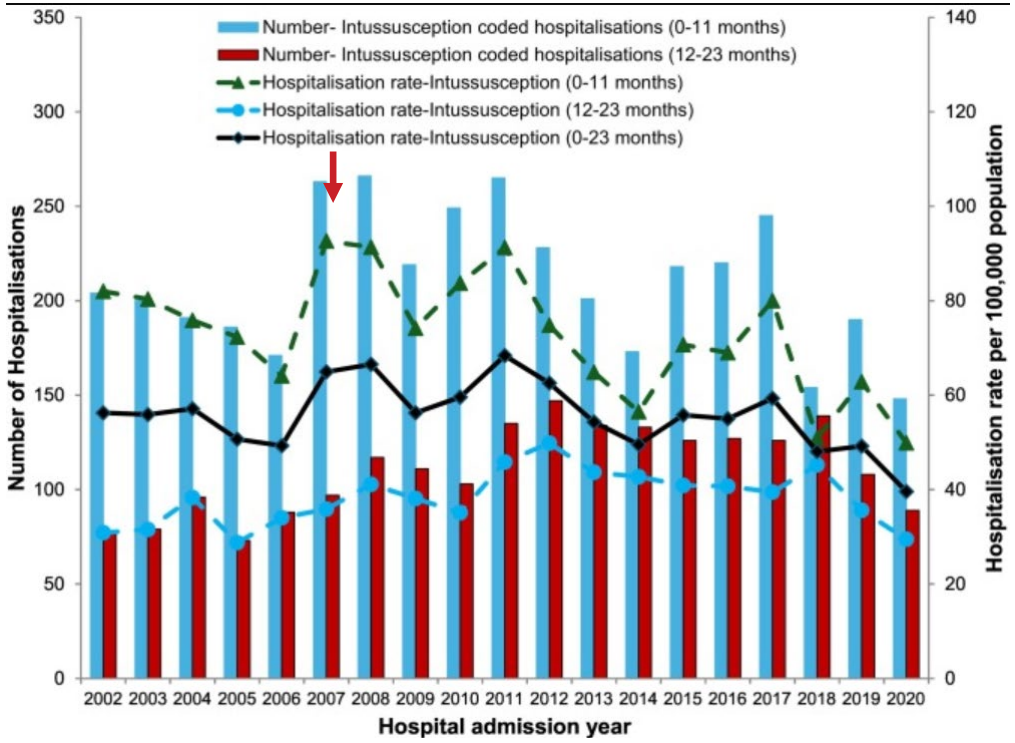


Table 1 Risk–benefit of rotavirus vaccination by country on rotavirus hospitalisations and deaths and associated intussusception risk for one vaccinated birth cohort to age 5 years

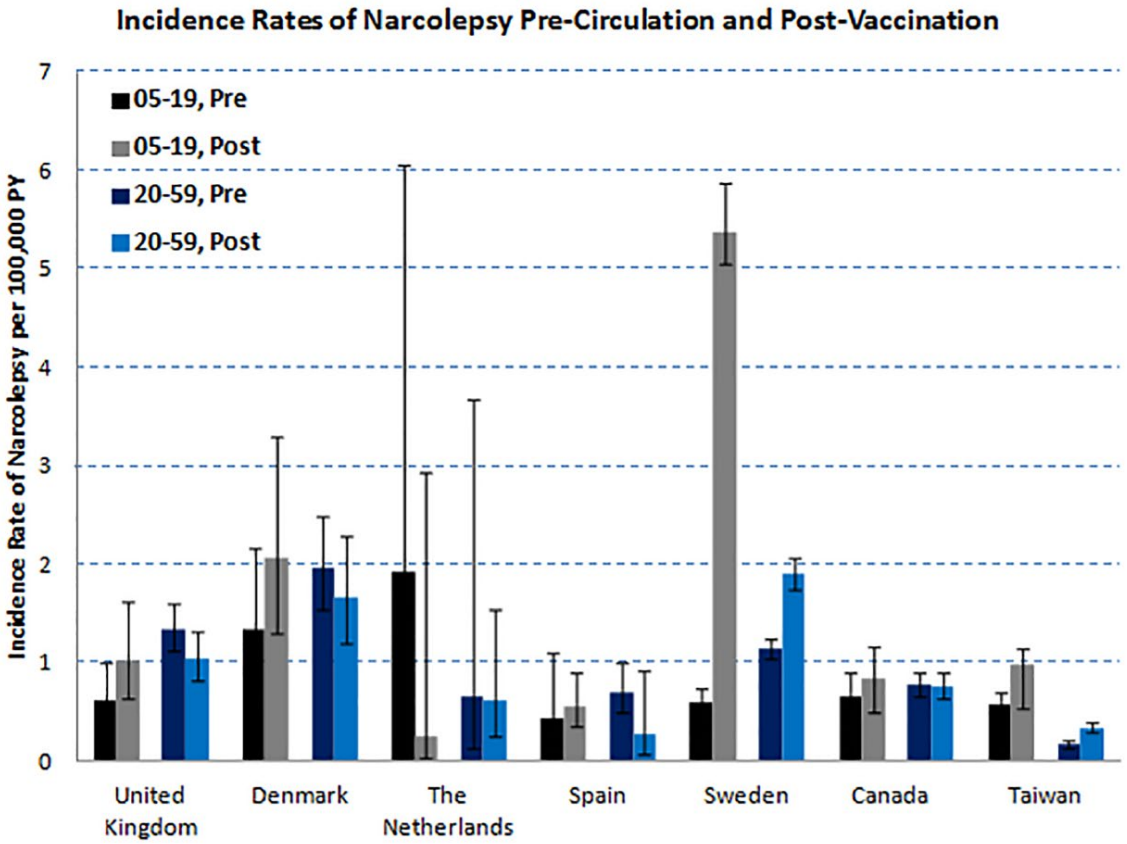
Country	Vaccine evaluated	Vaccine dose(s)	Overall attributable risk*	Rotavirus outcomes averted	Intussusception outcomes caused
Mexico[34]	Rotarix	Dose 1 only	2.0–3.7	Hospitalisations: 11 551 Deaths: 663	Hospitalisations: 41 Deaths: 2
Brazil[34]	Rotarix	Dose 2 only	1.5	Hospitalisations: 69 572 Deaths: 640	Hospitalisations: 55 Deaths: 3
Australia[35]	Rotarix	Doses 1 and 2	4.3	Hospitalisations: 6528 Deaths: not reported	Hospitalisations: 14 Deaths: not reported
	RotaTeq	Doses 1 and 2	7.0		
USA[36 39]	Rotarix	Doses 1 and 2	5.3	Hospitalisations: 53 444 Deaths: 14	Hospitalisations: 35–166 Deaths: 0.1–0.5
		Dose 2 only	7.3		
	RotaTeq	Dose 1 only	0.7–1.5	Not reported	Not reported
England[40]	Rotarix	Dose 1 only	1.68	Hospitalisations: 25 000 Deaths: not reported	Hospitalisations: 21 Deaths: not reported

Note: Table adapted from Reference.[87]
*Excess intussusception cases per 100 000 vaccinated infants.

https://gh.bmj.com/content/bmjgh/6/Suppl_2/e003814.full.pdf; Australia's rotavirus immunisation program: Impact on acute gastroenteritis and intussusception hospitalisations over 13 years - ScienceDirect

Narcolepsy

2010 - Safety signal of increase in incidence of narcolepsy in Finland, Sweden, and Norway but not other countries with Pandemrix (adjuvanted H1N1 pandemic vaccine)



Incidence rates were used to assess a signal of narcolepsy following AS03-adjuvanted monovalent pandemic H1N1 (pH1N1) influenza vaccination among children and adolescents in Sweden and Finland in 2010. We explored the utility of ecological data to assess incidence of narcolepsy following exposure to pandemic H1N1 virus or vaccination in 10 sites that used different vaccines, adjuvants, and had varying vaccine coverage.

- rare neurologic disease with sleep disturbance
- >90% of individuals with type 1 narcolepsy have HLA DQB1*06:02 gene
- long interval from onset of symptoms to diagnosis, especially in adults (10-20 years)

Is the cumulative exposure to aluminum from childhood vaccines associated with increased risk for developing chronic autoimmunity, atopy or allergy, or neurodevelopmental disorders?

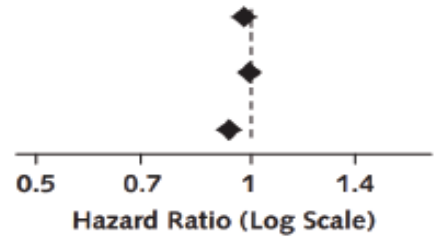
1 224 176 children born in Denmark between 1997 and 2018, alive

Cumulative aluminum amount received (per 1-mg increase) through vaccination by age 2 y



Incident events of 50 different chronic disorders including autoimmune, atopic or allergic, and neurodevelopmental disorders

Outcome	Cases, *n*	Person-Years	Adjusted Hazard Ratio (95% CI) per 1-mg Increase in Aluminum Received Through Vaccines by Age 2 y
Autoimmune outcomes	5174	3 400 369	0.98 (0.94–1.02)
Atopic and allergic outcomes	39 465	1 562 490	0.99 (0.98–1.01)
Neurodevelopmental outcomes	5200	3 409 893	0.93 (0.90–0.97)



Annals of Internal Medicine

Andersson NW, Bech Svalgaard I, Hoffmann SS, et al. Aluminum-adsorbed vaccines and chronic diseases in childhood A nationwide cohort study. Ann Intern Med. 15 July 2025. [Epub ahead of print]. doi:10.7326/ANNALS-25-00997
http://acpjournals.org/doi/10.7326/ANNALS-25-00997

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Aluminum-Adsorbed Vaccines and Chronic Diseases in Childhood: A Nationwide Cohort Study: Annals of Internal Medicine: Vol 0, No 0
Aluminium adjuvants in vaccines and potential health effects: systematic review | The BMJ

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Statement of the WHO Global Advisory Committee on Vaccine Safety (GACVS) on vaccines and autism

11 December 2025 | Statement | Reading time: 3 min (727 words)

On 27 November 2025, the WHO Global Advisory Committee on Vaccine Safety (GACVS) assessed two new systematic literature reviews, performed using robust methodology, on the potential relationship between vaccines and autism spectrum disorder (ASD)

Upon comprehensive review of the latest evidence published from January 2010 until August 2025, the Committee reaffirmed its previous conclusion based on extensive reviews conducted in 2002[1][2], 2004[3], and 2012[4], that there is no evidence of a causal relationship between vaccines and ASD.

A causal relationship between a vaccine and an event is suspected when several high-quality studies indicate a statistical association between exposure to the vaccine and the outcome of interest. In systematic reviews, databases are searched to ensure comprehensive capture of published studies and the quality of all included studies is evaluated according to well accepted methodologies. When reviewing the evidence to inform causality, the greatest weight is put on the high-quality well-designed studies with low risk of bias and little weight is given to those with methodological flaws and high risk of bias.

>25 years of high quality studies show now association

Studies that ‘support’ association are of low quality/design/inference

Thank you

NCIRS National Centre for Immunisation Research and Surveillance Australia