# Vaccine pharmacoepidemiology

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Australian Vaccinology Course 2026

NCIRS National Centre for Immunisation Research and Surveillance Australia

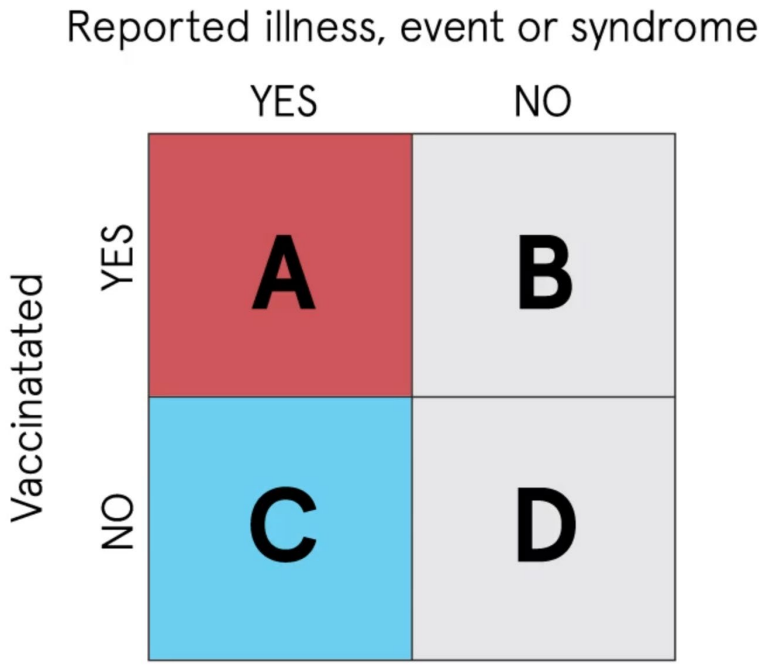
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Sydney Infectious Diseases Institute

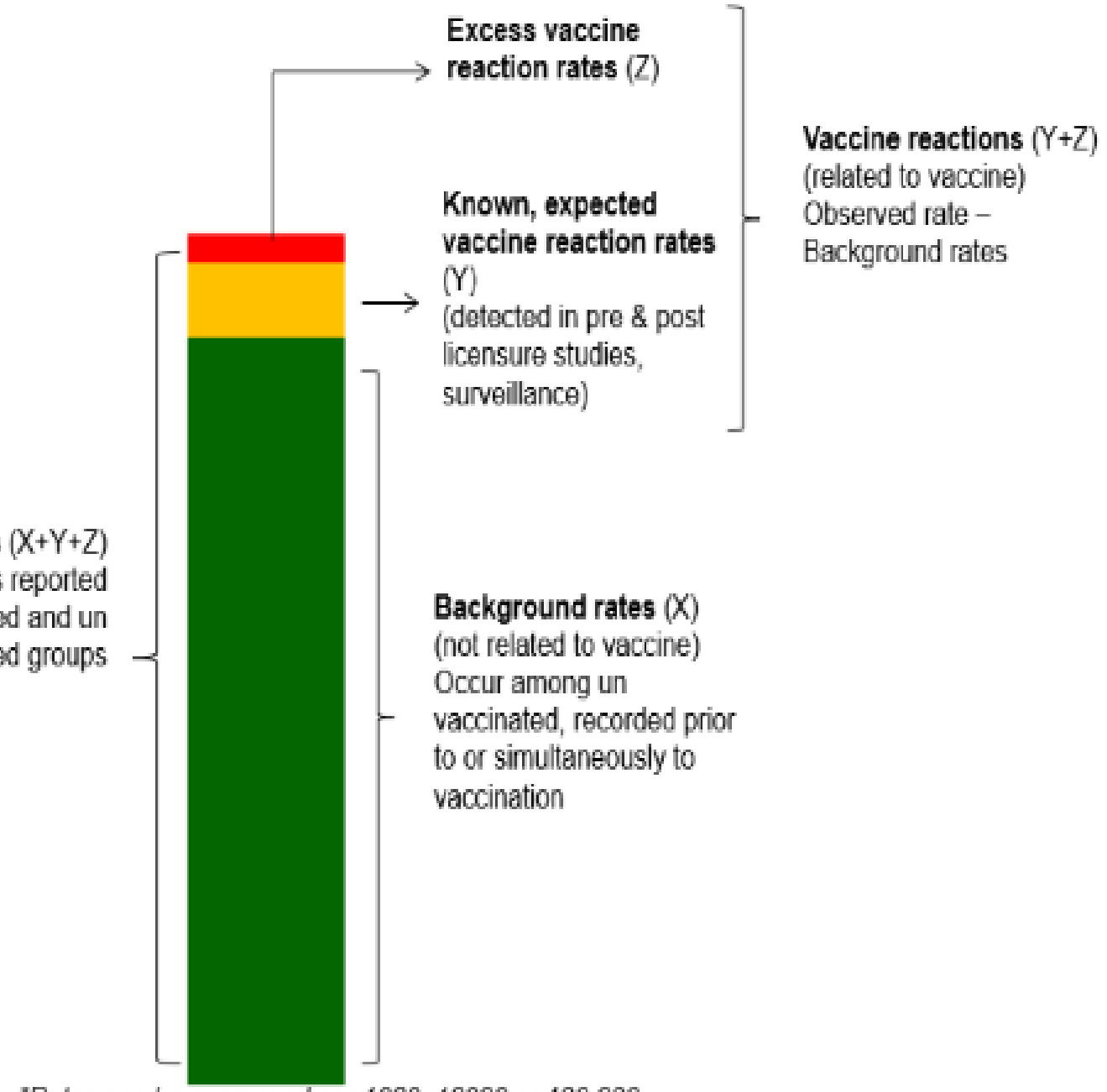
# Passive or ‘spontaneous’ AEFI surveillance (= A)

- 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)**




*"Rates can be expressed per 1000, 10000 or 100,000*

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

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

# 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'

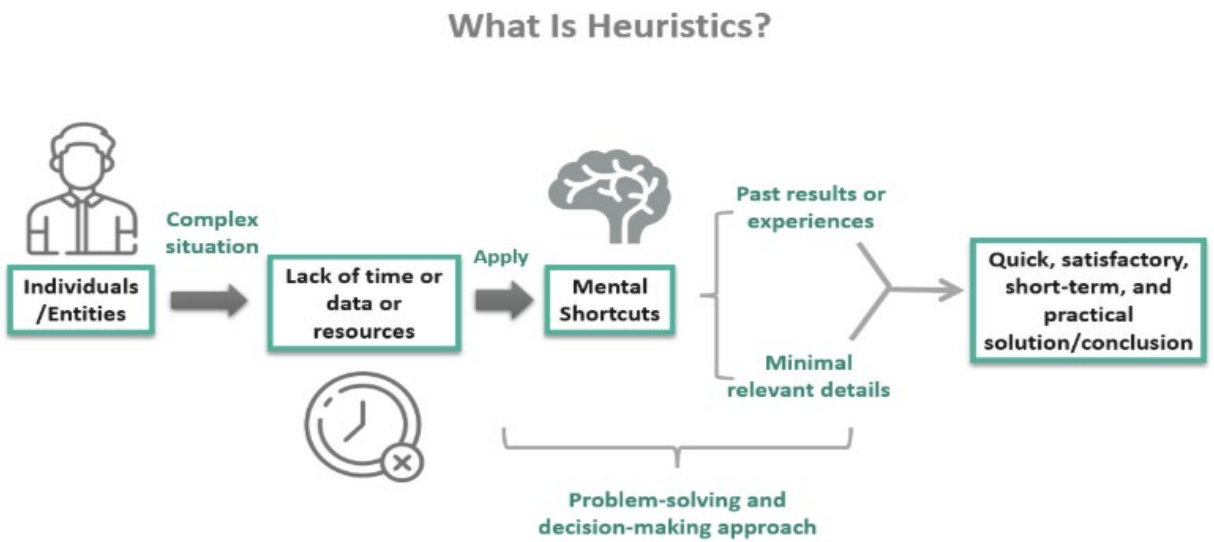
Especially if

- 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

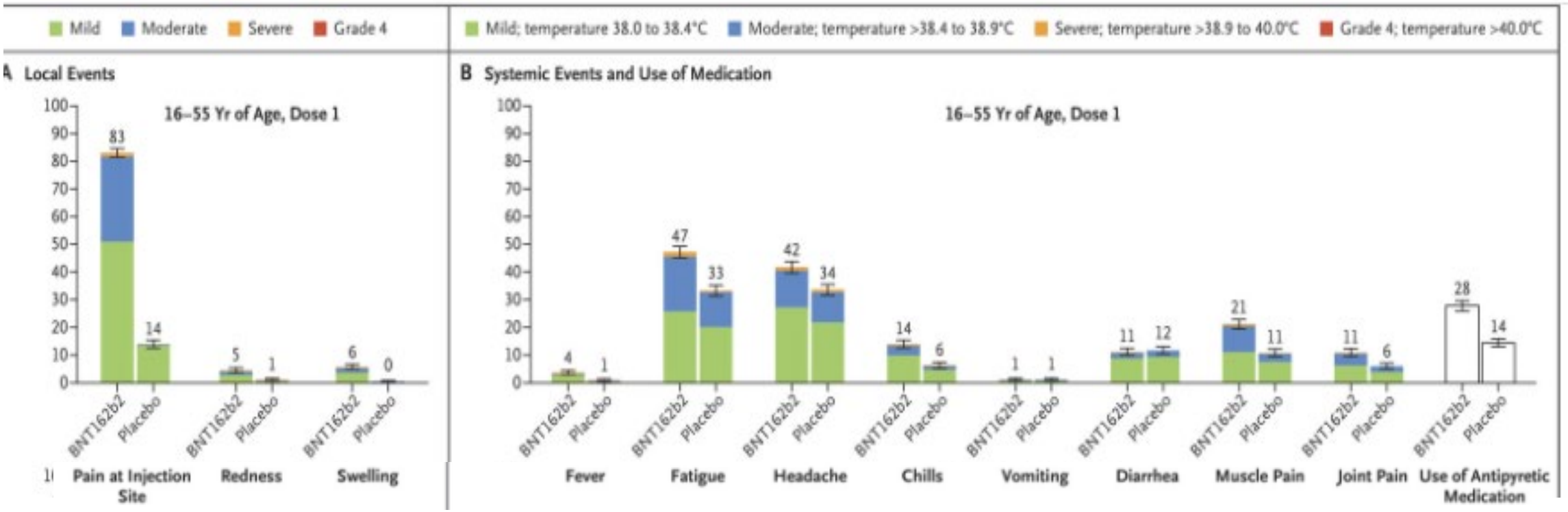
## Likelihood of a temporal association is proportional to

- 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




# "Background rates" in clinical trials

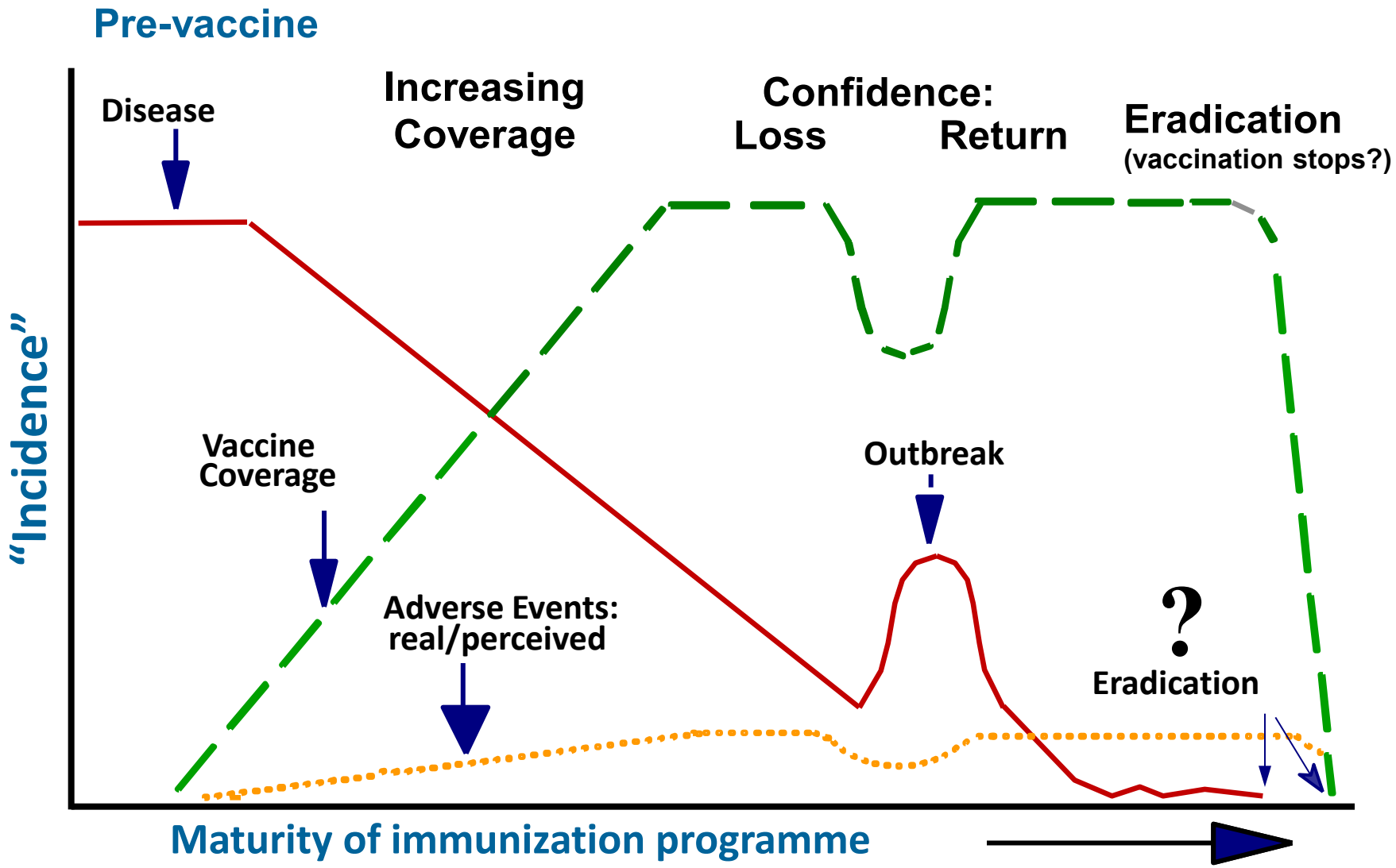
Adverse events of any/unknown cause are common every day!

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

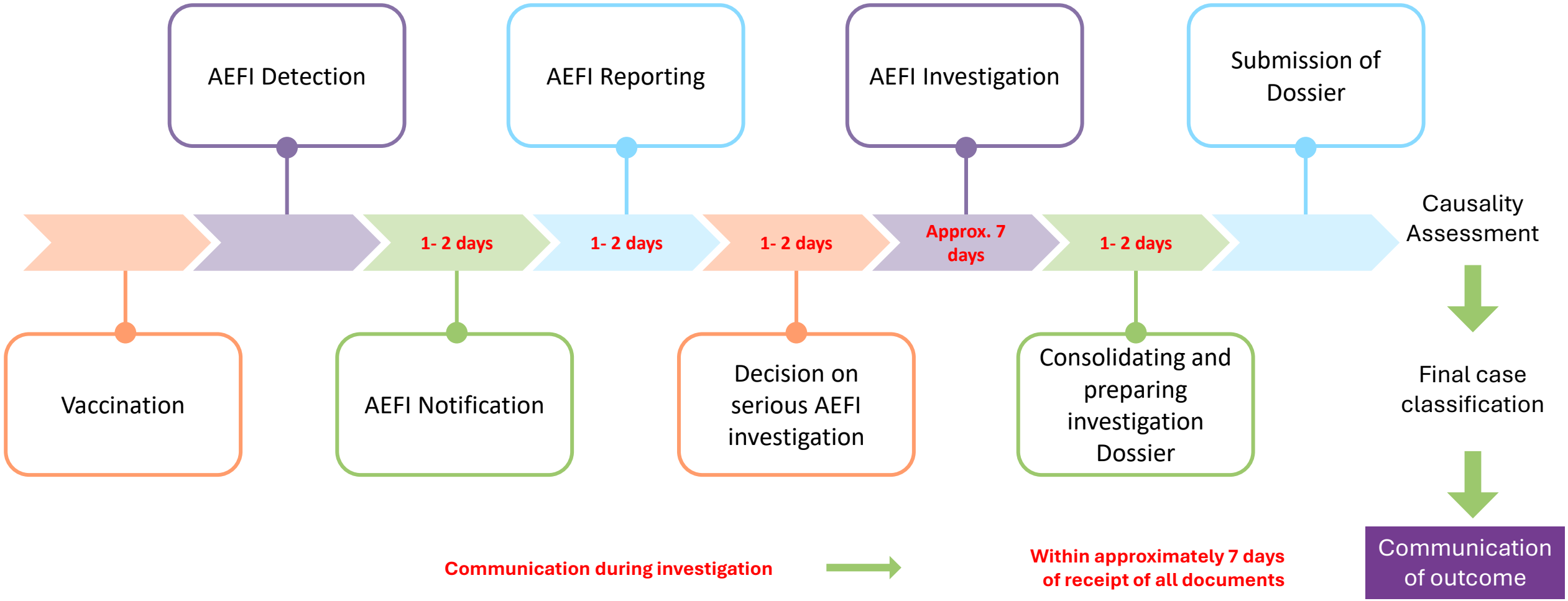
# Evolution of immunisation program and prominence of vaccine safety



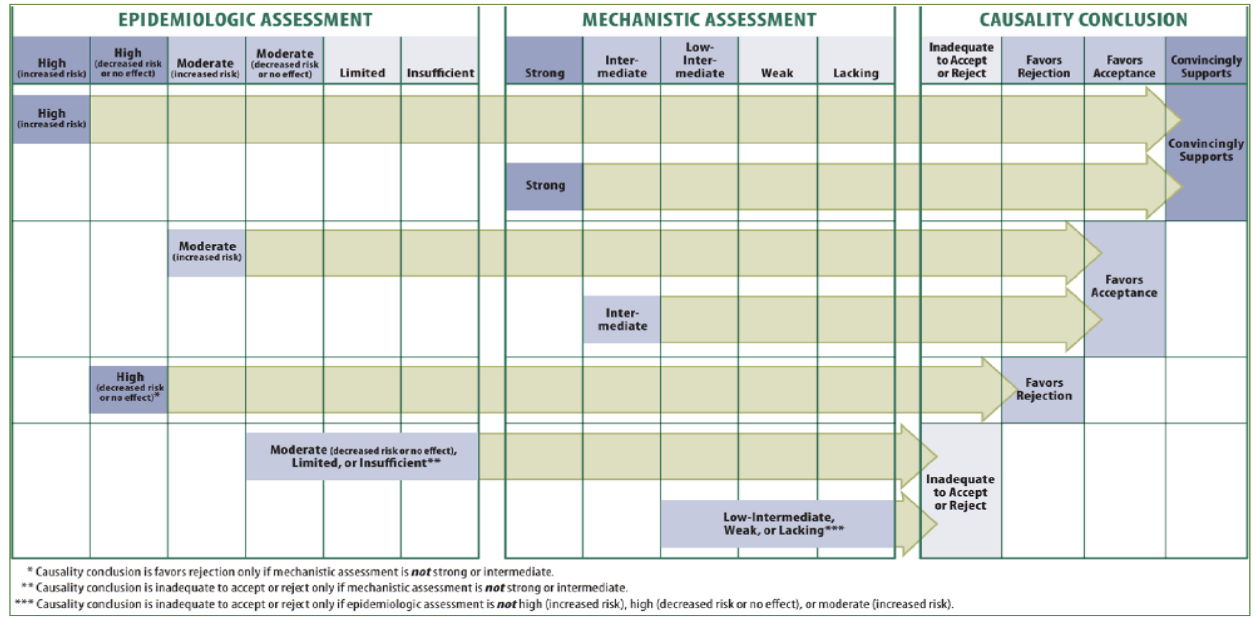

*Adapted from: Chen RT et al, Vaccine 1994; 12:542-50*

# Active surveillance / Ausvaxsafety

# Approximate timelines for AEFI Investigation

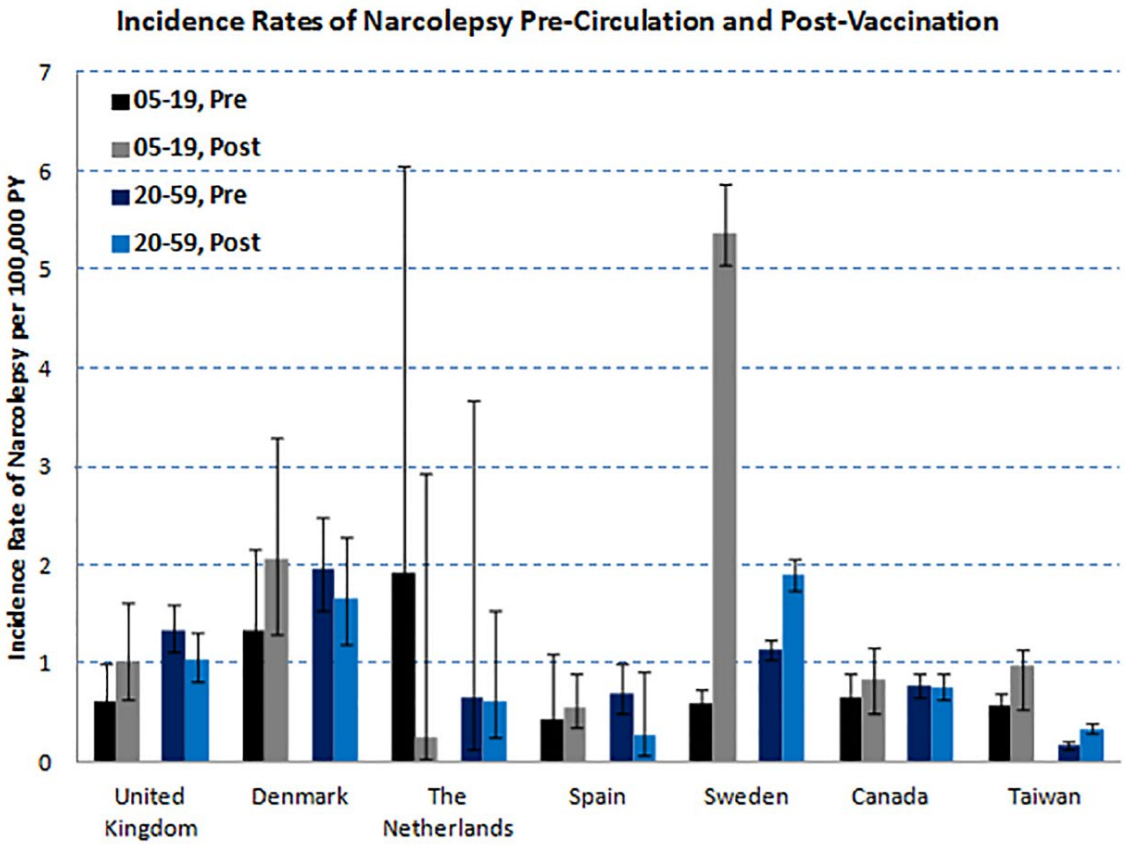



Biologic Plausibility
Prior evidence
Proof of association
AEFI
Alternate explanations
Population based evidence
Temporal Relationship


EPIDEMIOLOGIC ASSESSMENT
MECHANISTIC ASSESSMENT
CAUSALITY CONCLUSION
High (increased risk)
High (decreased risk or no effect)
Moderate (increased risk)
Moderate (decreased risk or no effect)
Limited
Insufficient
Strong
Inter-mediate
Low-Inter-mediate
Weak
Lacking
Inadequate to Accept or Reject
Favors Rejection
Favors Acceptance
Convincingly Supports
High (increased risk)
Strong
Moderate (increased risk)
Inter-mediate
Favors Acceptance
High (decreased risk or no effect)*
Favors Rejection
Moderate (decreased risk or no effect), Limited, or Insufficient**
Inadequate to Accept or Reject
Low-Intermediate, Weak, or Lacking***
* Causality conclusion is favors rejection only if mechanistic assessment is not strong or intermediate.
** Causality conclusion is inadequate to accept or reject only if mechanistic assessment is not strong or intermediate.
*** Causality conclusion is inadequate to accept or reject only if epidemiologic assessment is not high (increased risk), high (decreased risk or no effect), or moderate (increased risk).

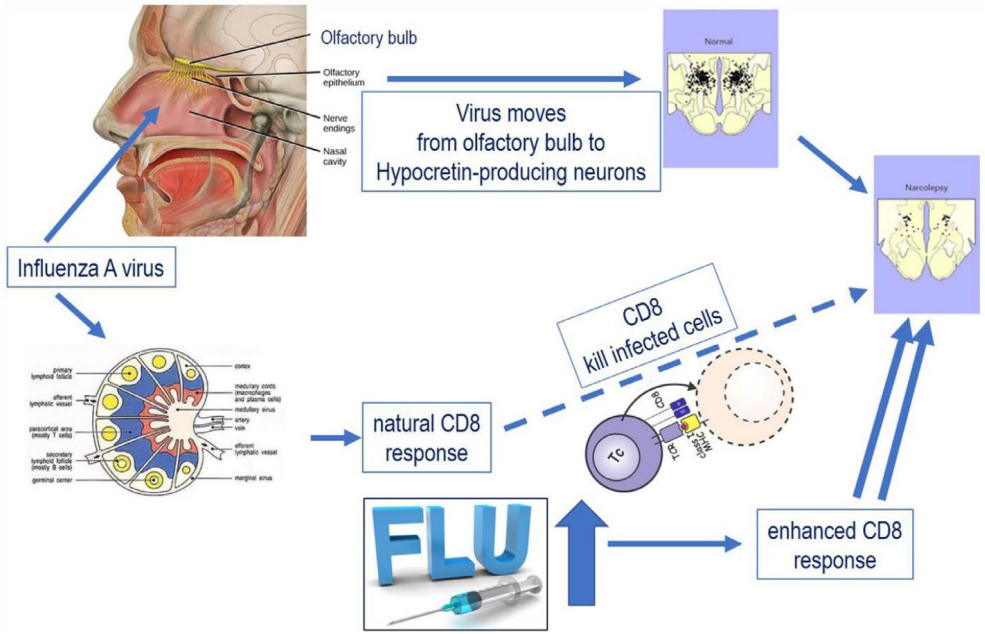
# Narcolepsy

**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)
- Pandemic Hypotheses: range from a causal effect of the AS03 adjuvant, the manufacturing process, presence of nucleoproteins in Pandemrix, molecular mimicry, to awareness and assessment biases, and residual confounding




The two hit hypothesis—a possible mechanism for an enhanced risk for narcolepsy following 2009 H1N1 pandemic influenza vaccine

# 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

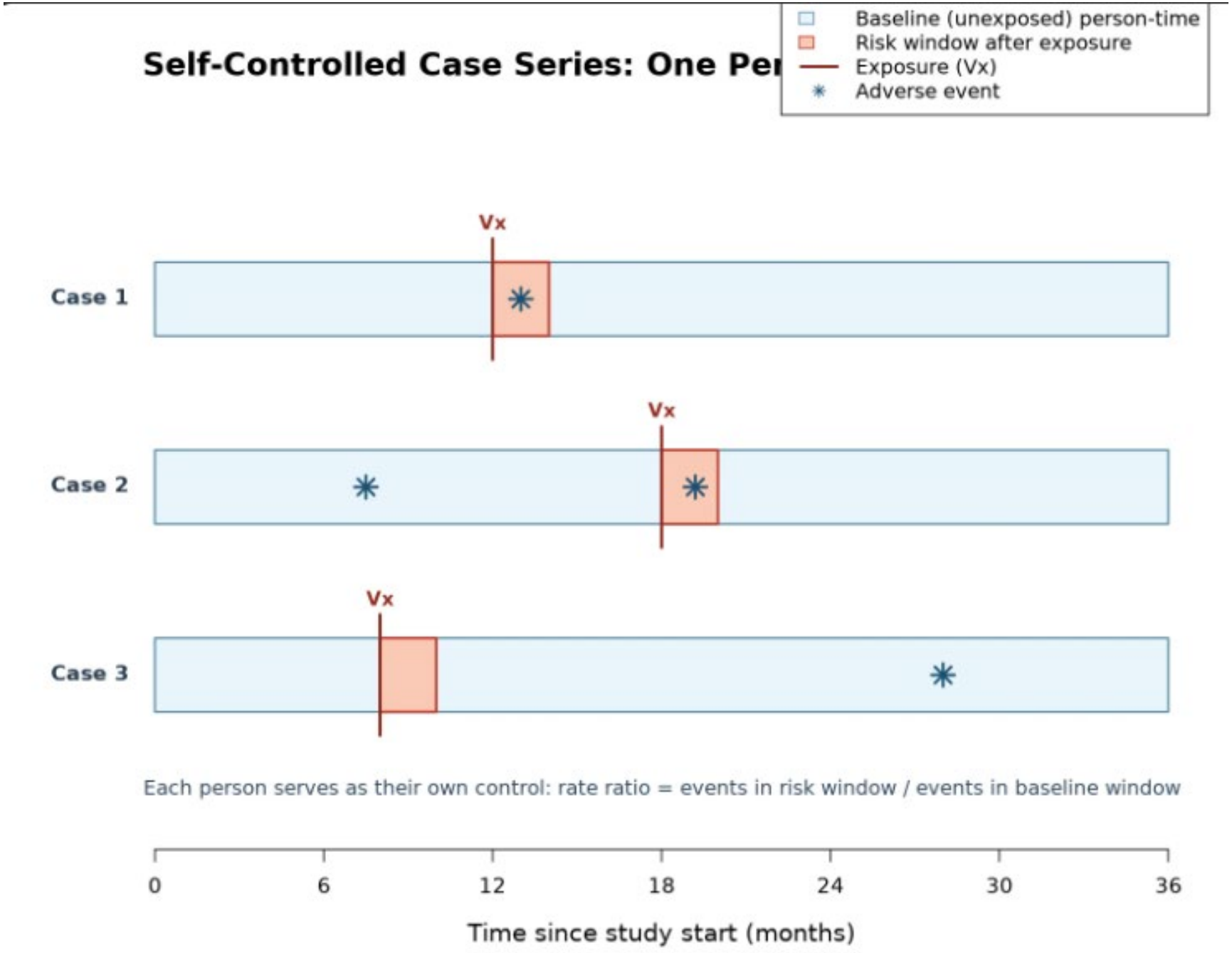
For more common events

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

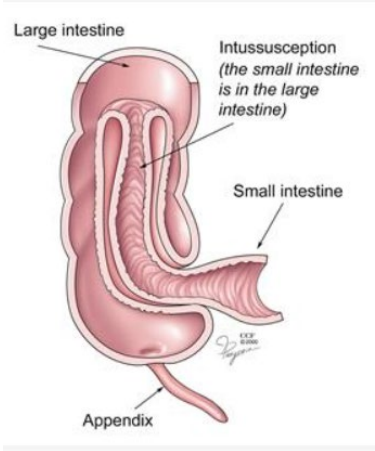
### 'SCCS' design

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

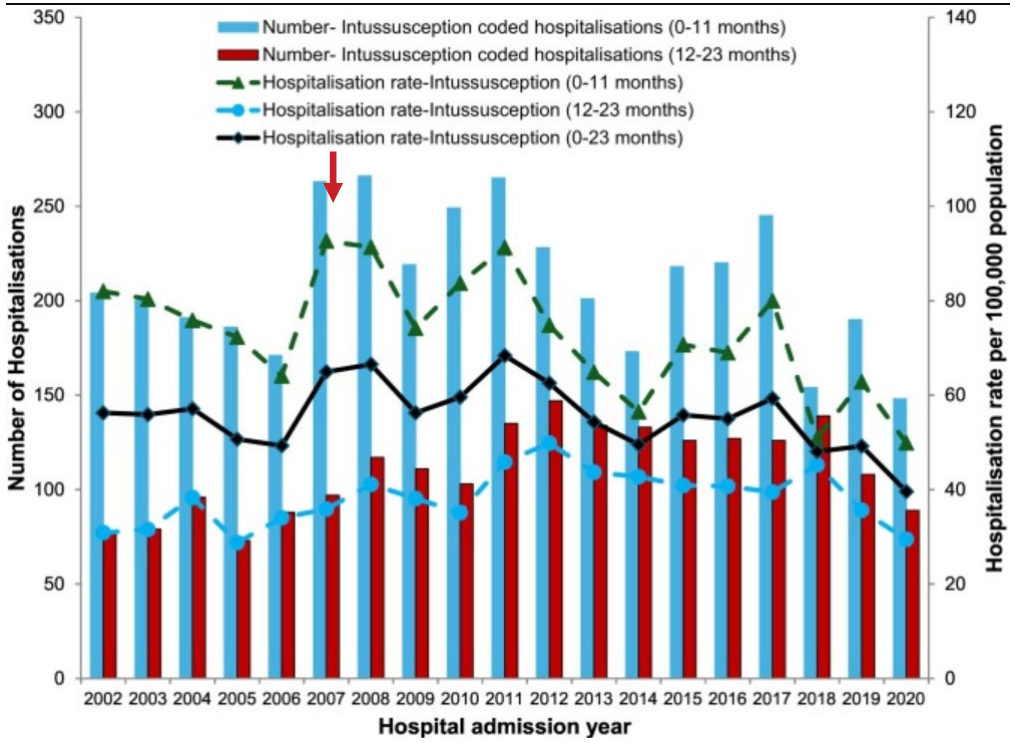
Useful for rare events, high vaccine coverage, multiple doses


Self-Controlled Case Series: One Per
Baseline (unexposed) person-time
Risk window after exposure
Exposure (Vx)
Adverse event
Vx
Case 1
Vx
Case 2
Vx
Case 3
Each person serves as their own control: rate ratio = events in risk window / events in baseline window
0
6
12
18
24
30
36
Time since study start (months)

# Rotavirus vaccines and intussusception




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



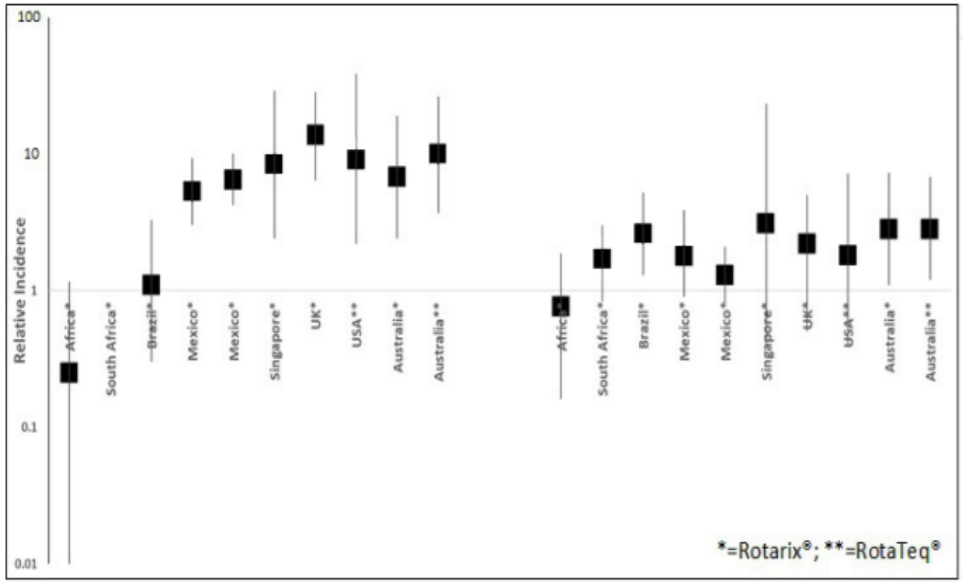




**Figure 3** Relative incidence of intussusception from self-controlled case-series analyses in the 1–7 days following dose 1 and dose 2 of rotavirus vaccine by country.

**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<br>Deaths: 663 | Hospitalisations: 41<br>Deaths: 2 |
| **Brazil**[34] | Rotarix | Dose 2 only | 1.5 | Hospitalisations: 69 572<br>Deaths: 640 | Hospitalisations: 55<br>Deaths: 3 |
| **Australia**[35] | Rotarix | Doses 1 and 2 | 4.3 | Hospitalisations: 6528<br>Deaths: not reported | Hospitalisations: 14<br>Deaths: not reported |
| | RotaTeq | Doses 1 and 2 | 7.0 | | |
| **USA**[36 39] | Rotarix | Doses 1 and 2 | 5.3 | Hospitalisations: 53 444<br>Deaths: 14 | Hospitalisations: 35–166<br>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<br>Deaths: not reported | Hospitalisations: 21<br>Deaths: not reported |

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

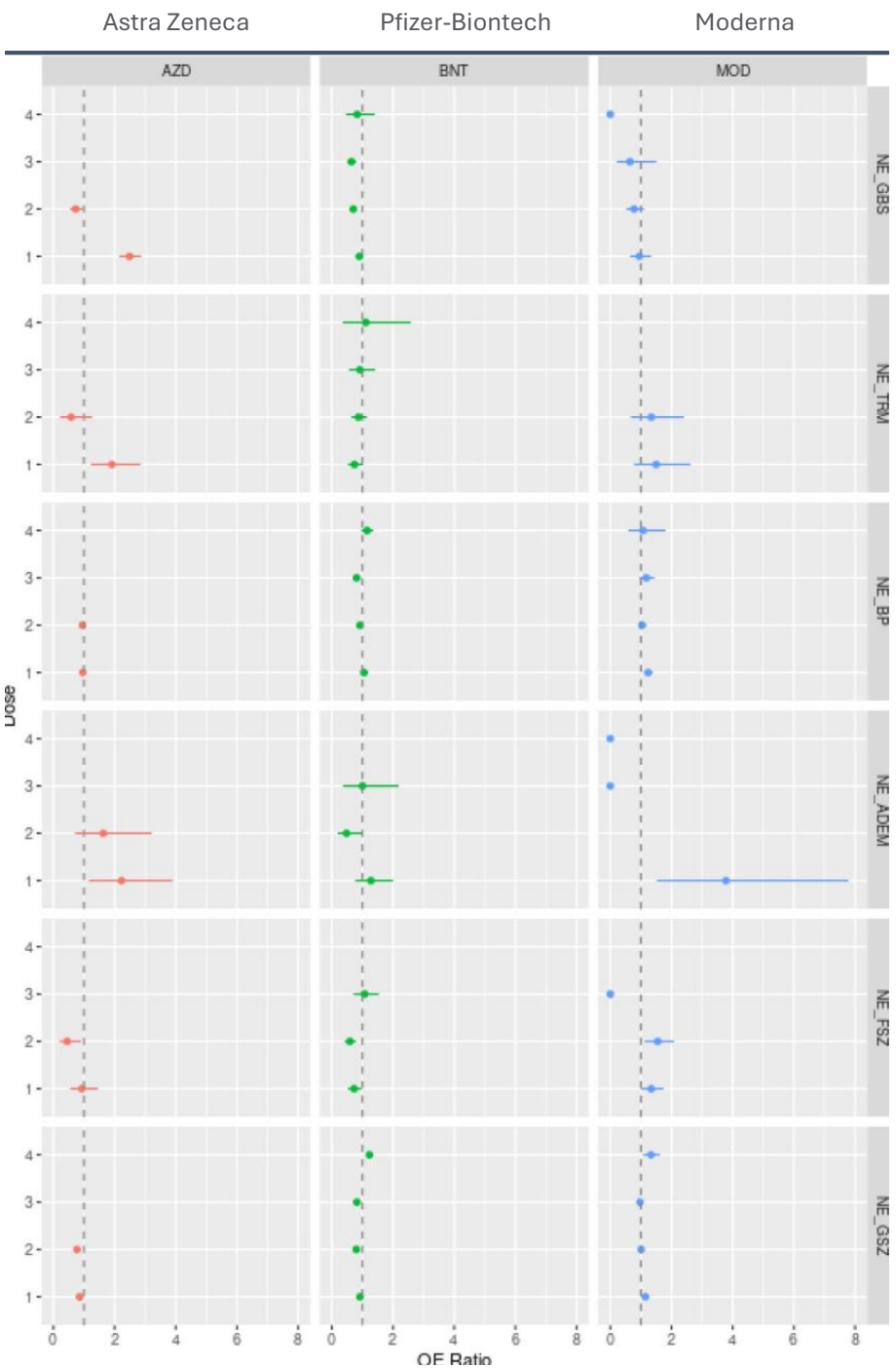


https://gh.bmj.com/content/bmjgh/6/Suppl_2/e003814.full.pdf; Australia's rotavirus immunisation program: Impact on acute gastroenteritis and intussusception hospitalisations over 13 years - ScienceDirect

# COVID-19 vaccines and adverse events:

## ←Observed Expected analysis - multi-country

## ↓ Nationwide cohort study - Denmark




Guillain-Barré syndrome

Transverse myelitis

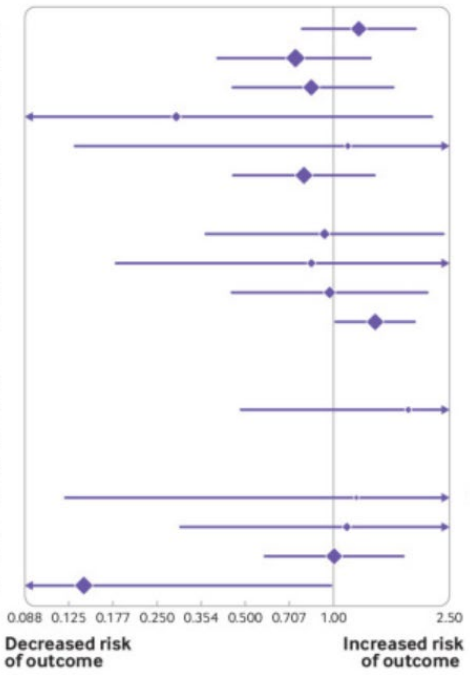
Facial (Bell's) palsy

Acute disseminated encephalomyelitis

Febrile seizures

Generalised seizures

| Outcome | No of events/person-years Heterologous | Homologous | Incidence rate ratio (95% CI) |
|---|---|---|---|
| **Main outcomes** | | | |
| Ischaemic cardiac events | 23/10 518 | 431/205 110 | 1.22 (0.78 to 1.91) |
| Cerebrovascular events | 12/10 521 | 326/205 223 | 0.74 (0.40 to 1.34) |
| Cerebrovascular infarction | 11/10 522 | 267/205 273 | 0.84 (0.45 to 1.59) |
| Intracranial bleeding | <3/10 529 | 61/205 450 | 0.29 (0.04 to 2.16) |
| Arterial thromboembolism | <3/10 529 | 20/205 485 | 1.12 (0.13 to 9.58) |
| Venous thromboembolism | 14/10 517 | 392/205 164 | 0.79 (0.45 to 1.38) |
| Cerebral venous thrombosis | 0/10 530 | 10/205 495 | NE |
| Pulmonary embolism | 5/10 526 | 135/205 376 | 0.93 (0.37 to 2.38) |
| Myocarditis or pericarditis | <3/10 529 | 93/205 465 | 0.84 (0.18 to 3.96) |
| Thrombocytopenia and coagulative disorders | 8/10 525 | 110/205 399 | 0.97 (0.45 to 2.10) |
| Other bleeding events | 48/10 507 | 729/205 022 | 1.39 (1.01 to 1.91) |
| **Secondary outcomes** | | | |
| Guillain-Barré syndrome | 0/10 530 | 4/205 495 | NE |
| Bell's palsy | 3/10 529 | 35/205 467 | 1.81 (0.48 to 6.79) |
| Transverse myelitis | 0/10 530 | 3/205 496 | NE |
| Encephalomyelitis or encephalitis | 0/10 530 | 9/205 489 | NE |
| Narcolepsy | <3/10 529 | 19/205 479 | 1.20 (0.12 to 12.01) |
| Anaphylaxis | 3/10 527 | 44/205 461 | 1.11 (0.30 to 4.09) |
| Appendicitis | 17/10 522 | 297/205 337 | 1.01 (0.59 to 1.73) |
| Death | <3/10 530 | 281/205 499 | 0.14 (0.02 to 0.99) |

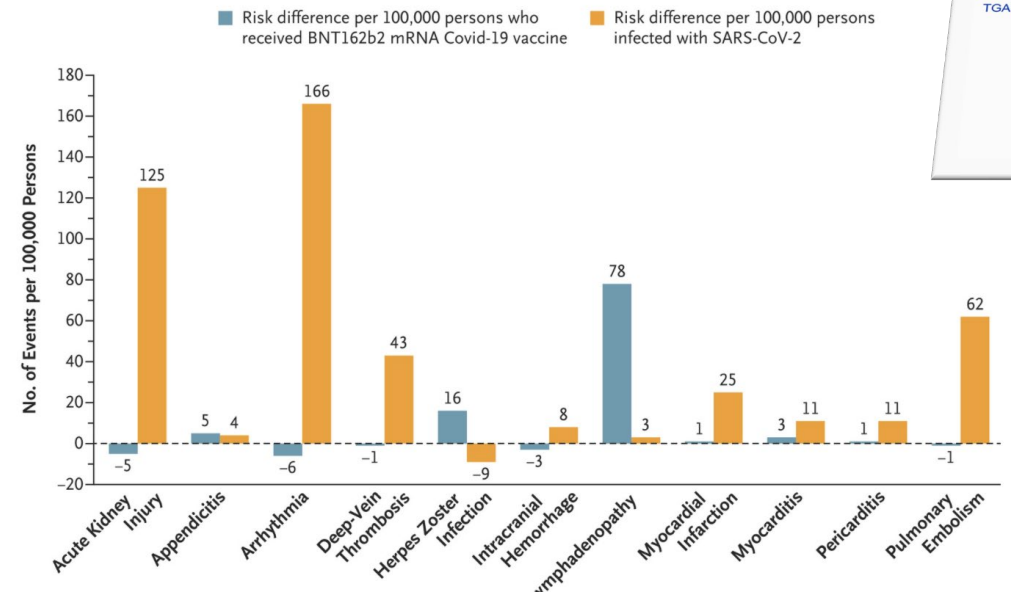


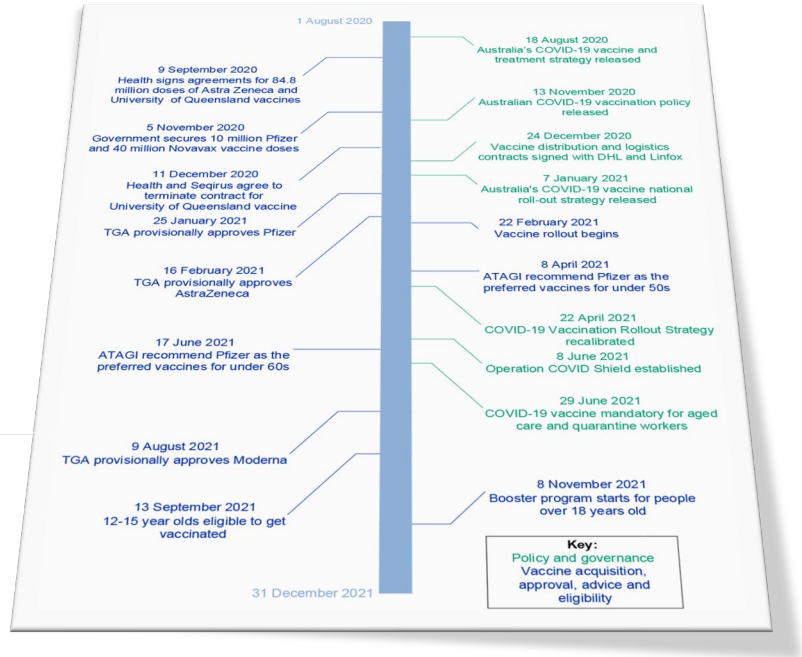

Safety of heterologous primary and booster schedules with ChAdOx1-S and BNT162b2 or mRNA-1273 vaccines: nationwide cohort study | The BMJ

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



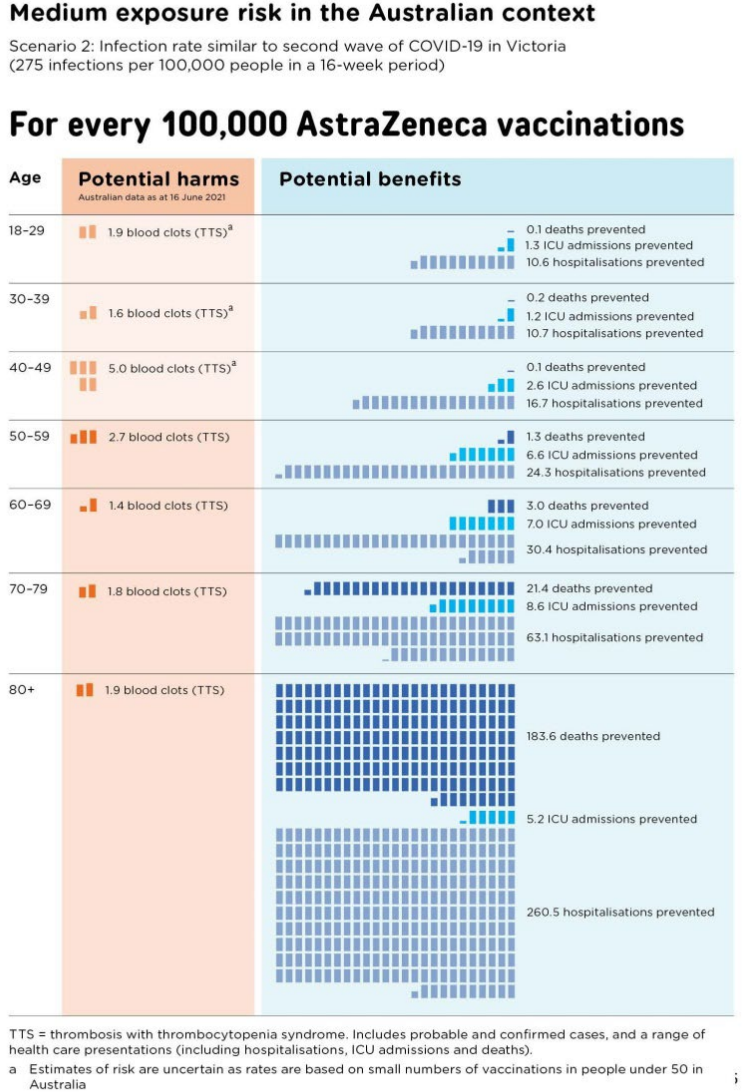
## COVID-19 vaccines: Myocarditis and Pericarditis




## 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

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

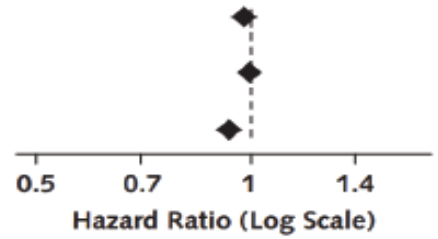
**1 224 176 children born in Denmark between 1997 and 2018, alive**

**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.

# Thank you

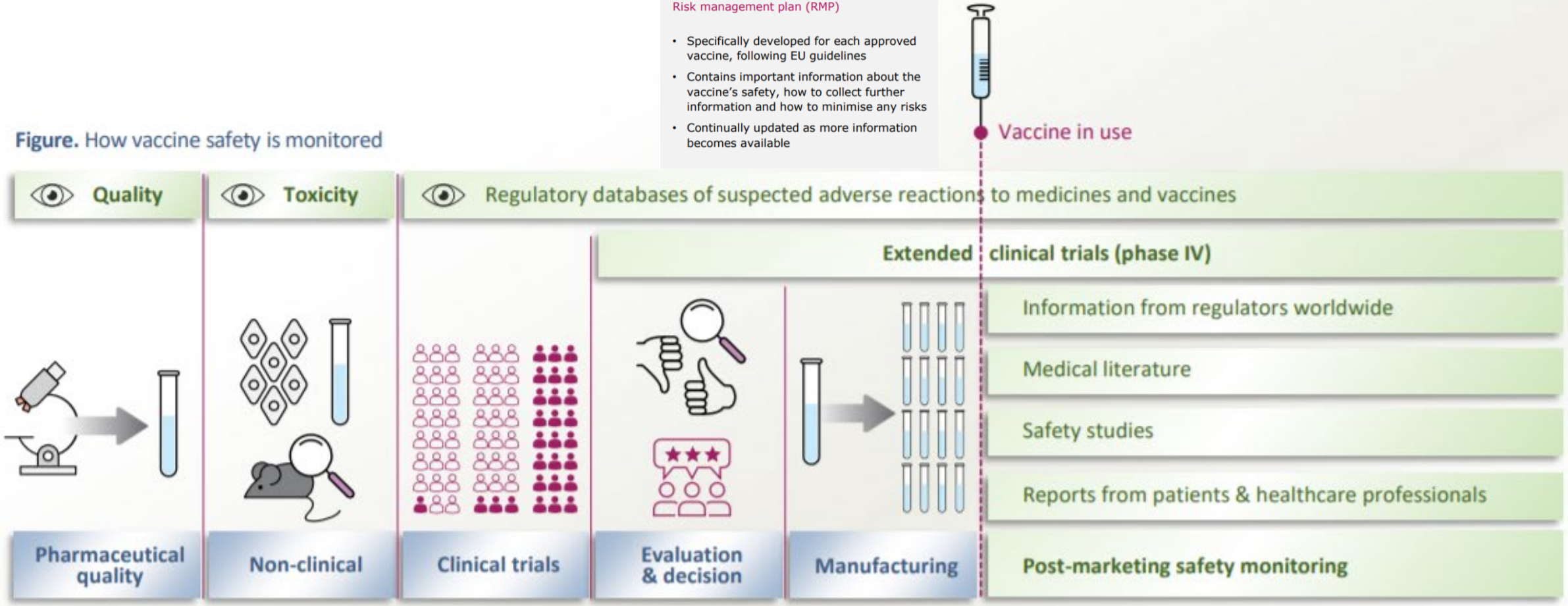
NCIRS National Centre for Immunisation Research and Surveillance Australia

# Safety studied from the first development stage through to use in the population

Risk management plan (RMP)

- Specifically developed for each approved vaccine, following EU guidelines
- Contains important information about the vaccine's safety, how to collect further information and how to minimise any risks
- Continually updated as more information becomes available

**Figure.** How vaccine safety is monitored




Source: adapted from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-development-evaluation-approval-monitoring#monitoring-vaccine-safety-and-use-in-real-life-sec

# What Is Risk Difference?

Attributable Risk

THE QUESTION

*"How much disease is actually due to the exposure?"*

DEFINITION

Risk difference is the extra risk caused by the exposure.

FORMULA

$$RD = Risk(exposed) - Risk(unexposed)$$