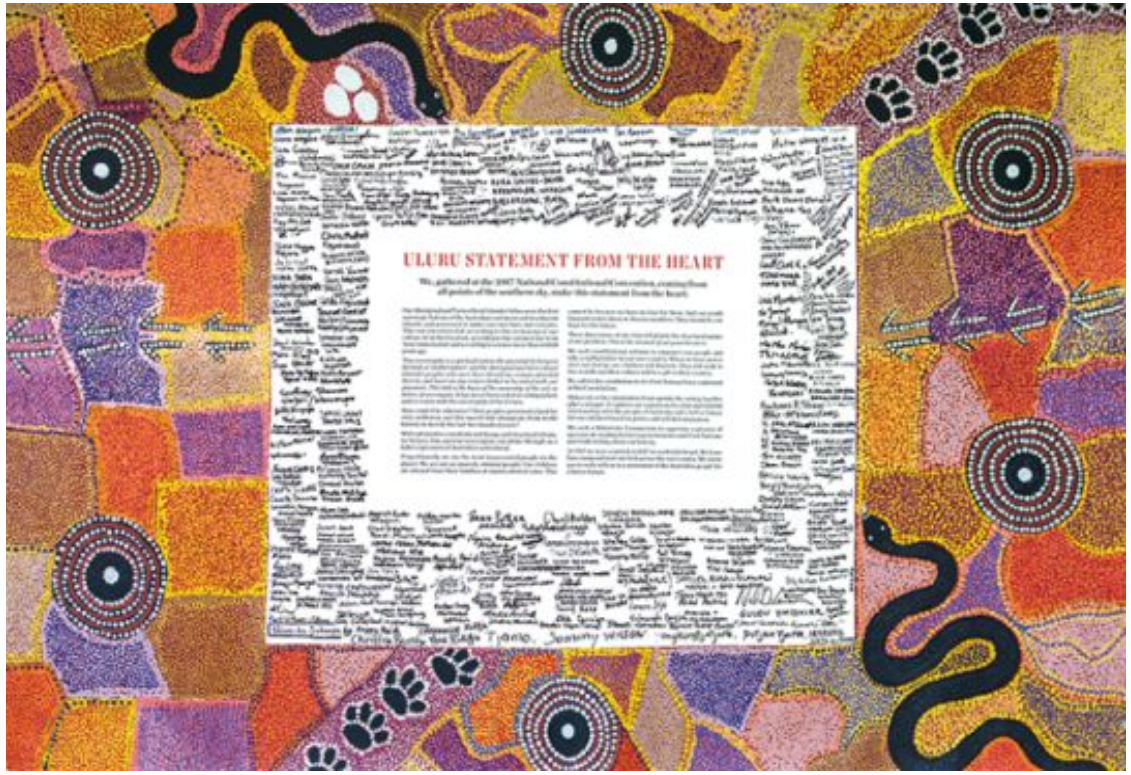
NCIRS National Centre for Immunisation Research and Surveillance

COVID-19 Vaccine Safety:

An update



Professor Kristine Macartney
Director, NCIRS

ISG Meeting Feb 2022

Overview of vaccine safety concepts

- Vaccine safety paramount
- Vaccines given to protect against disease – not treat it
- Benefits must outweigh risks

Careful surveillance continues even after a vaccine candidate has proven to be effective and has passed all safety checks. Image: Self Magazine CC-BY-2.0

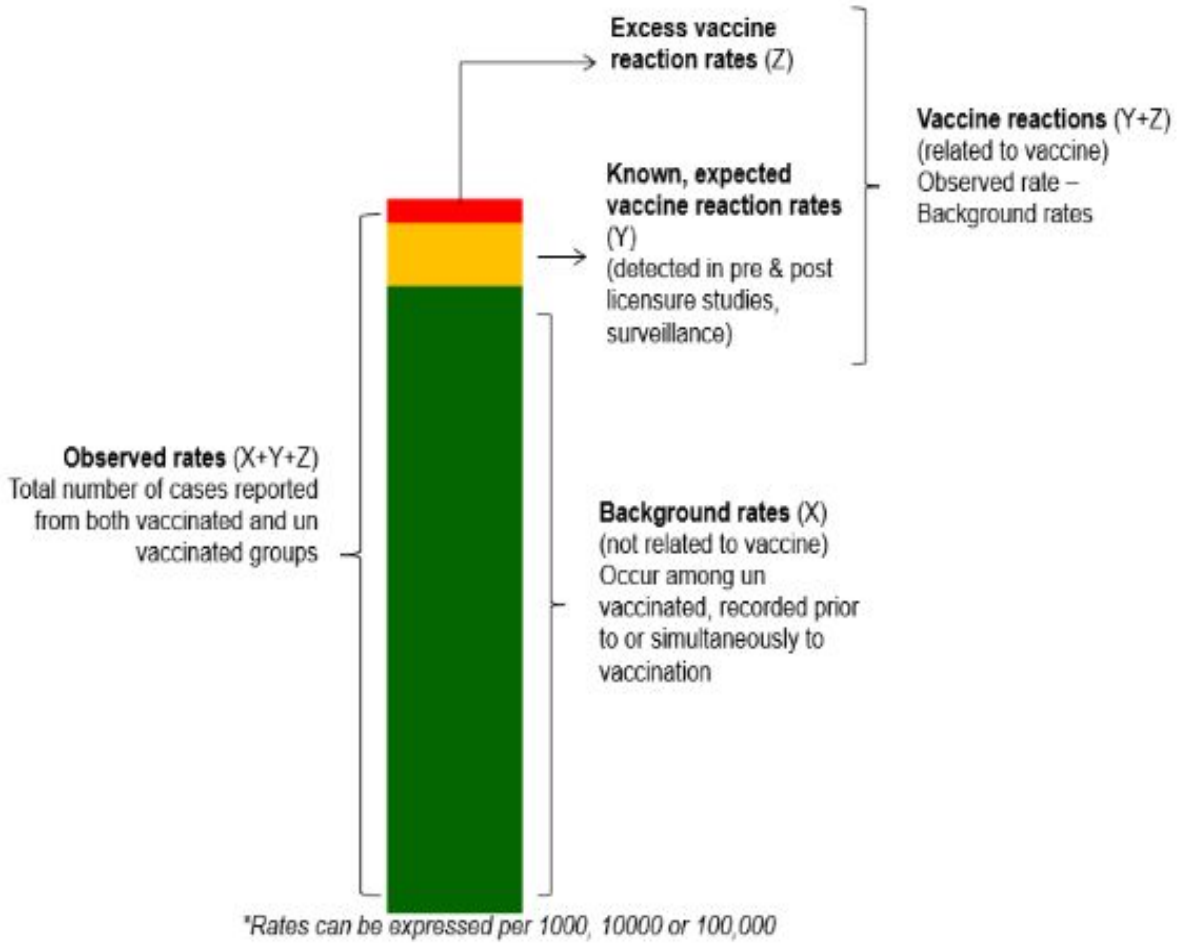
Adverse Event Following Immunisation (AEFI) Definition:

‘any untoward medical occurrence which follows immunisation and which <u>does not necessarily have a causal relationship</u> with the usage of the vaccine’

https://www.science.org.au/education/immunisation-climate-change-genetic-modification/science-immunisation/4-are-vaccines-safe

Causal versus coincidence? 5 categories of AEFI

Vaccine product related	• Febrile seizures with CSL Fluvax in 2010
Vaccine quality defect related	• Manufacturing error
Immunisation error related	• Live vaccine in immunocompromised patient
Immunisation stress related	• Fainting with vaccine in school
Coincidental	• Fall off a bike after vaccination



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

Safer vaccine design and manufacture

- Intelligent vaccine design
  - Safer, fewer antigens
  - Revolutionary science

⇧ ⇩

- Introduction of novel vaccines
  - requires alertness to the possibility of equally novel adverse effects

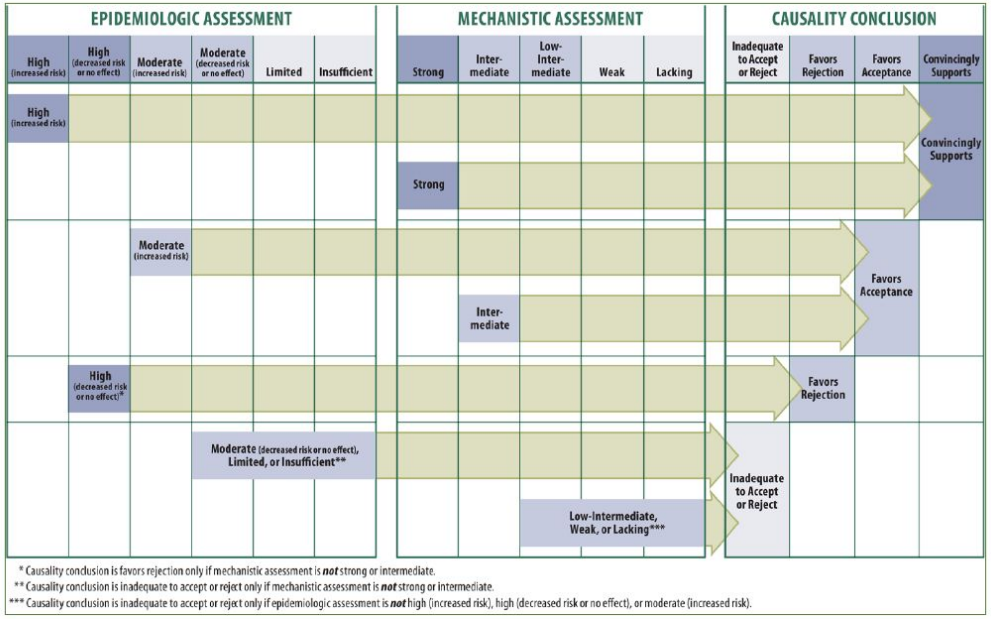
Vaccine design and manufacture is complex; high regulated

Slide courtesy of Saad Omer ADVAC presentation/Sanofi credit

Assessing causality is complex

- Very few adverse events have a unique ‘profile’ that absolutely defines them as being ‘vaccine related’ or ‘not vaccine related’

- Conditions that raise concern often don’t have known cause/trigger in absence of vaccination
  - Individual case assessment - challenging
  - Epidemiologic risk assessment - specialised

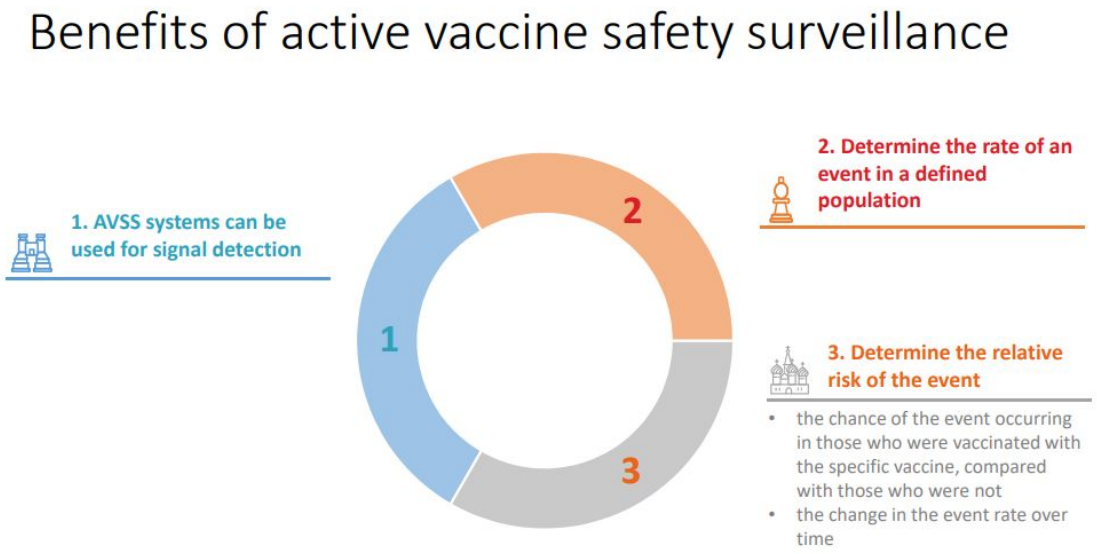


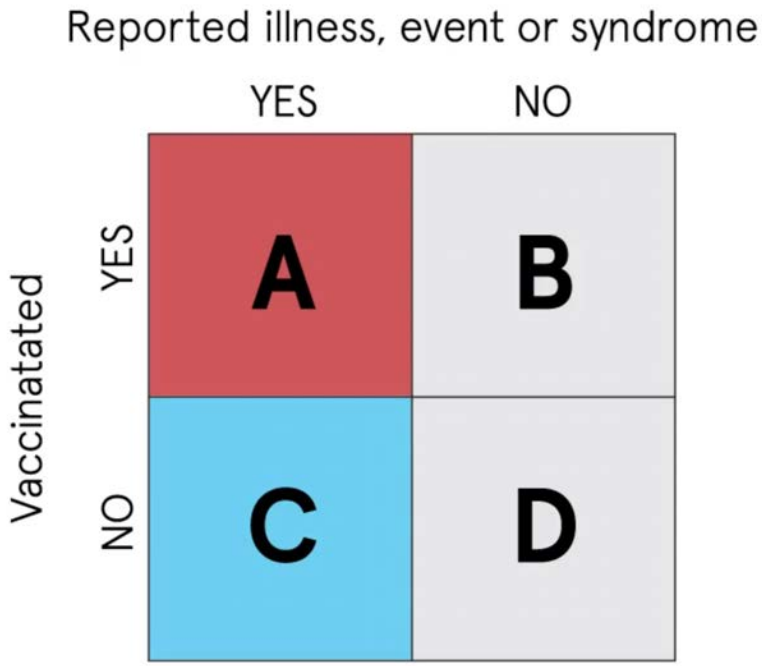
https://vaccine-safety-training.org/causality-assessment-of-aefis.html

Improving global AEFI surveillance

"A" = ~ Passive surveillance

- Relies on spontaneous report, data incomplete, quality variable
- For signal detection
- Incidence rates/vaccine attributable risk cannot be calculated





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

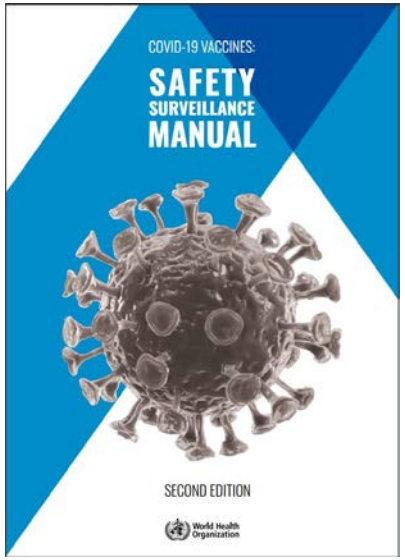
% of adverse event in unvaccinated = C/(C+D)

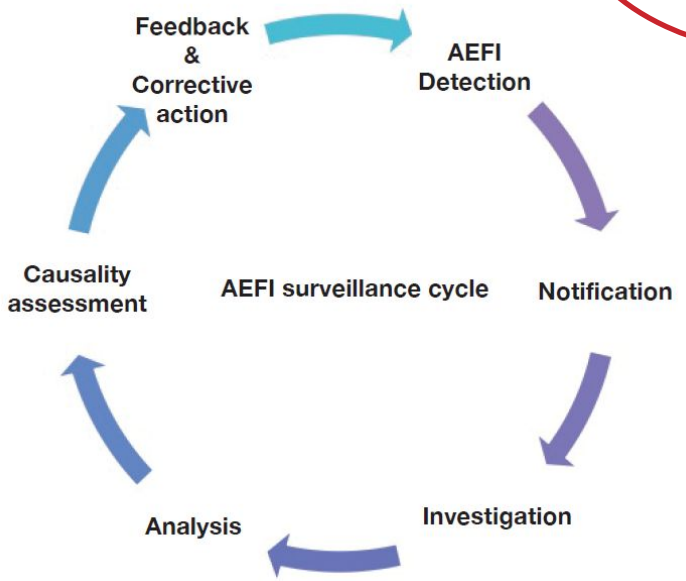
Improving global AEFI surveillance for COVID-19 vaccines

- Introduce AEFI surveillance in countries with none
- Improve AEFI surveillance in countries with limited
- Add/strengthen new modalities
  - More real-time data
  - Reporting, interpretation
  - Causality assessment
  - Monitoring AESI

Improve Program Safety

Improve Vaccine uptake





https://www.who.int/publications/i/item/10665345178

COVID-19 vaccines

Pharmaceutical Company RCTs – reactogenicity and long term follow-up

Other vaccine clinical trials

Surveillance (passive and active)

Observational/Epidemiologic studies

Adverse Events of Special Interest AESI

"pre-specified medically significant event with potential to be causally associated with a vaccine product that needs to be carefully monitored and to be confirmed by further special studies"

Extra monitoring for events that could potentially be

- serious events that have followed other immunizations (e.g. GBS, anaphylaxis)
- serious events potentially related to novel platforms
- serious events potentially related to adjuvants, serious events related to vaccine failure/immunogenicity (enhanced disease) or events that are potentially specific to special populations
- proven association with immunization
- proven association with a known vaccine platform and/or adjuvant that is being used in any COVID-19 vaccines
- theoretical concern based on immunopathogenesis of COVID-19 disease
- theoretical concern related to viral replication during COVID-19 infection; or

Table 4: List of AESI defined for COVID-19 vaccines (May 2020)

AESI	Brighton Collaboration case definition status	Link to access the definition	Recommended length of post-vaccine surveillance
Vaccine-associated enhanced disease	Case definition submitted for publication Sept 2020	Link will be provided-	1 year
Multisystem inflammatory syndrome in children	Under development and targeted for Oct 15, 2020	For all under development – they will be posted at time of submission for publication	1 year
Acute respiratory distress syndrome	Under development and targeted for Oct 15, 2020	-	1 year
Acute cardiovascular injury (microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia, myocarditis)	Under development and targeted for Nov 15, 2020	-	1 year
Coagulation disorder (thromboembolism, haemorrhage)	Under development and targeted for Nov 15, 2020	-	1 year
Acute kidney injury	Planned start in Sept and targeted completion by Nov 30, 2020	-	1 year
Generalized convulsion	Published 2004	10.1016/j.vaccine.2003.09.008	LA vaccines: 4 weeks Others: 1 week
Guillain Barré Syndrome	Published 2011	10.1016/j.vaccine.2010.06.003	4-6 weeks
Acute liver injury	Planned start in Sept and targeted completion by Nov 30, 2020	-	4-6 weeks
Anosmia, ageusia	Planned start in Sept and targeted completion by Nov 30, 2020	-	4-6 weeks
Chilblain – like lesions	Planned start Jan 2021 and targeted completion by Apr 30, 2021	-	4-6 weeks
Single organ cutaneous vasculitis	Published 2016	10.1016/j.vaccine.2016.09.032	4-6 weeks
Erythema multiforme	Planned start Jan 2021 and targeted completion by Apr 30, 2021	-	4-6 weeks
Anaphylaxis	Published 2007	10.1016/j.vaccine.2007.02.064	2 days
Acute aseptic arthritis	Published 2019	10.1016/j.vaccine.2017.08.087	
Meningoencephalitis	Published 2007	10.1016/j.vaccine.2007.04.060	LA vaccines: 4 weeks
Acute disseminated encephalomyelitis	Published 2007	10.1016/j.vaccine.2007.04.060	4-6 weeks
Thrombocytopenia	Published 2007	10.1016/j.vaccine.2007.02.067	4-6 weeks

https://www.who.int/vaccine_safety/committee/Module_AESI.pdf

Immunisation Stress Related Response

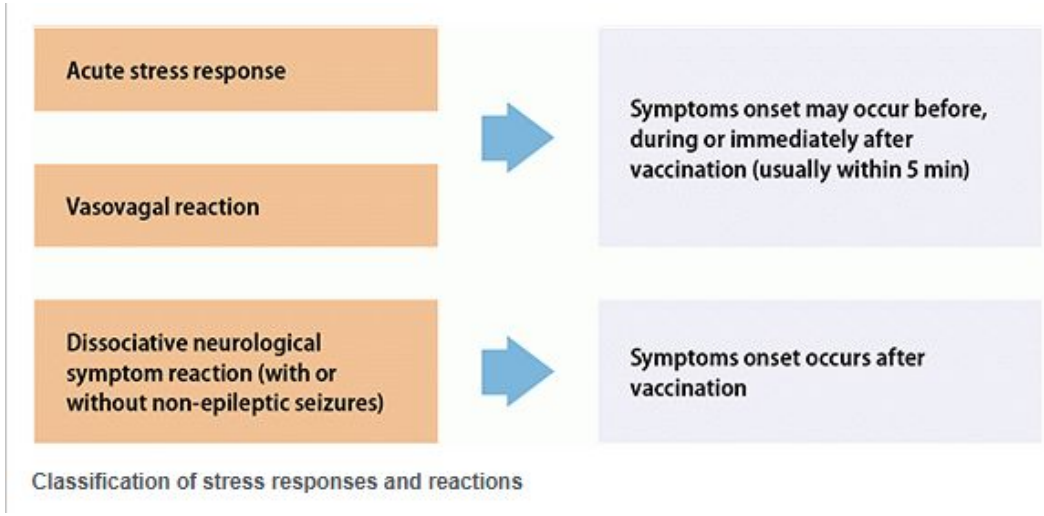
Responses before, during and after vaccine administration

Immunization is recognized as the event to which the stress response is related

Covers many different symptoms & signs that may occur

Not caused by the vaccine, a defect in its quality or an error in immunization.

- Vaccine product related
- Vaccine quality defect related
- Immunisation error related
- Immunisation stress related
- Coincidental



Classification of stress responses and reactions

2007 Victoria, Australia, School HPV program

PUBLIC HEALTH

Mass psychogenic response to human papillomavirus vaccination

Jim P Buttery, Simon Madin, Nigel W Crawford, Sonja Elia, Sophie La Vincente, Sarah Hanieh, Lindsay Smith and Bruce Bolam

https://vaccine-safety-training.org/immunization-anxiety-related-reactions.html; https://pubmed.ncbi.nlm.nih.gov/18759721/

‘Nocebo effect’ above background rates versus ‘healthy vaccine’ effect

“a negative reaction characterised by the expression of adverse symptoms largely driven by the expectation of the individual that some untoward events will occur following the administration of a drug, vaccine or other medical intervention”

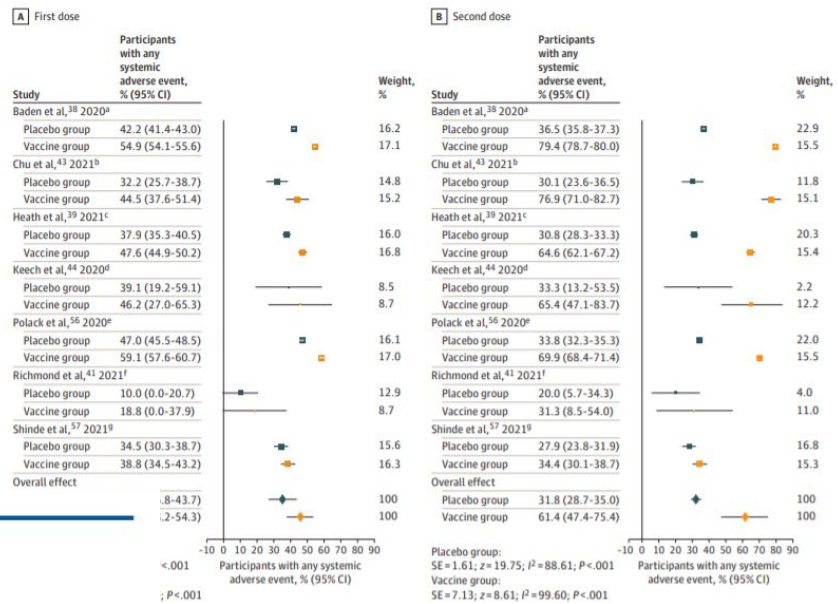
JAMA Network Open

Original Investigation | Public Health

Frequency of Adverse Events in the Placebo Arms of COVID-19 Vaccine Trials
A Systematic Review and Meta-analysis

Julia W. Haas, PhD; Friederike L. Bender, MS; Sarah Ballou, PhD; John M. Kelley, PhD; Marcel Wilhelm, PhD; Franklin G. Miller, PhD; Winfried Rief, PhD; Ted J. Kaptchuk

Figure 2. Forest Plots of Any Systemic Adverse Events After the First and Second Doses of the COVID-19 Vaccine or Placebo



Key Points

Question What was the frequency of adverse events (AEs) in the placebo groups of COVID-19 vaccine trials?

Findings In this systematic review and meta-analysis of 12 articles including AE reports for 45 380 trial participants, systemic AEs were experienced by 35% of placebo recipients after the first dose and 32% after the second. Significantly more AEs were reported in the vaccine groups, but AEs in placebo arms ("nocebo responses") accounted for 76% of systemic AEs after the first COVID-19 vaccine dose and 52% after the second dose.

Meaning This study found that the rate of nocebo responses in placebo arms of COVID-19 vaccine trials was substantial; this finding should be considered in public vaccination programs.

Nocebo affects after COVID-19 vaccination

Professor Peter Sever

National Heart and Lung Institute, Imperial College London, United Kingdom

Amanzio and colleagues are to be congratulated for their review of adverse events associated with vaccinations against corona virus-SARS-CoV-2.[1] Adverse events claimed to be caused by modern medicines be they tablets or injections, are the commonest reason given by patients for not accepting medication or for failing to adhere to prescribed drugs.

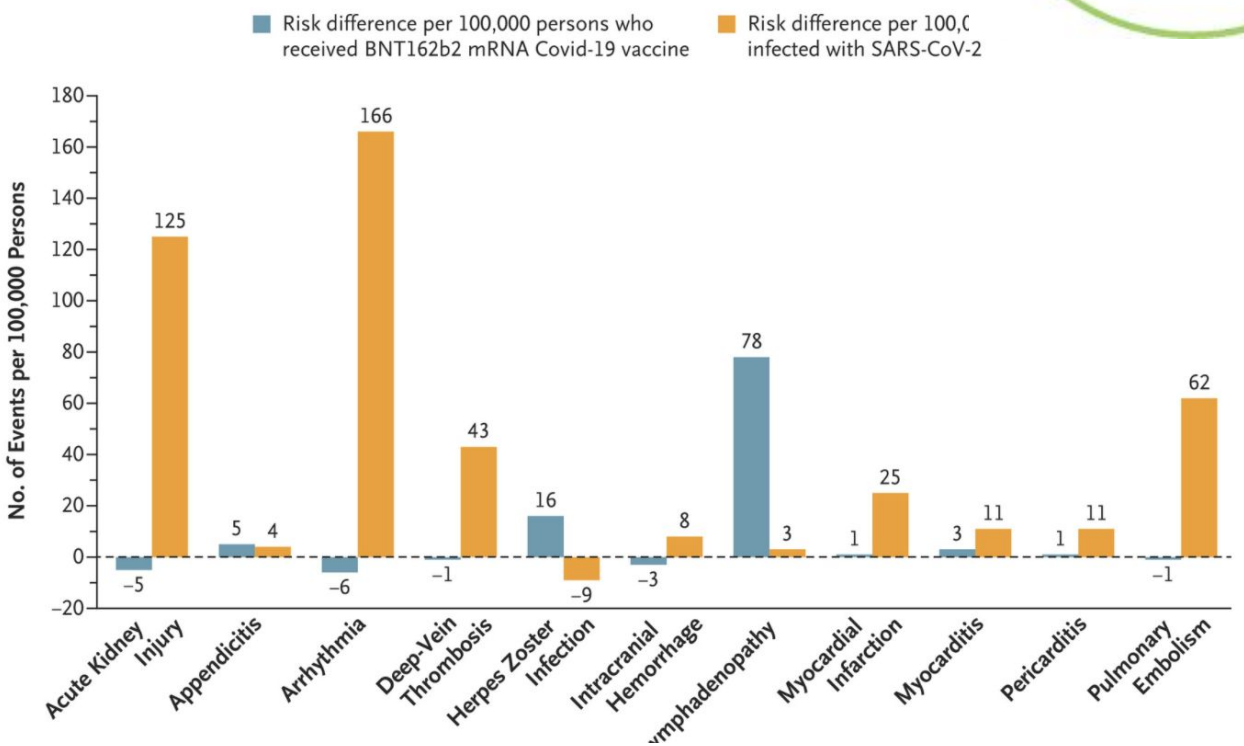
individual that some untoward events will occur following the administration of a drug, vaccine or other medical intervention.[2]

The phenomenon has been highlighted recently in relation to statin treatment where the majority of adverse events have been demonstrated not to be due to the statin but to the anticipation of adverse

The Lancet Regional Health - Europe 2022;12: 100273
Published online 29 November 2021
https://doi.org/10.1016/j.lanepe.2021.100273

COVID-19 vaccines: Thrombosis Thrombocytopenia Syndrome (TTS)

COVID-19 vaccines: Myocarditis and Pericarditis



Medium exposure risk in the Australian context

Scenario 2: Infection rate similar to second wave of COVID-19 in Victoria (275 infections per 100,000 people in a 16-week period)

For every 100,000 AstraZeneca vaccinations

Age	Potential harms (Australian data as at 16 June 2021)	Potential benefits
18–29	1.9 blood clots (TTS)[a]	0.1 deaths prevented 1.3 ICU admissions prevented 10.6 hospitalisations prevented
30–39	1.6 blood clots (TTS)[a]	0.2 deaths prevented 1.2 ICU admissions prevented 10.7 hospitalisations prevented
40–49	5.0 blood clots (TTS)[a]	0.1 deaths prevented 2.6 ICU admissions prevented 16.7 hospitalisations prevented
50–59	2.7 blood clots (TTS)	1.3 deaths prevented 6.6 ICU admissions prevented 24.3 hospitalisations prevented
60–69	1.4 blood clots (TTS)	3.0 deaths prevented 7.0 ICU admissions prevented 30.4 hospitalisations prevented
70–79	1.8 blood clots (TTS)	21.4 deaths prevented 8.6 ICU admissions prevented 63.1 hospitalisations prevented
80+	1.9 blood clots (TTS)	183.6 deaths prevented 5.2 ICU admissions prevented 260.5 hospitalisations prevented

TTS = thrombosis with thrombocytopenia syndrome. Includes probable and confirmed cases, and a range of health care presentations (including hospitalisations, ICU admissions and deaths).

a Estimates of risk are uncertain as rates are based on small numbers of vaccinations in people under 50 in Australia

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

Myocarditis

- Rare and usually mild, shortly after mRNA vaccine dose
- Rates highest post dose 2 in teen/young males; Moderna ~2-fold > Pfizer
- Rate post 3rd/booster dose appears lower than after 2nd dose (Israel, Australia, USA)
- Very few cases in children age 5-11 years (USA ~ 2 per million doses to date)

Australian (TGA) reported rate 27 Jan 2022

Pfizer

Table 2. Rates of likely myocarditis cases following the mRNA vaccines. A. Comirnaty (Pfizer)

Age (years)	All doses		Second doses	
	Rate* per 100,000 doses		Rate* per 100,000 doses	
	Male	Female	Male	Female‡
12-17	6.8	1.5	11.1	2.5
18-29	3.9	1.2	6.0	1.8
30-39	1.6	0.6	1.6	0.5
40-49	0.7	0.6	0.9	0.8
50-59	0.4	0.3	0.1	0.3
60-69	0.1	0.2	0.0	0.0
70+	0	0.1	0.0	0.0
All ages*	**2.1**	**0.6**	**3.1**	**1.0**

Moderna

B.Spikevax (Moderna)

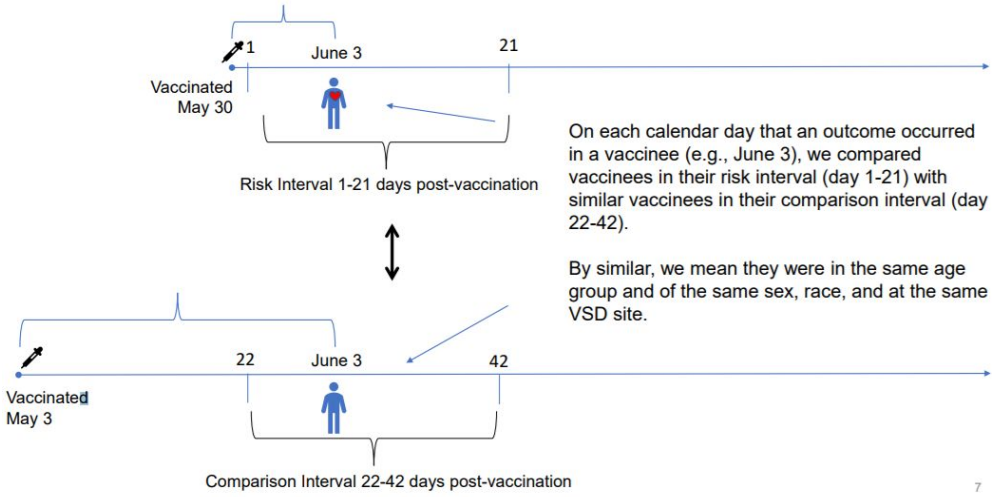
Age (years)	All doses		Second doses	
	Rate* per 100,000 doses		Rate* per 100,000 doses	
	Male	Female	Male	Female‡
12-17	8.6	2.0	15.6	2.8
18-29	6.2	0.5	12.2	0.0
30-39	3.4	0.5	5.6	0.0
40-49	1.0	0.5	0.0	0.0
50-59	0.5	0.9	0.0	0.0
60-69	0.0	0.0	0.0	0.0
70+	0.0	0.0	0.0	0.0
All ages*	**3.6**	**0.8**	**7.1**	**0.5**

COVID-19 vaccine weekly safety report | Therapeutic Goods Administration (TGA)

https://www.tga.gov.au/periodic/covid-19-vaccine-weekly-safety-report-27-01-2022

US Vaccine Safety Datalink: Detailed linked data analysis

Vaccinee with Myocarditis in Risk Interval and a Concurrent Comparator



On each calendar day that an outcome occurred in a vaccinee (e.g., June 3), we compared vaccinees in their risk interval (day 1-21) with similar vaccinees in their comparison interval (day 22-42).

By similar, we mean they were in the same age group and of the same sex, race, and at the same VSD site.

Validated Myocarditis/Pericarditis, among 12–17-Year-Olds in the 0-7 and 0-21 Day Risk Interval after Pfizer Vaccine by Dose

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

				Analysis			
Risk Interval	Dose	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1 Million Doses
Days 0-21	**Both Doses**	45	3	**10.16**	**3.41 – 42.39**	**<0.001**	**36.2**
	Dose 1	3	3	1.16	0.17 – 8.05	0.873	0.7
	Dose 2	39	3	**15.21**	**5.07 – 63.70**	**<0.001**	**70.8**
Days 0-7	**Both Doses**	41	3	**29.63**	**9.76 – 125.24**	**<0.001**	**34.6**
	Dose 1	1	3	1.25	0.04 – 13.93	0.836	0.3
	Dose 2	37	3	**46.18**	**15.07 – 196.40**	**<0.001**	**70.2**

Post dose 2 = 1 in 14,000

[1]**Comparison interval** is 22–42 days after either dose.
[2]**Adjusted** for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.

Follow-Up Information on Validated Myocarditis/Pericarditis Cases Aged 12-17 Years (N=24)*

Status at Time of Most Recent Follow-Up Visit	No. (%)
Current Status (not mutually exclusive)	
Recovered: no symptoms, medication, or exercise restrictions	11 (46%)
Still symptomatic	7 (29%)
Still on medication (e.g., NSAIDs, colchicine)	2 (8%)
Still on exercise/physical activity restrictions	6 (25%)

Myocarditis in Children 5-11 years

- In the VSD, there have been no safety signals among 5–11-year-olds (430K doses analysis point)
- In VAERS in children 5-11 years, 12 validated cases after 8.6 million doses (9 post dose 2)

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-01-05/04-COVID-Klein-508.pdf

We expect less vaccine associated myocarditis in younger ages

Background myocarditis age distribution (cases, hospitalisation)

Australian Government

COVID-19 VACCINATION

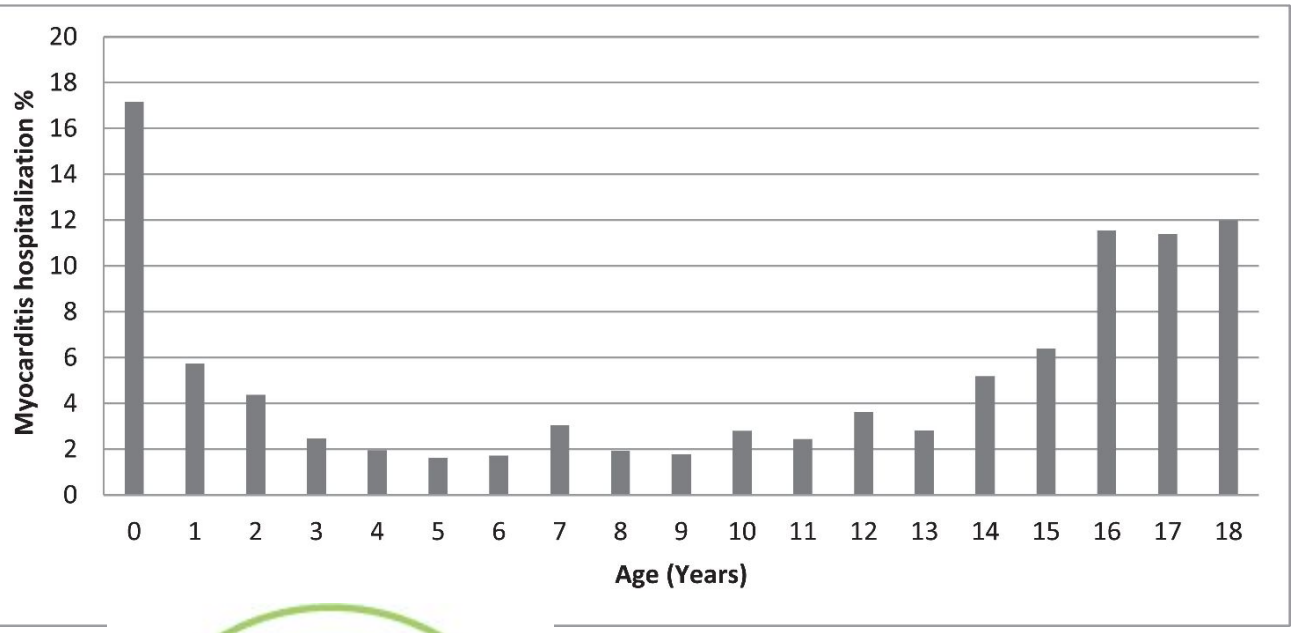
Guidance on Myocarditis and Pericarditis after mRNA COVID-19 Vaccines

The following guidance has been developed jointly by the Australian Technical Advisory Group on Immunisation (ATAGI), the Cardiac Society of Australia and New Zealand (CSANZ), the Royal Australian College of General Practitioners (RACGP), the Australian College of Rural and Remote Medicine (ACRRM), the Australasian College for Emergency Medicine (ACEM) and the Paediatric Research in Emergency Departments International Collaborative (PREDICT).

Updated 8 November 2021

What has been updated:

- Minor changes to **Figure 2:** Approach to revaccination in people with pericarditis attributed to an mRNA COVID-19 vaccine



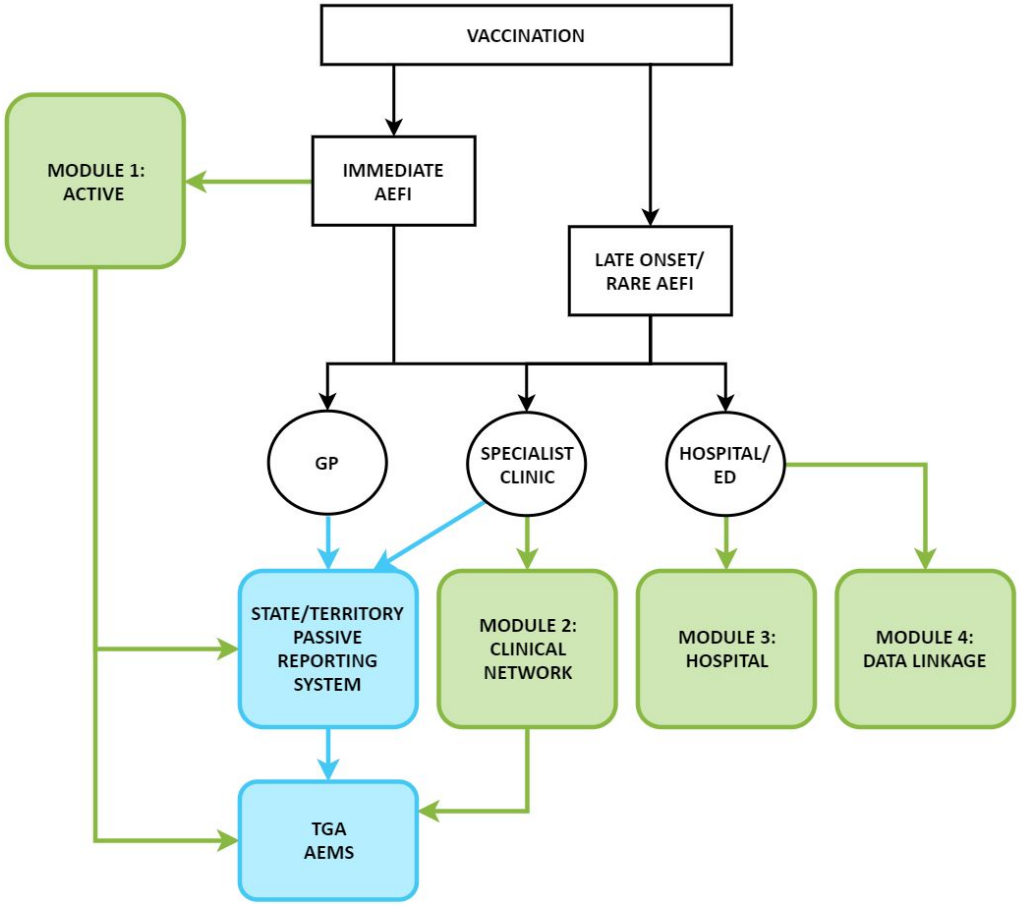
RISK of PIMS TS (post COVID-19 Inflammatory Syndrome) in NSW Children in Delta wave 2021
1 in 3000
(Williams P et al, Preprint)

AusVaxSafety
An NCIRS led collaboration

Active, enhanced, national vaccine safety surveillance

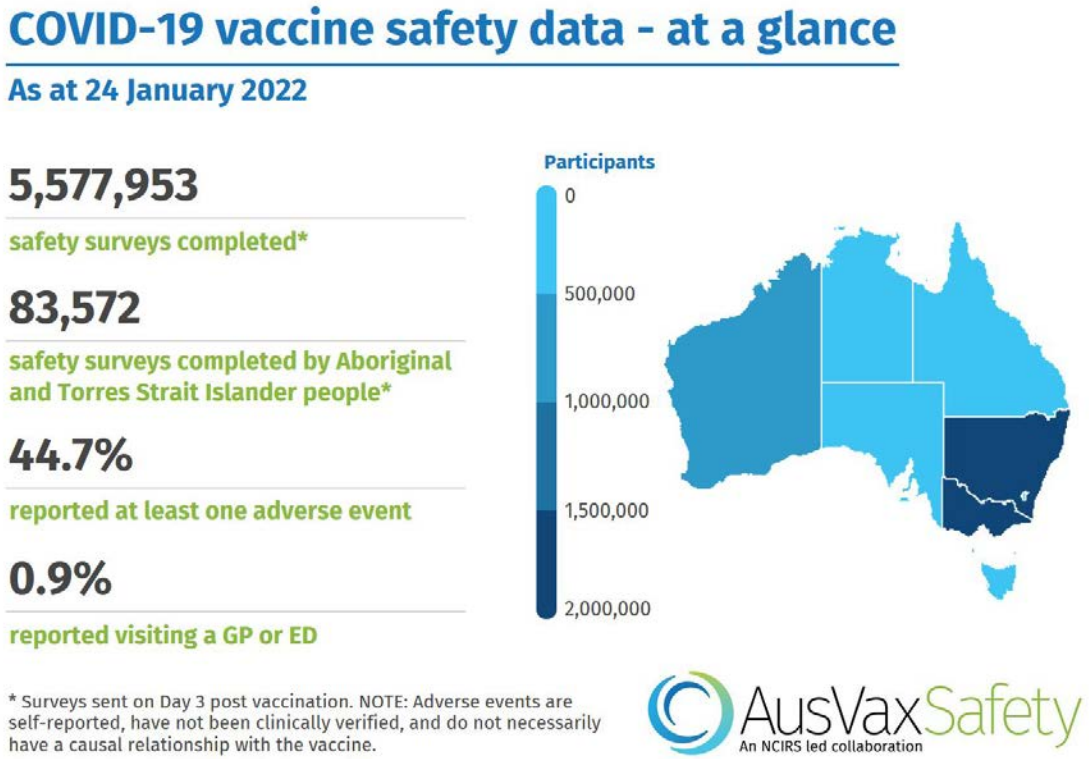
February 2022

AusVaxSafety Modules



Module	Role
1. Active	Cohort event monitoring of short term AEFIs using SMS/email
2. AEFI Clinical Assessment Network	AEFI case discussions for nationally consistent approach to complex cases
3. AESI Program of Research	Long term clinical follow up of patients with adverse events of special interest with States, Territories TGA and specialist groups • TTS • myocarditis
4. Linked data	Risk/Association studies using linked data

Active surveillance



COVID-19 vaccine safety data are published weekly and include:

- All participants
- Aboriginal and Torres Strait Island participants
- Children aged 5-11 years
- Adolescents aged 12-19 years
- Pregnant participants
- People affected by cancer

www.ausvaxsafety.org.au

Active surveillance – public data

Pfizer - all participants

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

37% Pfizer dose 1

53% Pfizer dose 2

52% Pfizer dose 3 / booster

Medical attendance

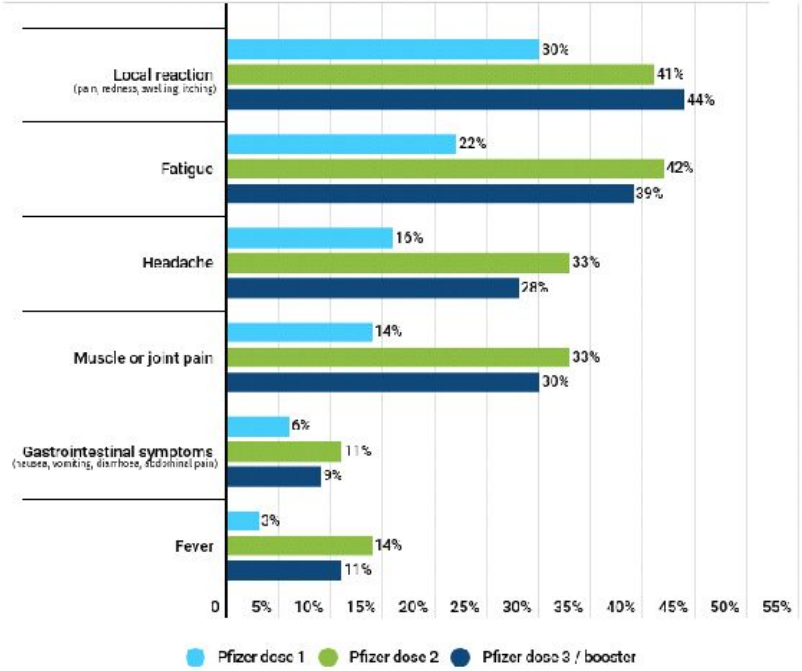
Less than 1 in 100 people reported seeing a doctor or going to the emergency department in the days after Pfizer dose 1

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

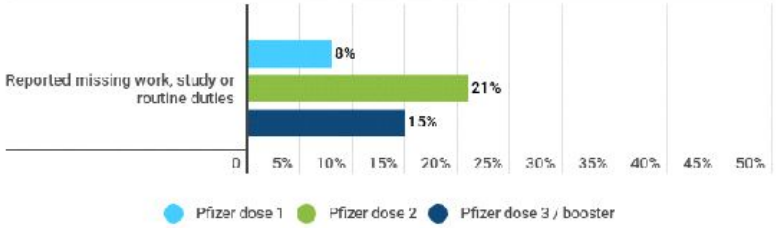
Less than 1 in 100 people reported seeing a doctor or going to the emergency department in the days after Pfizer dose 3 / booster

Data as at 16 January 2022

Commonly reported adverse events



Impact on routine activities



Pfizer - children aged 5-11

Data as at 16 January 2022

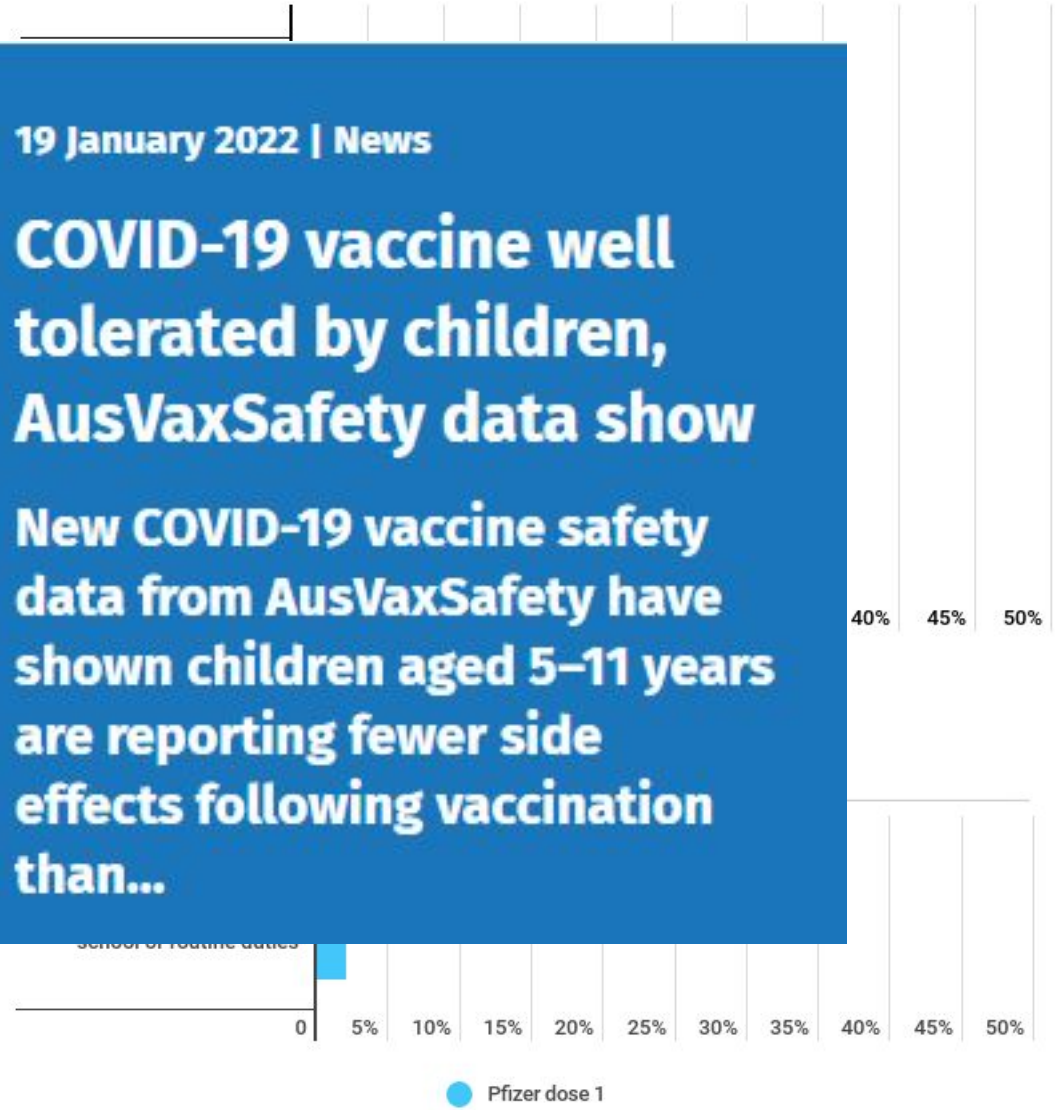
Safety surveys completed

Reported at l

Medical atter

Less than 1 in 10
the days after Pfi

Commonly reported adverse events



19 January 2022 | News

COVID-19 vaccine well tolerated by children, AusVaxSafety data show

New COVID-19 vaccine safety data from AusVaxSafety have shown children aged 5–11 years are reporting fewer side effects following vaccination than...

Australia's active vaccine safety system

AusVaxSafety
An NCIRS led collaboration

Pfizer - all participants

Data as at 16 January 2022

Safety surveys completed

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1,863,825 Pfizer dose 2

399,713 Pfizer dose 3 / booster

Reported at least one adverse event

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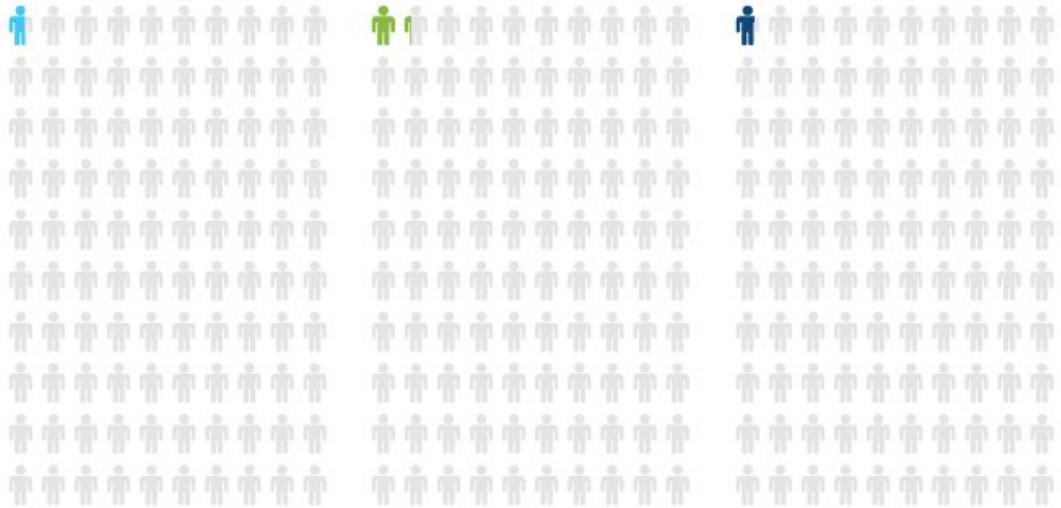
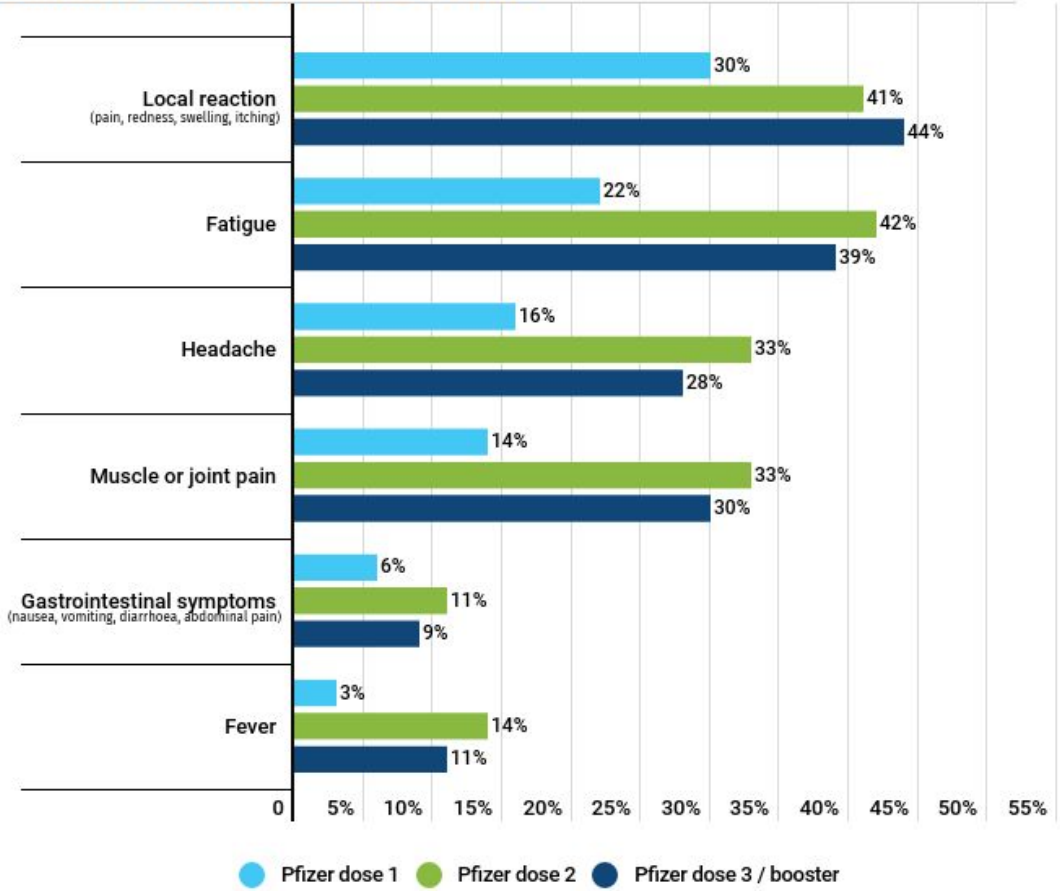
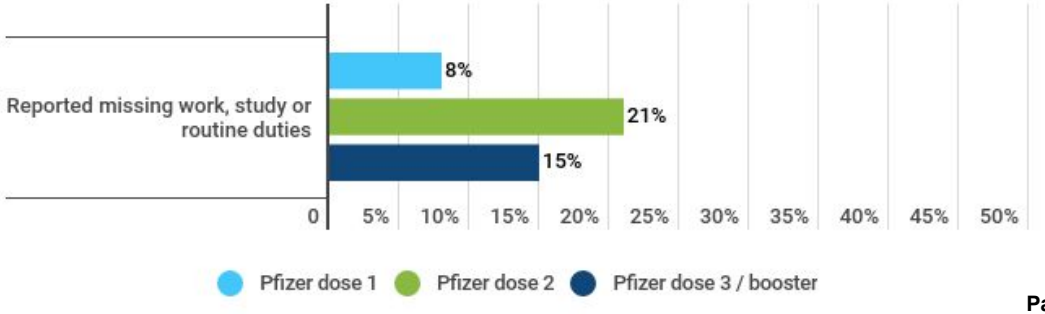


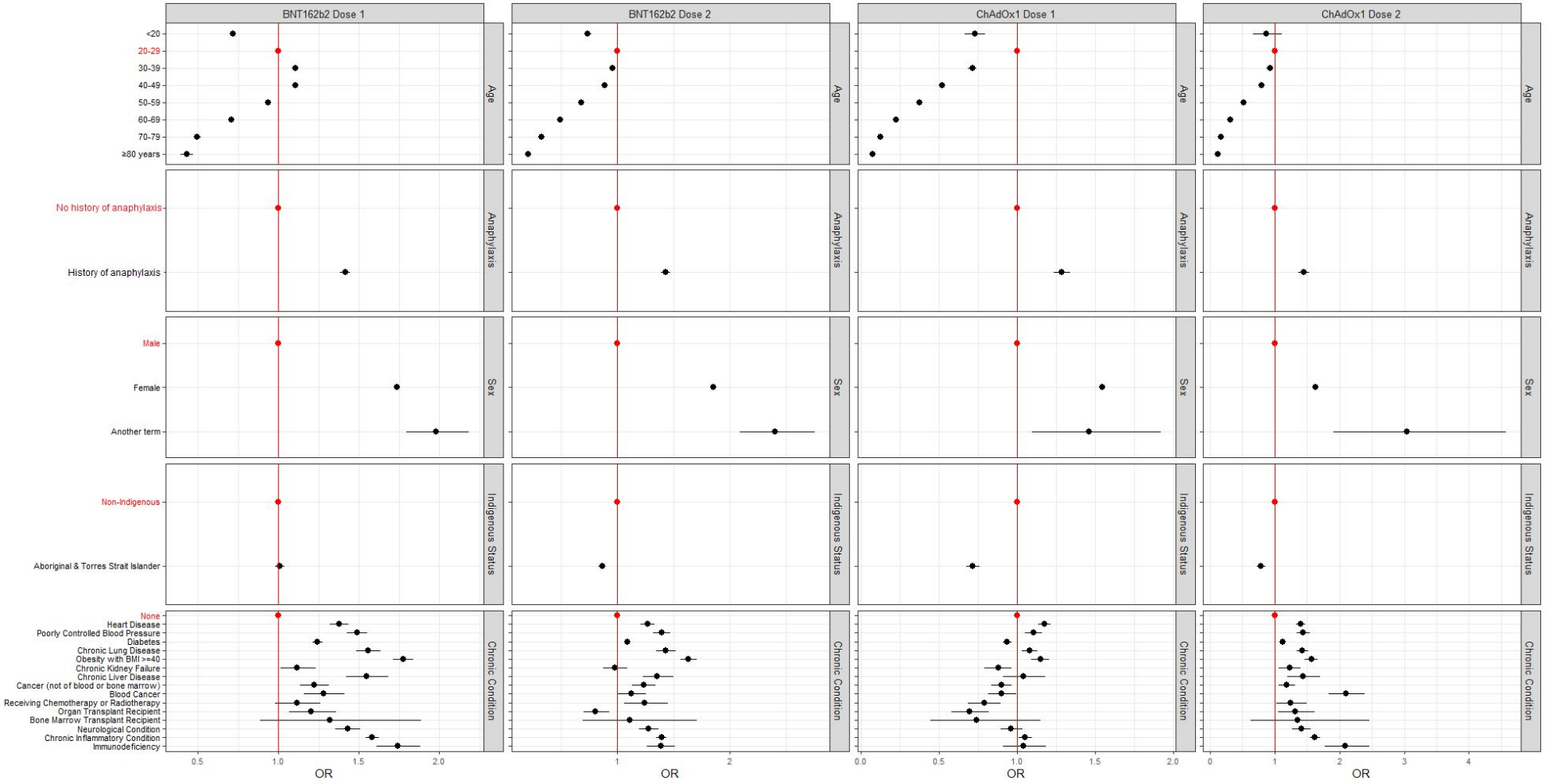
Commonly reported adverse events



Impact on routine activities

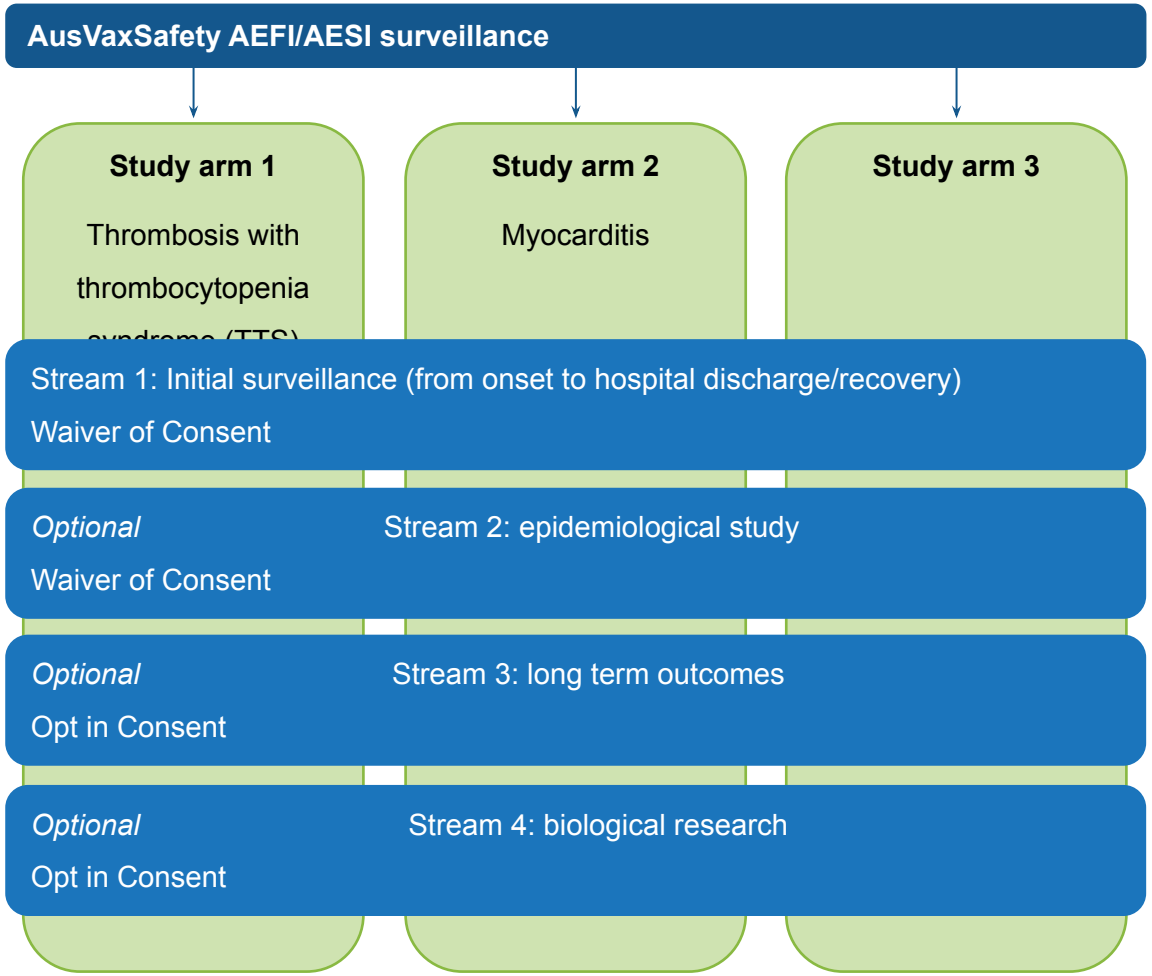


Active surveillance – detailed analyses



Risk of any adverse event following immunisation (AEFI) with Comirnaty and Vaxzevria vaccines by respondent demographics, history of anaphylaxis or other medical conditions (manuscript under review)

AESI Program of Research

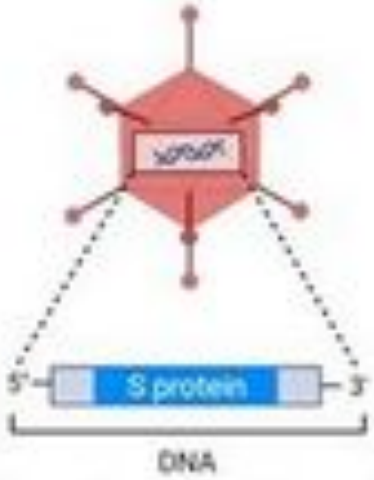


- Collaboration with TGA, S/T and specialist groups (THANZ, CSANZ)
- Data collection and recruitment in progress for TTS and myocarditis

New vaccines, populations and schedules

NOVAVAX COVID-19 Vaccine:
A protein nanoparticle vaccine co-formulated with a saponin-based Matrix-M adjuvant. The antigenic component is based on the full-length, wild-type SARS-CoV-2 rS glycoprotein; modified by mutation at the putative furin cleavage site to be protease resistant. Two additional proline amino acid substitutions inserted to stabilise the S protein in a prefusion conformation, which is believed to optimise presentation of neutralising epitopes.

Vaccine: University of Oxford/ AstraZeneca



Platform: Adenovirus with gene for the SARS-CoV-2 spike (S) protein

BioNTech/Pfizer

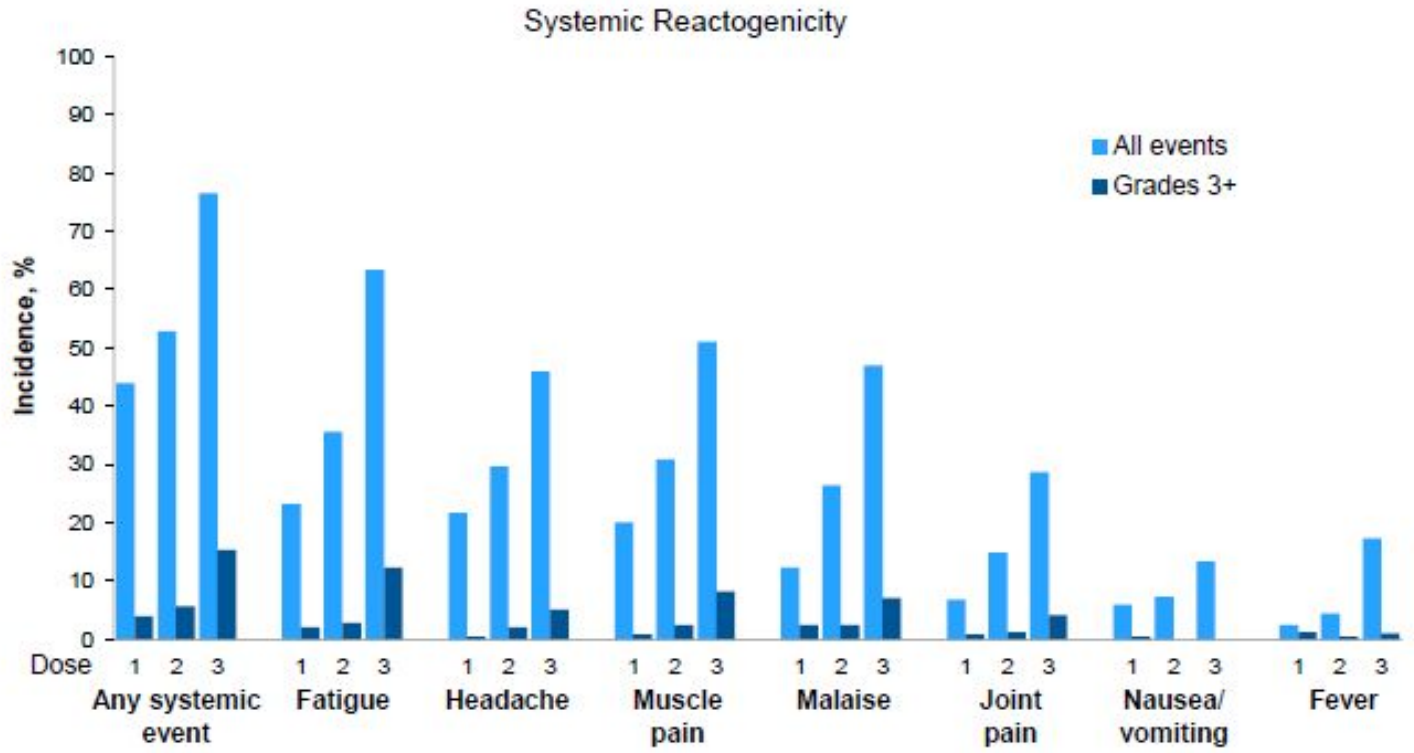
Platform: lipid nanoparticle-encapsulated mRNA vaccines encoding Spike protein

Novavax

Platform: Synthetic nanoparticle coated with trimer spike protein. Matrix M used an immune-boosting adjuvant

Novavax – Reactogenicity (Systemic) post doses 1-3

- Increased events across all 3 doses, local and systemic reactions short-lived
- Overall medically attended AEs - related events reported in few participants (1.9%, 0%, and 1.2%, respectively)



Timing of potential registration as booster dose, not yet known

Use now:

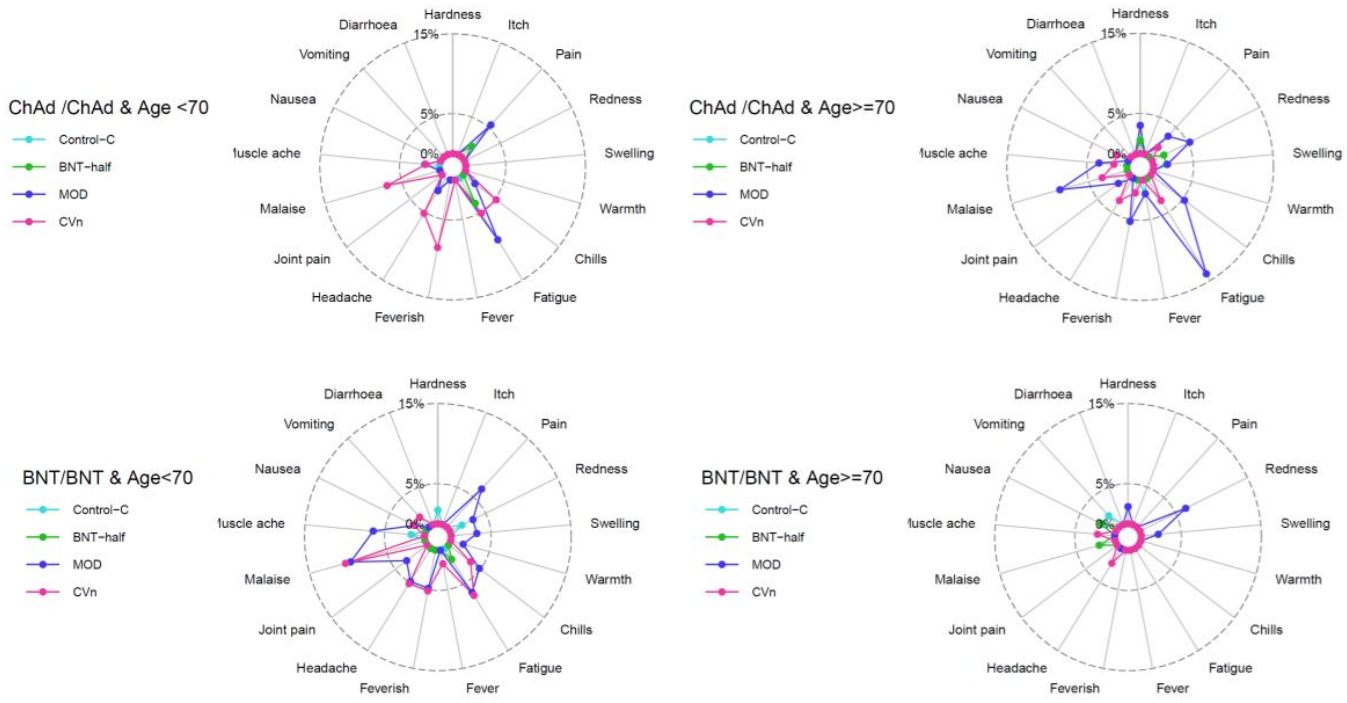
- Unvaccinated
- contraindications or reluctant to receive same brand as previous primary dose

Mallory et al. (25 Dec 2021). Immunogenicity and Safety Following a Homologous Booster Dose of a SARS-CoV-2 recombinant spike protein vaccine (NVX-CoV2373): A Phase 2 Randomized Placebo-Controlled Trial. *Preprint*. DOI: 10.1101/2021.12.23.21267374
https://www.medrxiv.org/content/10.1101/2021.12.23.21267374v1

UK COV-Boost Study

- 7 different booster vaccines after 2 dose AZ or Pfizer primary vaccination
- Immunogenicity and safety data

Supplementary Figure 2.C1 Group C severe



Munro et al, Lancet 2021
https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2902717-3

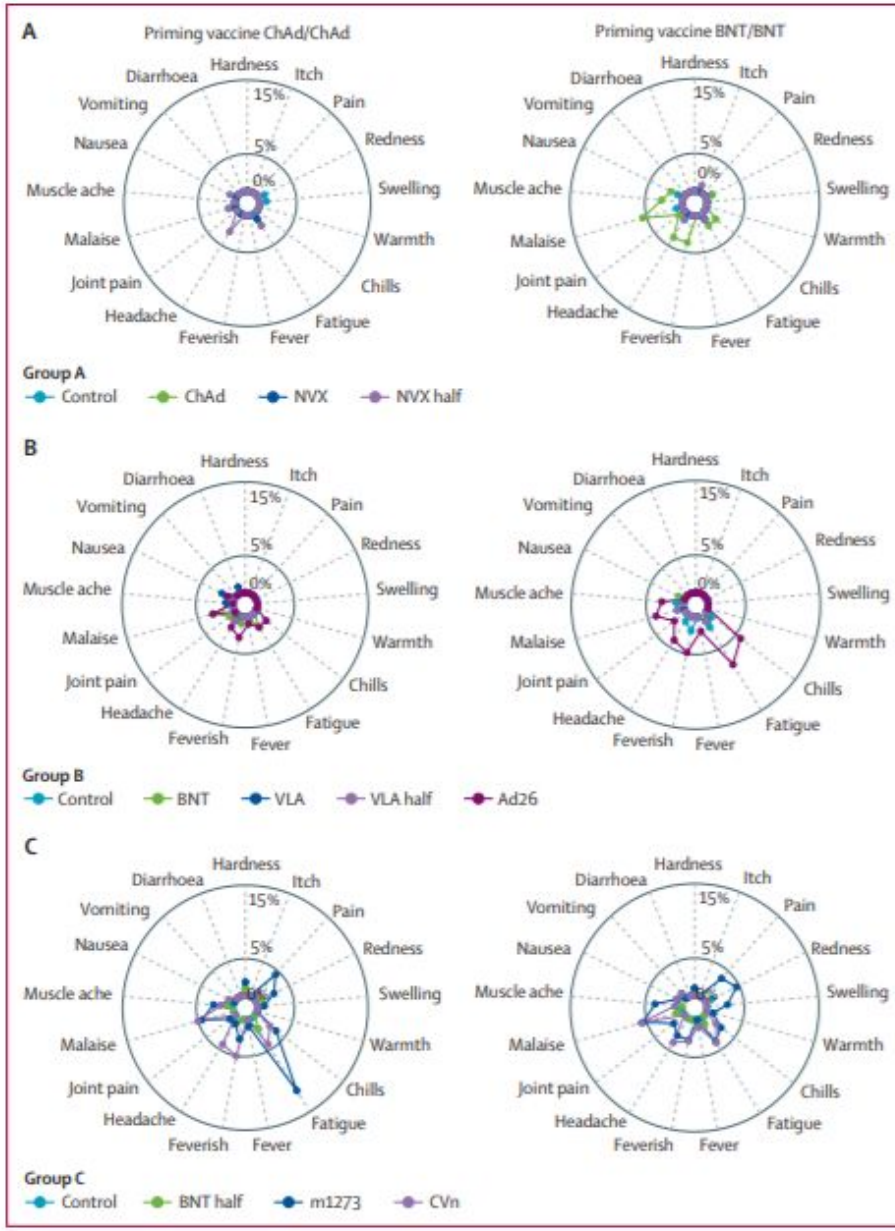


Figure 2: **Radial graph for the occurrence of severe local and solicited adverse events in the first 7 days post vaccination in groups A, B, and C**
Control=quadrivalent meningococcal conjugate vaccine. ChAd=ChAdOx1 nCoV-19 vaccine, Oxford–AstraZeneca. NVX=NVX-CoV2373 vaccine, Novavax. NVX half=half dose of NVX-CoV2373 vaccine. BNT=BNT162b2 vaccine, Pfizer–BioNTech. VLA=VLA2001 vaccine, Valneva. VLA half=half dose of VLA2001 vaccine. Ad26=Ad26.COV2.S vaccine, Janssen. m1273=mRNA1273 vaccine, Moderna. CVn=CVnCoV vaccine, Curevac.

Summary of risks conditions – with risk demonstrated

- **Anaphylaxis after COVID-19 vaccination is rare** and has occurred in approximately 5 people per one million
- **Guillain-Barré Syndrome (GBS)** signal after viral vector COVID-19 vaccines – very rare
- NEW **Thrombosis with thrombocytopenia syndrome (TTS)** after viral vector COVID-19 vaccination is rare
- **Idiopathic thrombocytopenic purpura (ITP) and** AZ vaccine adjusted rate ratio (aRR) = 5.77, 95% CI 2.41–13.83), estimated incidence of 1.13 (0.62–1.63) cases per 100,000 doses

Simpson et al Nature 2021 https://www.nature.com/articles/s41591-021-01408-4

Additional Reading

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The future of vaccine safety

EDITORIAL

Vaccine safety: looking forward and back (19 May, 2021)
Alexander Muir Walker, Walter A Orenstein

ANALYSIS

Vaccine safety issues at the turn of the 21st century (19 May, 2021)
Laura Conklin, Anders Hviid, Walter A Orenstein, Andrew J Pollard, Melinda Wharton, Patrick Zuber

Novel vaccine safety issues and areas that would benefit from further research (19 May, 2021)
Daniel A Salmon, Paul Henri Lambert, Hanna M Nohynek, Julianne Gee, Umesh D Parashar, Jacqueline E Tate, Annelies Wilder-Smith, Kenneth Y Hartigan-Go, Peter G Smith, Patrick Louis F Zuber

Evolving pharmacovigilance requirements with novel vaccines and vaccine components (19 May, 2021)
Patrick L F Zuber, Marion Gruber, David C Kaslow, Robert T Chen, Brigitte K Giersing, Martin H Friede

Methodological frontiers in vaccine safety: qualifying available evidence for rare events, use of distributed data networks to monitor vaccine safety issues, and monitoring the safety of pregnancy interventions (19 May, 2021)
Caitlin Dodd, Nick Andrews, Helen Petousis-Harris, Miriam Sturkenboom, Saad B Omer, Steven Black

Vaccine safety in the next decade: why we need new modes of trust building (19 May, 2021)
Heidi J. Larson, Isabelle Sahinovic, Madhava Ram Balakrishnan, Clarissa Simas

https://gh.bmj.com/content/6/Suppl_2; Lo Re et al 2021: https://www.bmj.com/content/373/bmj.n1416

"Some vaccine safety issues of the 20th century involved genuine and causal, through rare, severe adverse events, such as vaccine-associated poliomyelitis.

More frequently, the concerns that focused public interest were ill founded, with scientific evidence not supporting any harmful role for vaccines"


ANALYSIS

Global covid-19 vaccine rollout and safety surveillance—how to keep pace

An agile internationally harmonised surveillance system is essential to maintain safety and trust in vaccines, argue **Vincent Lo Re and colleagues**

Vincent Lo Re,[1] Olaf H Klungel,[2] K Arnold Chan,[3] Catherine A Panozzo,[4] Wei Zhou,[5] Almut G Winterstein[6]

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