Signal Detection Methods for COVID-19 Vaccine Safety Surveillance

Michael Dymock

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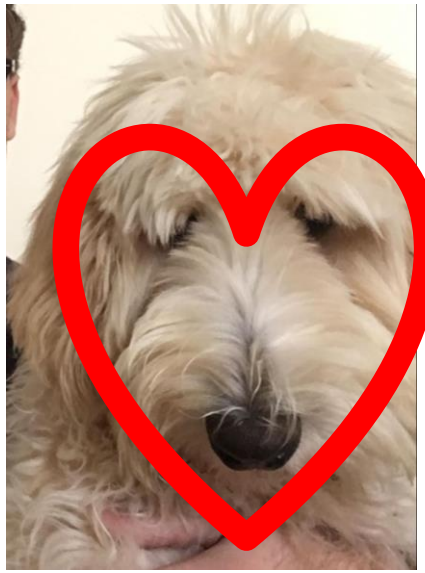
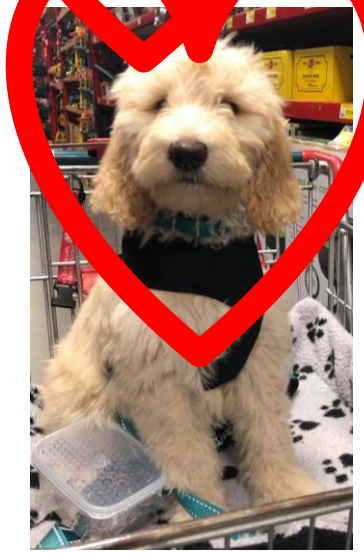
WESFARMERS CENTRE OF VACCINES & INFECTIOUS DISEASES

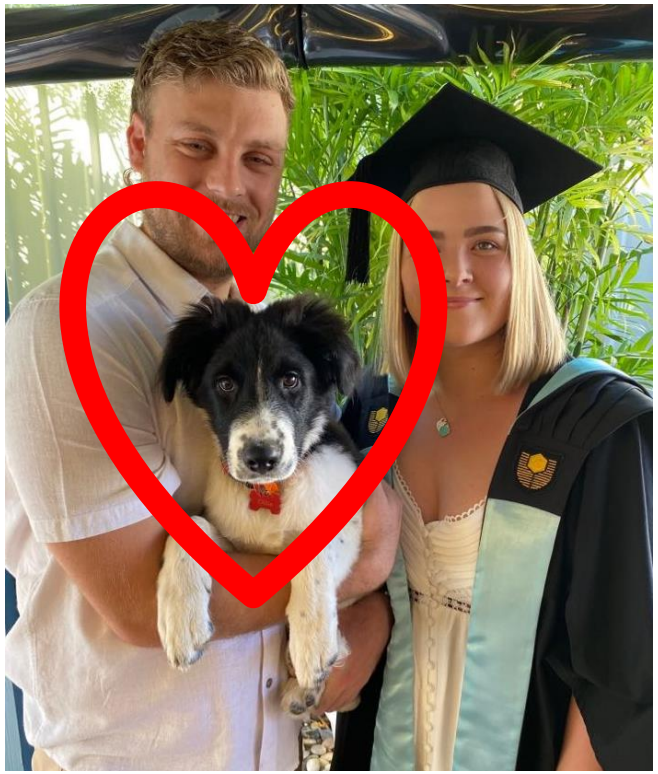
15st March 2021

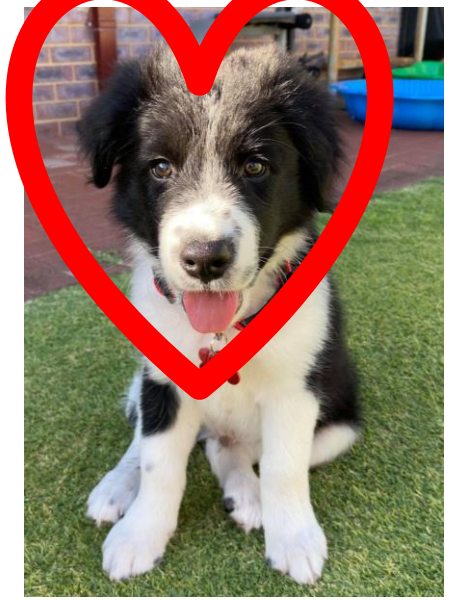
Proudly supported by the people of Western Australia through Channel 7's Telethon

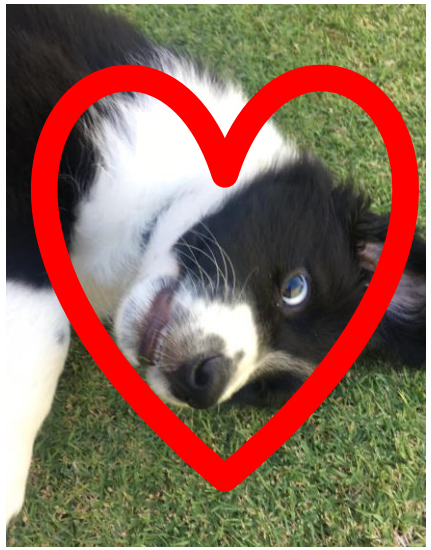
Who am I?

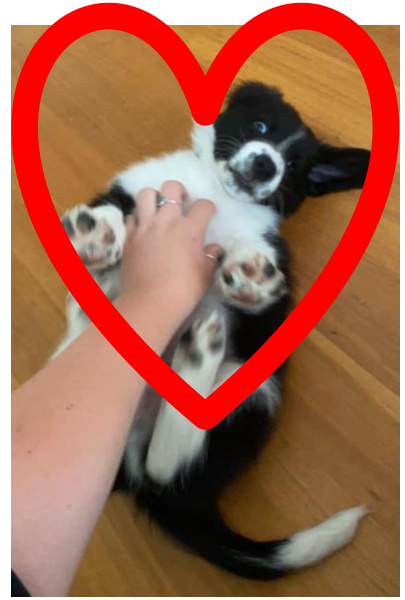












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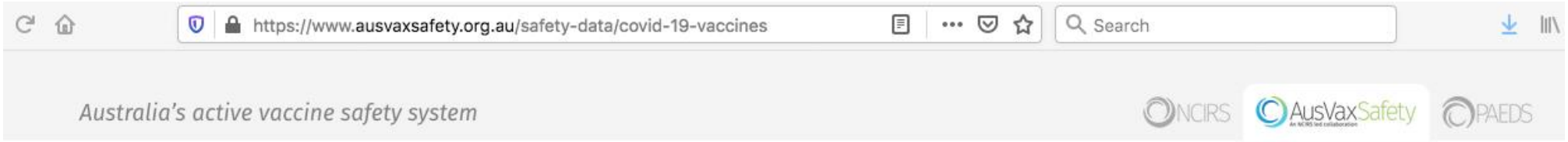

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Surveillance data have been provided by Vaxtracker and SmartVax. Surveys were sent on Day 3 after the vaccination, and data presented here are from surveys received up to 7 March 2021. These data are updated weekly.

Background

- Why do we use vaccines?
  - Immune system creates antibodies to fight a specific disease
  - Effective way to prevent disease (up to 3 million lives saved per year)
  - Protective against at least 20 diseases

- Why do we monitor safety?
  - Vaccination is safe and side effects are usually minor and temporary
  - All licensed vaccines are tested using clinical trials & monitored over time
  - You are far more likely to be seriously injured by a vaccine-preventable disease than by a vaccine
  - **BUT** there are always risks

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What happened with the influenza vaccine in 2010?

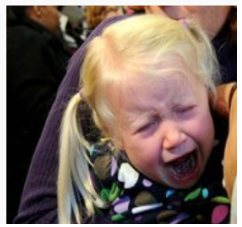
- Brand of TIV associated with febrile convulsions
- 38 cases of febrile convulsions in children under 5 presented to Perth emergency departments

The fallout from a batch of flu vaccine

Claire Krol

Updated 23 Nov 2010, 12:07pm

When the Health Minister Kim Hames announced in April he had suspended the flu vaccination program for children under five, hundreds had already fallen ill, some had come close to death.



Days earlier a pattern had begun emerging - all the children had received the flu vaccine in the 24 hours before they were admitted to hospital

APRIL 23 2010

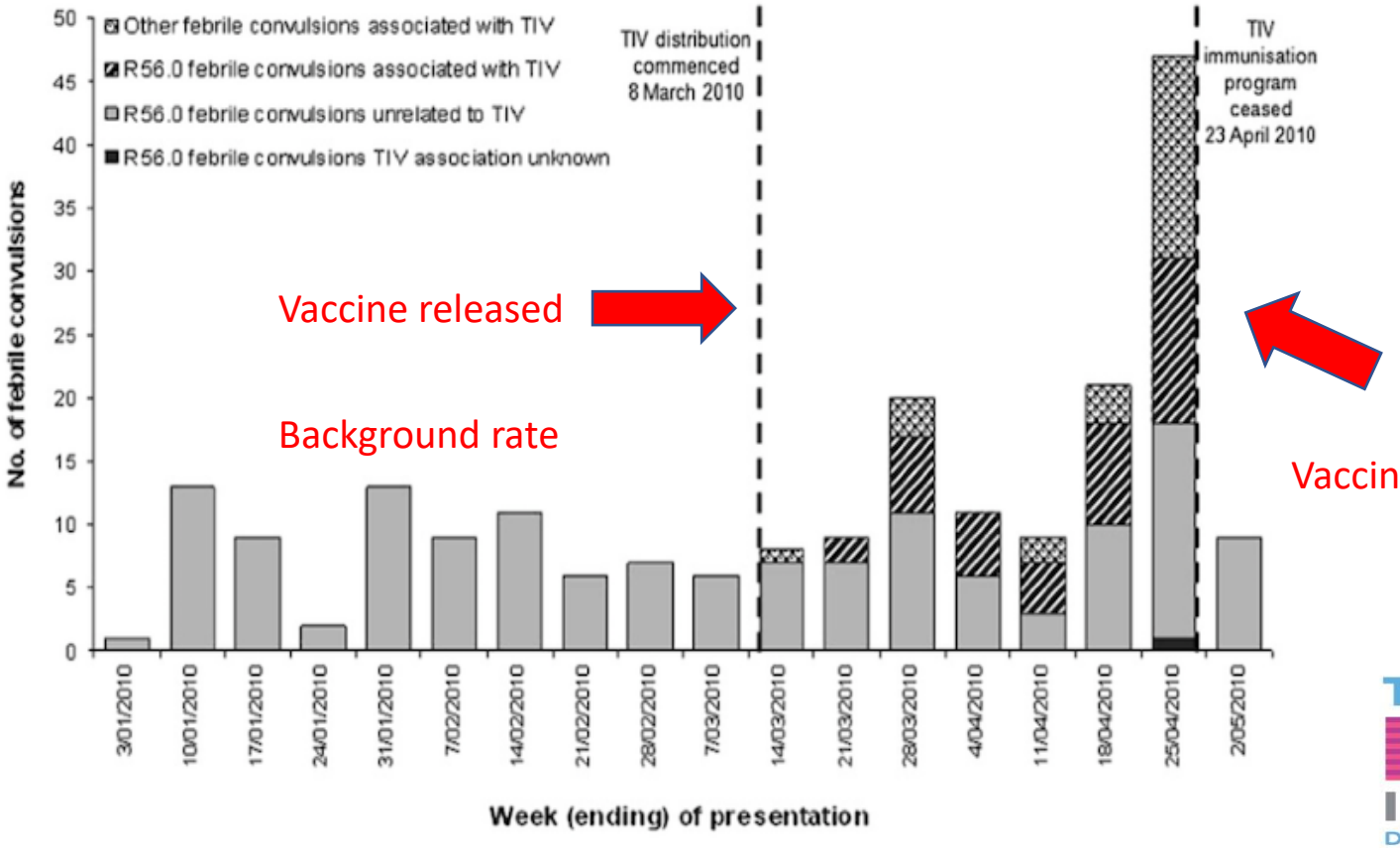
Flu vaccination ban goes national after fever, convulsions in children

Chris Thomson Show comments

SHARE TWEET MORE

Seasonal flu vaccinations across Australia for children under five have been suspended after 23 children in Western Australia were admitted to hospital with convulsions following their injections.

One child, aged 1, remains in a coma in a Perth hospital.



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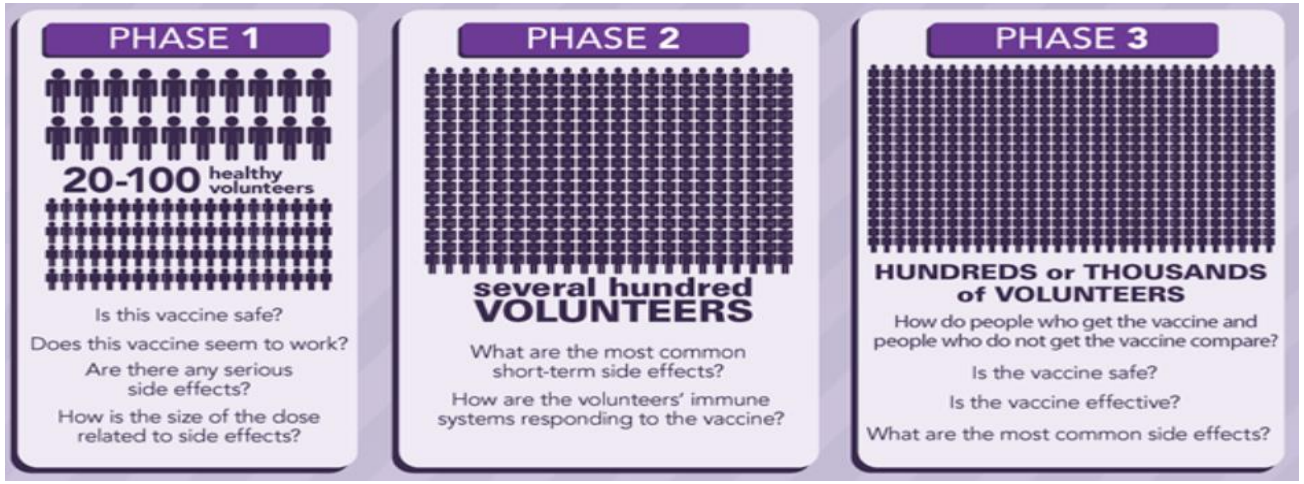
Pre-COVID-19 sources of vaccine safety

Clinical trials (pre-registration)



☺ Detection of **common** adverse events (site reactions, fever, etc.) in **healthy** individuals

☹ Detection of adverse events following immunisation (AEFI):

- **Rare** AEFI (sample size too small)
- **Delayed** onset AEFI (follow-up too short)
- Individuals with **comorbidities**
- Vaccine-vaccine & Vaccine-drug **interactions**

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Pre-COVID-19 sources of vaccine surveillance

- Vaccine safety surveillance systems:
  - Observed cluster of cases in hospital or clinic (media, TIV example)
  - Spontaneous reports to TGA (limitations?)
  - Mining records from hospital databases or General Practices (researchers)
  - SmartVax/VaxTracker (active surveillance)

- How does AusVaxSafety monitor other vaccines?
  - SmartVax/VaxTracker – SMS
  - **Signal detection methods**

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Sources of vaccine surveillance

Spontaneous reports of adverse events attributed to vaccines

☹ Passive reporting must be interpreted with caution
- Primarily hypothesis generating system
- Cannot determine if vaccine **caused** adverse event
- Under reporting of adverse events, especially known adverse events

☹ No gold standard for evaluating statistical methods

☹ No accepted threshold for declaring a signal

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Sources of vaccine surveillance

Mining records from hospital databases

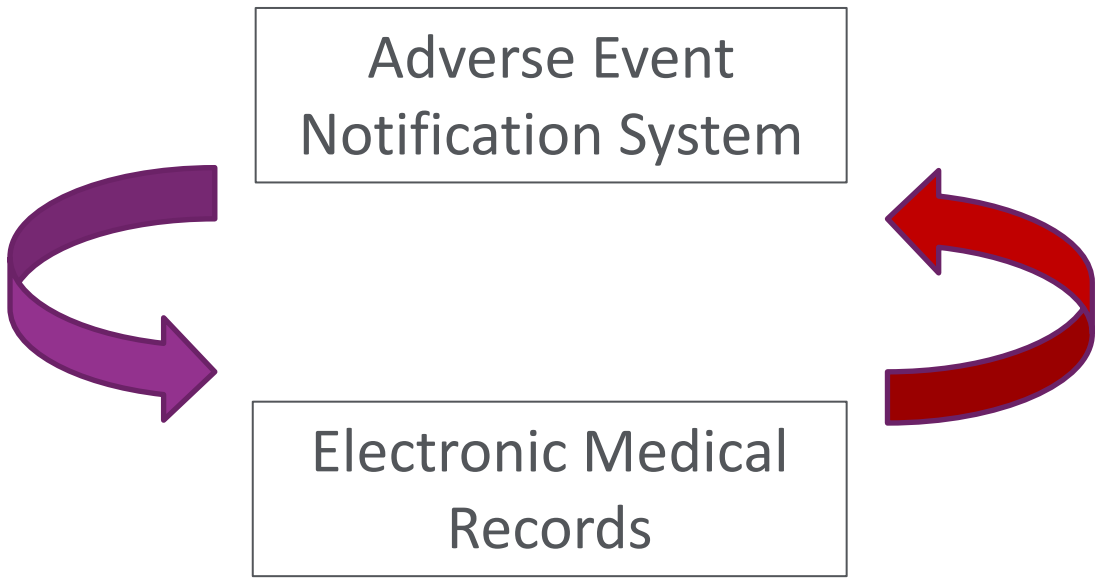
☹ Restricted to retrospective investigations following identification of potential safety issues

☺ Standardised coding is available (often non-hierarchical)

☹ Adverse events tend to be more severe (bias?)

Sources of vaccine surveillance

Mining records from General Practice



☺ GP records are a rich source for data mining and provide details on medications

☹ Lack of adverse event coding

☹ Difficult to determine onset date

☹ Difficult to determine comorbidities

☹ Inability to link patient across practices

☹ No links to hospital data

☹ No links to registries

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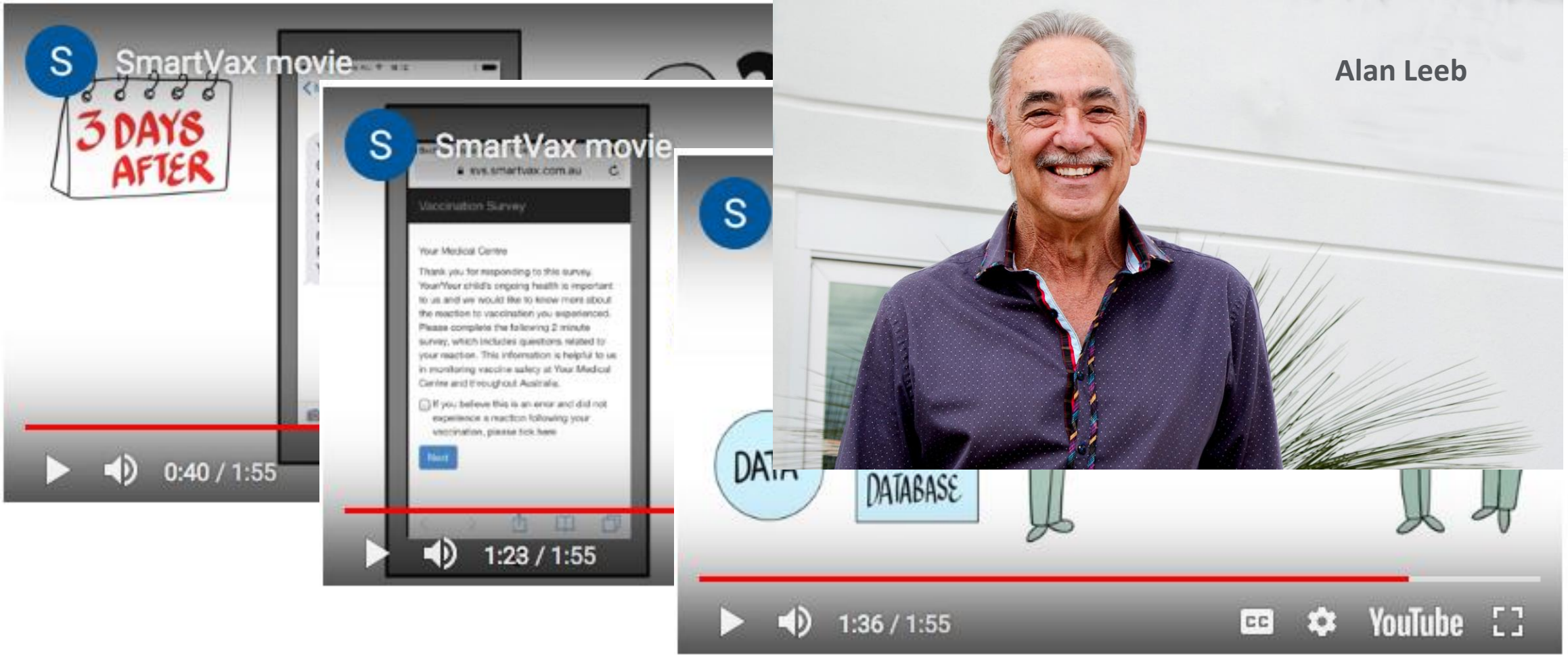
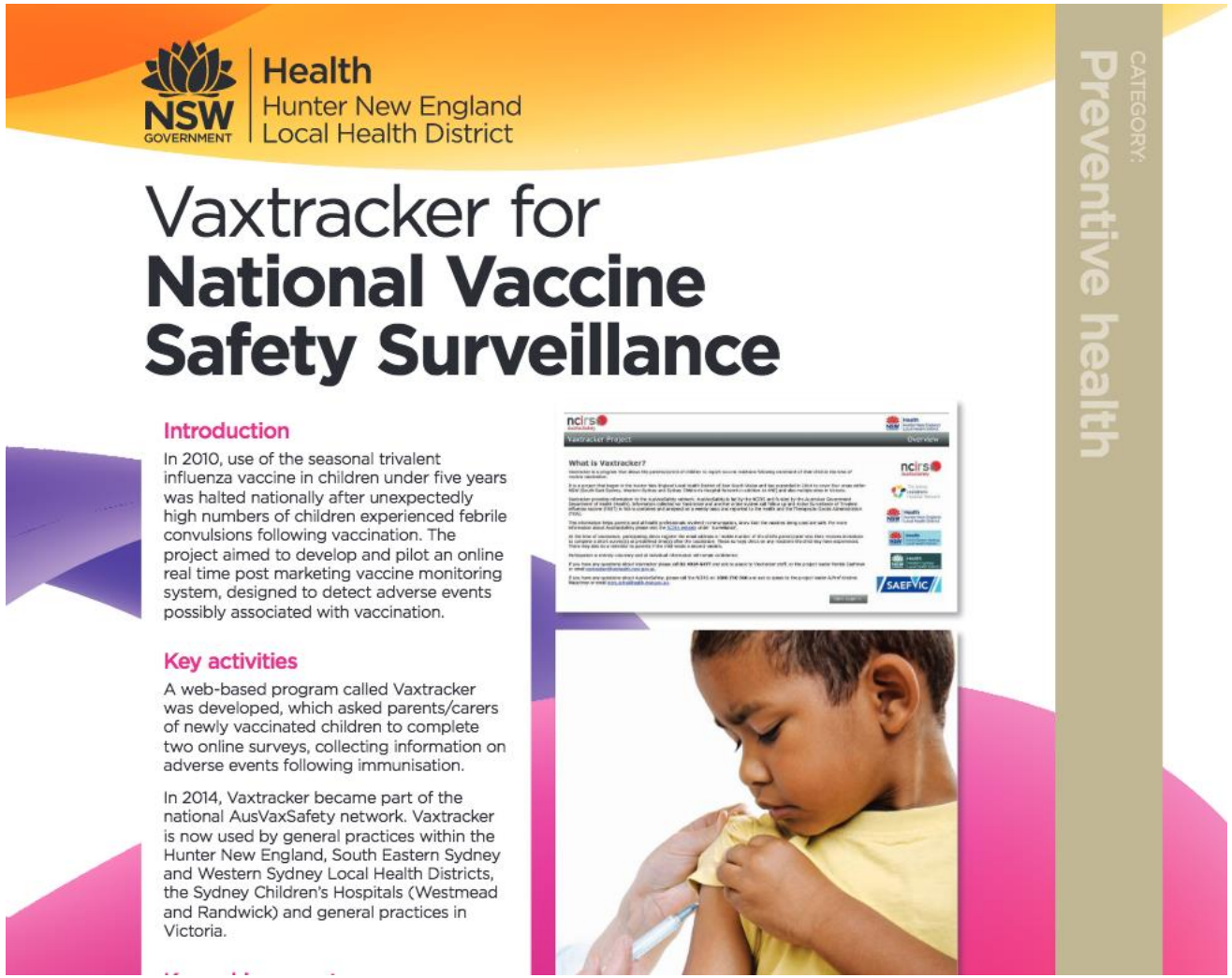
SmartVax and VaxTracker Systems



https://www.smartvax.com.au/about-smartvax-vaccine-surveillance-system/

SmartVax and VaxTracker Systems



https://www.vaxtracker.net/

Patrick Cashman

Sources of vaccine surveillance

Active surveillance from SmartVax/VaxTracker

- ☺ SMS sent to participants after vaccination
- ☺ Large number of participating sites across Australia
- ☹ Moderate participation rate and data quality
- ☺ **Signal detection methods**
- ☹ Dependence on manual analysis (potential for human error)

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Australia's active vaccine safety system

NCIRS AusVaxSafety PAEDS

AusVaxSafety
An NCIRS led collaboration

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Vaccine safety in Australia AusVaxSafety summary report 2019

Read more here

Influenza vaccine safety data

Vaccine safety resources

Specialist immunisation services

COVID-19 vaccine safety surveillance

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COVID-19 Vaccines

- COVID-19 pandemic – over 2.6 million deaths (and counting)
- Many vaccines developed – Pfizer/BioNTech & Oxford/AstraZeneca
- Public concerns?
  - Comparatively short time from design to approval
  - Do the vaccines work?
  - Are the vaccines safe?
- Research questions?
  - Are the efficacy/safety profiles the same for everyone? Age/Sex/Pregnant?
  - When should the second dose be given? Coadministration?

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What do we know?

- Pfizer/BioNTech Data
  - Over 43,000 participants, over 16 years of age, mainly USA & Argentina
  - 95% efficacy and similar safety profile to other viral vaccines
- Oxford/AstraZeneca Data
  - Over 23,000 participants, over 18 years of age, trials in UK, Brazil, South Africa
  - Approx. 70% efficacy and acceptable safety profile (maybe slightly higher?)

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How many approved (emergency use) COVID-19 vaccines are there???

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Approved COVID-19 Vaccines (emergency use)

- **Comirnaty [Pfizer-BioNTech]**
- Moderna COVID-19 Vaccine [Moderna]
- **COVID-19 Vaccine AstraZeneca [Oxford-AstraZeneca]**
- Sputnik V [Gamaleya Research Institute]
- CoronaVac [Sinovax]
- BBIBP-CorV [Beijing Institute of Biological Products]
- JNJ-78436735 [Janssen Vaccines, Johnson & Johnson]
- EpiVacCorona [Federal Budgetary Research Institution, Center of Virology & Biotechnology]
- Convidicea (Ad5-nCoV) [CanSino Biologics]
- Covaxin [Bharat Biotech, ICMR]
- CoviVac [Chumakov Federal Scientific Center for Research & Development Of Immune & Biological Products]
- ZF2001 [Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences]

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Table 15. Frequency of Solicited Local Reactions Within 7 Days After Each Vaccination, Reactogenicity Subset of the Phase 2/3 Safety Population*, 18 to 55 Years of Age

Local Reaction	BNT162b2 Dose 1 N=2238 n (%)	Placebo Dose 1 N=2248 n (%)	BNT162b2 Dose 2 N=2045 n (%)	Placebo Dose 2 N=2053 n (%)
Pain[a]				
Any				
Mild				
Moderate				
Severe				
Redness[b]				
Any				
Mild				
Moderate				
Severe				
Swelling[b]				
Any				
Mild				
Moderate				
Severe				

Source: adapted from
n = number of particip
N = number of particip
[a] Mild: does not interfe
[b] Mild: 2.0 to ≤5.0 cm;
* Participants in the re
least 1 dose of vaccin
Data analysis cutoff d

Table 21. Frequency of Solicited Local Adverse Reactions Within 7 Days Following Either the First or Second Dose of Vaccine, Participants Age 18 to <64 years, Solicited Safety Set*[a]

	Vaccine Group Dose 1	Placebo Group Dose 1	Vaccine Group Dose 2	Placebo Group Dose 2
				%)
				17
Grade 3				

FDA Briefing Documents for Comirnaty, Moderna & Janssen (Johnson & Johnson), respectively.

Results from clinical trials indicate low rates of serious adverse events but relatively high rates of minor adverse events.

g All Participants and by Age

	l (%) 895	Placebo n/N (%) N=21888
	(1.4)	408/21888 (1.9)
	(1.4)	272/14547 (1.9)
	(1.3)	136/7341 (1.9)
	(0.1)	22/21888 (0.1)
	(0.1)	18/14547 (0.1)
	(0.1)	4/7341 (0.1)
	(0.4)	96/21888 (0.4)
	(0.3)	56/14547 (0.4)
	(0.5)	40/7341 (0.5)
Related[b] serious adverse event	7/21895 (<0.1)	2/21888 (<0.1)[c]
18-59 years of age	4/14564 (<0.1)	1/14547 (<0.1)
≥60 years of age	3/7331 (<0.1)	1/7341 (<0.1)
Deaths	3/21895 (<0.1)	16/21888 (0.1)
18-59 years	1/14564 (<0.1)	7/14547 (<0.1)
≥60 years	2/7331 (<0.1)	9/7341 (0.1)
Related[b] deaths	0	0
AE leading to study discontinuation	0	0

What do we aim to do?

- Detailed break down of adverse event rates across subgroups
- Identify how these change over time
- Signal detection for possible **changes in safety profiles**
- Frequent reporting to TGA and Health
- Respond quickly to possible public concerns

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What are we doing?

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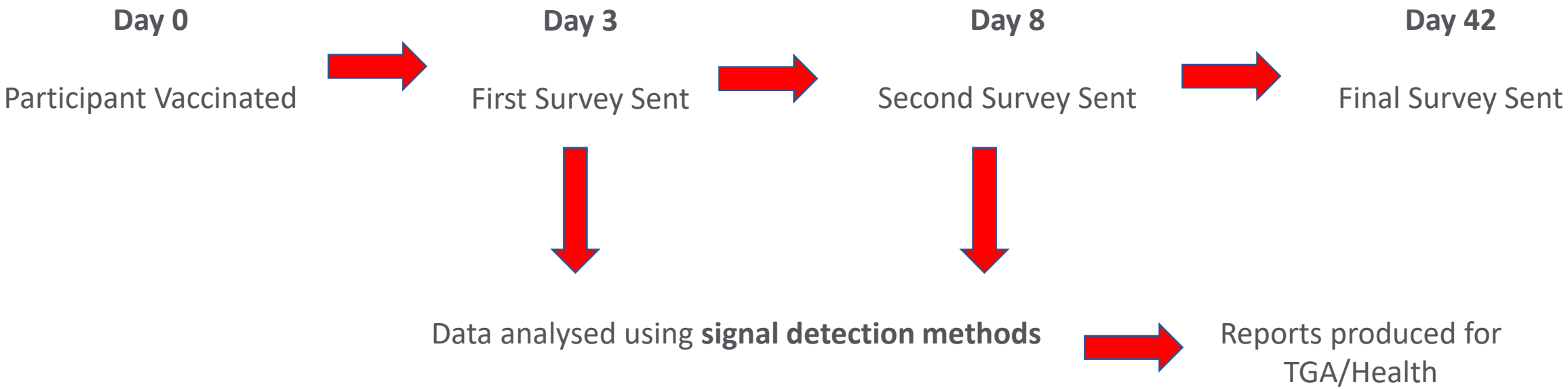
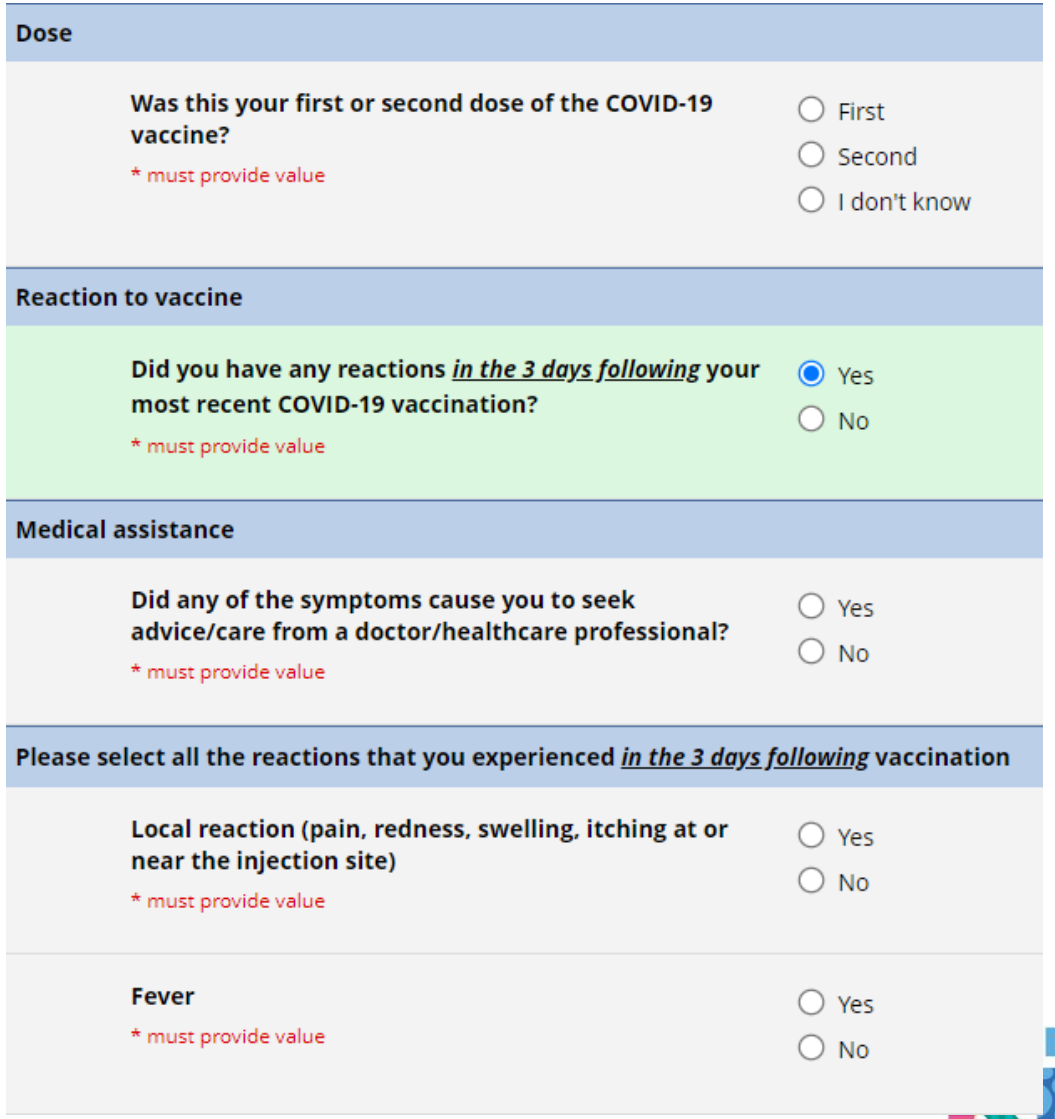
What are we doing?

- Automated surveillance system to monitor adverse events



The Survey

- How do you receive the survey?
- When is it completed?
- What does the survey look like?
- Why does it have these questions?



Dose

Was this your first or second dose of the COVID-19 vaccine?
* must provide value
- ○ First
- ○ Second
- ○ I don't know

Reaction to vaccine

Did you have any reactions *in the 3 days following* your most recent COVID-19 vaccination?
* must provide value
- ◉ Yes
- ○ No

Medical assistance

Did any of the symptoms cause you to seek advice/care from a doctor/healthcare professional?
* must provide value
- ○ Yes
- ○ No

Please select all the reactions that you experienced *in the 3 days following* vaccination

Local reaction (pain, redness, swelling, itching at or near the injection site)
* must provide value
- ○ Yes
- ○ No

Fever
* must provide value
- ○ Yes
- ○ No

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What do we do with the data?

- Clean the data – auto-populate, self report & missing
- Tabulate summaries of the data
- Analyse the data using **signal detection methods**:
  - **CUSUM for medical attendances**
  - **Bayesian hierarchical model for effect estimates**
- Produce reports for TGA/Health Departments
- Some data publicly available on AusVaxSafety and TGA websites

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What information is public?

As at 7 March 2021

NO SAFETY SIGNAL DETECTED

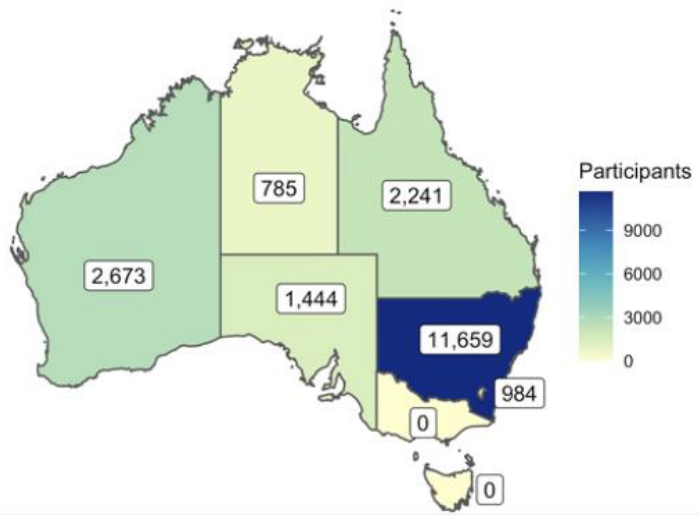
29,467 surveys sent Australia wide

19,786 participants (67.1% response rate)

64.3% of participants reported no adverse event

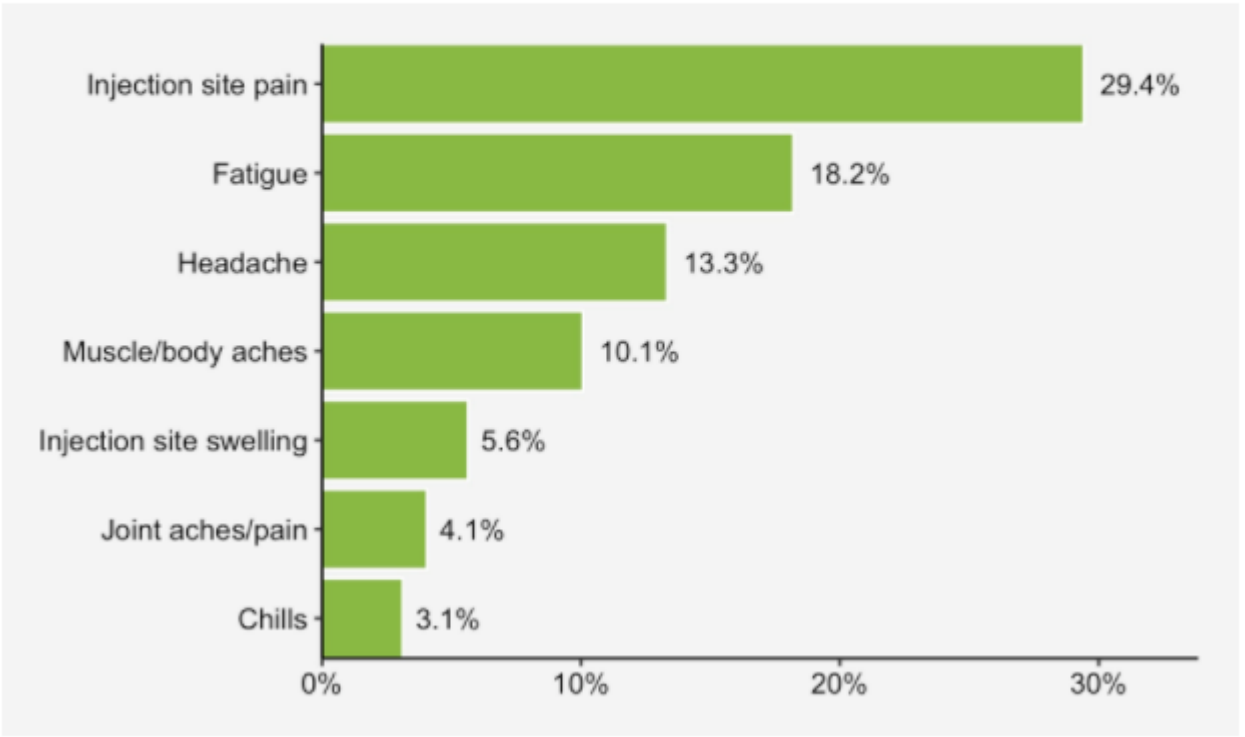
35.7% of participants reported any adverse event

0.7% of participants reported visiting a doctor or emergency department



7,061 people reported one or more adverse events.

The most commonly reported were:



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To illustrate how we monitor for safety signals and estimate AE rates, I will use some made up data.

We call this simulation, and it is how we evaluate the best analysis methods to use before the data even arrives.

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Worked Example

FAKE DATA

- Real data is **confidential**
- This is **simulated data**
- Suppose we consider:
  - Comirnaty, Pfizer/BioNTech
  - Dose 1
  - Survey Day 3

Age	Participants	Medical Attendances
<50	4356	20
51-60	1238	7
61-70	334	3
71-80	130	1
80+	24	0

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Worked Example

FAKE DATA

Age	Participants	Medical Attendances
<50	4356	20
51-60	1238	7
61-70	334	3
71-80	130	1
80+	24	0

	Participants		Medical Attendances	
Day	<55	55+	<55	55+
1	1074	138	10	2
2	406	12	1	2
3	1224	848	6	1
4	319	294	3	1
5	979	48	1	0
6	566	174	3	1

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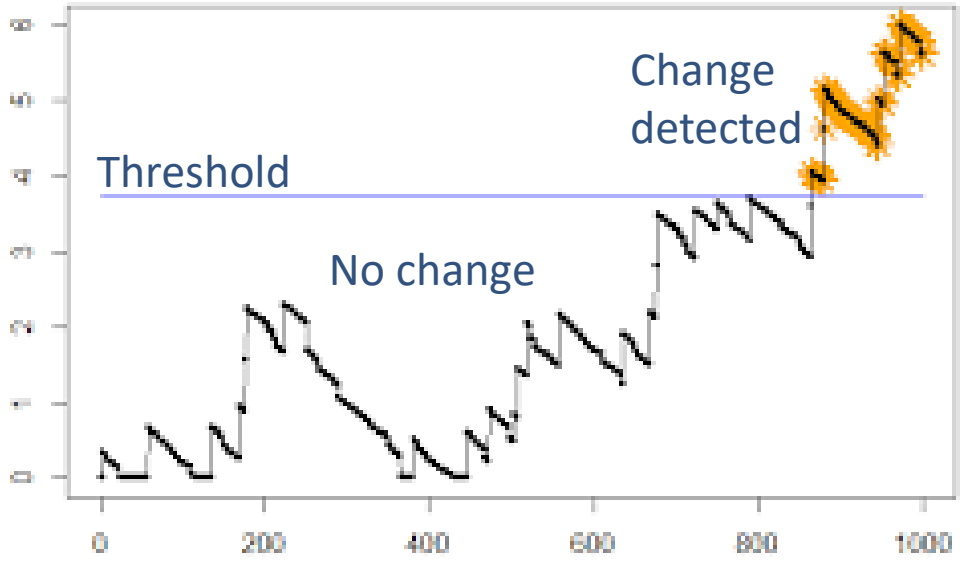
CUSUM Method

- CUSUM = **CU**mulative **SUM** Control Chart (change detection)
- **More** events → **Increased** signal
- **Less** events → **Decreased** signal
- Requires:
  - Control threshold
  - Expected probability
  - Maximum probability
- Signal > threshold → Signal Detected
- Operating characteristics explored using simulation



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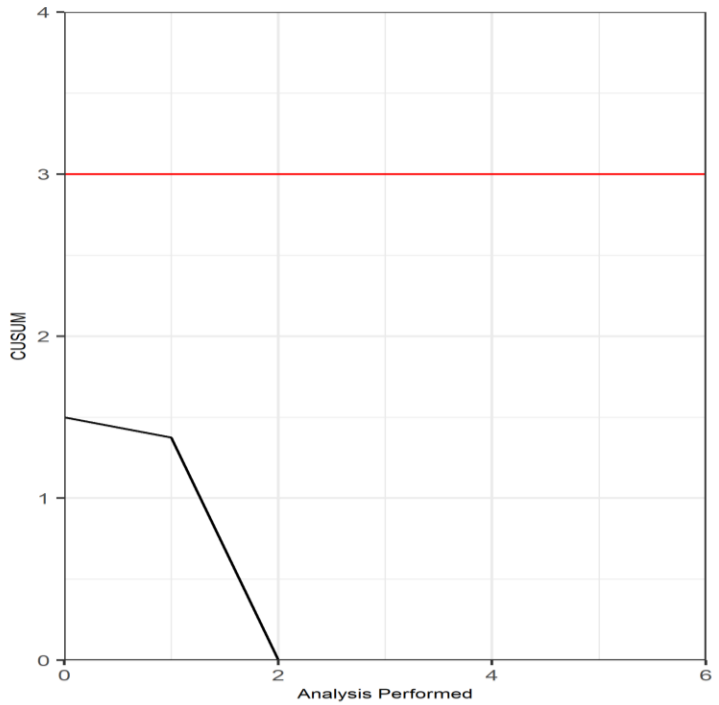
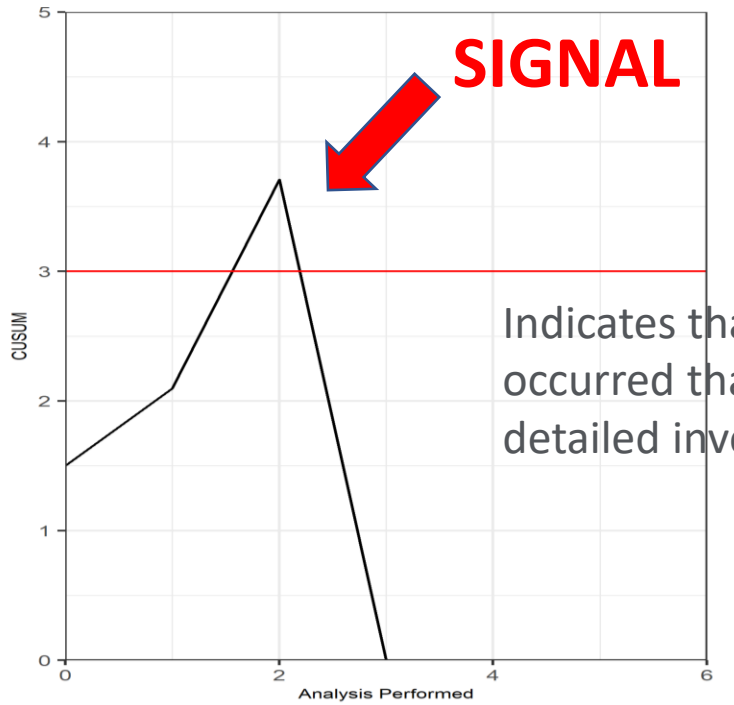
CUSUM Output

FAKE DATA

Age Group	No. of Records	CUSUM Status
<55	4,568	No Signal Detected
55+	1,514	Signal Detected





Indicates that a change has occurred that requires more detailed investigation.

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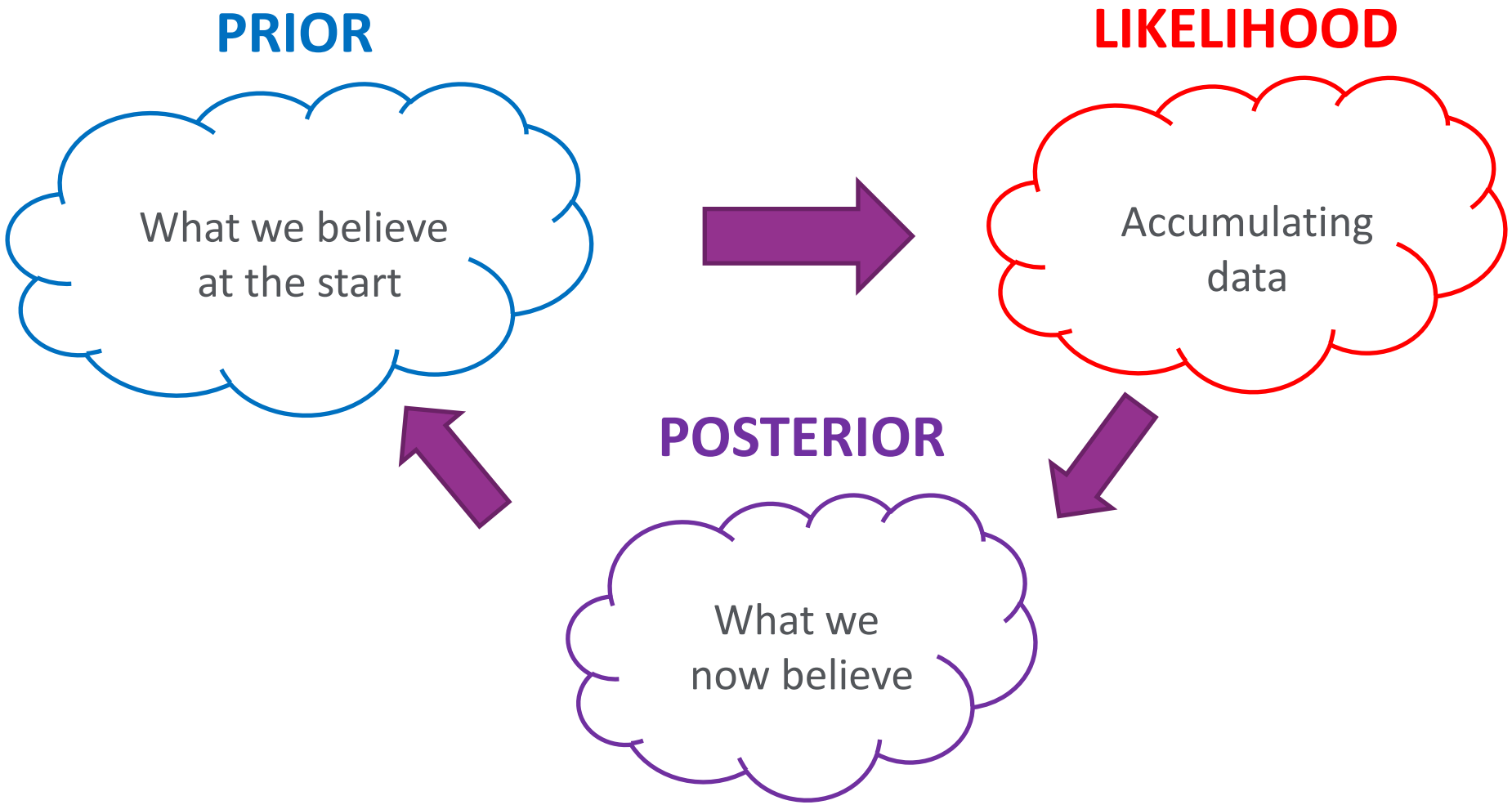
Bayesian Model



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Bayesian Hierarchical Model

- Estimate **probability** of medical attendance
- Estimate separately for each **group** (brand x age x sex x dose#)
- Let groups **share information**

Age	Probability of Medical Attendance
<50	p1
51-60	p2
61-70	p3
71-80	p4
80+	p5

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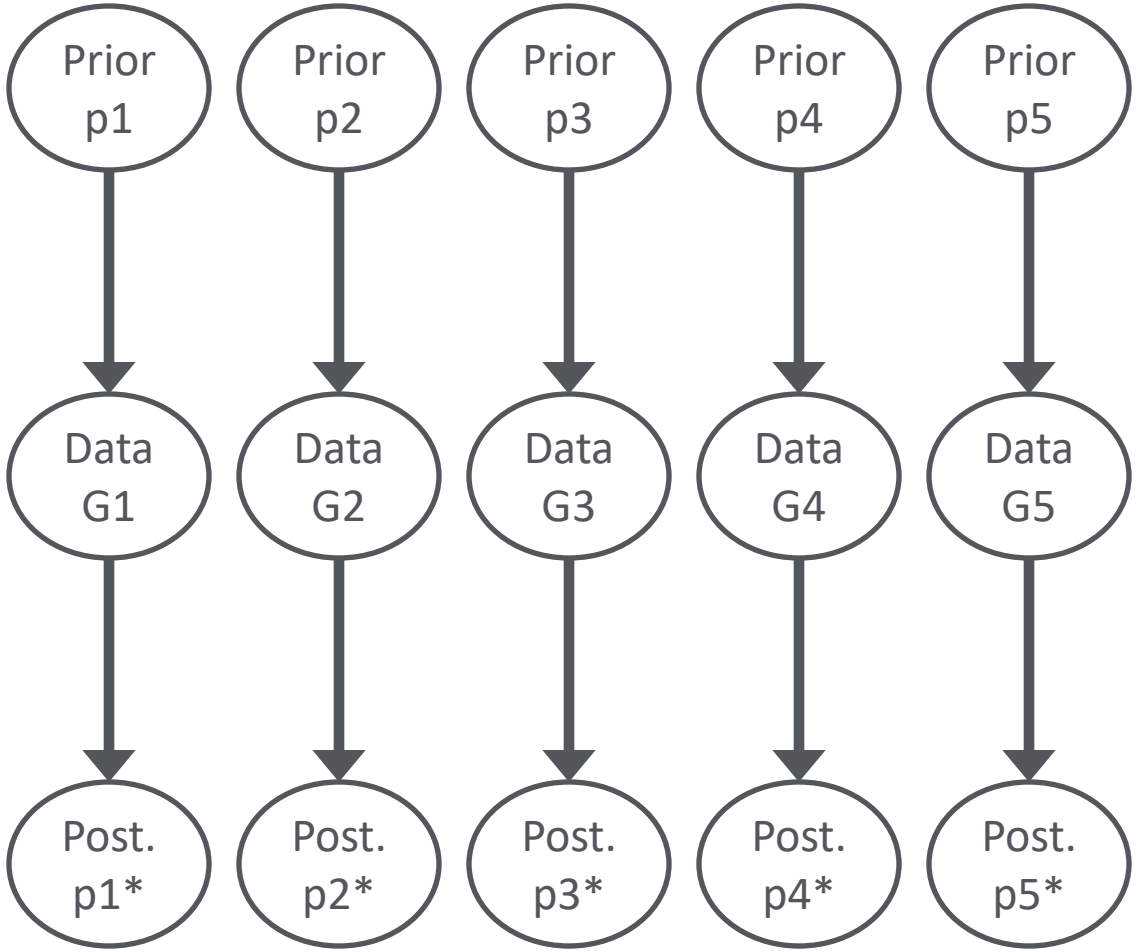
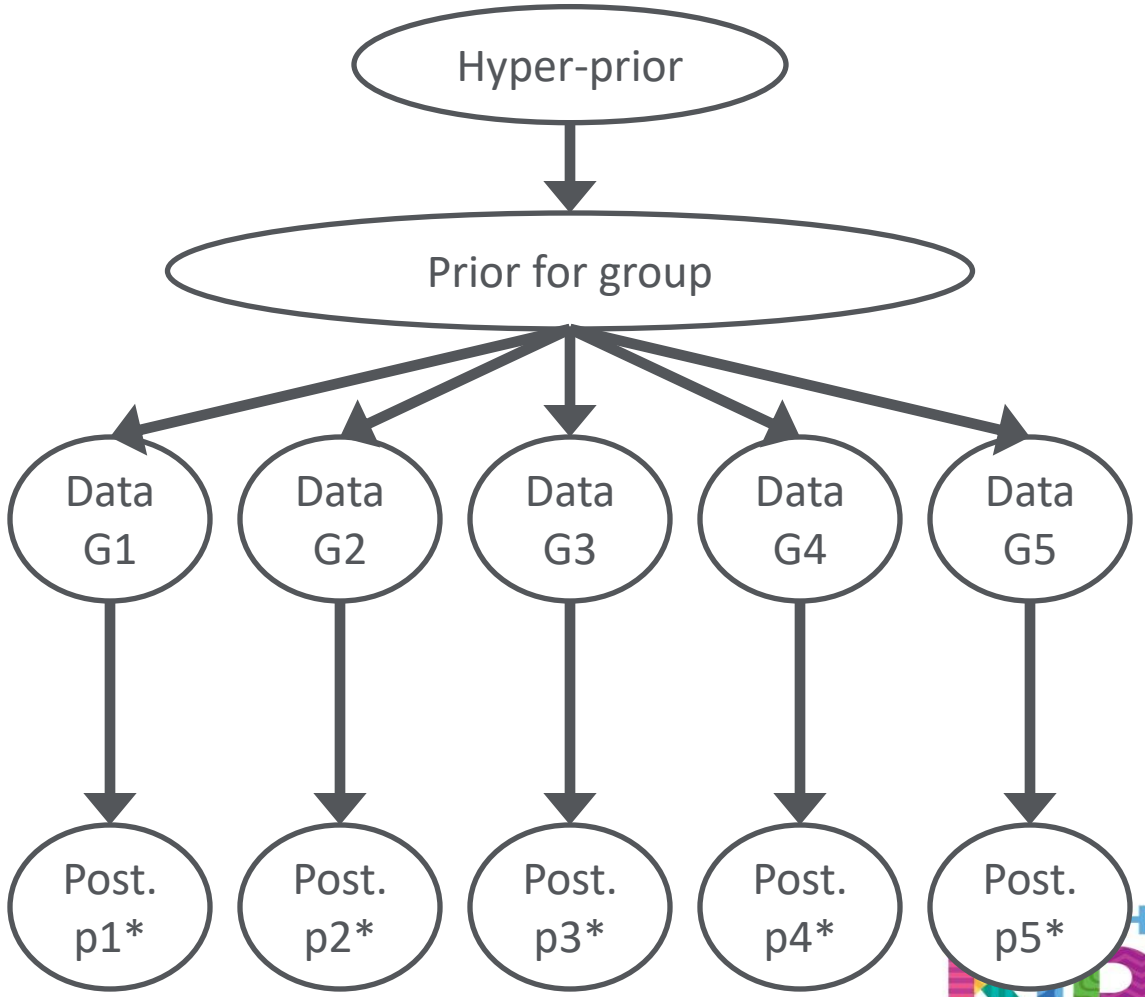
Independent Model



Hierarchical Model



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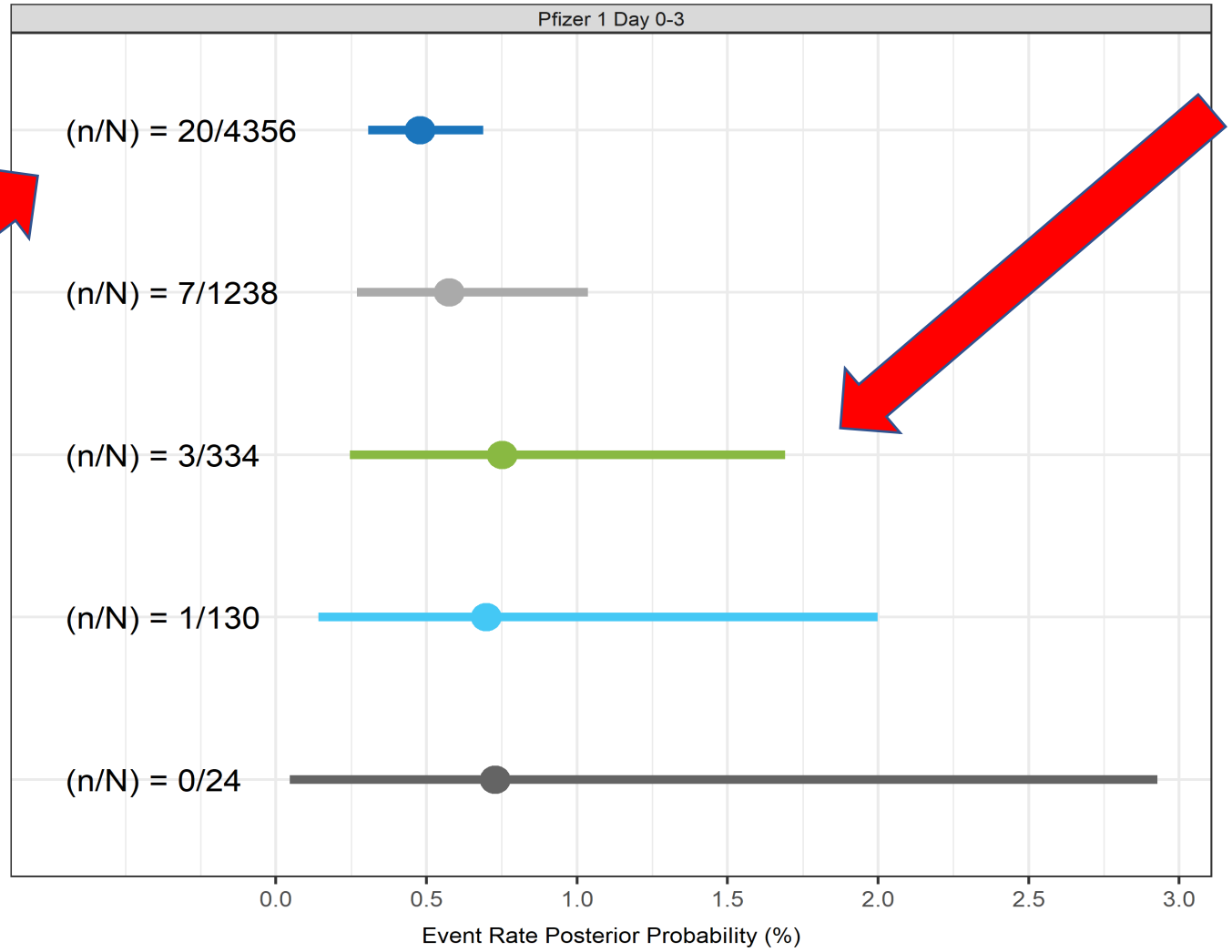
Bayesian Output

FAKE DATA



95% Credible Intervals

Number of medical attendances and participants

Age
- <50
- 51-60
- 61-70
- 71-80
- 80+

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Problems Encountered

- What issues have we encountered so far?
  - Double entry of participants in some jurisdictions
  - Dose 2's recorded for some jurisdictions: error or 1st dose abroad?
  - Missing demographic data
  - Delay in some jurisdictions collecting data
- How have they been resolved?
  - Careful quality control of reports
  - Regular meetings to discuss solutions (including weekends)
- Do we foresee more issues?

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What's next?

- More data sources becoming available
  - Other states and territories
  - General Practices and pharmacies
- More subgroups
  - AstraZeneca starting to rollout
  - Dose 2 data soon to be available
- Enhancement of signal detection methods
  - Beta-Binomial Posterior Predictive (BBPP) model
  - Hierarchical model across adverse event groups

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Acknowledgements

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An NCIRS led collaboration

NCIRS National Centre for Immunisation Research and Surveillance

SmartVax

PAEDS Paediatric Active Enhanced Disease Surveillance
An NCIRS led collaboration

Deloitte.

Vaxtracker
Monitoring Vaccine Safety

THE UNIVERSITY OF SYDNEY

TELETHON KIDS INSTITUTE
Discover. Prevent. Cure.

SPRINT SARI

FluCAN
The Influenza Complications Alert Network

MONASH University

TELETHON KIDS INSTITUTE
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