Signal Detection Methods for COVID-19 Vaccine Safety Surveillance

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WESFARMERS CENTRE OF VACCINES & INFECTIOUS DISEASES

5th July 2021

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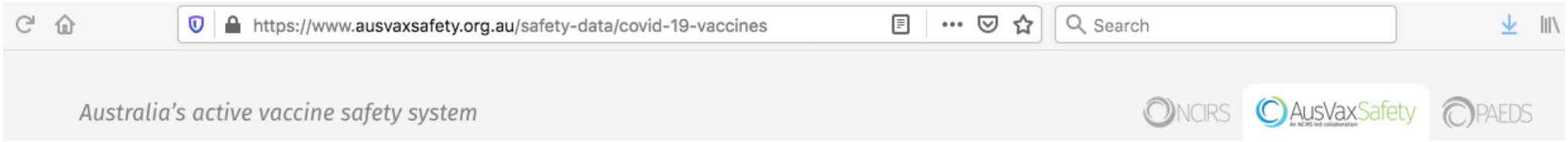

Acknowledgements

AusVaxSafety Leadership:
Kristine Macartney
Nick Wood
Chris Blyth
Tom Snelling
Paul Effler
David Durrheim
Mike Gold
Alan Leeb
Heather Gidding
Allen Cheng

NCIRS:
Alexis Pillsbury
Catherine Glover
Helen Quinn
Lucy Deng
Nicola Carter
Laura Lopez

SmartVax:
Ian Peters
Karin Orlemann

Vaxtracker:
Dave Durrheim
Patrick Cashman
Stephen Clarke

TKI/Uni Sydney
Julie Marsh
Michael Dymock
Yue Wu
Tim Spelman

Australian Government Department of Health
State & Territories Departments of Health
Therapeutic Goods Administration

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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COVID-19 Vaccines

- COVID-19 pandemic – over 3.9 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 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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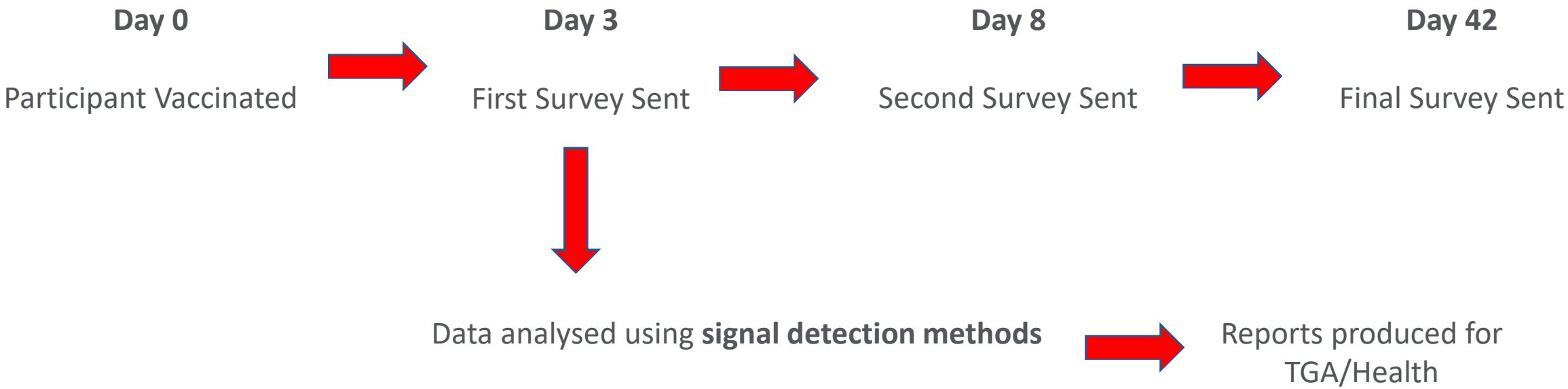
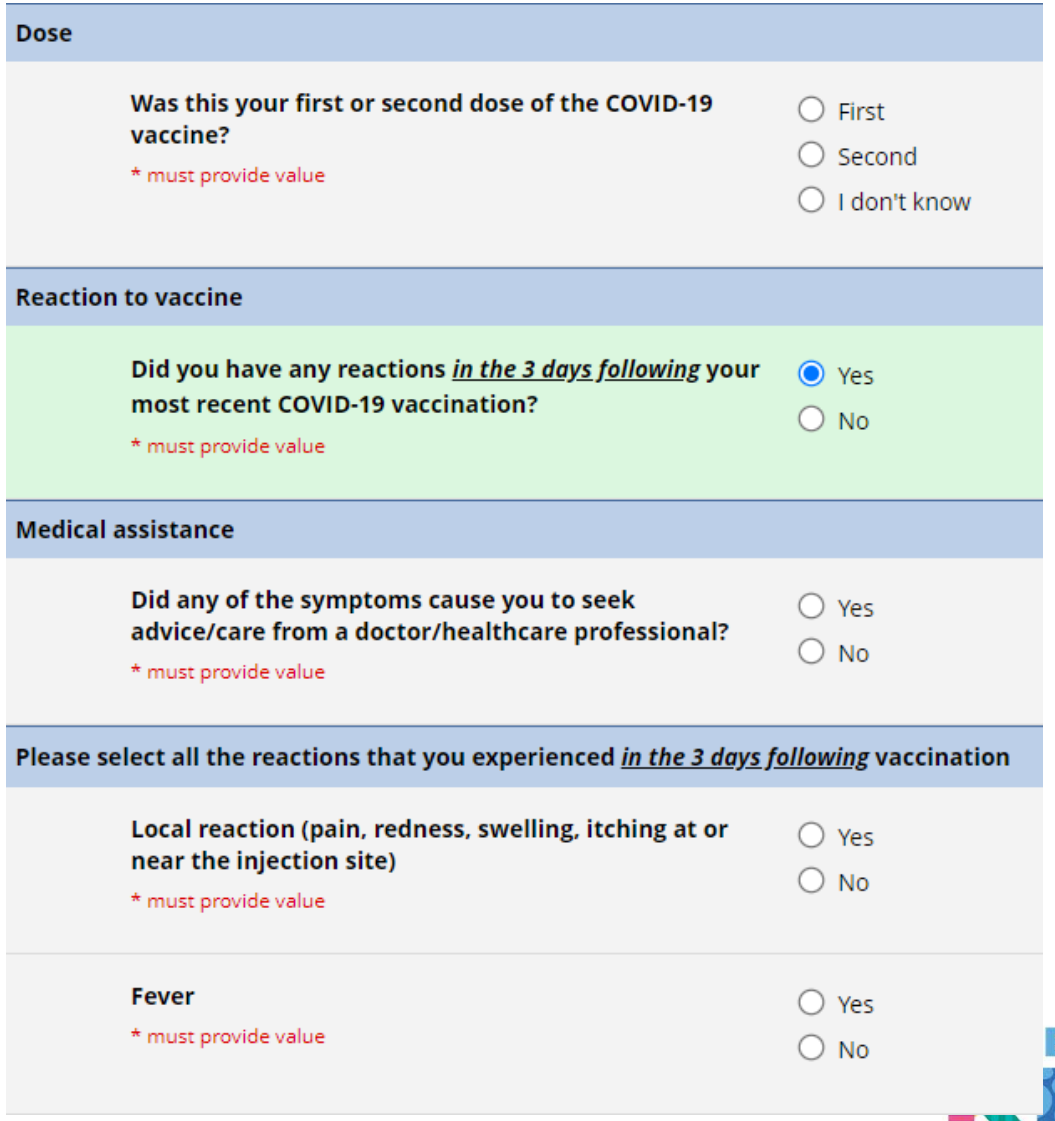
What are we doing?

- 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?



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
- Tabulate summaries of the data
- Analyse the data using **signal detection methods**:
  - **CUSUM Control Chart**
  - **Bayesian Logistic Model for Estimation and Predictive Probabilities**
- Produce reports for TGA/Health Departments
- Some data publicly available on AusVaxSafety and TGA websites

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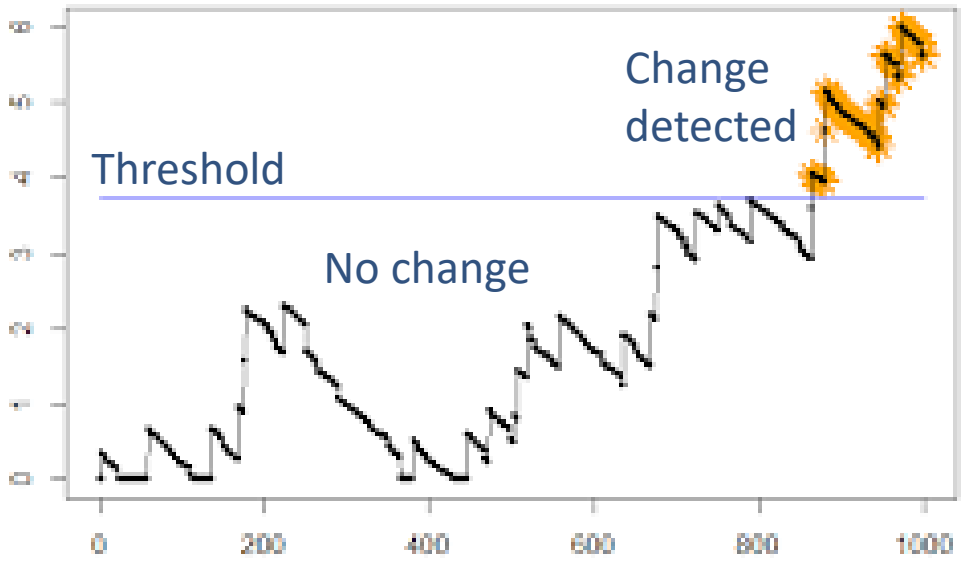
Worked Example – Simulated Data

Consider data only for one vaccine x dose combination

(e.g. Pfizer Dose 1).

CUSUM Method

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



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CUSUM Input

- Initial Condition:
  - $X_0 = \frac{3}{2}$
- Expected Probability:
  - $p_E = 0.6\%$
- Maximum Probability:
  - $p_M = 1.4\%$
- Control Threshold:
  - $C = 3$

Data:

	Participants		Medical Attendances	
Time	<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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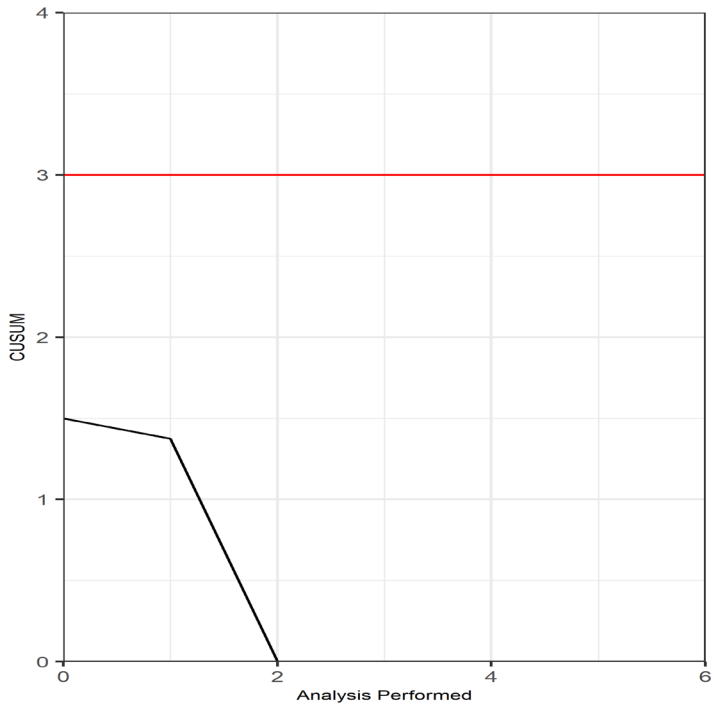
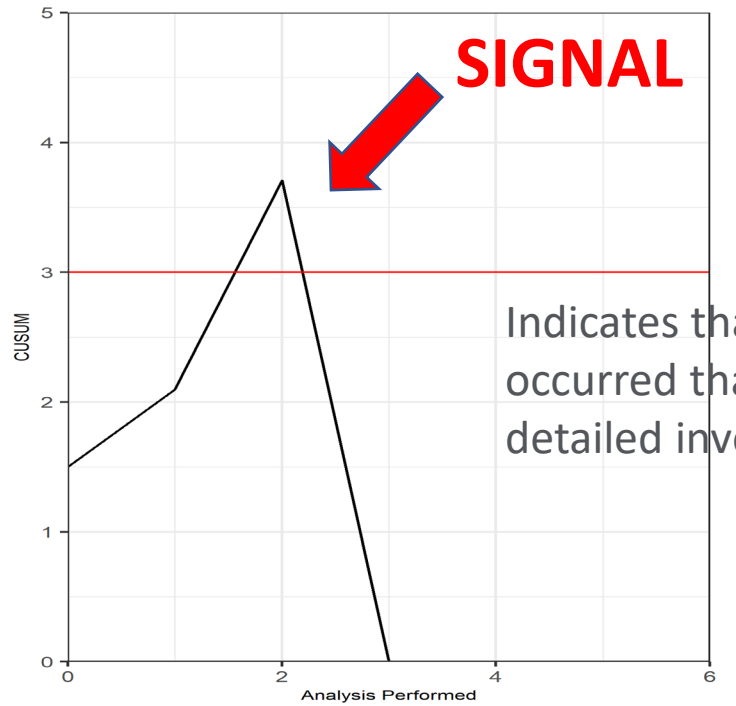
CUSUM Output

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 Logistic Model

- Participant subgroups: x = age, s = sex, g = covariate group
- Covariates include **state**, indigenous status and **medical history**
- Model no. of medical attendances (y) given no. of records (n) as Binomial with parameter (p) in each subgroup
- Model log odds of (p) with intercept (a), smooth function (g) and linear terms (B)

$$y_{xsg} \sim \text{Binomial}(n_{xsg}, p_{xsg})$$

$$\text{logit}(p_{xsg}) = a + g_s(x) + \sum_{q=1}^{Q} z_{gq}\beta_q$$

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Bayesian Logistic Model

- Define prior distributions on parameters:
  - Gaussian Process for smooth function over age by sex

$$
\begin{aligned}
a &\sim \mathrm{N}(-4, 2) \\
g_s(\cdot) &\sim GP(0, K(\cdot|\alpha_s, \rho_s)) \\
K(x, x'|\alpha_s, \rho_s) &= \alpha_s^2 \exp\left(-\frac{(x - x')^2}{2\rho_s^2}\right) \\
\alpha_s &\sim \mathrm{N}(0, 1) \\
\rho_s &\sim \mathrm{Gamma}(5, 0.5) \\
\beta_q &\sim \mathrm{N}(0, 3)
\end{aligned}
$$

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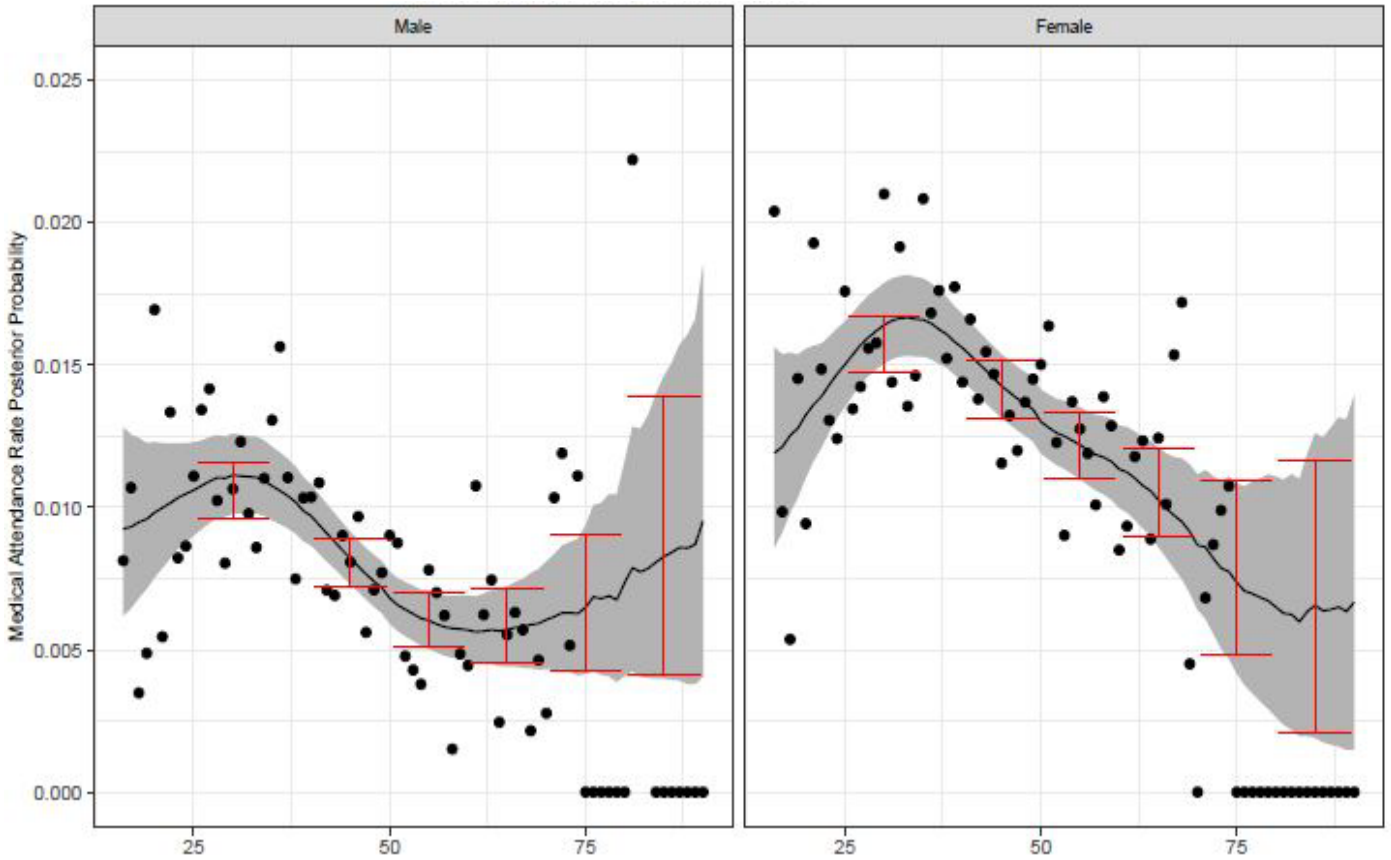
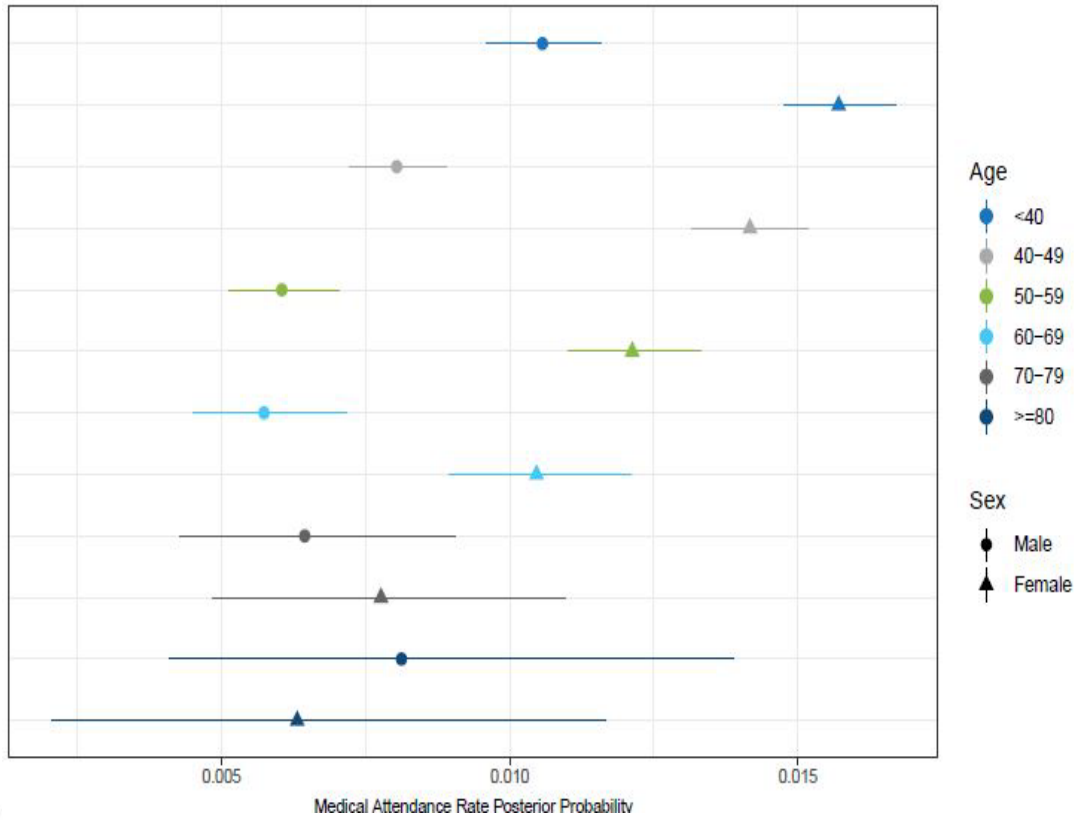
Fit of Gaussian Processes





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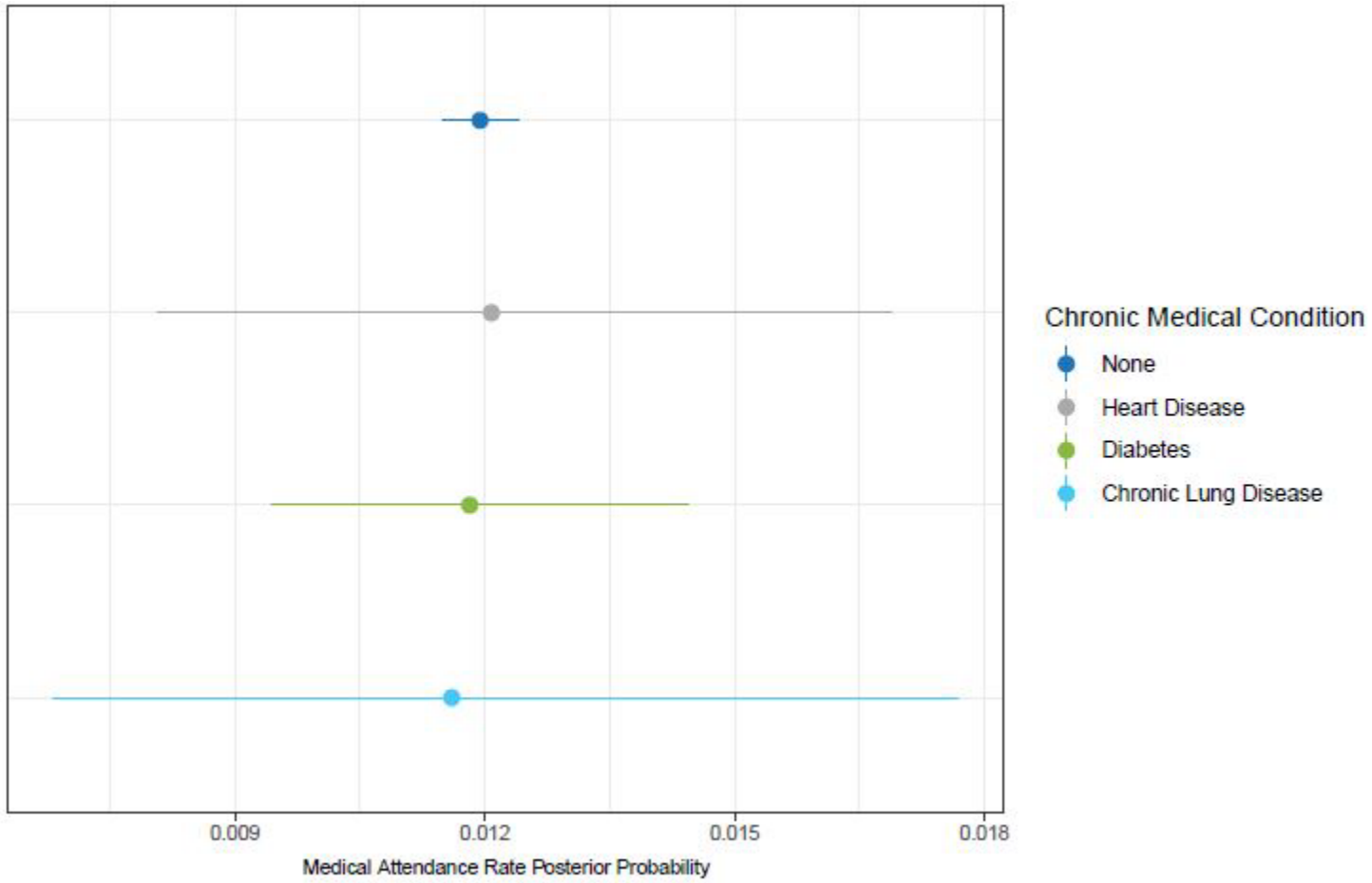
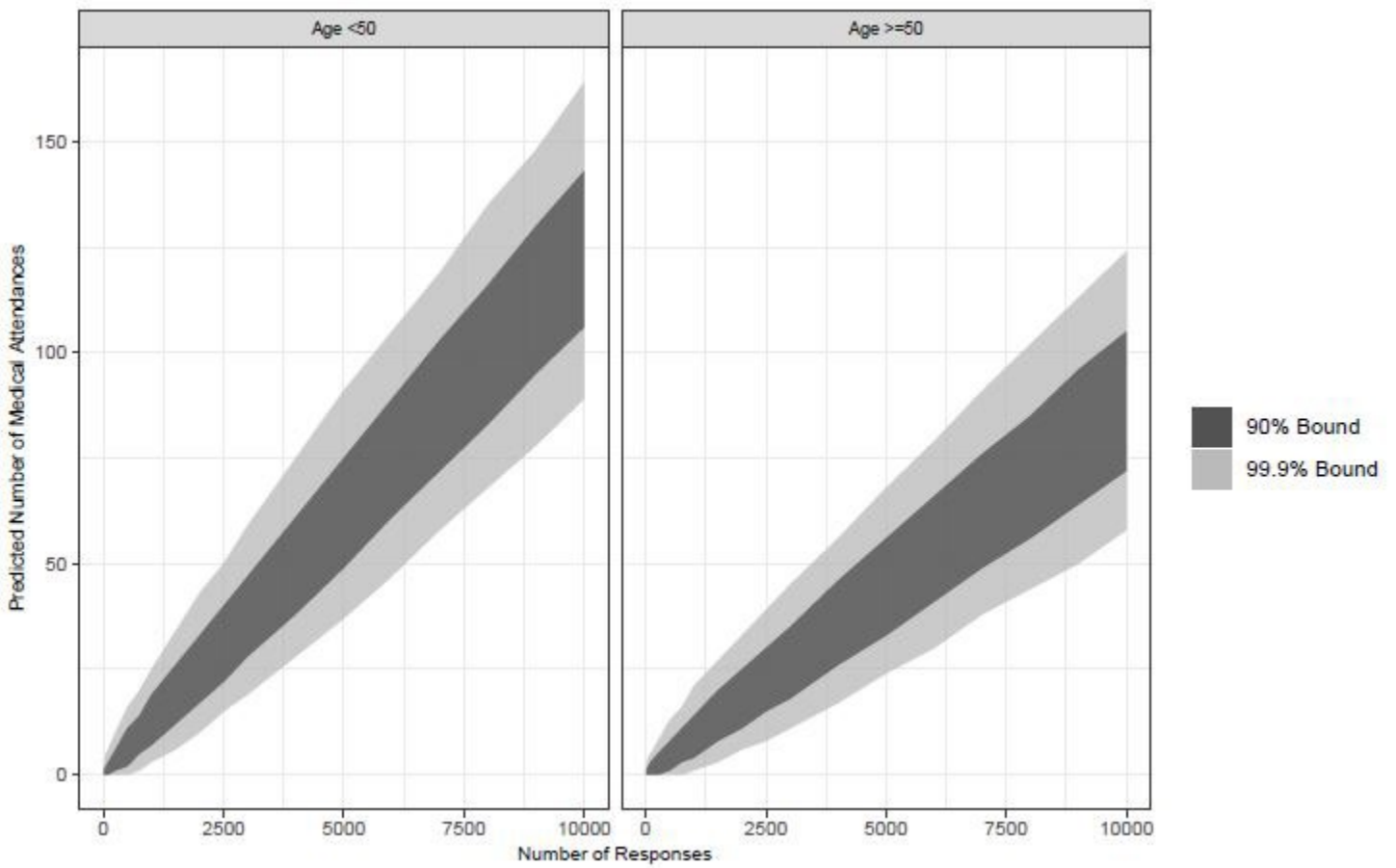
Estimation of Probabilities

- Estimate **probability** of medical attendance in various subgroups
- Posterior distribution of (p) “averaged” over nuisance parameters to get marginal distribution



Predictive Probabilities

- Posterior Predictive distribution to predict forward number of medical attendances given known demographics of population
- How many medical attendances would we expect to see this week?
- Compare distribution of predicted number of medical attendances to actual observed number of medical attendances



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Problems Encountered

- What issues have we encountered so far?
  - Data entry errors in some jurisdictions
  - Delay in some jurisdictions collecting data
  - Data storage and processing limitations
- How have they been resolved?
  - Careful quality control of reports
  - Regular meetings to discuss solutions

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What's next?

- Publish findings
  - First one million responses
- Wait and watch how the population evolves
  - Younger (healthier?) population groups
- More vaccines
  - Moderna? Novavax? Johnson & Johnson?

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Acknowledgements