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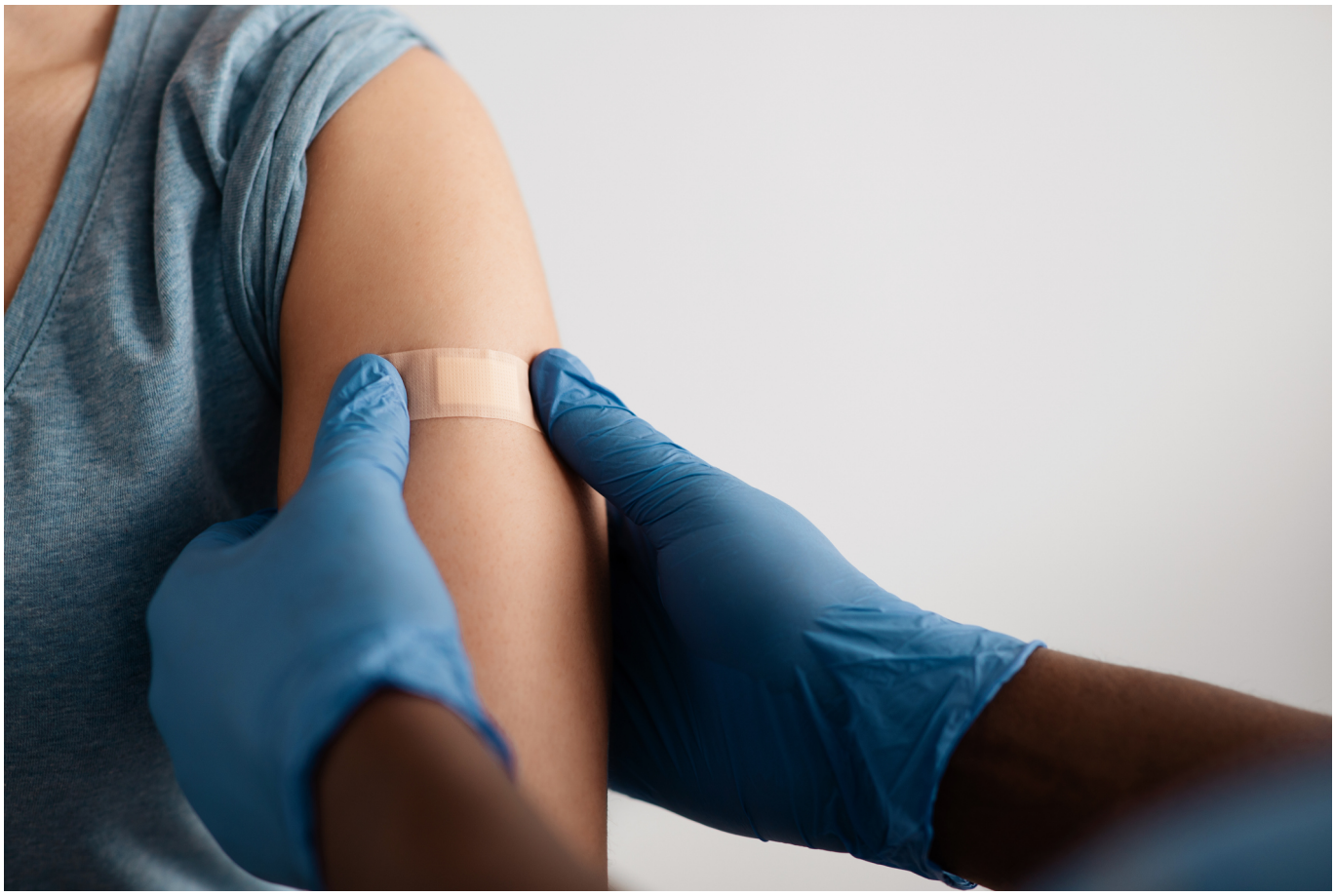

# Robust vaccine surveillance shows safety – we need to communicate this better

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# Summary

Vaccines have to meet high effectiveness and safety standards before they are offered to the public and continue to maintain a good ongoing safety record. In Aotearoa New Zealand (NZ) Medsafe has a well-established national system for pre-marketing approval of medical products and passive post-marketing pharmacovigilance.

For example, data from NZ and overseas show that the Pfizer/BioNTech Covid-19 mRNA vaccine is very safe. After billions of doses, the most serious adverse events with increased risk after vaccination are myocarditis and pericarditis – with a risk that is very small compared with the large benefits from vaccination in preventing both acute Covid-19 infection and Long Covid. Profiling the safety of vaccines and identifying rare risks is only possible with robust surveillance systems.

NZ's vaccine pharmacovigilance capacity is a valuable resource that needs to be maintained along with its ability for rapid expansion in response to future immunisation programme demands. To build trust and maintain confidence in vaccines, NZ health agencies need to be far more active in communicating the high capability and integrity of this independent vaccine safety surveillance function.

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This Briefing discusses modern approaches to vaccine safety surveillance and the need to generate critical data for policy and communication to maintain vaccine confidence. It focusses on describing the intense safety surveillance of the Pfizer/BioNTech Covid-19 mRNA vaccine and the findings from this surveillance.

## Vaccine safety surveillance

Since the 19th Century, concerns about the safety of vaccines have been a major reason some people hesitate to be vaccinated. Sometimes perceptions about safety are based on misinformation and misunderstandings. This situation is likely to have lowered uptake of Covid-19 vaccination and boosters[1], as well as other vaccines, such as measles[2], reducing their public health benefit.

Vaccine distrust is noted by the World Health Organization (WHO) to pose a major threat to public health.

Modern pharmacovigilance was born in 1961, in response to the thalidomide disaster. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine-related problem.[3] Today, there are a range of methods for tracking vaccine safety, from active signal detection to hypothesis testing (**Table 1, Appendix 1**).

In NZ, Medsafe is the government agency responsible for assessing the effectiveness and safety of medicines, including vaccines. This process includes pre-marketing approval of products and passive post-marketing surveillance. Pre-marketing approval involves rigorous review of submitted data on the quality, safety and effectiveness of the product for the purposes for which it is to be used.

Post-marketing surveillance is needed to detect uncommon adverse effects of the vaccine

or other medical products. Medsafe provides this service via an online Centre for Adverse Reaction Monitoring (CARM) reporting form.

Identification of rare potential vaccine safety signals often needs a population much larger than NZ has, especially for vaccines for subgroups such as pregnant people or older adults. The opportunity to pool data from countries around the world, using a standardised approach, means we can get a much clearer picture of the safety of medicines (see **Appendix 3** on the use of international collaboration for pharmacovigilance).

## Safety of the Covid-19 vaccines

The benefits of vaccine safety surveillance are clear when considering the Pfizer/BioNTech mRNA vaccine. All the approaches for vaccine safety surveillance described in **Table 1** were used across the globe, including NZ through Medsafe, the Ministry of Health, and the Vaccine Datalink and Research Group at the University of Auckland.

After billions of doses, the most serious (defined as requiring hospitalisation) adverse events with increased risk after Covid-19 vaccination are myocarditis and pericarditis with attributable risk of around three additional cases per million doses given. **Table 2 (Appendix 2)** summarises the safety profile of the Pfizer/BioNTech mRNA vaccine based on NZ and global data. The vaccine is very safe.

The low risks from Covid-19 vaccines need to be balanced against the benefit of the vaccine, which far outweighs these risks for most people. In NZ, use of these vaccines is estimated to have saved 6,650 lives and prevented 45,100 hospitalisations during the first major waves of infection (January 2022 to June 2023).[4] These vaccines continue to provide a high level of protection[1] against infection, hospitalisation, severe disease, mortality, long Covid, and in pregnancy.

## Requirements for NZ to sustain vaccine safety surveillance

Vaccine safety surveillance has tended to be low priority within public health, with no funding beyond the country's regulator. Two decades ago, NZ set the standard for vaccine safety surveillance for a meningococcal disease vaccination (MeNZB) campaign,[5] but has done little for the national programme since. While the technology and expertise are available to robustly and efficiently monitor vaccine safety and assess real or perceived concerns, there are also obstacles to achieving this in many countries,[6] including NZ. Politics and financial and human resource limits are constant barriers.

While the approaches in **Table 1** are relatively low-cost to operationalise in a timely and agile way, they need sustainable infrastructure[7] that allows them to operate with independence and provide timely, transparent information. Relying on building resource only when a safety concern arises can lead to delays in responsiveness, an information vacuum, and can open the door to a large-scale loss of confidence in vaccines.

An emerging vaccine safety issue (real or perceived) can rapidly lead to negative perception of a vaccine's safety. Mitigating a crisis in vaccine trust requires coordination and engagement. The relationship between health leadership, sector stakeholders, and media are critical factors. Communication requires the right messages and right messengers if trust is to be gained. The WHO has developed evidence-based frameworks[8]and case studies[9] to guide member nations on responding to crises, but they are rarely used.

The core requirements for a standard vaccine safety surveillance system in a country the size of NZ are sustained funding and support for international collaboration. To be well prepared for emerging infectious diseases, including pandemics, we need the great majority of people to have confidence in vaccine safety.

Access to excellent administrative data collections must include passive and active surveillance,[7] with observed vs expected studies for both hospitalisations and visits to primary care[10] and a platform for executing association studies when needed with a fast (weeks) turnaround. These platforms need to be 'shovel ready', agile, transparent, and independent. Alongside the generation of good data is an active communication strategy that follows best practice.

To do less falls short and risks both the health of the public and potentially exacerbating health inequities.

## What this Briefing adds

- Vaccine safety surveillance is now a highly evolved area of health science, drawing on a range of methods in active use across the world, including NZ. These systems are now proven to be effective, even for detecting extremely rare adverse events.
- NZ has a passive adverse vaccine event surveillance system operated by Medsafe with CARM providing independent review and assessment of reports of clinical significance and drawing on global data for additional information.
- Intense international surveillance of the Pfizer/BioNTech mRNA vaccine for preventing Covid-19 shows it is very safe. After billions of doses the most serious adverse events with increased risk after vaccination are myocarditis and pericarditis with an overall attributable risk around 3 additional cases per million doses. The benefits of the vaccine far outweigh this low risk.

## Implications for policy and practice

- The NZ vaccine safety surveillance platforms have previously demonstrated utility and need to be maintained along with their independence and capacity to be stood up rapidly in response to future vaccine safety issues and new vaccines for any novel pandemics. Risk assessment needs to be transparent and independent of the agencies tasked with risk management.
- NZ health agencies need to be far more active in communicating the high capability and integrity of the independent vaccine safety monitoring function to build trust, and maintain confidence in vaccines.

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## Appendices

## Appendix 1: Methods for pharmacovigilance / post-marketing surveillance

Post marketing surveillance involves systems for reporting adverse events that occur following administration of medicines, including vaccines. Today, most countries in the world have such a system, for example VAERS in the US. The systems rely on healthcare professionals, vaccine manufacturers, and the public to report any suspected adverse events following immunisation. Over the years such systems have successfully detected many vaccine safety signals, for example rotavirus vaccine and intussusception.

However, adverse event reporting systems are passive, meaning among other things, they rely on voluntary reporting, are subject to reporting bias, have no well-defined denominator, and cannot be used to assess causality—although they are valuable for identifying potential signals for further evaluation.

Today, there are a range of methods to complete the vaccine safety profile picture, from active signal detection methods to hypothesis testing. **Table 1** is a catalogue of methods and their use.

**Table 1. Summary of vaccine safety surveillance systems in use globally, including in NZ**

| Approach | Utility | Strengths and weaknesses | NZ capacity |
|---|---|---|---|
| Background rates of adverse events of special interest[11] | Performed prior to deployment of new vaccine so as there is a baseline of expected rates of events (year, age, sex, season, etc.) for risk assessment and communication. | Can include entire population and depending on incidence, information on population subgroups.<br>Prepares country for pharmacovigilance of new vaccine. | Excellent capacity. |
| Rapid cycle analysis (Repeated analysis in near-real time of pre-selected conditions by comparing the rates being observed with several comparator groups such as historical, unvaccinated and concurrently vaccinated). | Signal detection.<br>Hypothesis generating. | Identify clustering of adverse events.<br>Generate hypothesis.<br>Highly sensitive.<br>Need a very large, vaccinated population for many events.<br>Not hypothesis testing (cannot assess causality). | Limited for rapid cycle due to timely data and small population.<br>Could participate in global studies if timeliness of data resolved. |
| Observed vs. expected rates of adverse events of special interest[12] (Compares the rates being observed with historical pre-vaccine background rates (expected) in vaccinated persons. | Signal detection<br>Hypothesis generating | Identify clustering of adverse events.<br>Verify potential safety signals.<br>Generate hypothesis.<br>Highly sensitive.<br>Need large, vaccinated population for rare events.<br>Not hypothesis testing (cannot assess causality). | Excellent capacity.<br>Can use for both hospitalisation and primary care (less serious and more common).<br>Can participate in global studies to increase power and diversity. |
| Association studies<br>Usually a self-controlled case series (SCCS) or cohort study. | Hypothesis testing.<br>Assess risk. | Use of SCCS method excellent for specific rare events with low risk of bias.<br>Can contribute to causality assessment of relationship between vaccine and event. | Excellent capacity.<br>Can participate in global studies to increase power and diversity. |
| Can use the same protocol for of these across multiple sites/countries for meta-analysis.[6] | | | |

## Appendix 2: Safety of the Covid-19 vaccines

During the Covid-19 pandemic many new vaccines were developed and rapidly deployed. As of July 2024, over 13.5 billion doses of Covid-19 vaccines had been administered globally and over 4.5 billion doses were Pfizer/BioNTech. All the approaches for vaccine safety surveillance described in **Table 1** were used across the globe for Covid-19 vaccine safety surveillance, including in NZ.

These data show that the Pfizer/BioNTech mRNA vaccine is very safe. After billions of doses the most serious (defined as requiring hospitalisation) adverse events with increased risk after vaccination are myocarditis and pericarditis with attributable risk around three additional cases per million doses. **Table 2** summarises the safety profile of the Pfizer/BioNTech mRNA vaccine based on NZ and global data.

**Table 2. Summary of the safety profile of the Pfizer/BioNTech mRNA vaccine used for preventing Covid-19 based on global and NZ data**

| Adverse outcome | Incidence | Types of evidence |
|---|---|---|
| Injection site reactions<br>Redness, swelling, or pain at injection site. | Very common. | Randomised controlled trials. |
| Systemic reactions<br>Flu-like symptoms, headache, tiredness, muscle aches, joint pain, chills, fever, decreased appetite, nausea, diarrhoea, vomiting | Common. | Randomised controlled trials. |
| Tender arm pit, lymphadenopathy | Click on this link[13] to read a review of what is currently known. | Case reports. |
| Disrupted menstruation | Click on this link[14] for an explainer and evidence.<br>Can cause a delay to next period of 0–3.9 days. Return to normal after 1–2 cycles.<br>No changes to fertility. | Ten observational studies including a study of almost 3 million Swedish women aged 12–74 years.[15] |
| Myocarditis<br>Pericarditis | Click on this link[16] to read a review of what is currently known.<br>Estimates vary by population group but generally considered rare.<br>General incidence in population considered <4/100,000 and attributable risk around three additional cases per million doses. | Observational studies including self-controlled case series studies.<br>Largest study included 99 million vaccinated persons.[12] |
| Anaphylaxis | Very rare, 2–5 cases per million doses. | Case reports. |

| | | |
|---|---|---|
| Acute disseminated encephalomyelitis<br>Transverse myelitis | **No association**[17] between receipt of the Pfizer/BioNTech mRNA vaccine and transverse myelitis or acute disseminated encephalomyelitis* have been identified.<br><br>*Possible vaccine safety signals for transverse myelitis after viral vector vaccines and acute disseminated encephalomyelitis after viral vector and mRNA vaccines were identified in the largest vaccine safety study that included 99 million vaccinated persons.[12]<br><br>Investigation of the association between Covid-19 vaccination and the onset of each of these conditions was conducted by the GVDN site in Victoria, Australia.<br><br>The potential signal for onset of these conditions after receipt of a viral vector vaccine was confirmed. There was no evidence of an association between receipt of a mRNA vaccine and onset of either of these conditions.[17] | Observational self-controlled case series studies including Victoria, Australia (~6.7 million people)[17] and the resident population in England aged ≥5 years.[18] |
| Long Covid | Current studies on >600,000 people support up-to-date vaccination before infection is associated with a **reduction in risk** for Long Covid.[19] | Observational studies. |
| Other adverse events | Occur at the same rate in vaccinated vs unvaccinated persons. | Observational studies. |

## Appendix 3: International collaboration for increasing the effectiveness of pharmacovigilance

NZ has exceptional health and population data and is well placed to monitor the safety of vaccines used here. Also, there is now a large global community of vaccine safety scientists collaborating in vaccine safety surveillance. While NZ is somewhat limited by a small population, and therefore ability to detect and study very rare events, we can collaborate with other sites around the world.

The Vaccine Datalink and Research Group (VADAR) at Waipapa Taumata Rau | University of Auckland is a member site of the Global Vaccine Data Network™ (GVDN®), a multi-national investigator-led research network specialising in vaccine safety and effectiveness. Through

VADAR, implementation of common protocols, and the Auckland-based GVDN Global Coordinating Centre, NZ data can be pooled with data from multiple global sites for meta-analyses with the increased study power needed to detect rare potential vaccine safety signals.

NZ data stays in NZ, respecting some concerns of the Māori Data Sovereignty principles kaitiakitanga, whanaungatanga, and rangatiratanga.

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