Adverse events following the BNT162b2 mRNA COVID-19 Vaccine (Pfizer-BioNTech) in Aotearoa New Zealand

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ABSTRACT

Background

In February 2021, New Zealand began its largest ever immunisation programme with the BNT162b2 mRNA COVID-19 vaccine. We aimed to understand the association between 12 adverse events of special interest (AESIs) and a primary dose of BNT162b2 in the New Zealand population, aged ≥ 5 years, from 19 February 2021 through 10 February 2022.

Methods

Using national electronic health records, the observed rates of AESIs within a risk period (0-21 days) following vaccination were compared to the expected rates based on background data (2014 - 2019). The incidence rate ratio (IRR) for each AESI was estimated with 95% confidence intervals (CI) and adjusted by age. The risk difference was calculated to estimate the excess number of events per 100,000 persons vaccinated.

Findings

As of 10 February 2022, 4,277,163 first and 4,114,364 second doses of BNT162b2 were administered to the eligible New Zealand population, aged ≥ 5 years. The observed rates of most AESIs post-vaccination were not statistically different than the expected rates. The IRR (95% CI) of myo/pericarditis following the first dose was 2.6 (2.2– 2.9) with a risk difference (95% CI) of 1.6 (1.1– 2.1) per 100,000 persons vaccinated and was 4.1 (3.7– 4.5) with a risk difference of 3.2 (2.6– 3.9) per 100,000 persons vaccinated following the second dose. The highest IRR was 25.8 (95% CI 15.6– 37.9) in the 5-19 years age group, following the second dose of the vaccine, with an estimated 5 additional myo/pericarditis cases per 100,000 persons vaccinated. An increased incidence of acute kidney injury (AKI) was observed following the first (1.6 (1.5– 1.6)) and second (1.7 (1.6– 1.7)) dose of BNT162b2.

Interpretation

Although rare, a statistically significant association between BNT162b2 vaccination and myo/pericarditis and AKI was observed. While the association between BNT162b2 and myo/pericarditis has been confirmed internationally, further research is required to understand the association of AKI. BNT162b2 was not found to be associated with most of the AESIs investigated, providing reassurances around the safety of the vaccine.

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Keywords

COVID-19, mRNA Vaccines, BNT162b2, Adverse events, Pharmacoepidemiology

Evidence before this study

A rare but significant association between BNT162b2 and myocarditis and pericarditis has been observed in real-world studies internationally. However, there is a lack of evidence and real-world data on the rate and relative risk of myo/pericarditis in the New Zealand specific population and of other AESIs internationally.

Added value of this study

This population-based study, of over 4 million vaccinated persons in New Zealand, aged 5 years or older, contributes to the global and New Zealand specific understanding of the

safety profile of BNT162b2. BNT162b2 vaccination was not found to be associated with the majority of the selected AESIs. A rare but statistically significant association between the BNT162b2 vaccine and myo/pericarditis and acute kidney injury (AKI) was observed. To our knowledge, this is the largest ever post-marketing vaccine safety study carried out in New Zealand and includes the largest number of Māori (indigenous New Zealanders) and Pacific peoples (Pacific islanders living in New Zealand) in any vaccine surveillance study undertaken globally to date.

Implications of all the available evidence

Given the concern from the public, health care professionals and regulators around the safety profile of BNT162b2, this study provides important vaccine safety information not only for building public confidence, as vaccination was not associated with most of the AESIs investigated, but also for evidenced-based health-policy decisions. The associations produced by this study are considered statistical signals that indicate the need for additional analytic investigation and validation.

INTRODUCTION

New Zealand's national COVID-19 Vaccine and Immunisation Programme began vaccinations in February 2021 using the two-dose BNT162b2 messenger RNA (mRNA) COVID-19 vaccine (Pfizer-BioNTech, referred to as the BNT162b2 vaccine hereafter)[2]. The BNT162b2 vaccine demonstrated acceptable efficacy and safety in phase III clinical trials [3] and received provisional approval for use in adults, aged 16 and older, from Medsafe, New Zealand's Medicines and Medical Devices Safety Authority on 3 February 2021 [4]. This provisional approval was renewed on the 28 October 2021, with additional conditions for use in adolescents, aged 12 years and older [5]. Provisional consent of a paediatric formulation of the BNT162b2 vaccine for use in children aged 5-11 years old was also granted by Medsafe on 16 December 2021 [6]. However, rare, and potentially serious adverse events following immunisation (AEFI) are often impossible to detect in clinical trials due to limited sample size, narrow patient selection criteria, and constraints on the duration of the study [7]. Responses to a new vaccine and a particular AEFI can also differ among population subgroups depending on various factors e.g., age, ethnicity, and sex, and minority groups are often underrepresented in clinical trials [8]. This is a concern as New Zealand has a unique demographic, consisting of three main minority ethnic groups, Māori (indigenous New Zealanders), Pacific peoples (Pacific islanders living in New Zealand), and Asian, alongside the majority group, New Zealand Europeans [9]. Therefore, the safety profile of the vaccine in New Zealand specific subpopulations, particularly indigenous Māori, cannot be gleaned from the clinical trial outcomes or subsequent international post-marketing studies alone.

New Zealand has also been in a unique position globally during the pandemic. The implementation of strict public health measures such as imposed lockdowns, and border controls led to the successful elimination of COVID-19 transmission for sustained periods from May 2020 [10]. However, the emergence of more transmissible COVID-19 variants (e.g., BA.1, BA.1.1, BA.2 and BA.3) and the subsequent outbreak in the community at the beginning of 2022 [11], rendered the elimination strategy unsustainable [12]. Ensuring high equitable uptake of safe and effective vaccines is the most important tool for protecting the population against COVID-19. Vaccine hesitancy poses a serious challenge to achieving this, with fear and aversion to potential side effects one of the causes for concern [13]. Robust post-marketing vaccine safety surveillance is crucial to detect rare and unexpected vaccine reactions in a timely manner and provides information for risk-benefit assessments that can inform health policy decisions. This helps minimise the risks associated with serious

adverse reactions and ensures that accurate and credible information regarding side effects is communicated outwardly to maintain public confidence and trust [14].

The safety of BNT162b2 is monitored predominantly through a spontaneous reporting (passive) system by Medsafe, in collaboration with the Centre for Adverse Reactions Monitoring (CARM), with support from the COVID-19 Vaccine and Immunisation Programme within the Ministry of Health New Zealand [15]. This system relies on reports being voluntarily submitted by health care professionals and the public. Although it is effective at signal detection, it can be subject to several limitations, namely underreporting, incomplete reports, limited information on cases and reporting biases [16].

To address some of these shortcomings, the COVID-19 Vaccine and Immunisation Programme, in collaboration with Medsafe established an active surveillance system to monitor the BNT162b2 vaccine in a real-world setting. Unlike spontaneous reporting, the active system is not contingent upon voluntary reports and instead uses electronic health records (EHRs) to assess the risk of prespecified adverse events of special interest (AESI) following vaccination compared to a non-vaccinated group i.e., historical background rate data. This includes linking all national COVID-19 vaccination data to public hospitalisation records. As of 10 February 2022, approximately 95% of the eligible New Zealand population, aged 12 years and above, and 43% of children aged 5 to 11 years old, have received at least one dose of the adult or paediatric BNT162b2 vaccine respectively. The high vaccination coverage ensures representation across the entire population, including main ethnic groups. This coupled with the low infection rates of COVID-19 in the community during the study period, provides an ideal and unique setting to evaluate the safety profile of the BNT162b2 vaccine. We therefore aimed to understand the incidence and excess risk of several AESIs for COVID-19 vaccines following BNT162b2 vaccination in a largely COVID-19 naïve New Zealand population.

METHODS

Study Design and Setting

We used a retrospective historical comparative cohort design to compare the incidence rates of each prespecified AESI within a defined risk period (0-21 days) following administration of the BNT162b2 vaccine to the expected rate based on background incidence rates from a pre-vaccination period (2014-2019). The monitoring period was from 19 February 2021 (start of the COVID-19 vaccine rollout) through 10 February 2022.

Study Population

The study population comprised of individuals, aged 5 years or older, who received a primary dose of the adult [5] and paediatric [6] formulation of the BNT162b2 vaccine. Individuals that received a second dose within 21 days after their first were excluded. We also excluded all individuals who tested positive for COVID-19, received a COVID-19 vaccine overseas, or received a different COVID-19 vaccine. For each of the first and second dose cohorts, an individual was followed from their vaccination date (day 0) until the earliest of one of the following dates: the end of their follow up period (21 days), date of AESI onset, end of the monitoring period (10 February 2022), or with the occurrence of a death.

The study population also comprised of a historical comparison group identified from the background rate study for COVID-19 AESIs in New Zealand [17, 18]. This study estimated the incidence per 100,000 persons, per year, of several predefined AESI associated with COVID-19 vaccines in the New Zealand population. The incidence rates were stratified by calendar year, 20-year age groups (0-19, 20-39, 40-59, 60-79, ≥80), sex, ethnicity,

deprivation, and region over the period 2008 (start of ICD-10 coding) to 2019 (preceding the start of the COVID-19 pandemic). The background incidence rates were not stratified by more than one factor e.g., sex was not stratified by age, ethnicity was not stratified by sex, etc. Due to significant changes to ICD-10-AM coding practices implemented in 2014 [19], we only included the incidence rates of AESI from 2014 through to 2019 for comparison to our study period from 2021 through to 2022.

Prespecified Events of Interest

Twelve adverse events of special interest (AESI) for COVID-19 vaccines [20] were analysed: acute kidney injury (AKI), acute liver injury, Guillain-Barré syndrome (GBS), erythema multiforme, herpes zoster, single organ cutaneous vasculitis, myo/pericarditis (includes all events coded as myocarditis, pericarditis and myopericarditis), arterial thrombosis, cerebral venous thrombosis (CVT), splanchnic thrombosis, venous thromboembolism (VTE) (including deep vein thrombosis and pulmonary embolism) and thrombocytopenia. We identified these events from a list of diagnosis codes published on the Global Vaccine Data Network (GVDN) shiny app that was developed by the University of Auckland to estimate the background rates of AESIs for COVID-19 vaccines in New Zealand [17]. The *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification* (ICD-10-AM) Eleventh Edition diagnosis codes were used to identify AESIs.

Clinical record assessment was also conducted by the University of Auckland in an unpublished study using the same New Zealand population data [18] to validate the accuracy (positive predictive value (PPV)) of the ICD-10-AM codes used to identify the AESI's. We omitted an AESI from our study if the codes selected to identify the condition had a low PPV (approximately ≤50%) and following consultation with Medsafe. There is no ICD-10-AM code for myopericarditis. As such, we combined the ICD-10-AM codes used to identify cases of myocarditis and pericarditis to capture cases of myopericarditis and avoid duplication of these events. We also combined the ICD-10-AM codes relating to pulmonary embolism and deep vein thrombosis to capture cases of venous thromboembolism as a new ICD-10-AM code for deep vein thrombosis was only developed in the ICD-10-AM Eleventh Edition implemented in July 2019 [19]. The full table of ICD-10-AM codes used are presented in the supplementary information, Table S1.

Data source

We used a de-identified dataset, prepared by the Ministry of Health New Zealand. Prespecified events were identified from the National Minimum Data Set (NMDS), a national collection of all public hospitalisations, including coded clinical data for inpatients and day patients [21]. All New Zealand citizens (including Cook Islands, Niue, or Tokelau), residents, or individuals with a work visa that is valid for two years or more, are eligible for publicly funded health and disability services [22]. A National Health Index (NHI) number is provided to each person who uses these services. The NHI number was used to link the hospitalisation information with the BNT162b2 vaccination records in the national COVID Immunisation Register (CIR), a database of all COVID-19 vaccination information in New Zealand [23]. The BNT162b2 vaccine is freely available to all eligible individuals in New Zealand (as of 10 February 2022 this refers to individuals aged 5 years and above), regardless of eligibility to public health and disability services. The Pandemic Minimum Dataset, which registers all reported COVID-19 polymerase chain reaction (PCR) and rapid antigen tests, was used to check if an individual tested positive for SARS-CoV-2 infection. During the study period, the PCR test was the predominant form of COVID-19 testing in New Zealand. Rapid antigen tests were made widely available by the government in early March

2022 [24]. The Health Service User (HSU) population was used to estimate the New Zealand population eligible for COVID-19 vaccination in New Zealand.

Statistical analysis

We compared the observed incidence of each AESI following vaccination with the expected incidence using historical background rate data from 2014 through 2019 [17, 18]. We estimated our observed incidence rates from the number of events that occurred in the risk period (0-21 days) following both doses of the vaccine in the vaccinated cohorts. If there were multiple hospital admissions for an individual, the event recorded closest to vaccination was included. We calculated the expected incidence of each AESI from the historical comparison group and the person-time at risk per 100,000 person years. Rates were stratified by 20-year age groups (0-19 years to ≥80 years) using the age-specific background rates. We were unable to adjust other factors by age (e.g., sex) as this was not provided in the background rate dataset. We estimated the incidence rate ratio (IRR) for each AESI by dividing the observed counts by the expected counts. Corresponding 95% confidence intervals were calculated using the parametric percentile bootstrap method [25] based on 100,000 draws to account for variation in the observed and expected incidence rates. To calculate the risk difference, we estimated the excess number of events per 100,000 persons after vaccination (21-day period) for each AESI. Analyses were performed using the R software, version 4.1.0.[26].

Patient and Public Involvement

This observational study did not involve patients or members of the public. Their input was not sought in the systematic review design, interpretation of results, or drafting or editing this document.

Ethics Approval

The study did not require informed consent of individual participants as we used a de-identified dataset and received an exemption from New Zealand's Health and Disability Ethics Committee (HDEC) of New Zealand (Reference #:2022 OOS 11950).

RESULTS

Study population

From the 19 February 2021 through 10 February 2022, within a population of 4,685,351 individuals, aged 5 years and above, and eligible for COVID-19 vaccination in New Zealand, 4,277,163 and 4,114,364 individuals were included in the vaccinated cohorts who received a first and second dose of the BNT162b2 vaccine (adult and paediatric formulations), respectively. During the study period, 13,597 individuals tested positive for COVID-19 and were excluded from the vaccinated cohorts.

The demographics of the study participants, including the historical comparison cohort (2014- 2019) and the vaccinated cohorts (first and second dose recipients) are shown in Table 1. The proportion of females included was 50.5%, 50.5% and 50.6% in the historical comparison group, and first and second dose vaccinated cohorts, respectively. New Zealand European was the predominant ethnic group across the historical comparison (62.7%) and first (63.0%) and second (63.6%) dose vaccinated cohorts. The proportion of Māori participants in the historical comparison cohort (16.2%) was greater than that in the first (13.2%) and second (12.7%) dose vaccinated cohorts. Conversely, there was a greater number of Asian participants in the vaccinated cohorts (both 16.2%) compared to the comparison cohort (13.8%).

The highest proportion of participants were in the 20–39-year-old group with 27.2%, 30.3% and 31.0% in the historical comparison group, and first and second dose vaccinated cohorts, respectively. The proportion of participants in the youngest age group, under 19 years, in the historical comparison cohort was 25.7% and was 17.8% in the first dose and 15.3% in the second dose vaccinated cohorts since the background rate data includes information on individuals of all age groups (0-19 years to ≥80 years), while the vaccinated cohort was restricted to those aged 5 years and above (as of 10 February 2022, the BNT162b2 vaccine is not approved in New Zealand for individuals under 5 years of age).

Demographic characteristics of patients who were discharged from hospital with an event of interest in a period between 2014-2019 in New Zealand are provided in Supplementary Table S2.

Observed versus expected analyses

The age-adjusted incidence rate ratio (IRR) for each AESI within the 21 days following a first and second dose of the BNT162b2 vaccine, as projected from the incidence in the historical comparison group, are presented in Table 2 and Figure 1. The observed incidence rates of acute liver injury (second dose only), GBS, herpes zoster, single organ cutaneous vasculitis, arterial thrombosis, splanchnic thrombosis, VTE (first dose only) and thrombocytopenia (first dose only) following one or both doses of BNT162b2 were not statistically different than the expected incidence rates for those AESIs'. The observed incidence rate of acute liver injury following the first dose was statistically less than the expected incidence rate for that AESI. Thrombocytopenia and VTE following the second dose of the vaccine only had an IRR of 1.3 (1.1– 1.5) and 1.2 (1.1– 1.3), respectively. There were 6 events or less of erythema multiforme and CVT observed following vaccination and the IRR calculated for these events was not statistically significant.

The age-stratified IRRs of these ten AESIs are presented in Supplementary Table S3 and S4. There was no statistically significant increased incidence of the ten AESIs in any specific age-group except for single organ cutaneous vasculitis in the 20–39-year-old age group and VTE in the 40-59-year-old age group following the first dose of the BNT162b2 vaccine (Supplementary Table S3). There were six events or less of single organ cutaneous vasculitis observed following the first dose of the vaccine in the 20–39-year-old age group, with an IRR (95%) of 3.7 (1.1– 7.0) and a risk difference (95%) of 0.3 (0.0– 0.7) events per 100,000 persons vaccinated. The IRR of VTE following the first dose of the vaccine in the 40-59-year-old age group was 1.4(1.1– 1.7) with a risk difference of 1.6 (0.3– 3.0). These two associations were not observed in any other age group following either dose of the vaccine. The IRR of GBS, erythema multiforme, herpes zoster, arterial thrombosis, CVT, and splanchnic thrombosis could not be calculated in certain age groups as there were 6 events or less in both the historical comparison group and vaccinated cohorts.

Compared with the expected, the incidence rates of myo/pericarditis were greater post-vaccination, with an IRR (95%CI) of 2.6 (2.2– 2.9) and 4.1 (3.7– 4.5) following the first and second dose of BNT162b2 respectively (Table 2 and Figure 1). The risk difference (95%) in the 21 days after the first and second dose was 1.6 (1.1– 2.1) and 3.2 (2.6– 3.9) per 100,000 persons vaccinated, respectively. The IRRs of myo/pericarditis in the 21 days following both doses of the vaccine stratified by age (20-year age group) are presented in Table 3. The highest IRR was 25.8 (95% CI 15.6– 37.9) in the 5-19 years age group, following the second dose of the vaccine. The number of excess cases of myo/pericarditis in this age group was 4.6 (2.7– 6.7) per 100,000 persons vaccinated. The IRR of myo/pericarditis following the first and second dose of the vaccine was 4.1 (2.9– 5.3) and 6.6 (5.1– 8.3), respectively, in 20 and

39 years old, and 2.4 (1.6– 3.2) and 3.7 (2.7– 4.7), respectively, in the 40- and 59-year-old age group. The rates of myo/pericarditis were as expected for individuals aged 60 years and above.

The IRR for AKI following the first dose was 1.6 (1.5– 1.6) with a risk difference of 19.2 (17.1– 21.4) per 100,000 persons and was 1.7 (1.6– 1.7), with a risk difference of 23.1 (20.7– 25.4) per 100,000 persons following the second dose (Table 2 and Figure 1). In the subgroup analysis, stratified by 20-year age groups, an increased incidence of AKI was seen following the first and second dose of the vaccine in all age groups except the 5–19-year-olds (Supplementary Table S3 and S4).

DISCUSSION

This nationwide cohort study, involving more than 4 million vaccinated persons in New Zealand, aged 5 years or older, found no association between BNT162b2 vaccination and the majority of the 12 selected AESIs, including acute liver injury, GBS, erythema multiforme, herpes zoster, arterial thrombosis, CVT and splanchnic thrombosis. To our knowledge, this is the largest ever post-marketing vaccine safety study carried out in the country and includes representation across the population (including main ethnic groups). Our findings provide reassurance on the overall safety profile of the BNT162b2 vaccine.

However, vaccination was associated with a rare but significant increased risk of myo/pericarditis following both doses of the BNT162b2 vaccine. The association was found to be highest in the youngest recipients, under 39 years old, and following the second dose, with an estimated 5 additional myo/pericarditis cases per 100,000 persons vaccinated. Importantly, this risk was not limited to younger age groups, and an increased risk of myo/pericarditis was seen in individuals between the ages of 40 and 59 years old. We also observed more events than expected of AKI following both doses of the vaccine. A slight increased incidence of thrombocytopenia and VTE was observed following the second dose of the vaccine. Moreover, we observed more events than expected of single organ vasculitis in the 20–39-year-old age group only.

Although no cases of myo/pericarditis were reported during the BNT162b2 vaccine phase III clinical trials [3], this was detected through reports to New Zealand's spontaneous system and in many international post-marketing studies and case series reports [27-32]. As a result, both myocarditis and pericarditis were included in the New Zealand product information by the sponsor, Pfizer-BioNTech, in July 2021 at the request of Medsafe [33]. Our findings align with these reports and studies that suggest a relationship, especially in younger people and after the second dose [29]. Consistent with our results (2 and 3 excess hospitalisation events per 100,000 persons after the first and second dose, respectively), a population-based cohort study in Israel of 884,828 vaccinees using health care data estimated the excess risk of myocarditis to be 3 events per 100,000 persons vaccinated with the BNT162b2 vaccine [28]. Another Israeli study provides further evidence with the addition of clinical review assessments and found that the risk of myocarditis was highest in young males after the second dose [29]. They estimated a standardised incidence ratio of 13.60 (95% CI, 9.30 to 19.20), that translates to 14 additional events of myocarditis per 100,000 persons in vaccinated recipients aged 16 to 19 years old.

In our study, the higher incidence rates of myo/pericarditis observed following vaccination in the youngest age group is most likely due to differences in the way age groups were stratified in the observed versus expected datasets. The background incidence data used to calculate the expected rate includes information on persons between the ages of 0 and 19

years, while our observed rate includes persons between the ages of 5 and 19 years. The incidence of myocarditis has been found to increase with age in children [34], and the inclusion of children under 5 years of age may have led to an underestimate of our expected rates, and thereby an overestimate of the rate for myo/pericarditis after vaccination in this age-group.

Importantly, the risk of myo/pericarditis is still low in individuals under 19 years old, with an excess of 2 and 5 events per 100,000 persons after the first and second dose of the vaccine respectively. Furthermore, given the increased public and medical awareness around myo/pericarditis as a rare adverse reaction of COVID-19 mRNA vaccines, BNT162b2 vaccination might lead to increased hospitalisations and over-identification of the event compared to pre-pandemic years. Most importantly, studies have found that the risk of myocarditis following SARS-CoV-2 infection is substantially greater than after COVID-19 mRNA vaccination[28, 32, 35]. It is generally considered that the benefits of vaccination with the BNT162b2 vaccine against COVID-19 continue to outweigh the risks from the disease [36].

Unlike myo/pericarditis, AKI has not been identified as an adverse reaction to the BNT162b2 vaccine. We observed a statistically significant increased incidence of AKI following both doses of the vaccine. This increased incidence was seen in all age groups except the 5-19-year-olds. The number of large real-world studies investigating the incidence of AKI following COVID-19 vaccination is limited. One study used data from the Vaccine Adverse Event Reporting System (VAERS) and identified 616 cases of AKI reported after BNT162b2 vaccination during a year and a half of vaccinations in the United States. The analyses indicated an increased risk of AKI after BNT162b2 vaccination, however, as the data is self-reported, it is subject to several limitations such as inaccurate and incomplete information on reports. Moreover, the majority of patients who reported AKI were older than 65 years, and more than 50% had underlying diseases that could contribute to AKI such as hypertension, diabetes, and chronic kidney disease. As such, further investigation is needed to understand this association.

Similarly, thrombocytopenia, VTE and single organ cutaneous vasculitis have not been identified as adverse reactions to the BNT162b2 vaccine. Although we observed more events than expected of thrombocytopenia (1.3 (1.1– 1.5)), and VTE (1.2 (1.1– 1.3)) following the second dose of the vaccine, the rate increases were low and the confidence intervals near 1.00. This suggests that there is very little difference between the observed and expected events. Furthermore, there were no statistically significant increases of thrombocytopenia in our subgroup analysis stratified by 20-year age groups. There was a slight increased incidence of VTE following the first dose in the 40–59-year-old age group only (1.4 (1.1-1.7)) but this association was not seen in any other age group following either dose of the vaccine. There have been case reports of these AESIs occurring after dose one and/or two of the BNT162b2 vaccine internationally. However, no clear association has been confirmed and several large real-world studies observed no increased risk of VTE or thrombocytopenia following BNT162b2 vaccination [28, 37-42].

We also observed an increased rate of single organ cutaneous vasculitis following the first dose of the BNT162b2 vaccine in the 20–39-year-old age group only. However, both the observed and expected numbers were extremely low (less than 6 events), resulting in wide confidence intervals. To our knowledge, the rate of vasculitis following BNT162b2 vaccination has not been evaluated in any other population-based observational study, and there have only been a few case reports and reviews in the literature. Cases that were

reported occurred after both doses, with no differences in gender or age [43-46]. Given the low incidence rates of VTE, thrombocytopenia and single organ cutaneous vasculitis observed following vaccination, and lack of evidence from international studies, further research and continued safety monitoring are required to establish an association between these AESIs and the BNT162b2 vaccine.

Our study has several strengths, including the robustness and completeness of the datasets used. We linked data on all individuals vaccinated with a first or second dose of BNT162b2 to national hospitalisation records for all persons who use public health and disability services in New Zealand. Importantly, BNT162b2 is freely available to all eligible individuals in New Zealand (as of 10 February 2022, this is individuals aged 5 years and above), regardless of eligibility to public health and disability services. This enabled us to rapidly assess, analyse, and contextualise the risk for all vaccine-related outcomes of interest that that were hospitalised in the public setting from 19 February 2021 through to 10 February 2022. The same hospitalisation dataset and diagnosis codes were also used to determine the number of AESI from the background rates (2014-2019), making our study less susceptible to misclassification bias. Furthermore, during the study period, New Zealand suppressed community transmission of SARS-CoV-2 [10] and experienced one of the lowest incidence of infection and COVID-19 related mortality among the Organisation for Economic Co-operation and Development (OECD) countries [47, 48]. High community transmission of the virus in other countries can introduce bias to pharmacovigilance studies, especially as many of the adverse events observed following immunisation, such as myocarditis, are also associated with SARS-CoV-2 infection. New Zealand also achieved extremely high vaccination coverage, particularly in individuals over 12 years of age, with 95% of this population vaccinated with at least one dose of the BNT162b2 vaccine. To put this in context, approximately 86% of Māori, 88% of Pacific Peoples, and 90% of NZ European and Asian, aged 12 years and older, received at least one dose of the vaccine during the study period. This allowed us to study the true effects of the vaccine in nearly an entire population, that includes representation across the main ethnic groups in New Zealand. We therefore believe that our analysis includes the largest number of Māori and Pacific peoples in any vaccine surveillance study undertaken globally to date.

Our study is subject to several limitations. Firstly, only hospital discharge information was used to identify the outcomes of interest in the vaccinated and historical comparator cohorts. Although many of the AESI analysed in this study result in hospitalisation, less serious conditions such as herpes zoster are commonly treated in primary care settings. Therefore, diagnoses made in general practice are not included in our analyses and the rate for certain AESI following vaccination could be underestimated. Secondly, ICD-10-AM codes were used to identify outcomes of interest. There is potential for misclassification as clinical record assessments were not conducted to validate the diagnoses or codes used. Thirdly, we are limited with the use of hospitalisation data from the pre-pandemic years, 2014 to 2019, as our reference for the background incidence rates of AESI. Comparisons between these years and 2021 to 2022 might be limited due to secular trends in disease, seasonal variations in outcomes and changes to viral circulation, especially in the context of the pandemic. For example, the influenza virus circulation in New Zealand was almost non-existent during the 2020 winter [49], with a 99.9% reduction from previous years. This trend continued, with no cases of influenza reported during the 2021 winter season [50, 51]. Furthermore, variation in diagnostic or coding practices from 2014 through to 2022 can lead to an under or overestimate of risks for certain AESI. Fourthly, although the study population included more than 4 million people, for extremely rare outcomes (e.g., CVT and GBS), too few events were observed, particularly in specific age groups, to draw any conclusions from

the estimated IRR. Fifthly, we used one risk period of 0-21 days, and the IRRs may be underestimated or overestimated if the real risk period was longer or shorter. Finally, although we adjusted for age in our analysis, we could not adjust for other factors such as sex, ethnicity, or comorbidities. Stratification by both age and another factor e.g., sex and ethnicity, was not provided in our background rate data, making further subgroup analysis impossible. Additional observational studies that are not reliant on background rates, such as the self-controlled case series (SCCS) or revised background rates that stratify by multiple factors are required to allow for this. However, given that this study is representative of nearly the entire eligible New Zealand population, including 86% of Māori and 88% of Pacific peoples aged 12 years and above, we are confident that the overall safety profile of the vaccine in these groups is understood.

CONCLUSION

This nationwide study of more than 4 million people in New Zealand, identified a rare but statistically significant association between myo/pericarditis in the 21 days following both doses of the BNT162b2 vaccine. The risk was highest following the second dose and in the youngest age groups. We also observed more events than expected of AKI following both doses of the vaccine. A slight increased incidence of thrombocytopenia and VTE was observed following the second dose of the vaccine. Moreover, we observed more events than expected of single organ vasculitis in the 20–39-year-old age group only. However, the increased rates of thrombocytopenia, VTE and single organ cutaneous vasculitis following BNT162b2 vaccination were low and there is insufficient evidence to establish an association. We found no other significant associations between the BNT162b2 vaccine and any other outcome of interest. These findings provide further reassurance on the safety profile of the vaccine, particularly from a New Zealand specific context. Importantly, studies have found that the risk of any of these AESI following SARS-CoV-2 infection is substantially greater than after COVID-19 mRNA vaccination.

TABLES AND FIGURES

Table 1. Baseline demographics of study participants in observed (2021-2022) and expected (2014-2019) cohorts, New Zealand

Characteristics		Historical Comparison group 2014-2019 (%)[a]	Vaccinated Cohort: First dose (%)	Vaccinated Cohort: Second dose (%)
Total		29,269,989	4,277,163	4,114,364
Sex	**Female**	14,770,293 (50.5)	2,159,097 (50.5)	2,082,166 (50.6)
	Male	14,496,951 (49.5)	2,112,089 (49.4)	2,026,359 (49.3)
	Unknown	2,748 (0.01)	5,977 (0.1)	5,839 (0.1)
Age group	**5-19** [b]	7,526,508 (25.7)	761,322 (17.8)	628,049 (15.3)
	20-39	7,949,337 (27.2)	1,294,892 (30.3)	1,276,399 (31.0)
	40-59	7,590,234 (25.9)	1,181,252 (27.6)	1,171,458 (28.5)
	60-79	5,032,203 (17.2)	857,393 (20.1)	856,397 (20.8)
	80+	1,171,701 (4.0)	182,304 (4.3)	182,061 (4.4)
Ethnicity	**Māori**	4,734,330 (16.2)	562,895 (13.2)	522,548 (12.7)
	Pacific people	1,997,523 (6.8)	297,833 (7.0)	280,243 (6.8)
	Asian	4,035,918 (13.8)	691,935 (16.2)	666,566 (16.2)
	NZ European or other	18,339,789 (62.7)	2,693,945 (63.0)	2,615,230 (63.6)
	Unknown	162,423 (0.6)	30,555 (0.7)	29,777 (0.7)

a. Figures taken from the background rate study of COVID-19 AESIs in New Zealand (2014-2019) **[17, 18]**.
b. The background rate data includes information on individuals age ≥0. The vaccination data contains information on

Table 2. Age-adjusted incidence rate ratios (95% confidence intervals) of prespecified AESI in the 21 days following the first and second dose of the BNT162b2 vaccine, 19 February 2021 to 10 February 2022, New Zealand

Adverse Event	No. Doses administered	Person years	Observed events	Expected events [a]	Incidence Rate Ratio (95% CI)	Risk Difference (95% CI) (per 100,000 persons)
Acute Kidney Injury						
First dose	4197826	90962276	2279	1446.2	1.6 (1.5– 1.6)	19.2 (17.1– 21.4)
Second dose	3926047	86025950	2370	1424.9	1.7 (1.6– 1.7)	23.1 (20.7– 25.4)

Acute Liver Injury						
First dose	4197851	90962805	43	61.7	0.7 (0.5– 0.9)	-0.4 (-0.7– -0.1)
Second dose	3926078	86026624	49	60.5	0.8 (0.6– 1.1)	-0.3 (-0.6– 0.2)
Guillain-Barré syndrome						
First dose	4197852	90962827	9	≤6	1.6 (0.6– 2.7)	0.1 (-0.1– 0.2)
Second dose	3926078	86026624	≤6[b]	≤6	0.9 (0.2– 1.8)	-0.0 (-0.1– 0.1)
Erythema multiforme						
First dose	4197852	90962827	≤6	≤6	1.1 (0.2– 2.3)	0.0 (-0.1– 0.1)
Second dose	3926078	86026624	≤6	≤6	0.3 (0.0– 0.9)	-0.1 (-0.1– -0.0)
Herpes Zoster						
First dose	4197852	90962827	38	50.2	0.8 (0.5– 1.0)	-0.3 (-0.6– 0.0)
Second dose	3926077	86026602	48	49.5	1.0 (0.7– 1.3)	-0.0 (-0.4– 0.3)
Single Organ Cutaneous Vasculitis						
First dose	4197852	90962827	15	12.6	1.2 (0.6– 1.9)	0.1 (-0.1– 0.3)
Second dose	3926078	86026624	11	11.2	1.0 (0.4– 1.6)	-0.0 (-0.2– 0.2)
Myo/pericarditis						
First dose	4197851	90962805	112	43.7	2.6 (2.2– 2.9)	1.6 (1.1– 2.1)
Second dose	3926078	86026624	175	42.8	4.1 (3.7– 4.5)	3.2 (2.6– 3.9)
Arterial Thrombosis						
First dose	4197852	90962827	29	34.0	0.9 (0.6– 1.2)	-0.1 (-0.4– 0.1)
Second dose	3926078	86026624	22	33.7	0.7 (0.4– 1.0)	-0.3 (-0.5– -0.0)
Cerebral Venous Thrombosis						
First dose	4015821	86965857	≤6	≤6	2.3 (0.0– 6.4)	0.0 (-0.0– 0.1)
Second dose	3744568	82043434	≤6	≤6	0.8 (0.0– 3.1)	-0.0 (-0.0– 0.1)
Splanchnic Thrombosis						
First dose	4197852	90962827	11	9.9	1.1 (0.5– 1.9)	0.0 (-0.1– 0.2)
Second dose	3926078	86026624	15	9.7	1.5 (0.8– 2.4)	0.1 (-0.1– 0.3)
Venous thromboembolism						
First dose	4197851	90962805	261	237.3	1.1 (1.0– 1.2)	0.6 (0.1– 2.2)
Second dose	3926077	86026602	275	235.1	1.2 (1.1– 1.3)	1.0 (0.8– 3.1)
Thrombocytopenia						
First dose	4197851	90962805	134	125.6	1.1 (0.9– 1.3)	0.2 (-0.3– 0.7)
Second dose	3926078	86026624	157	122.2	1.3 (1.1– 1.5)	0.9 (0.3– 1.5)

a. Expected events taken from the background rate study of COVID-19 AESI in New Zealand (2014-2019). Rates are per 100,000 person years [17, 18].
b. Events with fewer than six occurrences have been suppressed for privacy reasons.

Table 3. Age-adjusted incidence rate ratios (95% confidence intervals) of myo/pericarditis in the 21 days following the first and second dose of the BNT162b2 vaccine, stratified by 20-year age group, 19 February 2021 to 10 February 2022, New Zealand

Vaccine Dose	Age Group (years)	No. Doses administered	Person years	Observed events	Expected events [a]	Incidence Rate Ratio (95% CI)	Risk Difference (95% CI) (per 100–000 persons)

First dose	**5-19**[b]	693704	13990513	11	1.2	9.0 (4.1–15.0)	1.5 (0.6– 2.5)
	20-39	1287414	28251623	46	11.3	4.1 (2.9–5.3)	2.6 (1.6– 3.6)
	40-59	1178336	25894383	34	14.4	2.4 (1.6– 3.2)	1.6 (0.7– 2.6)
	60-79	856366	18829316	19	14.3	1.3 (0.8–2.0)	0.5 (-0.4– 1.5)
	80+	182031	3996970	≤6[b]	≤6	0.8 (0.00– 2.1)	-0.3 (-1.4– 1.4)
	Total	4197851	90962805	112	43.7	2.6 (2.2– 2.9)	1.6 (1.1– 2.1)
Second dose	**5-19**	465201	10129517	23	0.9	25.8 (15.6– 37.9)	4.6 (2.7– 6.7)
	20-39	1260122	27572612	73	11.0	6.6 (5.1– 8.3)	4.7 (3.5– 6.0)
	40-59	1164895	25565746	52	14.2	3.7 (2.7– 4.7)	3.1 (2.0– 4.3)
	60-79	854350	18775559	23	14.2	1.6 (1.0– 2.3)	1.0 (-0.02– 2.1)
	80+	181510	3983190	4	2.5	1.6 (0.4– 3.4)	0.8 (-0.9–3.0)
	Total	3926078	86026624	175	42.8	4.1 (3.7– 4.5)	3.2 (2.6– 3.9)

a. Expected events taken from the background rate study of COVID-19 AESI in New Zealand (2014-2019). Rates are per 100–000 person years [17, 18].
b. Events with fewer than six occurrences have been suppressed for privacy reasons.

FIGURE TITLE

Figure 1. Age-adjusted incidence rate ratios (95% confidence intervals) of prespecified AESI in the 21 days following the first and second dose of the BNT162b2 vaccine, 19 February 2021 to 10 February 2022, New Zealand. Bars indicate 95% confidence intervals.

Contributors

MW contributed to the statistical design, supported the analysis, interpreted the data, wrote the manuscript, and revised the content. VP contributed to the statistical design, carried out the analysis, and interpreted the data. TT contributed to the conception of the study,

statistical design, supported the analysis and interpreted the data. TL provided consultation on the statistical analysis and research. TH contributed to the conception of the study, supervised the study, and reviewed the content. All authors critically reviewed the manuscript and provided final approval of the version to be published.

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Data sharing statement

The data that support the findings of this study are not able to be made publicly available due to privacy and ethical restrictions outlined by New Zealand Legislation.

Declaration of Interest

The authors have no conflicts of interest to disclose.

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