

SAFE Project:

Background rates of adverse events of special interest (AESIs) for COVID-19 vaccination

Part 1: Background rates of AESIs in New Zealand 2008–2019

Final report

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Executive summary

Background

The first COVID-19 vaccines became available at the end of 2020 and mass vaccination programmes were implemented rapidly across many countries. Careful safety monitoring for adverse events of special interest (AESIs) following vaccination was, and continues, to be a critical activity. To understand if increased AESI incidences are attributable to COVID-19 vaccination/s, baseline reference data from before vaccine deployment is required. Baseline data serve as preparation for signal verification and risk assessment should they be required during the programme as well as risk communication. As with other countries, New Zealand did not have the baseline data required to form the basis of robust vaccine safety monitoring.

In 2018 the Coalition for Epidemic Preparedness and Innovation (CEPI) contracted with the Brighton Collaboration, through The Task Force for Global Health, to harmonise the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) project. In response to the pandemic SPEAC established and prioritised a set of AESIs for COVID-19 vaccines. SPEAC and the Brighton Collaboration have also engaged in a long-term programme establishing case definitions for AESIs following vaccination. Internationally agreed case definitions for each of the AESIs enable consistent assessment and diagnosis of AESIs across multiple healthcare networks and countries, support measurement of baseline rates for the conditions and reporting and contributes to harmonised vaccine safety surveillance. The Brighton Collaboration case definitions provide key criteria to define the level of diagnostic certainty that the presentation is a case.

The outcomes of the *Background rates of AESIs in New Zealand 2008–2019* project has helped prepare New Zealand for local assessment of COVID-19 vaccine safety by establishing baseline rates for 20 AESIs extracted from the SPEAC prioritised list and myocarditis, pericarditis, multisystem inflammatory syndrome, a range of haematological conditions potentially associated with the newly identified thrombosis with thrombocytopenia syndrome (TTS), herpes zoster (shingles), narcolepsy, and sudden death for the New Zealand population overall and key subgroups from 2008–2019. These background rates may be used as a first step to contextualise data from prospective monitoring studies, spontaneous reports from the *Centre for Adverse Reaction Monitoring* and other databases, and case reports, and thereby form a basis for identifying potential COVID-19 vaccine safety signals. With the baseline established, signals may be verified through the conduction of observed over expected analysis with the same population cohort.

There are two components to the SAFE Project. First, the *Background rates of AESIs in New Zealand 2008–2019* reports on the incidence of predefined AESIs and a range of other conditions of interest. Second, the *Assessing accuracy of search strategies for AESIs* reports on clinical record assessment provides insight into the disease codes used in the administrative health data. The primary objectives were to estimate the incidence of predefined AESIs and other conditions of interest in the general population by calendar year,

age band, sex, ethnicity, deprivation, and region over the period 2008–2019 and use clinical record assessment to identify the accuracy (positive predictive value (PPV)) of the ICD-10-AM codes used in the health data to estimate the incidence of AESIs.

The *Background rates of AESIs in New Zealand 2008–2019* also reports on the prevalence of predefined high-risk medical conditions for developing severe COVID-19 disease.

Approach

Background rates

This project aligned our approach to the *Vaccine monitoring Collaboration for Europe (VAC4EU) vAccine Covid-19 monitoring readinESS (ACCESS)* protocol. Alignment of New Zealand methodology with global practices enables direct data comparisons and knowledge sharing internationally, with the overall aim of developing robust surveillance systems for vaccine safety.

This was a retrospective multi-database cohort assessment over the years 2008–2019 conducted in the *Stats NZ Integrated Data Infrastructure (IDI)*. The period was selected due to the combined quality and quantity of data available at the time. Data was sourced from multiple existing databases, including but not limited to the *Laboratory Claims Data, National Health Index (NHI) Database, National Maternity Collection, National Minimum Data Set, National Non-admitted Patient Collection, and Pharmaceutical Collection* to collate a longitudinal data set linked by NHI number for 2008–2019. Data includes age band, sex, ethnicity, and region, and by the seasonal and/or annual incidence of AESI-related medical conditions and events, and a range of other conditions of interest and high-risk conditions for developing severe COVID-19 disease. The *New Zealand Customs Service Journey Data Table* was used to accurately censor individuals where data sets were incomplete.

Initially, 20 AESIs from the SPEAC prioritised list, plus multisystem inflammatory syndrome, narcolepsy, and sudden death were identified for documentation of background rates. Three new AESIs (myocarditis, pericarditis, and thrombosis with thrombocytopenia syndrome (TTS)) and one condition of interest (herpes zoster (shingles)) were identified through real-world use of the COVID-19 vaccines. Myocarditis, pericarditis, a range of haematological conditions potentially associated with the newly identified thrombosis with thrombocytopenia syndrome (TTS), and herpes zoster were added to this investigation. Clinical records were assessed to validate selected ICD-10-AM and SNOMED codes for all Tier 1 AESI conditions identified by SPEAC, except anaphylaxis.

High-risk medical conditions for developing severe COVID-19 disease were defined in line with the ACCESS protocol and the information available on the *Centers for Disease Control and Prevention Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers*, which is updated regularly. These conditions include diabetes mellitus and five conditions (arrhythmia, coronary artery disease, heart failure, microangiopathy, stress cardiomyopathy) that overlap with potential vaccine safety indicators for the acute cardiac injury AESI.

Outcomes were defined dichotomously by the presence of specified ICD-10-AM codes in the primary or any of the other 99 possible diagnosis fields available in the *National Minimum Data Set* (NMDS). A list of ICD-10-AM codes for these conditions was developed and relevant clinical expertise sought as required.

Incidence rates, and 95% confidence interval (CI), of AESI and pregnancy outcomes by calendar year were calculated by dividing the number of incidence (new) cases by the total person-time at risk. Confidence intervals are based on Poisson distribution of counts.

Each outcome was summarised with total frequencies, incidence rates and 95% CIs. Incidence rates for each identified AESI were stratified by age, calendar year of hospitalisation, ethnicity, region, and socioeconomic status.

The *Assessing accuracy of search strategies for AESIs* project outcomes complement the use of background rates in identifying and verifying potential vaccine safety signals by contributing context, predictive value, and insight into coding reliability and practice.

Clinical record assessment was divided into two parts:

Part A: Codes to cases documented and assessed the accuracy of search strategies to identify patient events in New Zealand that met the *Brighton Collaboration* case definitions for each AESI, except for anaphylaxis, prioritised in Tier 1 by SPEAC, myocarditis, and pericarditis. Anaphylaxis was excluded as when vaccine related the condition generally occurs within a short time after vaccination, less than 15 minutes, and has a clear association.

Part B: Cases to codes focused on cases of thrombocytopenia, described the associated ICD-10-AM and SNOMED codes. Thrombocytopenia was selected as this is one requirement for diagnosis of the newly identified TTS and there are no specific ICD-10-AM or SNOMED codes that represent diagnosis of the syndrome.

Candidate ICD-10-AM and SNOMED codes were developed based on advice from senior coders and content experts – a haematologist, a neurologist, a paediatric cardiologist, an infectious diseases physician and a general practitioner. Specificity was favoured over sensitivity, all instances of codes were included, not just the primary diagnosis. Only the first event was sought for each patient.

Eight *District Health Boards* (DHBs) were approached as a convenience sample, including all those who used SNOMED codes for emergency department (ED) visits, and those that had remote access available for some or all the clinical record assessments. Included DHBs were Northland, Auckland, Counties Manukau, Bay of Plenty, Hutt Valley, Capital and Coast, Nelson Marlborough, and Canterbury. Between them the DHBs covered approximately 55% of the national population and covered the country geographically.

For hospital admissions, data was requested for all events coded with one or more of the target ICD-10-AM codes admitted between 1 January 2016 and 31 December 2019; except that for thrombocytopenia and Bell's palsy (also termed peripheral facial nerve palsy), for which data to 31 March 2021 was requested to allow comparison with SNOMED codes from ED visits. If there were fewer than eight cases, the DHB was asked to search data back to 1 January 2008. For ED visits, data was requested for all events coded with one or more of the target SNOMED codes seen between the start of coding in 2019 to 31 March 2021.

The decision to limit most data collection to 2019 and earlier was because data from 2020 may have been affected by either COVID-19 disease or the public health response to manage the pandemic, and data in 2021 may be affected by the COVID-19 vaccine roll-out.

From each of the eight DHBs, four events for each ICD-10-AM code up to 31 December 2019 were randomly selected using an online random generator. From each of the four DHBs using SNOMED codes eight events up to 31 March 2021 were randomly selected. This gave 32 events per code for clinical record assessment, which was conducted by an experienced coder, either in person or remotely depending on availability and agreement with each DHB.

As a case study, all people with thrombocytopenia attending one DHB over a specified period were identified and coding patterns described.

Results

The study population was representative of people living in New Zealand during the study period, and the demographic profile remained stable. Over the 12-year study period the size of the denominator population gradually increased by over 600,000 persons, with over five million persons in 2019.

A total of 761 events in clinical records were assessed. With a 95% confidence interval (CI), codes selected for the following AESIs had the greatest PPV: thrombocytopenia (94–100%), Guillain-Barré syndrome (81%), generalised convulsion (69–100%), and myocarditis (34–100%). With a 95% CI, codes selected for the following AESIs had the lowest PPV: acute disseminated encephalomyelitis (21–60%) and pericarditis (33–66%). Nuances were identified during the review that should be considered when using the ICD10-AM codes to identify and refine AESIs. For generalised convulsions, some cases had been included that were recorded from a previous admission rather than the current admission. For Bell's palsy, it is common practice in New Zealand to discharge patients to primary care prior to full resolution, therefore the case definition criterion "full recovery" is unlikely to be met and the level of diagnostic certainty that the presentation is a case unable to be applied.

There were 88,178 thrombocytopenia-associated hospital admissions, including only the first event per patient, recorded between 1 January 2008 and 31 December 2019. Of these, only 3% (n=2493) of cases had an associated ICD-10-AM code that specified thrombocytopenia. There are no ICD-10-AM 11th edition

codes specific to disseminated intravascular coagulation (DIC) or deep vein thrombosis (DVT), either of which together may mimic TTS.

Summary

Established population background rates of conditions that are potential AESIs following vaccination are an essential component for vaccine safety surveillance. However, in May 2020 no countries had these available and few had commenced planning to undertake this activity. Stimulated by the COVID-19 pandemic and rapid availability of vaccines to protect against COVID-19, lists of AESIs for COVID-19 vaccination were developed, along with case definitions for newly identified events.

The background rates presented here should be viewed with the understanding that that trends over time and the consistent use of codes can change. The purpose of background rates is not an exercise in precision but rather consistency in definitions and approach – comparing like with like to be useful for vaccine safety signal detection and verification. These rates have been established for their role in crude signal detection during the delivery of new vaccines to the New Zealand population.

While there was considerable variation in the PPV for the Tier 1 AESIs using ICD-10-AM codes selected in this review, consistent use of codes over time should allow signal detection.

The denominator cohort derived from the IDI compares well with other New Zealand population denominators and has slightly better representation of younger healthy individuals than the health service user population.

Recommendations

We have four recommendations for the ongoing utility of this work.

1. That this work be extended to include 2020 and 2021.
2. That observed versus expected rates are undertaken using the same source population to complement other safety surveillance activities and to compare like with like.
3. That this activity be repeated on a regular basis for the duration that COVID-19 pandemic vaccines are in use.
4. That this activity be activated in the future should monitoring of a new vaccine be required.

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Conflict of interest statement

All members of the research team involved in this project and production of the final report are employed by either Waipapa Taumata Rau, University of Auckland or Auckland UniServices Limited. They have no conflicts of interest to this project to declare.

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Abbreviations

Abbreviation	Description
ACCESS	vAccine Covid-19 monitoring readinESS project
AEFIs	adverse events following immunisation
AESIs	adverse events of special interest
AF	atrial fibrillation
AHREC	Auckland Health Research Ethics Committee
ALIVE	African Local Initiative for Vaccinology Expertise
CEPI	Coalition for Epidemic Preparedness Innovations
CI	confidence interval
COVID-19	disease caused by SARS-CoV-2
DHB	District Health Board
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
ED	emergency department
EMA	European Medicines Agency
GMS	General Medical Subsidy Collection
GTPS	HealthPAC General Transaction Processing System
GVDN	Global Vaccine Data Network
HDEC	Health and Disabilities Ethics Committee
HIV	human immunodeficiency virus
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Australian Modification
IDI	Stats NZ Integrated Data Infrastructure
IR	incidence rate
IQR	interquartile range
LMP	last menstrual period
MMR	measles, mumps, and rubella
NHI	National Health Index
NMDS	National Minimum Data Set
NZDep	New Zealand Deprivation Index
NZPhvC	New Zealand Pharmacovigilance Centre
PHO	Primary Health Organisation
PIPS	Pertussis Immunisation in Pregnancy Study
PPV	positive predictive value
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SNOMED	SNOMED Clinical Terms SNOMED CT
SPEAC	The Brighton Collaboration Safety Platform for Emergency Vaccines project
TTS	thrombosis with thrombocytopenia syndrome
VAC4EU	VAccine monitoring Collaboration for Europe
BWHO	World Health Organization

Background rates of adverse events of special interest for COVID-19 vaccination

1. Introduction

1.1 Deployment of COVID-19 vaccines

The first COVID-19 vaccines became available at the end of 2020. They were approved under emergency conditions based on clinical trial data from a few tens of thousands of human participants, and with a short follow-up time. Mass vaccination programmes were implemented at speed across many countries. Under such circumstances, it is essential that vaccines are first used in populations where intensive safety monitoring is possible. Vaccine deployment is ideally accompanied by enhanced safety surveillance in countries where mature enough systems are in place, with the resulting data being provided to those countries without such capability.^{1,2}

Careful safety monitoring for adverse events of special interest (AESIs) following vaccination was, and continues, to be a critical basic activity. To begin to understand if increased AESI incidences are attributable to COVID-19 vaccination/s, baseline reference data prior to vaccine deployment is required. Baseline data serve as preparation for signal verification and risk assessment should they be required during the programme as well as risk communication. As with other countries, early in the pandemic New Zealand did not have the baseline data required to form the basis of robust vaccine safety monitoring.

In addition to trial size limitations, current phase III studies of COVID-19 vaccines are occurring at sites with high rates of disease, such as South Africa and Brazil, and excluding areas such as New Zealand and the Pacific Islands. Therefore, there is limited or no data on people of Polynesian descent. New Zealand is one of several strongly placed countries to deploy new vaccines with the ability to rigorously monitor safety. However, it is essential that this is conducted with full consideration of the safety and equity risks to all ethnic groups.

1.2 Importance of post-licensure safety studies

Adverse events following immunisation (AEFIs) are any untoward medical occurrence which follows immunisation, but do not necessarily have a causal relationship with the vaccine. AESIs are a subset of AEFIs, that are defined as events of scientific and medical concern specific to the sponsor's product or programme. Assessment of AEFIs that have a delayed onset or diagnosis and occur beyond clinical trial follow-up, are rare, or occur among sub-populations are often beyond the scope of initial clinical programmes.² This makes post-licensure studies critical. In the past decade, international collaborations have demonstrated the ability to supply background rates of events of interest in anticipation of the use of new vaccines (e.g., H1N1 pandemic vaccines), develop tools and procedures for collaborative studies of vaccine safety and efficacy, and implement vaccine safety studies globally.^{2,3}

Based on the progress and evaluation of the *World Health Organization (WHO) Global Vaccine Safety Initiative Blueprint 1.0*, strategies that have been highlighted in *Blueprint 2.0* for the next decade^{4,5} include using and coordinating existing active surveillance and sentinel systems regionally, nationally and globally to measure background rates of events of interest, taking advantage of variability in vaccination practices, and increase power and timeliness.

1.3 Vaccine safety equity in New Zealand

The improvement in equitable delivery of vaccines in New Zealand has had a dramatic effect on disease incidence, most notably for Māori and Pasifika children, and those with the lowest socioeconomic status. While vaccines have reduced inequities in vaccine preventable disease burden in New Zealand and are therefore equitably effective when delivered well, there is still the question of equitable safety. Our own research has demonstrated that there can be measurable differences in vaccine reactogenicity between ethnicities. For example, fever following 2010 H1N1 influenza vaccines was more likely in New Zealand European, Māori and Indian children and adolescents, and less likely in Pasifika and non-Indian Asian populations, indicating population-level genetic differences (unpublished data). During the 2010 H1N1 immunisation programme, febrile reactions also resulted in febrile convulsions.⁶ Data from the 2002–2004 school-based clinical trial for the *MeNZB™* vaccine in South Auckland, showed that ethnicity was one of the main factors associated with vaccine reactogenicity (redness, induration, swelling and pain at the injection site).⁶

While common vaccine responses and reactions are easily measured, rare events are often not. In 2018, an infant was airlifted from Samoa to Auckland's Starship hospital where she died several days later. The cause of death was diagnosed as hemophagocytic lymphohistiocytosis, a severe systemic inflammatory syndrome that is often fatal. She had received her measles, mumps, and rubella (MMR) vaccine two weeks earlier. A family history indicated her brother had died two years earlier in Samoa with a similar presentation, also two weeks after receiving an MMR vaccination. The cause of death at the time was thought to be septic shock. Subsequent genetic investigations suggest the adverse events and immunisation may be linked. International discussions and publications reveal that several similar, albeit extremely rare, cases may have occurred.⁷

Another example of a rare vaccine related adverse vaccine event is narcolepsy onset following a single brand of 2010 pandemic influenza vaccine. This vaccine (*Pandemrix™*) triggered narcolepsy in individuals with HLA haplotype HLA-DQB1*06:02,⁸ most notably in Sweden and Finland, but not other countries.⁹ These examples stress the importance of assessing rare events in genetically diverse populations where genetic polymorphisms may favour a risk.

Vaccine hesitancy has increased among Māori to such an extent that it has become a contributor to the decline in coverage of the routine childhood vaccines, particularly in some regions.¹⁰ An important driver

behind such hesitancy is concern about vaccine safety.¹¹ Trust and effective communication strategies are pivotal to addressing community concerns about vaccines and attaining and maintaining confidence in a vaccine, but these must be underpinned by rigorous population-specific data and transparent action.

1.4 Global need and response

The WHO highlighted an urgent need to establish background rates for potential AESIs that may be related to COVID-19 vaccines. A list of these events was developed by the *Safety Platform for Emergency vAccines* (SPEAC) project,¹² a *Brighton Collaboration* project funded by the *Coalition for Epidemic Preparedness Innovations* (CEPI). There are currently around 35 adverse conditions identified as worthy of special attention, most requiring hospitalisation, yet robust background rates for many of these are not established for most countries/regions. In addition to being scientifically important, knowledge about background rates for these conditions is vital when communicating risk and addressing concerns and misinformation. Such data will be essential for informing the COVID-19 vaccine communication and implementation strategy.

SPEAC and the *Brighton Collaboration* have also engaged in a long-term programme establishing case definitions for AESIs following vaccination. Internationally agreed case definitions for each of the AESIs enable consistent assessment and diagnosis of AESIs across multiple healthcare networks and countries, support measurement of baseline rates for the conditions and reporting and contributes to harmonised vaccine safety surveillance. The *Brighton Collaboration* case definitions provide key criteria to define the level of diagnostic certainty that the presentation is a case.

Finally, there are several multi-national collaborations conducting COVID-19 vaccine safety related activities. These include the *Vaccine monitoring Collaboration for Europe* (VAC4EU) consortium, the *African Local Initiative for Vaccinology Expertise* (ALIVE) network, and the *Global Vaccine Data Network* (GVDN).^{2,13,14}

1.5 Establishing background rates – the first step.

The outcomes of the *Background rates of AESIs in New Zealand 2008–2019* project has provided initial data to support the local assessment of COVID-19 vaccine safety by establishing rates for 20 AESIs extracted from the SPEAC prioritised list (Table 1) and myocarditis, pericarditis, multisystem inflammatory syndrome, a range of haematological conditions potentially associated with the newly identified thrombosis with thrombocytopenia syndrome (TTS), herpes zoster (shingles), narcolepsy, and sudden death for the New Zealand population overall and key subgroups from 2008–2019. These background rates may be used to contextualise data from prospective monitoring studies, spontaneous reports from the *Centre for Adverse Reaction Monitoring* and other databases, and case reports, and thereby form a basis for identifying potential COVID-19 vaccine safety signals. With the baseline established, signals may be verified through the conduction of observed over expected analysis with the same population cohort.

The second component to the SAFE Project, the *Assessing accuracy of search strategies for AESIs* project, documented and assessed the accuracy of search strategies to identify patient events that met the case definition of Tier 1 AESIs¹⁵ (Table 1), except anaphylaxis, and reported on clinical record assessment to provide insight into the disease codes used in the administrative health data in New Zealand. That project also conducted a case study that identified cases of thrombocytopenia, a condition required for diagnosis of the newly identified TTS.

2. Objectives

2.1 Primary objectives

1. Estimate the incidence of predefined AESIs in the general population by calendar year, age band, sex, ethnicity, deprivation, and region over the period 2008–2019.
2. Use clinical record assessment to validate the accuracy (positive predictive value (PPV)) of the ICD-10-AM codes used in the health data to estimate the incidence of AESIs.

2.2 Secondary objectives

1. Estimate the prevalence of predefined high-risk medical conditions for developing severe COVID-19 disease by calendar year and season.

There are two main components to the SAFE Project. First, the *Background rates of AESIs in New Zealand 2018–2019* project that addresses the first primary objective and secondary objectives of the *SAFE Project*. The methodology and results for which are provided in this report. Second, the *Assessing accuracy of search strategies for AESIs* project that addresses the second primary objective of the *SAFE Project*. The methodology and results for which are provided in a separate report.

Information for the predefined high-risk medical conditions was collated from the existing published and grey literature (Appendix 1). A comprehensive collection of the background rates of adverse conditions in pregnancy, childbirth, and the neonatal period from the *Pertussis Immunisation in Pregnancy Study* (PIPS) are provided in the results section and Appendix 6.

3. Methods

3.1 Ethics approval

Ethics approval for the *Background rates of AESIs in New Zealand 2018–2019* project was granted by the *Auckland Health Research Ethics Committee (AHREC)* on 21 June 2021 (reference number AH22547).

The AHREC provides ethical oversight and approval of clinical/health research that is not eligible for review by the *Health and Disability Ethics Committee (HDEC)* and is carried out by staff of *The University of Auckland*, or staff of the Auckland or Counties Manukau District Health Boards (DHBs).

While this research did not undertake any clinical work, there was no intervention, the team observed the *Guiding Principles for Conducting Research with Human Participants* that also provided how the AHREC ensured this research conformed with the highest ethical standards. Details about the AHREC and the principles are available through this link <https://www.auckland.ac.nz/en/research/about-our-research/human-ethics/ahrec.html>.

3.2 Study design

VAC4EU, the *Vaccine monitoring Collaboration for Europe*, generates robust, timely data on the effects of vaccines in Europe. VAC4EU partnered with the *European Medicines Agency (EMA)* and established the *vACcine Covid-19 monitoring readinESS (ACCESS)* project to ensure that European infrastructure will be in place to effectively monitor COVID-19 vaccines in the real-world. The project has a *Memorandum of Understanding* with VAC4EU and designed the research in close alignment with the ACCESS protocol *for Background Rates of AESIs for Monitoring COVID-19 Vaccines (September 2021)*. Alignment of New Zealand methodology with global practices enables direct data comparisons and knowledge sharing internationally, with the overall aim of developing robust surveillance systems for vaccine safety.

We conducted a retrospective multi-database cohort assessment over the years 2008–2019. This period was selected due to the combined quality and quantity of data available. Some hospital discharge codes were clinically validated. Clinical criteria were used to support the reported codes, which were collected for administrative purposes and may have differed from this research enquiry. The New Zealand research team validated codes for all Tier 1 conditions identified by the SPEAC project, except for anaphylaxis.

3.3 AESI numerator

A comprehensive data set for AESI incidence by age band, sex, ethnicity, year, and region was constructed using the *National Minimum Data Set (NMDS)*. This dataset includes records of all public hospital discharges in New Zealand. Data fields relevant to this research include *National Health Index (NHI)* number (encrypted), admission event ID, facility code, admission date, discharge date, length of stay and ICD-10-AM diagnosis code (up to 100 diagnosis codes are available for each admission event). A list of the ICD-10-AM diagnosis codes used are available in Appendix 2, Table 1.

3.4 Population denominator

To accurately estimate population denominators for each year between 2008 (~4.3 million) and 2019 (~5 million), a whole of population cohort was constructed in the *Stats NZ Integrated Data Infrastructure (IDI)* for each calendar year taking an activity-based approach. This approach used datasets available within the IDI, which contain records of an individual's interaction, i.e., activity, with certain centrally funded services (e.g., within births, deaths, education, taxation, health, and immigration data sets). Use of ethnicity data from the census is considered gold standard for New Zealand. These records of activity were used to determine whether individuals were present and resident in New Zealand for at least six months during the observation period. Individuals who met all the following criteria were selected and linked to form the IDI population cohort:

- were within the *IDI Spine*;

AND

- were active in at least one of the following data sources: health, tax, education, and injury claims in the in-scope year, or in the births or visa dataset in last five years; **or**
- died in the year, which was recorded in at least one of the following data sources: deaths, health population cohort demographics, and personal detail (i.e., the *IDI Spine*);

OR

- were active in at least one of the following health datasets, primary health organisation enrolment, community laboratory test claims, the national non-admitted patient collection, the community pharmaceutical collection, and the publicly funded hospitalisation discharge collection, in each in-scope year;

AND

- were present in New Zealand and did not travel away from New Zealand to overseas for more than six months within the year; **or**
- arrived in New Zealand for the first time and did not spend more than six months overseas within the year;

AND

- were aged between 0 to 115 years.

To calculate incidence per event, individuals were followed until the earliest date of the event, death, exiting the data source, or last data draw down. Because person-time was censored at the occurrence of the event, person-time may have varied between events.

3.4.1 Population denominator data sources

In addition to the NMDS, the following data sources were accessed to compile a comprehensive data set linked by NHI number for 2008–2019 for AESI incidence, age band, sex, ethnicity, year, and region.

3.4.1.1 ACC claims data – were used to identify individuals who were active in this dataset in the study period for constructing the population denominator.

3.4.1.2 Department of Internal Affairs – birth and death registrations were used to flag if an individual was alive or had died in the study period for constructing the population denominator.

3.4.1.3 General Medical Subsidy Collection – contains data on the fee-for-service payments made to doctors for patient visits.

3.4.1.4 Laboratory Claims Collection – contains data on claim and payment information for laboratory tests. Data fields relevant to this research include NHI (encrypted), visit date, laboratory test code, and laboratory test type.

3.1.4.5 Ministry of Education datasets – were used to identify individuals who were active in these datasets in the study period for constructing the population denominator.

3.1.4.6 Mortality Collection – contains information on the underlying cause of all deaths (including fetal and infant deaths). Data fields relevant to this study include age at death, date of death, clinical code.

3.1.4.7 National Health Index (NHI) Database – contains demographic information for all New Zealanders. A person's NHI number, date of birth, date of death and gender are static, but the remaining data fields may change over time. Data fields relevant to this research include NHI (encrypted), date of birth, date of death, sex, prioritised ethnicity, geographic area of residence and socioeconomic deprivation level.

3.1.4.8 National Non-Admitted Patient Collection – provides nationally consistent data on non-admitted patient (outpatient and emergency department) activity.

3.1.4.9 New Zealand Census – provides the official count of the people and dwellings in New Zealand every five years. The 2013 and 2018 census data and sociodemographic information was used to construct the population denominator and meshblock level information on patient's residential address.

3.1.4.10 New Zealand Customs Service Journey Data Table – provides information on permanent or long-term departure from New Zealand so that individuals can be accurately censored where data sets are incomplete.

3.1.4.11 Pharmaceutical Collection – contains claim and payment information from pharmacists for subsidised dispensing. Data fields relevant to this research include NHI (encrypted), date dispensed, dose, frequency, day's supply, quantity dispensed, therapeutic group, chemical ID, and chemical name.

3.1.4.12 Primary Health Organisation Enrolment Collection – provides a national collection that holds Primary Healthcare System patient enrolment data.

3.1.4.13 Stats NZ Integrated Data Infrastructure (IDI) main tables – a collection of tables supplied by Stats NZ also provided information on personal detail such as gender and ethnicity, and census area unit information that was used to summarise the population and AESI events by region of residence and income data.

3.5 Outcome variables

Variables of interest for the calculation of background incidence rates were those relevant for creation of:

- Person-time: birth and death dates as well as periods of observation.
- Events: dates of medical and/or procedure codes to identify AESIs.

The AESIs focused on in this project were extracted from the lists of AESIs established and prioritised by SPEAC for COVID-19 vaccines¹⁵ (Table 1), endorsed by the WHO *Global Advisory Committee on Vaccine Safety*, and agreed by the EMA, based on one or more of the following criteria:

- Proven association with immunisation encompassing several different vaccines.
- Proven vaccine association that could theoretically be true for CEPI vaccines under development.
- Theoretical concern related to viral replication during wild type disease.
- Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

Initially, 20 AESIs from the SPEAC prioritised list, plus multisystem inflammatory syndrome, narcolepsy, and sudden death were identified for documentation of background rates. Three new AESIs (myocarditis, pericarditis, and thrombosis with thrombocytopenia syndrome (TTS)) and one condition of interest (herpes zoster (shingles)) were identified through real-world use of the COVID-19 vaccines. Myocarditis, pericarditis, a range of haematological conditions potentially associated with the newly identified thrombosis with thrombocytopenia syndrome (TTS), and herpes zoster were added to this investigation. TTS was a newly identified syndrome; thrombocytopenia was an existing Tier 1 AESI, and venous and arterial thrombosis were added to the conditions for this investigation. Clinical records were assessed to validate codes for all Tier 1 AESI conditions identified by SPEAC, except anaphylaxis.

High-risk medical conditions for developing severe COVID-19 disease were defined in line with the ACCESS protocol and the information available on the *Centers for Disease Control and Prevention Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Providers*, the webpage for which,¹⁶ is updated regularly. These conditions included diabetes mellitus and five conditions (arrhythmia, coronary artery disease, heart failure, microangiopathy, stress cardiomyopathy) that overlap with potential vaccine safety indicators for the acute cardiac injury AESI.

Outcomes were defined dichotomously by the presence of specified ICD-10-AM codes in the primary or any of the other 99 possible diagnosis fields available in the NMDS. A list of ICD-10-AM codes for these conditions was developed and relevant clinical expertise sought as required (Appendix 2, Table 1).

Table 1. SPEAC adverse events of special interest prioritised by tier of importance

Tier 1 (most important)	Tier 2	Tier 3	Tier 4
Anaphylaxis	Vaccine associated enhanced disease	Sensorineural hearing loss	Acute/chronic inflammatory rheumatism
Thrombocytopenia	Acute respiratory distress syndrome	Anosmia/ageusia	Total/partial loss of vision
Generalised convulsion	Acute cardiovascular injury (Includes arrhythmia, coronary artery disease, heart failure, microangiopathy, stress cardiomyopathy)	Chilblain-like lesions	Optic neuritis
Aseptic meningitis	Coagulation disorder (Includes arterial thrombosis, idiopathic thrombocytopenia, lower limb venous thrombosis, other venous thrombosis, pulmonary embolism, venous thromboembolism)	Erythema multiforme	Alopecia
Encephalitis	Acute kidney injury	Acute aseptic arthritis	
Myelitis	Acute liver injury	Single organ cutaneous vasculitis	
Acute disseminated encephalomyelitis			
Guillain-Barré and Miller Fisher syndromes			
Peripheral facial nerve palsy			

 AESI background rates calculated

3.6 Data management

Individuals were linked by an assigned identification code. This code was based on probabilistic linkage of individuals across data sets using a defined set of identifying variables such as first and last names and date of birth. Individuals are linked across health data with an encrypted version of the NHI. Due to the administrative nature of the data sources, there was little missing data. Where health information for a single data field was missing in 5% or less of records, complete case analysis was used to compile full data sets. Where health information was missing in 6% or more of records, consideration of the reasons for missing data, missing data patterns, and the availability of auxiliary information was used to determine the appropriate method (complete case analysis or multiple imputation) for dealing with missing data. To further harmonise with the ACCESS protocol, we worked with our collaborators to ensure a use of a common data model and common analytics programme.

Outputs from the IDI with a count less than six were suppressed ('S') as per IDI output rules. Aggregated results data outputted from the IDI were stored on a secure research drive on a server at The University of Auckland in restricted access folders. Data on servers were backed up every night in three physical

locations. Only members of the research team had access to the folders. This research was fully documented using The University of Auckland's *Data Management Plan*.

3.7 Covariates

The covariates were:

- a) Calendar year
- b) Sex
- c) Age group
 - a. Based on year of age at date of outcome grouped into the following:
0-19, 20–39, 40–59, 60–79, 80+ years
- d) Ethnicity
 - a. Prioritisation consistent with *Ministry of Health and Stats NZ*
- e) Deprivation score
- f) Region

3.8 Analysis

Incidence rates, and 95% confidence interval (CI), of AESIs and pregnancy outcomes by calendar year were calculated by dividing the number of incidence (new) cases by the total person-time at risk. Confidence intervals were calculated based on Poisson distribution. Prevalence rates, and 95% CI, of high-risk medical conditions for developing severe COVID-19 disease are reported from the published and grey literature and summarised in Appendix 1. Statistical analysis was performed using SAS version 9.4 (*SAS Institute Inc.*, Cary, NC, USA).

Each outcome was summarised with total frequencies, incidence rates and 95% CIs. Incidence rates for each identified AESI (Table 1) were stratified by age, calendar year/and or season of hospitalisation, ethnicity, region, and socioeconomic status. Annual trends in incidence are still to be examined by plotting incidence over time. Seasonal patterns in AESIs may indicate a seasonal cause, and any patterns that are detected pre-emptively will help to refine signal detection depending on when a vaccine is introduced (e.g., if vaccine delivery coincides with increased incidence of one or more AESIs, it is important to account for normal seasonal variation in attributing causality).

4. Results

4.1 Objectives

1. Estimate the incidence of predefined AESIs in the general population by calendar year, age band, sex, ethnicity, deprivation, and region over the period 2008–2019.
 - a. Estimate the prevalence of predefined high-risk medical conditions for developing severe COVID-19 disease by calendar year and season.
 - b. Provide estimates of the prevalence of AESIs in the sub-population most at risk for developing severe COVID-19 disease.

4.2 Population denominator

The study population was representative of people living in New Zealand during the study period, and the demographic profile remained stable. Over the 12-year study period the size of the denominator population gradually increased by over 600,000 persons, with over five million persons in 2019 (Appendix 3, Table 1).

The proportion of females over this period ranged from 51% to 50%. The age distribution was stable across the study period with the 0–19, 20–39 and 40–59 groups contributing the largest, approximately equal proportions. The proportion of Māori and Pasifika remained stable across the study period at 16% and 7% respectively. The deprivation profile remained stable across the study period with approximately one third of the population in each the least, moderately, and most deprived tertiles. The regional distribution remained relatively stable across the study period with the Northern region contributing the highest proportion, approximately one third.

4.3 Background rates for AESI, other conditions of interest, and high-risk medical conditions for severe COVID-19 disease

Background rates per 100,000 person years for AESI, other conditions of interest, and high-risk medical conditions for severe COVID-19 disease were calculated for the New Zealand population for each of the years from 2008 to 2019 and for the aggregated data 2008–2019 inclusively.

The most common adverse events of special interest, with over 10,000 cases per year each, were acute kidney injury, arrhythmias, coronary artery disease diabetes mellitus and heart failure. These were followed by acute liver injury, anaphylaxis, coagulation disorder, generalised convulsion, lower limb venous thrombosis, multisystem inflammatory syndrome, pulmonary embolism, thrombocytopenia, and venous thromboembolism, each between 1000 and 10,000 cases per year. The rarest events seen in hospital were anosmia and ageusia, aseptic meningitis, cerebral venous thrombosis, chilblain-like lesions, encephalitis, microangiopathy, myelitis, pregnancy thrombosis, and sudden death.

Table 2 lists each AESI and condition with the associated background rate per 100,000 person years for 2008–2019 and shows the number of cases recorded for the year 2019. With TTS being a newly defined syndrome and no specific ICD-10-AM or SNOMED codes that represent diagnosis of the syndrome, a range of haematological conditions potentially associated with the syndrome have been grouped and listed in Table 3 with the associated background rate per 100,000 person years for 2008–2019 and shows the number of cases recorded for the year 2019.

Myocarditis and pericarditis case numbers and rates by sex, age band, prioritised ethnicity and deprivation for the year 2019 are described. Following this, the prevalence of high-risk medical conditions for severe COVID-19 disease is briefly described, and the background rates overall and trends by sex, age band, ethnicity, deprivation, and region over 2008–2019 described for each AESI and condition.

Table 2. Background rate per 100,000 person years 2008–2019 and number of cases in 2019 for AESI, other conditions of interest and high-risk medical conditions in New Zealand

Condition	Rate per 100,000 person years 2008–2019	N 2019
Acute disseminated encephalomyelitis	8.47	312
Acute kidney injury	461.18	26,931
Acute liver injury	20.72	1,137
Acute respiratory disease	33.15	810
Anaphylaxis	60.72	3,213
Anosmia and ageusia	0.32	21
Arrhythmia	375.19	23,886
Arterial thrombosis	11.75	579
Aseptic meningitis	0.65	33
Cerebral venous thrombosis	0.36	30
Chilblain-like lesions (seen in Primary Care)	0.12	<6
Coagulation disorder	202.73	9,186
Coronary artery disease	343.61	12,732
Diabetes mellitus	399.21	16,254
Encephalitis	0.36	15
Erythema multiforme	2.28	105
Generalised convulsion	95.17	4,413
Guillain-Barré and Miller Fisher syndromes	2.23	102
Heart failure	261.17	12,228
Idiopathic thrombocytopenia	6.52	285
Lower limb venous thrombosis	12.02	1,284
Meningoencephalitis	5.25	306
Microangiopathy	0.40	18

Condition	Rate per 100,000 person years 2008–2019	N 2019
Multisystem inflammatory syndrome	120.03	6,711
Myelitis	0.54	27
Myocarditis	2.01	114
Narcolepsy	4.25	234
Other venous thrombosis	13.08	522
Pericarditis	12.17	723
Peripheral facial nerve palsy	17.79	582
Pregnancy thrombosis	0.34	75
Pulmonary embolism	49.52	3,045
Single organ cutaneous vasculitis	5.67	327
Splanchnic thrombosis	3.05	183
Stress cardiomyopathy	5.70	393
Sudden death	0.38	<6
Thrombocytopenia	45.79	2,373
Venous thromboembolism	63.56	3,648
Zoster (shingles)	17.57	819

4.3.1 Thrombosis with thrombocytopenia syndrome

Thrombosis with thrombocytopenia syndrome (TTS) is newly identified and there are no specific ICD-10-AM or SNOMED codes that represent diagnosis of the syndrome. Background rates for a range of haematological conditions potentially associated with the syndrome are described, including arterial thrombosis, cerebral venous thrombosis, coagulation disorder, idiopathic thrombocytopenia, lower limb venous thrombosis, other venous thrombosis, pregnancy thrombosis, pulmonary embolism, splanchnic thrombosis, thrombocytopenia, and venous thromboembolism.

The *Assessing accuracy of search strategies for AESIs* project provides insight into the potential utility of existing combinations of codes to identify TTS cases. The methodology and results for which are provided in a separate report.

Table 3. Background rate per 100,000 person years 2008–2019 and number of cases in 2019 for haematological conditions potentially associated with thrombosis with thrombocytopenia syndrome

Condition of interest	Rate per 100,000 person years 2008–2019	N 2019
Arterial thrombosis	11.75	579
Cerebral venous thrombosis	0.36	30
Coagulation disorder	202.73	9,186
Idiopathic thrombocytopenia	6.52	285
Lower limb venous thrombosis	12.02	1,284
Other venous thrombosis	13.08	522

Condition of interest	Rate per 100,000 person years 2008–2019	N 2019
Pregnancy thrombosis	0.34	75
Pulmonary embolism	49.52	3,045
Splanchnic thrombosis	3.05	183
Thrombocytopenia	45.79	2,373
Venous thromboembolism	63.56	3,648

4.3.2 Myocarditis and pericarditis in 2019

In 2019, there were a total of 114 cases of myocarditis and 723 cases of pericarditis. Combined (n=837), there are an average of 2–3 cases of heart-related inflammation per day. Pericarditis was more common and the incidence in males was double that of females. Similarly, myocarditis was also more common in males and almost double that of females. The myocarditis and pericarditis data tables for 2019 are presented in Appendix 4, Table 26 and Table 29 respectively.

While older adults, aged 60–79 years, were the most likely to present with pericarditis, this was only slightly higher than adults aged 40–59 years. The age groups presenting most often with myocarditis were those aged 40–59 years and 20–39 years. In 2019, there were no cases of pericarditis in the age group 0–19 years and 39 cases of myocarditis.

‘Other’ followed by European ethnicities were more likely to present with pericarditis, and there was insignificant variation across presentations from the least, moderately, and most deprived. For myocarditis, Pasifika followed by European and then Māori ethnicities were more likely to present, as were those from the most then moderate deprivation levels.

4.3.3 High-risk medical conditions for severe COVID-19 disease

The prevalence of predefined high-risk medical conditions for developing severe COVID-19 were varied with human immunodeficiency virus (HIV) infection being among the rarest conditions and hypertension being among the most prevalent in New Zealand (Appendix 1). There were gaps in the literature, for example, New Zealand prevalence rates were not available for solid organ or blood stem cell transplant and liver disease. The cardiac conditions, arrhythmia, coronary artery disease, heart failure, microangiopathy, and stress cardiomyopathy, are included as high-risk medical conditions and conditions of interest for identification of the Tier 2 acute cardiac injury AESI (Table 1).

4.3.4 Acute disseminated encephalomyelitis

Rates of acute disseminated encephalomyelitis per 100,000 person years decreased between 2008 and 2019, despite some fluctuations. The overall rate for this period is 8.47 (8.23–8.71). Rates among females were greater than twice those seen among males (Appendix 4, Table 1). There was some variation by DHB region, with rates in the South Island being the highest (Appendix 5, Figure 1).

4.3.5 Acute kidney injury

Rates of acute kidney injury per 100,000 person years increased between 2008 and 2019 (Appendix 4, Table 2). The overall rate for this period is 461.18 (459.41–462.95). There was some slight variation in rates by region with the South Island having a lower rate compared to other regions (Appendix 5, Figure 2). Rates of acute kidney injury increase with age and were higher among males compared to females (Appendix 4, Table 2). Rates were slightly higher in Pasifika and European ethnicities compared to other groups.

4.3.6 Acute liver injury

Rates of acute liver injury per 100,000 person years gradually increased between 2008 and 2019 (Appendix 4, Table 3). The overall rate for this period is 20.72 (20.35–21.10). There was some slight variation in rates by region with the top of the North Island having the lowest rate compared with the rest of the North Island and South Island (Appendix 5, Figure 3). Rates were higher in males compared with females (Appendix 4, Table 3).

4.3.7 Acute respiratory distress syndrome

Rates of acute respiratory distress syndrome per 100,000 person years decreased between 2008 and 2019 (Appendix 4, Table 4). The overall rate for this period is 33.15 (32.68–33.63). There was some slight variation in rates by region with the bottom of the North Island having the highest rate and the South Island having the lowest rate (Appendix 5, Figure 4). Rates were similar in females compared to males (Appendix 4, Table 4).

4.3.8 Anaphylaxis

Rates of anaphylaxis per 100,000 person years increased (Appendix 4, Table 5). The overall rate for this period is 60.72 (60.08–61.36). There was some slight variation in rates by region with the upper and middle North Island having the highest rates (Appendix 5, Figure 5). Rates of anaphylaxis were higher in females compared with males (Appendix 4, Table 5).

4.3.9 Anosmia and ageusia

Rates of anosmia and ageusia per 100,000 person years increased slightly between 2008 and 2019 (Appendix 4, Table 6). The overall rate for this period is 0.32 (0.27–0.36). Rates by region were similar (Appendix 5, Figure 6) and rates by sex were also similar (Appendix 4, Table 6).

4.3.10 Arrhythmia

Rates of arrhythmia per 100,000 person years increased between 2008 and 2019 (Appendix 4, Table 7), with a sudden and remarkable increase in 2014 that was due to a change in coding practice.[#] The overall rate for this period is 375.19 (373.59–376.79). There was some slight variation in region with the middle of the North Island having the highest rate and the top of the North Island the lowest rate (Appendix 5, Figure 7). Rates of arrhythmia were higher in males compared with females (Appendix 4, Table 7).

[#]Prior to 1 January 2014, one ICD-10-AM code (I48) was used to identify atrial flutter and atrial fibrillation (AF). The 8th edition of the ICD-10-AM coding system, introduced into New Zealand on 1 January 2014,

expanded the I48 category with the addition of more specific ICD-10-AM codes (I48.0, I48.1, ..., I48.9) to classify atrial flutter and AF separately, and further classify AF as paroxysmal or persistent, and typical or atypical.

4.3.11 Arterial thrombosis

Rates of arterial thrombosis per 100,000 person years remained relatively stable between 2009 and 2019 (Appendix 4, Table 8). The overall rate for this period is 11.75 (11.47–12.03). In general, rates were higher among males compared to females and increase with age. Rates of arterial thrombosis were also greatest among Māori and European ethnic groups and increased with deprivation level (Appendix 4, Table 8). There was limited variation by region, though rates were consistently highest in the Southern region compared to other regions (Appendix 5, Figure 6).

4.3.12 Aseptic meningitis

Rates of aseptic meningitis per 100,000 person years remained stable between 2009 and 2019, despite some variation by year (Appendix 4, Table 9). The overall rate for this period is 0.65 (0.59–0.72). While trends in rates were difficult to interpret due to suppressed data, there did not appear to be variation by sub-population or region (Appendix 4, Table 9 and Appendix 5, Figure 9).

4.3.13 Cerebral venous thrombosis

Rates of cerebral venous thrombosis per 100,000 person years remained stable between 2009 and 2019 (Appendix 4, Table 10). The overall rate for this period is 0.36 (0.31–0.40). Trends by sub-population are difficult to comment on due to the suppression of small values (Appendix 4, Table 10 and Appendix 5, Figure 10).

4.3.14 Chilblain-like lesions

Rates of chilblain-like lesions per 100,000 person years between 2008 and 2019 have suppression of small values for most years (Appendix 4, Table 11). The overall rate for this period is 0.12 (0.09–0.15). There was negligible variation by region (Appendix 5, Figure 11). Rates of chilblain-like lesions were higher in males compared with females (Appendix 4, Table 11).

4.3.15 Coagulation disorder

Rates of coagulation disorder per 100,000 person years decreased between 2008 and 2019 (Appendix 4, Table 12). The overall rate for this period is 202.73 (201.55–203.90). There was some variation by region with the South Island having the highest rate (Appendix 5, Figure 12). Rates of coagulation disorder were higher in females compared with males (Appendix 4, Table 12).

4.3.16 Coronary artery disease

Rates of coronary artery disease per 100,000 person years decreased between 2008 and 2019 (Appendix 4, Table 13). The overall rate for this period is 343.61 (342.08–345.14). There was some variation in region with the South Island having the highest rate (Appendix 5, Figure 13). Rates of coronary artery disease were higher in males compared with females (Appendix 4, Table 13).

4.3.17 Diabetes mellitus

Rates of diabetes mellitus per 100,000 person years were the highest in 2008. They were lower in 2009 and remained stable since then (Appendix 4, Table 14). The overall rate for this period is 399.21 (397.56–400.86). There was some variation by region with the top of the North Island having the highest rate and the South Island having the lowest rate (Appendix 5, Figure 14). Rates of diabetes mellitus were higher in males compared with females (Appendix 4, Table 14).

4.3.18 Encephalitis

Rates of encephalitis per 100,000 person years gradually decreased between 2008 and 2019 (Appendix 4, Table 15). The overall rate for this period is 0.36 (0.31–0.41). There was negligible variation by region (Appendix 5, Figure 15). Rates of encephalitis were similar in females compared with males (Appendix 4, Table 15).

4.3.19 Erythema multiforme

Rates of erythema multiforme per 100,000 person years remained relatively stable between 2008 and 2019 (Appendix 4, Table 16). The overall rate for this period is 2.28 (2.16–2.41). There was negligible variation by region (Appendix 5, Figure 16). Rates of erythema multiforme were generally higher in males compared with females (Appendix 4, Table 16).

4.3.20 Generalised convulsion

Rates of generalised convulsion per 100,000 person years gradually decreased between 2008 and 2019 (Appendix 4, Table 17). The overall rate for this period is 95.17 (94.37–95.98). There was some slight variation by region with the middle and lower North Island having the highest rates compared with the upper North Island and South Island (Appendix 5, Figure 17). Rates of generalised convulsion were higher in males compared with females (Appendix 4, Table 17).

4.3.21 Guillain-Barré and Miller Fisher syndromes

Rates of Guillain-Barré and Miller Fisher syndromes per 100,000 person years gradually decreased in between 2008 and 2019 (Appendix 4, Table 18). The overall rate for this period is 2.23 (2.11–2.35). There was negligible variation by region (Appendix 5, Figure 18). Rates of Guillain-Barré and Miller Fisher syndromes were higher in males compared with females (Appendix 4, Table 18).

4.3.22 Heart failure

Rates of heart failure per 100,000 person years gradually decreased between 2008 and 2019 (Appendix 4, Table 19). The overall rate for this period is 261.17 (259.84–262.50). There was some slight variation in rates by region with the middle of the North Island and the South Island having higher rates compared to the upper and lower North Island (Appendix 5, Figure 19). Rates of heart failure were higher in males compared with females (Appendix 4, Table 19).

4.3.23 Idiopathic thrombocytopenia

Rates of idiopathic thrombocytopenia per 100,000 person years remained relatively stable between 2008-2019 (Appendix 4, Table 20). The overall rate for this period is 6.52 (6.31–6.73.) There was negligible variation by region (Appendix 5, Figure 20). Rates of idiopathic thrombocytopenia tended to be higher in females compared with males (Appendix 4, Table 20).

4.3.24 Lower limb venous thrombosis

Rates of lower limb venous thrombosis per 100,000 person years remained relatively stable between 2008 and 2016, but increased from 2017 (Appendix 4, Table 21). The overall rate during for this period is 12.02 (11.73 - 12.31). There was some slight variation in rates by region with the middle of the North Island and the South Island having higher rates compared to the upper and lower North Island (Appendix 5, Figure 21). Rates of lower limb venous thrombosis tended to be slightly higher in males compared with females (Appendix 4, Table 21).

4.3.25 Meningoencephalitis

Rates of meningoencephalitis per 100,000 person years gradually increased between 2008 and 2019 (Appendix 4, Table 22). The overall rate for this period is 5.25 (5.06–5.44). There were slight variations in rates by region, with the lower North Island having the highest rate compared with other regions in New Zealand (Appendix 5, Figure 22). Rates of meningoencephalitis tended to be higher amongst males compared to females (Appendix 4, Table 22).

4.3.26 Microangiopathy

Rates of microangiopathy per 100,000 person years remained relatively stable between 2008 and 2019 (Appendix 4, Table 23). The overall rate for this period is 0.40 (0.35–0.46). They did not vary significantly by region (Appendix 5, Figure 23) and were slightly higher in females compared with males (Appendix 4, Table 23).

4.3.27 Multisystem inflammatory syndrome

Rates of multisystem inflammatory syndrome per 100,000 person years increased between 2008 and 2019 (Appendix 4, Table 24). The overall rate for this period is 120.03 (119.13–120.94). For the 0–19-year age group, rates of multisystem inflammatory syndrome per 100,000 person years also increased. There was some slight variation in rates by region with the central and lower North Island having higher rates compared with the upper North Island and the South Island (Appendix 5, Figure 24). Rates of multisystem inflammatory syndrome were higher in males compared with females (Appendix 4, Table 24).

4.3.28 Myelitis

Rates of myelitis per 100,000 person years remained relatively stable between 2008 and 2019 (Appendix 4, Table 25). The overall rate for this period is 0.54 (0.48–0.60). Rates did not vary meaningfully by region (Appendix 5, Figure 25). There were no marked differences in rates between males and females (Appendix 4, Table 25).

4.3.29 Myocarditis

Rates of myocarditis per 100,000 person years gradually increased between 2008 and 2019 (Appendix 4, Table 26). The overall rate for this period is 2.01 (1.89–2.12). There was some slight variation in rates by region with the middle of the North Island having a lower rate compared to the South Island (Appendix 5, Figure 26). Rates of myocarditis were higher amongst males 2.70 (2.50 - 2.89) compared to females 1.32 (1.19–1.45) (Appendix 4, Table 26). With exception of the very young and very old the rates were similar across the age bands.

4.3.30 Narcolepsy

Rates of narcolepsy per 100,000 person years remained stable between 2008 and 2019 (Appendix 4, Table 27). The overall rate for this period is 4.25 (4.08–4.42). There was some variation in rates by region with the central North Island and South Island having higher rates compared to the rest of New Zealand (Appendix 5, Figure 27). Rates of narcolepsy were higher amongst males compared to females (Appendix 4, Table 27).

4.3.31 Other venous thrombosis

Rates of other venous thrombosis per 100,000 person years increased between 2008 and 2019 (Appendix 4, Table 28). The overall rate for this period is 13.08 (12.78–13.38). There was some slight variation in rates by region with the upper and lower North Island having higher rates compared to the central North Island and South Island (Appendix 5, Figure 28). Rates of other venous thrombosis were slightly higher in males compared to females (Appendix 4, Table 28).

4.3.32 Pericarditis

Rates of pericarditis per 100,000 person years gradually increased between 2008 and 2019 (Appendix 4, Table 29). The overall rate for this period is 12.17 (11.88–12.46). There was some slight variation in rates by region with the South Island having a higher rate compared with the North Island (Appendix 5, Figure 29). Rates of pericarditis were significantly higher in males 17.74 (17.25–18.24) compared with females 6.75 (6.45–7.05) and increases with age. (Appendix 4, Table 29).

4.3.33 Peripheral facial nerve palsy

Rates of peripheral facial nerve palsy (also termed Bell's palsy) per 100,000 person years gradually decreased between 2008 and 2019 (Appendix 4, Table 30). The overall rate for this period is 17.79 (17.45–18.14). There was some slight variation in rates by region with the top and central North Island having higher rates than the lower North Island and South Island (Appendix 5, Figure 30). Rates of peripheral facial nerve palsy were slightly higher in females compared with males (Appendix 4, Table 30).

4.3.34 Pregnancy thrombosis

Rates of pregnancy thrombosis per 100,000 person years between 2008 and 2019 were low but increased over time (Appendix 4, Table 31). The overall rate for this period is 0.34 (0.30–0.39). Trends by sub-population are suppressed due to small values (Appendix 5, Figure 31 and Appendix 4, Table 31).

4.3.35 Pulmonary embolism

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Rates of pulmonary embolism per 100,000 person years increased in New Zealand from 2008 to 2019 (Appendix 4, Table 32). The overall rate for this period is 49.52 (48.94–50.10). There was some slight variation in rates by region with the South Island having a higher rate than the North Island, and the upper North Island having the lowest rate (Appendix 5, Figure 32). Rates of pulmonary embolism between males and females were similar but increase significantly with age. (Appendix 4, Table 32).

4.3.36 Single organ cutaneous vasculitis

Rates of single organ cutaneous vasculitis per 100,000 person years were stable between 2008 and 2019 (Appendix 4, Table 33). The overall rate for this period is 5.67 (5.47–5.86). There were no meaningful differences in rates by region (Appendix 5, Figure 33). Males tended towards a higher rate of single organ cutaneous vasculitis compared with females (Appendix 4, Table 33).

4.3.37 Splanchnic thrombosis

Rates of Splanchnic thrombosis per 100,000 person years slightly increased between 2008 and 2019 (Appendix 4, Table 34). The overall rate for this period is 3.05 (2.90–3.19). There were no significant differences in rates by region (Appendix 5, Figure 34). Males had a higher rate of splanchnic thrombosis compared with females (Appendix 4, Table 34).

4.3.38 Stress cardiomyopathy

Rates of stress cardiomyopathy per 100,000 person years increased between 2008 and 2019 (Appendix 4, Table 35). The overall rate for this period is 5.70 (5.50–5.90). There was some slight variation in rates by region with the top of the North Island having the highest rate compared with the rest of New Zealand (Appendix 5, Figure 35). Females had a higher rate of stress cardiomyopathy compared with males (Appendix 4, Table 35).

4.3.39 Sudden death

Rates of sudden death per 100,000 person years between 2008 and 2019 have suppression of small values for seven of the most recent years (Appendix 4, Table 36). Overall, the rate of sudden death appeared to decrease. The overall rate for this period is 0.38 (0.33–0.43). The rate of sudden death increased with age. There was variation in rates by region with the highest rate seen in the lower North Island compared with the rest of New Zealand (Appendix 5, Figure 36).

4.3.40 Thrombocytopenia

Rates of thrombocytopenia per 100,000 person years remained stable between 2008 and 2019 (Appendix 4, Table 37). The overall rate for this period is 45.79 (45.23–46.35). There were no significant differences by region (Appendix 5, Figure 37). Rates of thrombocytopenia were higher in males compared with females (Appendix 4, Table 37).

4.3.41 Venous thromboembolism

Rates of venous thromboembolism per 100,000 person years increased between 2008 and 2019 (Appendix 4, Table 38). The overall rate for this period is 63.56 (62.90–64.22). There were some differences in rates by

region with the South Island having the highest rate and the top of the North Island having the lowest rate (Appendix 5, Figure 38). Rates of venous thrombosis by sex were similar (Appendix 4, Table 38).

4.3.32 Zoster (shingles)

Rates of zoster per 100,000 person years were stable between 2008 and 2019 (Appendix 4, Table 39). The overall rate for this period is 17.57 (17.22–17.91). There were no significant differences in rates by region (Appendix 5, Figure 39). Rates of zoster were higher for females compared with males (Appendix 4, Table 39).

4.4 Background rates for maternal and infant events of special interest

The *Pertussis Immunisation in Pregnancy Study* (PIPS) included three main objectives, and these included establishing the annual background rates for hospital-related outcomes in pregnant women stratified by timing of the outcome (<28 weeks or ≥28 weeks gestation) and the background rates for birth outcomes and hospital-related outcomes of infants. The maternal study population included all women who were pregnant between 01 January 2009 and 31 December 2013 with a surviving fetus at 20 weeks gestation or who delivered an infant weighing at least 400 grams. The infant study included all live-born infants of the women.

The data sources for the study were the *National Health Index* (NHI) *Database*, which contains demographic information for all New Zealanders; the *National Minimum Data Set* (NMDS), which includes records of all hospital discharges in New Zealand; the *National Maternity Collection*, which contains data on primary maternity services and on inpatient and day-patient health event data during pregnancy, birth and the postnatal period for women and their babies; and the *Mortality Collection*. Outcomes were defined dichotomously by the presence of specified ICD-10-AM codes, see Appendix 6, Table 1, in the primary or any of the other 99 possible diagnosis fields available in the NMDS. Key terms for the assessment of the safety of vaccines in pregnancy developed by two *Brighton Collaboration* task forces were used to define and prioritise study outcomes.

Each outcome was described quantitatively with total frequencies, risks, incidence rates (IRs) and 95% CIs. The median and interquartile range (IQR) of women's age and gestation at the time of each outcome was also calculated. Risks were stratified by hospitalisation timing. Incidence rates were stratified by gestational timing (<28 of ≥28 weeks' gestation), hospitalisation timing, calendar year of hospitalisation, maternal age at hospitalisation, ethnicity, and socioeconomic status. The timing of hospitalisations occurring before delivery was plotted as the distribution over the number of weeks between last menstrual period (LMP) and hospitalisation. The timing of hospitalisations that occurred during the 42 days post-delivery were plotted as the distribution over the number of weeks between delivery and hospitalisation.

In this cohort, there were 350,041 women who contributed pregnancy person-time from 2009–2013.

4.4.1 Still birth

ICD-10-AM code Z37

There were 859 hospitalisations for stillbirth among the full cohort of women with a surviving fetus at 20 weeks gestation. The incidence of hospitalisation was 215.2 per 100,000 person-years at <28 weeks gestation (95% CI 192.7–237.7) and was higher from 28 weeks gestation to delivery (IR=753.0; 95% CI 87.5–818.5). The median age at hospitalisation was 30 years (IQR: 10.0) and the median gestation at hospitalisation was 32 weeks (IQR: 15.0) (Appendix 6, Table 2). The overall risk of hospitalisation through the post-partum period for stillbirth was 245.4 per 100,000 maternities. The incidence was highest in women 40+ years (IR=474.3; 95% CI 345.4–603.2); with New Zealand Deprivation Index (NZDep) of 9–10 (IR=394.8; 95% CI 349.6–440.0); and <20 years (IR=380.3; 95% CI 288.6–472.1) (Appendix 6, Table 3).

4.4.2 Spontaneous abortion and ectopic pregnancy

As these events occur prior to 24 weeks gestation they have not been included.

4.4.3 Pathways to preterm birth and preterm birth

4.4.3.1 Preterm labour

ICD-10-AM code O60.02

There were 1,981 hospitalisations prior to delivery for preterm labour in pregnancy among the full cohort of women with a surviving fetus at 20 weeks gestation. The incidence of hospitalisation was 256.9 per 100,000 person-years at <28 weeks gestation (95% CI 232.3–281.5) and was higher from 28 weeks gestation to delivery (IR=2,321.2; 95% CI 2,206.1–2,436.4). The median age at hospitalisation was 26 years (IQR: 10.0) and the median gestation at hospitalisation was 32 weeks (IQR: 6.0) (Appendix 6, Table 2). The overall risk of hospitalisation through the post-partum period for preterm labour was 565.9 per 100,000 maternities. The incidence was highest in women <20 (IR=1,566.2; 95% CI 1,379.7–1,752.7); of Māori ethnicity (IR=1,226.7; 95% CI 1,143.6–1,309.9); and 20–24 years (IR=1,093.5; 95% CI 1,001.9–1,185.0) (Appendix 6, Table 4).

4.4.3.2 Premature rupture of membranes (PROM)

ICD-10-AM code O42.0

There were 67,998 hospitalisations for PROM among the full cohort of women with a surviving fetus at 20 weeks gestation. The incidence of hospitalisation was 450.7 per 100,000 person-years at <28 weeks gestation (95% CI 418.1–483.3) and was higher from 28 weeks gestation to delivery (IR=39,144.8; 95% CI 38.672.0–39.617.7). The median age at hospitalisation was 29 years (IQR: 9.0) and the median gestation at hospitalisation was 39 weeks (IQR: 3.0) (Appendix 6, Table 2). The overall risk of hospitalisation through the post-partum period for PROM was 7,733.4 per 100,000 maternities. The incidence was highest in women with Asian ethnicity (IR=12,786.4; 95% CI 12,399.6–13,173.3); with NZDep 1–2 (least deprived) (IR=11,166.1; 95% CI 10,822.6–11,509.6); and with NZ Dep 3–4 (IR=10,770.5; 95% CI 10,445.0–11,096.0) (Appendix 6, Table 5).

4.4.3.3 Preterm delivery

ICD-10-AM code O60.13

There were 17,401 hospitalisations for preterm delivery among the full cohort of women with a surviving fetus at 20 weeks gestation. The incidence of hospitalisation was 1,035.7 per 100,000 person-years at <28 weeks gestation (95% CI 986.3–1,085.0) and was higher from 28 weeks gestation to delivery (IR=23,332.7; 95% CI 22,967.8–23,697.5). The median age at hospitalisation was 29 years (IQR: 10.0) and the median gestation at hospitalisation was 35 weeks (IQR: 4.0) (Appendix 6, Table 2). The overall risk of hospitalisation through the post-partum period for preterm delivery was 4,972.8 per 100,000 maternities. The incidence was highest in women 40+ years (IR=8,335.6; 95% CI 7,792.5–8,878.7); <20 years (IR=7,937.0; 95% CI 7,515.9–8,358.0); and with NZDep 9–10 (most deprived) (IR=7,307.6; 95% CI 7,111.3–7,503.8) (Appendix 6, Table 6).

4.4.3.4 Preterm birth

There were 23,574 preterm births among infants born to women pregnant between January 2009 and December 2013. The incidence of hospital related extreme, very, and moderate to late preterm outcomes among infants aged under one year of age born to women pregnant between 01 January 2009 and 31 December 2013 in New Zealand are shown in Appendix 6, Table 7.

4.4.3.4.1 Extreme preterm: <28 weeks

ICD-10-AM code P07.2

Of these 1,372 were extreme preterm born at less than <28 weeks gestation (IR=409.2; 95% CI 387.5–430.8) (Appendix 6, Table 7). The rates varied by year of birth with the lowest reported in 2011 (IR=359.1; 95% CI 311.7–406.4) and the highest reported in 2014 (IR=482.3; 95% CI 399.7–564.9). The risk for extreme preterm birth was lowest among European infants (IR=331.2; 95% CI 303.6–358.9) and highest among Pasifika infants (IR=552.8; 95% CI 477.5–628.1). The risk for extreme preterm birth increased linearly from least deprived to most deprived quintiles. There were 133 infants born extremely prematurely in the least deprived quintile (IR=284.2; 95% CI 235.9–332.5) and 552 in the most deprived quintile (IR=547.2; 95% CI 501.5–592.8). (Appendix 6, Table 8).

4.4.3.4.2 Very preterm: 28 to <32 weeks

ICD-10-AM code P07.31

There were 2,654 infants born very preterm, between 28 to <32 weeks gestation, to women pregnant between January 2009 and December 2013 (IR=795.3; 95% CI 765.0–825.6) (Appendix 6, Table 7). The risk for very preterm birth was lowest in 2013 (IR=743.2; 95% CI 673.3–813.2) and highest in 2014 (IR=883.3; 95% CI 771.3–995.3). The lowest risk for very preterm birth was among Asian infants (IR=634.1; 95% CI 557.3–710.8) and the highest among Māori infants (IR=892.9; 95% CI 831.0–954.8). The risk for very preterm birth increased linearly. There were 326 infants in the least deprived quintile born very prematurely (IR=699.7; 95% CI 623.8–775.7) and 859 in the highest deprivation quintile (IR=855.5; 95% CI 798.2–912.7). (Appendix 6, Table 9).

4.4.3.4.3 Moderate to late preterm: 32 to <37 weeks

ICD-10-AM code P07.323

There were 19,548 infants born moderate to late preterm from 32 weeks to <37 weeks gestation to women pregnant between January 2009 and December 2013, (IR=6,154.3; 95% CI 6,068.0–6,240.6) (Appendix 6, Table 7). The risk increased each year with 3,407 moderate to late preterm births in 2009 (IR=5,670.2; 95% CI 5,479.8–5,860.6) and 2,308 in 2014 (IR=8,971.3; 95% CI 8,605.3–9,337.3). Māori and European infants had the highest risk for moderate to late preterm birth (IR=6,381.8; 95% CI 6,212.0–6,551.6 and IR=6,305.5; 95% CI 6,181.5–6,429.6 respectively). The lowest risk was among Pasifika infants (IR=5,409.8; 95% CI 5,168.7–5,651.0). There was no linear pattern observed with increasing deprivation. (Appendix 6, Table 10).

4.4.4. Maternal death

ICD-10-AM code O95

There were no reported hospitalisations for maternal death in the current study.

4.4.5 Neonatal death

4.4.5.1 Stillbirth

ICD-10-AM code Z37

There were 859 stillbirths among the cohort of infants born to women who delivered between January 2009 and 31 December 2013, a total of 350,041 maternities. The risk of stillbirth was 254.4 (95% CI 229.0–261.8). Of these 350 occurred in the second trimester (IR=428.6; 95% CI 383.7–473.5) and 508 during the third trimester (IR=753.0; 95% CI 687.5–818.5). The IR=ranged from a low in 2010 of 270.5 (95% CI 226.9–314.1) to a high of 381.3 (95% CI 329.6–433.0) in 2009. The lowest risk for stillbirth was observed in women aged 25–29 (IR=283.5; 95% CI 243.8–323.1) and 30–39 years (IR=274.7; 95% CI 237.6–311.9). The highest risk was among women aged over 40 years (IR=474.3; 95% CI 345.4–603.2). There was little difference in risk for stillbirth between ethnicities with the lowest risk observed among European women (IR=303.4; 95% CI 274.4–332.4) and the highest among Pacific women (IR=362.7; 95% CI 294.9–430.5). Risk for stillbirth increased linearly over deprivation quintiles. There were 101 still births reported for the least deprived (IR=272.6; 95% CI 219.4–325.8) and 293 reported for the most deprived (IR=394.8; 95% CI 349.6–440.0).

4.4.5.2 Infant death, perinatal/neonatal death

There were 354,511 live-born infants, of these, 1,593 died after birth within one year of age. Of the 1,593, 703 (44%) died within 48 hours.

4.4.5.3 Sudden infant death

Among infants born to women pregnant between January 2009 and December 2013 there were 89 hospital related cases of sudden infant death syndrome (IR=26.5; 95% CI 21.0–32.0). The median age at outcome was 65 days (IQR 110.0). There were five other infant deaths (ICD-10-AM codes R96, R98 and R99) among these infants (IR=1.5; 95% CI 0.2–2.8). The media age at outcome was 152 days (IQR 18.0).

4.4.6 Neonatal sepsis

ICD-10-AM code P36 – Infection including sepsis

Among infants born to women pregnant between January 2009 and December 2013 there were 2,839 cases of sepsis of the newborn reported. There was no pattern associated with year of birth, deprivation quintile or for Māori or Pasifika ethnicity for the overall sepsis outcome. Premature infants were at greatest risk for all sepsis outcomes.

Sepsis of the newborn due to *Streptococcus* group B (ICD-10-AM code P36.0) occurred in 298 infants (IR=88.7; 95% CI 78.6–98.8). While infants of European ethnicity had the lowest risk (IR=82.8; 95% CI 69.0–96.6) and Māori the highest (IR=106.5; 95% CI 85.2–127.8) the CIs overlapped. Infants in the least deprived quintile had the lowest risk (IR=61.9; 95% CI 39.4–84.4) and the risk increased over quintiles to the highest risk, in the most deprived quintile (IR=99.9; 95% CI 80.4–119.4) although the CIs overlapped.

Sepsis of newborn due to other and unspecified *Streptococci* (ICD-10-AM code P36.1) occurred in 108 infants (IR=32.1; 95% CI 26.1–38.2). Asian infants had the lowest risk (IR=16.8; 95% CI 4.4–29.3) and Māori infants the highest IR=51.0; 95% CI 36.3–65.7). There was a linear association with deprivation quintile. There were five cases among the least deprived (IR=10.7; 95% CI [1.3–20.0]) and 42 cases among the most deprived quintile IR=41.5; 95% CI [29.0–54.1]).

Sepsis of the newborn due to *Staphylococcus aureus* (ICD-10-AM code P36.2) occurred in 139 infants. European infants had the lowest risk (IR=31.8; 95% CI 23.2–40.4) and Māori infants the highest risk (IR=63.2; 95% CI 46.8–79.6). While infants in the least deprived quintile had the lowest risk (IR=25.6; 95% CI 11.1–40.1), infants in the 5–6 deprivation quintile had the same risk as those in the highest deprivation quintile (IR=51.2; 95% CI 33.1–69.2) and (IR=58.3; 95% CI 43.4–73.2) respectively.

Sepsis of the newborn due to other and unspecified *Staphylococci* (ICD-10-AM code P36.3) occurred in 326 infants (IR=97.1; 95% CI 86.5–107.6). Asian infants had the lowest risk (IR=57.8; 95% CI 34.7–80.9) and European infants the highest risk (IR=109.9; 95% CI 93.9–125.8). There was no linear trend across deprivation quintiles with the lowest risk among quintile 5–6 (IR=84.2; 95% CI 61.1–107.3).

Sepsis of the newborn due to *Escherichia coli* (ICD-10-AM code P36.4) occurred in 135 infants. European infants had the lowest risk (IR=22.2; 95% CI 15.0–29.3) and Māori the highest (IR=63.2; 95% CI 46.8–79.6). While lowest risk was among the lowest deprivation quintile (IR=25.6; 95% CI 11.1–40.1) the highest risk was among the mid decile 5–6 (IR=49.5; 95% CI 31.8–67.2).

Four infants were reported to have sepsis of the newborn due to anaerobes (ICD-10-AM code P36.5).

Bacterial sepsis of newborn specified or unspecified (ICD-10-AM code P36.89) occurred in 1,829 infants (IR=546.7; 95% CI 521.7–571.8). The risk increased annually from 2009 (IR=439.9; 95% CI 388.2–491.7) to 2014 (IR=967.9; 95% CI 850.7–1,085.1). The lowest risk was among Asian and Pacific infants (IR=408.1; 95%

CI 346.6–469.6) and (IR=475.7; 95% CI 405.8–545.6) respectively. The highest risk was among Māori and European (IR=603.9; 95% CI 553.0–654.7) and (IR=566.1; 95% CI 529.9–602.3) respectively. There was no linear pattern with deprivation.

4.4.7 Neonatal encephalopathy

Neonatal encephalopathy/Hypoxic ischemic encephalopathy (ICD-10-AM code P91.6)

Among infants born to women pregnant between January 2009 and December 2013 there were 660 cases of neonatal encephalopathy. (IR=196.6; 95% CI 181.6–211.6) There no pattern associated with gestation at birth. There was little difference between Māori, European and Asian infants, and a non-significant higher risk among Pacific infants (IR=258.8; 95% CI 207.3–310.2). There was a general trend to increase risk over the deprivation quintiles with the lowest risk in the least deprived quintile (IR=153.7; 95% CI 118.2–189.2) and the highest risk among infants in the second to highest deprivation quintile (IR=218.3; 95% CI 184.9–251.7).

5. Discussion

Introduction of novel vaccines, such as during an emergency, requires additional active surveillance of vaccine recipients.⁴

To help prepare New Zealand for safety monitoring of COVID-19 vaccines, we established the background rates of AESIs in New Zealand for the period 2008–2019 and reported on incidence by calendar year, ethnicity, age, sex, region and deprivation. To assess the accuracy of selected search strategies, clinical record assessments of selected conditions were undertaken to provide insight into the disease codes used in the administrative data.

5.1 Context – how background rates fit in with vaccine safety surveillance

5.1.2 Importance of enhancing vaccine safety surveillance

The *WHO Vaccine Safety Blueprint 1.0 (2012)*⁴ laid the framework for minimal capacity for AEFI reporting, investigation, data management, causality assessment and communications. This blueprint included eight overarching objectives.

- Strengthen vaccine safety monitoring in all countries.
- Strengthen the ability of countries to evaluate vaccine safety signals.
- Develop vaccine safety communication plans at country level to promote awareness of vaccine risks and benefits, understand perceptions of risk and prepare for managing any adverse events and concerns about vaccine safety promptly.
- Develop internationally harmonised tools and methods to support country vaccine safety activities
- Promote a legal, regulatory, and administrative framework for the safety of vaccines at national, regional, and international levels.
- Strengthen regional and global technical support platforms that meet countries' expressed needs.
- Provide expert advice on vaccine safety issues at national, regional, and international levels.
- Put in place systems for appropriate interaction between national governments, multilateral agencies, and manufacturers at national, regional, and international levels.

Progress by 2019 indicated that AEFI notification and reporting had improved globally. High AEFI reporting rates improve the potential of detecting vaccine safety signals. An effective spontaneous reporting system requires a minimum reporting rate of at least 10 serious and non-serious AEFIs per 100,000 surviving infants.^{17,18} By this measure New Zealand has excelled for many years, with one of the highest reporting rates in the world. New Zealand has always had well-functioning spontaneous reporting system, established 1965, based at the *New Zealand Pharmacovigilance Centre (NZPhvC)*,¹⁹ at the University of Otago. While such systems have demonstrated they are effective at detecting vaccine safety signals, they do not allow for the establishment of causality or risk assessment. There is no denominator and no

unvaccinated persons for comparison. As such this type of surveillance is but one component in a comprehensive vaccine safety programme.

Globally, development in the areas of investigation, capacity for data analysis, causality assessment and communication has not made as much progress as that for notifications and reporting. Active surveillance, causality assessment and methodologies for vaccine safety are identified as priority areas moving into this next decade.^{2,5}

Countries deploying newly available vaccines require additional approaches to safety surveillance such as stimulated reporting and cohort studies. For these additional activities, there are harmonised tools and technologies available so that countries with the capability can conduct advanced epidemiological studies that control for important co-variates. Such harmonised tools include the *Brighton Collaboration* AEFI case definitions, now expanded to include AESIs following COVID-10 vaccines. Ideally, background rates of conditions of special interest should be developed in advance of vaccine introduction.⁴

Requirements for safety signal verification begin with the review of cases reported to the surveillance system. The second step is to determine if the observed AEFI/AESI is associated with the vaccine and then to determine the causal relationship and quantify the risk. This second step requires well-controlled epidemiological studies and the assessment of background rates including the rates of appropriate denominators. The use of electronic databases that can facilitate unbiased case ascertainment and evaluation from various sources are important.¹⁴ New Zealand has high quality health-care databases allowing for the assessment of causal associations and given the lack of such capacity in all countries can contribute to the landscape, particularly through harmonised approaches and collaborations.

Vaccine concerns can be based on both real and perceived safety issues. Rumours about vaccine safety can quickly escalate into crisis and communication about vaccine safety is more than just crisis management. Any evidence that a vaccine might cause should be taken seriously and prompt communication is critical in maintaining trust. Communications should not only include regulators, programme managers and health workers but also the communities. A country level communication strategy should exist and include a crisis-management plan enabling the prompt response to vaccine safety events either real or perceived, including misinformation.⁴ Country level data about health conditions that might occur after receipt of a vaccine (the normal background rates) can assist with these important communications.

5.2 Importance of establishing background rates

The background rates of medical conditions vary over time, geography, sex, socioeconomic status, ethnicity, and age. Establishing a list of AESIs then describing their rates is an essential component of the monitoring of new vaccines, this is the first step required to assess the incidence in the absence of a vaccine. Early in the COVID-19 pandemic the SPEAC project developed a list of AESIs that is reviewed and updated quarterly.^{12,20}

The background rate of any adverse event is the incidence of that event observed in the population of interest in the absence of a vaccine. To show if a vaccine is associated with an event the risk of the event will be higher than in a comparable non-vaccinated group. The availability of these rates is important for rapid evaluation of a safety signal that may have been identified through spontaneous reporting, clinical observations, or social media.

It is important to use appropriate comparisons. To reliably assess the rate of an AESI and compare it to a background rate it is important to use a standard case definition to validate cases. Many published rates are 'crude' in that the cases have not been validated. Therefore, like must be compared with like – validated rates with validated rates and unvalidated with unvalidated. Seasons should be considered where possible. Factors that can impact background rates include the year, age and gender distribution of the population, geography, comorbidities, socioeconomic status, medication use and the study approach.¹⁴

5.3 Value of using the IDI

Rather than only a health user population or census population, we used the *Stats NZ Integrated Data Infrastructure* to develop the population cohort and estimate the incidence rates.

Health service user populations are compiled using records of receipt of publicly funded health services and/or are enrolled with a primary health organisation. While this tends to capture a large portion of the population it is over-represented by those who are more likely to need and seek healthcare. Healthier individuals and demographic sub-groups who attend health care setting less frequently will be under-represented. Census populations are more likely to include healthier individuals, however still have undercount issues, for example; those with less secure residency.²¹

Data source selection for pharmacoepidemiologic studies are a key consideration as selection biases can result in serious concerns about result validity.²² As a source of data to develop a population denominator a health service user population can lead to selection biases, for example, healthy user bias, unhealthy user bias, and health care access bias.²² Biases resulting from the selection of a study population (e.g., health service user population) which are different to the target population (all living in New Zealand) are serious and study results require complicated and careful interpretation, with questions of validity difficult to resolve.²³

Integrating datasets from multiple sources, which include health service users and the census but add more such as inland revenue, helps to balance the bias because an income earning population will be biased towards a younger, health population. Our use of the IDI environment enables the most accurate denominator estimates, which are important for smaller population subgroups and the capture of individuals who may not have contact with health services.²¹

When monitoring trends over time in a population there are different perturbations that can contribute to changes in rates even when the underlying rate of disease doesn't change. Of particular relevance to health and disease rates are changes in the health care system. We see a stark example of this with the background rate of arrhythmia. A sharp increase in rates was caused by a change in coding as opposed to there being an increase in rates of arrhythmia. The other important source of error is a change in the use of the denominator population. If these background rates are used to detect changes in the rate of disease occurring in within a different denominator population, particularly one that is underrepresented in the new denominator, then this can cause errors due to reduced precision. For example young healthy males are a subgroup most at risk from myocarditis however they are underrepresented in the health service user population. The precision of the estimate that you are comparing with the background rate may be compromised, particularly if you are gathering data from a short time interval. The consequence is that a signal may not appear or will appear months later, only after a lot more data has been collected. In addition if you are only comparing an overall (total population) rate as opposed to a subgroup rate with the overall population rate calculated with a different denominator this will introduce larger errors and increase risk of missed or false safety signals.

5.4 Confirming and communicating a vaccine safety signal

Verification of a vaccine safety signal can be assessed using a retrospective database assessment. One approach is to establish the incidence of the condition of interest for a period prior to the use of the vaccine and compare it with a period that includes the use of the vaccine. The establishment of background rates can facilitate this in several ways.

1. Allow rapid comparison of observed number of events against a benchmark – while this is 'quick and dirty' it can be done in almost real time.
2. Provide information for communications as to what to expect by chance.
3. Provide the foundation to perform observed versus expected in the same population cohort.
4. Provide the foundation to perform rapid-cycle analysis¹⁷ – this is more robust than the 'real time' approach and can be done with a frequency of weeks to months.
5. Inform case-based and cohort association studies that can apprise public health risk.

Strategies for communicating vaccine safety should be in place throughout the life cycle of all vaccines. There are several ways that the establishment and maintenance of background rates can contribute to this. First, they can inform risk-benefit communications and second, they can be used to communicate what to expect without a vaccine.

To assist with vaccine safety communications, we uploaded these background rates onto an unrestricted access dashboard accessible at [placeholder for weblink]. These can be viewed by immunisation programme personnel, providers, and the public to assist with messaging.

6. Conclusions and recommendations

Established population background rates of potential adverse events following immunisation are an essential component for vaccine safety monitoring. However, in May 2020 no countries had these available and few had commenced planning to undertake this activity. Stimulated by the COVID-19 pandemic and rapid availability of vaccines to protect against COVID-19, lists of AESIs for COVID-19 vaccination were developed, along with case definitions for newly identified events.

The background rates presented here should be viewed with the understanding that that trends over time and the consistent use of codes can change. The purpose of background rates is not an exercise in precision but consistency in definitions and approach – comparing like with like to be useful for signal detection and verification. These rates have been established for their role in crude signal detection during the delivery of new vaccines to the New Zealand population.

While some codes have better predictive value than others, consistent use of codes over time should allow signal detection. There is considerable variation in the PPV for the Tier 1 AESIs using ICD10-AM codes selected in this review.

The denominator cohort derived from the IDI compares well with other New Zealand population denominators and has slightly better representation of younger healthy individuals than the health service user population.

We have four recommendations for the ongoing utility of this work.

- That this work be extended to include 2020 and 2021.
- That observed versus expected rates are undertaken using the same source population to complement other safety surveillance activities and to compare like with like.
- That this activity be repeated on a regular basis for the duration that COVID-19 pandemic vaccines are in use.
- That this activity be activated in the future should monitoring of a new vaccine be required.

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8. Appendices

Appendices 1–6 are provided in a separate PDF file.

Appendix 1 – Prevalence of high-risk medical conditions

Table 1. Prevalence of high-risk medical conditions, including multimorbidity, in New Zealand that increase risk of severe COVID-19 disease

Appendix 2 – AESI ICD-10-AM codes

List of broad conditions included

Acute disseminated encephalomyelitis	Lower limb venous thrombosis
Acute kidney injury	Meningoencephalitis
Acute liver injury	Microangiopathy
Acute respiratory disease	Multisystem inflammatory syndrome in children
Anaphylaxis	Myelitis
Anosmia and ageusia	Myocarditis
Arrhythmia	Narcolepsy
Arterial thrombosis	Other venous thrombosis
Aseptic meningitis	Pericarditis
Cerebral venous thrombosis	Peripheral facial nerve palsy
Chilblain-like lesions	Pregnancy thrombosis
Coagulation disorder	Pulmonary embolism
Coronary artery disease	Single organ cutaneous vasculitis
Diabetes mellitus	Splanchnic thrombosis
Encephalitis	Stress cardiomyopathy
Erythema multiforme	Sudden death
Generalised convulsion	Thrombocytopenia
Guillain-Barré and Miller Fisher syndromes	Venous thromboembolism
Heart failure	Zoster (Shingles)
Idiopathic thrombocytopenia	

Appendix 3 – Characteristics of the denominator population 2008–2019

Table 1. Characteristics of the denominator population

Appendix 4 – AESI data tables 2008–2019

Table 1. Acute disseminated encephalomyelitis

Table 2. Acute kidney injury

Table 3. Acute liver injury

Table 4. Acute respiratory distress syndrome

Table 5. Anaphylaxis

Table 6. Anosmia and ageusia

Table 7. Arrhythmia

Table 8. Arterial thrombosis

Table 9. Aseptic meningitis

Table 10. Cerebral venous thrombosis

Table 11. Chilblain-like lesions

Table 12. Coagulation disorder

Table 13. Coronary artery disease

Table 14. Diabetes mellitus

Table 15. Encephalitis

Table 16. Erythema multiforme

Table 17. Generalised convulsion

Table 18. Guillain-Barré and Miller Fisher syndromes

Table 19. Heart failure

Table 20. Idiopathic thrombocytopenia

Table 21. Lower limb venous thrombosis

Table 22. Meningoencephalitis

Table 23. Microangiopathy

Table 24. Multisystem inflammatory syndrome

Table 25. Myelitis

Table 26. Myocarditis

Table 27. Narcolepsy

Table 28. Other venous thrombosis

Table 29. Pericarditis

Table 30. Peripheral facial nerve palsy

Table 31. Pregnancy thrombosis

Table 32. Pulmonary embolism

Table 33. Single organ cutaneous vasculitis

Table 34. Splanchnic thrombosis

Table 35. Stress cardiomyopathy

Table 36. Sudden death

Table 37. Thrombocytopenia

Table 38. Venous thromboembolism

Table 39. Zoster (Shingles)

Appendix 5 – AESI data visualisations 2008–2019

Figure 1. Acute disseminated encephalomyelitis

Figure 2. Acute kidney injury

Figure 3. Acute liver injury

Figure 4. Acute respiratory distress syndrome

Figure 5. Anaphylaxis

Figure 6. Anosmia and ageusia

Figure 7. Arrhythmia

Figure 8. Arterial thrombosis

Figure 9. Aseptic meningitis

Figure 10. Cerebral venous thrombosis

Figure 11. Chilblain-like lesions

Figure 12. Coagulation disorder

Figure 13. Coronary artery disease

Figure 14. Diabetes mellitus

Figure 15. Encephalitis

Figure 16. Erythema multiforme

Figure 17. Generalised convulsion

Figure 18. Guillain-Barré and Miller Fisher syndromes

Figure 19. Heart failure

Figure 20. Idiopathic thrombocytopenia

Figure 21. Lower limb venous thrombosis

Figure 22. Meningoencephalitis

Figure 23. Microangiopathy

Figure 24. Multisystem inflammatory syndrome

Figure 25. Myelitis

Figure 26. Myocarditis

Figure 27. Narcolepsy

Figure 28. Other venous thrombosis

Figure 29. Pericarditis

Figure 30. Peripheral facial nerve palsy

Figure 31. Pregnancy thrombosis

Figure 32. Pulmonary embolism

Figure 33. Single organ cutaneous vasculitis

Figure 34. Splanchnic thrombosis

Figure 35. Stress cardiomyopathy

Figure 36. Sudden death

Figure 37. Thrombocytopenia

Figure 38. Venous thromboembolism

Figure 39. Zoster (Shingles)

Appendix 6 – Background rates for maternal and infant events of special interest

Table 1. ICD-10-AM codes

Table 2. Incidence of hospital-related outcomes among women who contributed pregnancy person-time between 01 January 2009 and 31 December 2013, New Zealand

Table 3. Risk and incidence of hospitalisation for stillbirth among pregnant women who delivered between 01 January 2009 and 31 December 2013, New Zealand

Table 4. Risk and incidence of hospitalisation for preterm labour among pregnant women who delivered between 01 January 2009 and 31 December 2013, New Zealand

Table 5. Risk and incidence of hospitalisation for premature rupture of membranes among pregnant women who delivered between 01 January 2009 and 31 December 2013, New Zealand

Table 6. Risk and incidence of hospitalisation for preterm delivery among pregnant women who delivered between 01 January 2009 and 31 December 2013, New Zealand

Table 7. Incidence of hospital-related outcomes among infants under 1 year of age who were born to women pregnant between 01 January 2009 and 31 December 2013, New Zealand

Table 8. Incidence of extreme preterm: <28 weeks in infants under 1 year of age who were born to women pregnant between 01 January 2009 and 31 December 2013, New Zealand

Table 9. Incidence of very preterm: 28 to <32 weeks in infants under 1 year of age who were born to women pregnant between 01 January 2009 and 31 December 2013, New Zealand

Table 10. Incidence of moderate to late preterm: 32 to <37 weeks in infants under 1 year of age who were born to women pregnant between 01 January 2009 and 31 December 2013, New Zealand