SAFE Project:

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

Part 2: Assessing accuracy of search strategies for AESI

Final report

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VACCINE DATALINK AND RESEARCH GROUP

uniservices
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Disclaimer

The findings and conclusions expressed in this report are those of the researchers, not the funder.

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Conflict of interest statement

Members of the research team involved in this project and production of the final report are employed by The University of Auckland, Auckland UniServices Limited, Auckland District Health Board, Counties Manukau District Health Board, or ACT Coding Ltd. They have no conflicts of interest to this project to declare.

Contents

Abbreviations

Abbreviation	Description
ADEM	acute disseminated encephalomyelitis
AESI	adverse event of special interest
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
DPT	diphtheria, whole-cell pertussis, and tetanus
DVT	deep vein thrombosis
ECG	electrocardiograph
ED	emergency department
EEG	Electroencephalogram
HDEC	Health and Disabilities Ethics Committee
HIT	heparin induced thrombocytopenia
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
ID	identification
IDI	Integrated Data Infrastructure
ITP	Idiopathic thrombocytopenic purpura
MRI	magnetic resonance imaging
N	number (count)
NHI	National Health Index
NMDS	National Minimum Data Set
NPAC	National Non-admitted Patient Collection
PPV	positive predictive value
PUC	Purchasing Unit Code
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
TMA	thrombotic microangiopathy
TTP	thrombotic thrombocytopenic purpura
TTS	thrombosis with thrombocytopenia syndrome

Assessing accuracy of search strategies for AESI

1. Introduction

To understand if increased adverse events of special interest (AESI) incidences are attributable to COVID-19 vaccination/s, baseline reference data from before vaccine deployment is required. The *Assessing accuracy of search strategies for AESI* project addresses and reports on the second primary objective of the *SAFE Project*. Clinical record assessment was used to validate the accuracy (positive predictive value (PPV)) of the ICD-10-AM codes used in the health data to estimate the incidence of AESI. The background, rationale, national and international context of the *SAFE Project*, are described in detail in the *Background rates of AESI in New Zealand 2008–2019* report.

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. SPEAC established and prioritised a set of AESIs for COVID-19 vaccines[1] (Table 1), that were endorsed by the *World Health Organization Global Advisory Committee on Vaccine Safety*, and agreed by the *European Medicines Agency*, 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.

SPEAC and the *Brighton Collaboration* also engaged in a long-term programme to establish 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 contribute 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.

2. Objectives

The *Background rates of AESI in New Zealand 2008–2019* project addresses and reports on the first primary objective and both secondary objectives of the *SAFE Project*. The *Assessing accuracy of search strategies for AESI* project addresses and reports on the second primary objective of the *SAFE Project*.

2.1 Primary objectives

1. Estimate the incidence of predefined AESI 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 AESI.**

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.
2. Estimate the prevalence of AESI in the sub-population most at risk for developing severe COVID-19 disease.

3. Methods

3.1 Ethics approval

Ethics approval was granted by the national *Health and Disabilities Ethics Committee* (HDEC) on 20 April 2021 following expedited review, reference 21/NTB/95. The HDEC provides independent ethical review health research and innovative practice to safeguard the rights, health and wellbeing of consumers and research participants. Locality approval was sought and obtained from each participating DHB.

3.2 Study design

This study 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 of the AESIs, except anaphylaxis, prioritised in Tier 1 by SPEAC[1] (Table 1), 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 and described the associated ICD-10-AM and SNOMED codes and assessed whether coding differed by ethnicity. Thrombocytopenia was selected as this is one condition required for diagnosis of the newly identified thrombosis with thrombocytopenia syndrome (TTS) and there are no specific ICD-10-AM or SNOMED codes that represent diagnosis of the syndrome.

3.3 Data management

The data collection form only identified the patient by a unique study identification (ID) number. To enable re-review of the medical record for training or adjudication, the principal investigator (Associate Professor Helen Petousis-Harris) and investigator (Associate Professor Timothy Kenealy) maintained a list, stored separately from the patient data, that included the patient *National Health Index* (NHI) number and the study ID number. This NHI/study ID number list will be destroyed after the end-of-contract report has been accepted.

The de-identified data extracted for each patient was entered into a master *Excel* sheet maintained by the research auditor and investigator Timothy Kenealy on *The University of Auckland Microsoft OneDrive*, which is one of the University preferred secure storage systems for research data.

4. Part A: Codes to cases

For each AESI, except anaphylaxis, prioritised in Tier 1 by SPEAC[1] (Table 1), myocarditis, and pericarditis, we sought to establish a small number of hospital discharge codes that consistently point to each AESI as defined by the *Brighton Collaboration* case definitions. An estimate of the positive predictive value (PPV) of the chosen code/s for the target AESI was calculated to indicate how likely the selected ICD-10-AM code would be to identify a case that met the *Brighton Collaboration* AESI definition from ED visit/hospital discharge records. 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.

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			

☐ AESIs included in *Part A: Codes to cases*

For the purposes of surveillance to monitor trends, high specificity of searches (low number of false positives) is more important than high sensitivity (low number of missed cases). We did not need a comprehensive list of all codes that might indicate a target AESI as this would inevitably lead to searches with high sensitivity and low specificity.

This work was not an audit of coding accuracy *per se*. Hospital discharge codes are collected for administrative purposes that differ from this research enquiry. Codes are assigned by professional coders according to clearly specified rules that include a requirement they code only diagnoses that are explicitly recorded by clinicians; they are prohibited from making their own clinical interpretation of data. In this research, we were required to clinically interpret the data to determine whether it met the *Brighton Collaboration* case definition.

Searches were based on ICD-10-AM codes assigned following hospital discharge and SNOMED codes assigned following emergency department (ED) visits. No widespread or consistent coding is available from primary care. Hospital admission ICD-10-AM codes are available from all *District Health Boards* (DHBs) and from the *National Minimum Dataset* (NMDS). The current code version is ICD-10-AM 11th edition. Up to 99 ICD-10-AM diagnosis or procedure codes are allowed per admission, with the first-recorded being the primary reason for admission as determined by a DHB coder.

ED visits are reported with SNOMED codes and have been recorded from 2019 in four DHBs – Auckland, Bay of Plenty, Nelson Marlborough, and Canterbury. All other DHBs were required to start SNOMED coding by 1 July 2021. National ED visit data are held in the *National Non-admitted Patients Collection* (NNPAC). A single chief complaint is recorded – this is generally a patient symptom. Up to five diagnoses are allowed. These are entered by a clinician (not a professional coder), with no explicit requirement that the first-entered is the principal reason for attendance. Up to 15 procedure codes are allowed.

4.1 Approach

We drew up a list of candidate ICD-10-AM and SNOMED codes based on advice from senior coders and content experts – a haematologist, a neurologist, a paediatric cardiologist, an infectious diseases physician and a general practitioner. As noted above, we sought specificity over sensitivity; where coding allowed, we sought to minimise events where an underlying cause for a target condition had been assigned, anticipating that vaccine related AESIs would be coded as cause unknown or unspecified. We searched on all instances of codes, not just the primary diagnosis. We sought only the first event for each patient.

We approached eight DHBs as a convenience sample, including all those who used SNOMED codes for ED attendances, and those we knew had remote access available for some or all the medical record reviews. 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 and included areas with high Māori and Pacific populations.[2]

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), we asked for data to 31 March 2021 to allow comparison with SNOMED codes from ED attendances. If there were fewer than eight cases, we asked the

DHB to search data back to 1 January 2008. For ED visits data was requested for all events coded with one of 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 we considered that data from 2020 might be affected either the disease or the response to COVID-19, and data in 2021 would be affected by the vaccine roll-out.

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

A data extraction form was constructed in *Google Sheets* (*Google Workspace* platform) to facilitate shared work from the coder and reviewers. The data extraction forms are available on request. Patients were de-identified and each assigned a unique study-specific identification code. We held an initial zoom session to train coders and reviewers, with follow up support by phone or e-meeting as needed. The coder was tasked with providing summary text against each criterion set by each case definition, sufficient to make a judgement that each criterion was met, or not, and sufficient for a reviewer to confirm or request further data from the coder. First reviews of the extracted data were conducted by the infectious disease specialist or the general practitioner, with adjudication as needed by the neurologist, haematologist, or paediatric cardiologist.

4.1.1 Decisions required during data collection

- Cases that were not the first admission with a condition were classified as 'Not a Case', except for convulsions. We wanted to identify new cases and count them only once.
- Cases where data from the index admission met a case definition – but subsequent admissions provide an alternative or more specific diagnosis – were classified according to the data from the index admission. We sought to develop search strategies that could be used for surveillance of discrete admissions rather than, for example, identifying cases for full longitudinal record review.
- Cases that met a case definition but were attributed to a specific cause e.g., myelitis caused by zoster, acute disseminated encephalomyelitis (ADEM) caused by anti-NDMA receptor antibodies – were classified as 'Not a Case'. We sought to develop search strategies that would find cases of unexplained conditions. Most case definitions explicitly exclude cases where an alternative diagnosis is available.
- Cases that include a time component were a special case.
    - For Bell's palsy the case definition requires partial or full recovery. However, most cases admitted to hospital were discharged before recovery was observed, and most had no further follow up in the hospital record. Most would be followed up in primary care. We

decided to report Bell's palsy in two ways – meeting the case definition including and excluding the recovery criteria.

  - For ADEM the case definition required a monophasic illness with no recurrence within three months to meet level 1 of diagnostic certainty. Evidence for a pattern over time can be sought from secondary care records but cannot be detected based only on surveillance of ICD-10-AM codes. We decided to report ADEM in two ways – meeting the case definition including and excluding the recovery criteria.

- Interpreting ECGs (electrocardiographs) was difficult for the auditor. There was usually a limited text comment or summary that did not provide the details required by myocarditis or pericarditis case definitions. This differed from scans that included a full formal report.
- Generalised convulsions were often missing explicit evidence of *witnessed* loss of consciousness. They were also mostly a chronic recurrent condition that could meet the case definition but would not be considered as caused by a vaccination if the need arose.
- Sometimes there was insufficient detail in a scan, lumbar puncture, ECG or EEG (electroencephalogram) report if the investigation was performed at another hospital (such as when patients transferred between hospitals).
- Pericarditis criteria to assign a level of diagnostic certainty include pericardial friction rub, distant heart sounds (infant/children), and pulsus paradoxus. We were concerned that New Zealand clinicians do not use or document these terms now, and this would affect being able to assign level 1 or level 2 of diagnostic certainty to cases. In the records reviewed, 'no rub' was recorded several times and 'pulsus paradoxus' only recorded once.
- There were several instances of thrombocytopenia (too few platelets) being miscoded as thrombocythemia (too many platelets); these events could not meet the case definition for thrombocytopenia.

Further background information and methods description can be found in Appendix 1, the *Protocol for assessing accuracy of search strategies for AESI*.

4.2 Results

The results are presented in tables, one for each condition. Details of raw data are shown in the Appendix 2. A total of 761 events were reviewed, of which 17 (2%) were from 2020 or 2021 and inadvertently included in this report.

Table 2. Thrombocytopenia

Number of record reviews, positive predictive value (PPV) and 95% confidence intervals (CI) for each code as a search strategy to identify events meeting the **c**ase **d**efinition with level 1, 2 or 3 of diagnostic certainty

Code	Short description	N	PPV	95% CI
32273002	Idiopathic thrombocytopenic purpura (ED visit)	5*	100%	48–100%
D69.3	Idiopathic thrombocytopenic purpura	32	94%	79–99%
D69.4	Other primary thrombocytopenia	32	100%	89–100%
D69.5	Secondary thrombocytopenia	32	100%	89–100%
D69.6	Thrombocytopenia, unspecified	32	100%	89–100%

Note

- *Four cases were excluded due to missing data.

Table 3. Aseptic meningitis

Number of record reviews, positive predictive value (PPV) and 95% confidence intervals (CI) for each code as a search strategy to identify events meeting the **c**ase **d**efinition with level 1, 2 or 3 of diagnostic certainty

Code	Short description	N	PPV	95% CI
G03.0	Non-pyogenic meningitis	32	78%	60–91%
G03.8	Meningitis due to other specified causes	27	56%	35–75%

Notes

- ICD-10-AM code G03.0. Sleepiness and confusion are manifestation of encephalopathy rather than meningitis *per se*.
- ICD-10-AM code G03.8. Several code selections were judged by the expert coder and specialist neurologist to be in error: inflammation of the dura coded as meningitis, arachnoiditis coded as meningitis, and enterococcal meningitis that should be coded explicitly. These cases were classified as coding errors.

Table 4. Encephalitis

Number of record reviews, positive predictive value (PPV) and 95% confidence intervals (CI) for each code as a search strategy to identify events meeting the **c**ase **d**efinition with level 1, 2 or 3 of diagnostic certainty

Code	Short description	N	PPV	95% CI
G04.0	Acute disseminated encephalitis	30	53%	34–72%

Notes

- Only one case had a biopsy, which is required to meet level 1 of diagnostic certainty.
- Eleven cases assigned as level 2 of diagnostic of certainty.
    - One was difficult to classify due to uncertainty in assigning the encephalopathy and altered response to environment criteria.
    - Four cases were considered to be ADEM rather than encephalitis.

- Four cases assigned as level 3a of diagnostic certainty, insufficient information available to classify a case.
    - Three cases were considered to be ADEM.
    - One case was described in the discharge summary as "autoimmune encephalitis possibly related to flu vaccine".
- Thirteen cases were excluded. Eleven cases were ADEM. One case was myelin oligodendrocyte glycoprotein (MOG) antibody positive, one case was secondary to a viral infection (chickenpox), two were post vaccination (varicella vaccine and whooping cough vaccine), and one case consistent with immune therapy related encephalitis. None of these cases meet the case definition of encephalitis.

Table 5. Myelitis

Number of record reviews, positive predictive value (PPV) and 95% confidence intervals (CI) for each code as a search strategy to identify events meeting the **c**ase **d**efinition with level 1, 2 or 3 of diagnostic certainty

Code	Short description	N	PPV	95% CI
G04.8	Other encephalitis, myelitis and encephalomyelitis	28	B18%	6–37%
G04.9	Encephalitis, myelitis and encephalomyelitis, unspecified	28	11%	2–28%
G37.3	Acute transverse myelitis in demyelinating disease of central nervous system	28	86%	67–96%

Note

- Most cases that did not meet the case definition for myelitis were cases of encephalitis, ventriculitis (five cases), ADEM or aseptic meningitis with no evidence of brain involvement.

Table 6. Acute disseminated encephalomyelitis

Number of record reviews, positive predictive value (PPV) and 95% confidence intervals (CI) for each code as a search strategy to identify events meeting the **c**ase **d**efinition with level 1, 2 or 3 of diagnostic certainty

Code	Short description	N	PPV	95% CI
G04.0	Acute disseminated encephalitis	30	60%	41–77%
G04.8	Other encephalitis, myelitis and encephalomyelitis	28	21%	8–41%
G04.9	Encephalitis, myelitis and encephalomyelitis, unspecified	28	36%	19–56%

Notes

- Most cases that did not meet the case definition did not have an acute event, rather they had a recurrence or chronic issues from prior ADEM.
- The second most common reason to not meet the case definition was the event was considered secondary to a specific diagnosis of autoimmune or paraneoplastic disease.
- Magnetic resonance imaging (MRI) findings were most likely to confirm a case or identify an alternative diagnosis.

Table 7. Generalised convulsion

Number of record reviews, positive predictive value (PPV) and 95% confidence intervals (CI) for each code as a search strategy to identify events meeting the **c**ase **d**efinition with level 1, 2 or 3 of diagnostic certainty

Code	Short description	N	PPV	95% CI
G40.30	Generalised idiopathic epilepsy and epileptic syndromes, not intractable epilepsy	31*	77%	59–90%
G40.31	Generalised idiopathic epilepsy and epileptic syndromes, with intractable epilepsy	32	91%	75–98%
G40.50	Special epileptic syndromes, not intractable epilepsy	32	69%	50–84%
G40.51	Special epileptic syndromes, with intractable epilepsy	3	100%	29–100%

Notes

- *One case was excluded due to missing data.
- Events that did not meet the case definition included focalised rather than generalised seizures, and instances of generalised seizures on prior admission but not the current admission.
- One case (level 2 of diagnostic certainty) was associated with an infant DPT (diphtheria, whole-cell pertussis, and tetanus) vaccination.
- Five events were stated to be a case of generalised convulsions, but there was insufficient evidence to meet the case definition. In one case we could not access mental health records, which were stored and accesses separately from the general medical records. In other instances, there was insufficient information to meet the case definition criteria about the type of seizure and generalised motor manifestation.

Table 8. Bell's palsy

Number of record reviews, positive predictive value (PPV) and 95% confidence intervals (CI) for each code as a search strategy to identify events meeting the case definition with level 1, 2 or 3 of diagnostic certainty

Code	Short description	N	PPV	95% CI
193093009	Bell's palsy (including recovery criterion) (ED visit)	9*	11%	0.3–48%
	Bell's palsy (excluding recovery criterion) (ED visit)	9*	89%	52–100%
G51.0	Bell's palsy (including recovery criterion)	31†	29%	14–48%
	Bell's palsy (excluding recovery criterion)	31†	52%	33–70%

Notes

- *Three cases were excluded due to missing data.
- †One case was excluded due to missing data. The principal reason for failure to meet the case definition was because of the requirement to show resolution over time. However, patients were typically discharged before resolution had taken place and there was no follow up in the secondary care system.
- Bell's palsy is also termed peripheral facial nerve palsy.

Table 9. Guillain-Barré syndrome

Number of record reviews, positive predictive value (PPV) and 95% confidence intervals (CI) for each code as a search strategy to identify events meeting the **c**ase **d**efinition with level 1, 2 or 3 of diagnostic certainty

Code	Short description	N	PPV	95% CI
G61.0	Guillain-Barre syndrome	32	81%	64–93%

Note

- G61.0 is also the ICD-10-AM code for Miller Fisher syndrome.

Table 10. Myocarditis or pericarditis after exclusions

Number of record reviews, positive predictive value (PPV) and 95% confidence intervals (CI) for each code as a search strategy to identify events meeting the **c**ase **d**efinition with level 1, 2 or 3 of diagnostic certainty

Code	Short description	N	PPV	95% CI
I40.1	Isolated myocarditis	4	100%	40–100%
I40.8	Other acute myocarditis	19	37%	16–62%
I40.9	Acute myocarditis, unspecified	28	89%	72–98%
I51.4	Myocarditis, unspecified	22	84%	67–95%
I30.0	Acute nonspecific idiopathic pericarditis	32	66%	46–82%
I30.8	Other forms of acute pericarditis	4	33%	16–55%
I30.9	Acute pericarditis, unspecified	18	47%	29–65%
I31.9	Disease of pericardium, unspecified	32	47%	29–65%

Notes

- Twenty-six cases of pericarditis codes I30.8, I30.9 or I31.9 did not meet the case definition, mostly due to pericardial effusion following repair of aortic dissection, or being after coronary artery surgery, or secondary to radiotherapy or specified viral or bacterial infection.
- Table 13 in Appendix 2 describes the codes excluded from myocarditis and pericarditis events for medical record review.

4.2.1 Summary of *Codes to cases* results

Common coding and clinical practices in the New Zealand context need to be considered when interpreting these codes.

- There was considerable variation in the PPV for the Tier 1 AESI using ICD10-AM codes selected in this review.
    - 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%).
    - 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 ICD-10-AM codes to identify and refine AESI.
    - For generalised convulsions, some cases had been included that were recorded from a previous admission rather than the current admission.

- For Bell's palsy (also termed peripheral facial nerve 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.

5. Part B. Cases to codes: Thrombocytopenia in depth

We sought to identify all people with thrombocytopenia attending a *District Health Board* (DHB) over a specified period, then described this group in terms of ethnicity and coding patterns. This approach had two purposes. First, we address the possibility that coding, attendance at an emergency department (ED) and admission rates vary by ethnicity. Second, we sought to develop search strategies that may screen for the recently identified thrombosis with thrombocytopenia syndrome (TTS). This syndrome is unusual for two reasons. First, thrombocytopenia is generally associated with too little clotting of blood rather than too much. Second, the sites of blood clots are unusual, especially the cerebral venous sinus and splanchnic vein that drains the spleen, stomach and pancreas.

Diagnosis of TTS rests on finding thrombocytopenia (relatively common) and unusual clots (relatively rare). We determined whether thrombocytopenia, confirmed by laboratory test, is consistently coded in SNOMED and ICD-10-AM codes.

Clinical notes about thrombocytopenia

- Peak incidence in young adults likely to be immune-mediated and self-limiting.
- Immune thrombocytopenia gets worse in pregnancy and is more important to manage and may first come to light when pregnant.
- Maturity-onset tend to be more chronic and need treatment.
- Thrombocytopenia may be seen in 2% of term infants and 20% of premature ones.
- Only unwell neonates will have blood test so expect a substantial proportion of these to show thrombocytopenia.
- Main causes of thrombocytopenia in infants are placental insufficiency, alloimmune, and infections including necrotising enterocolitis.
- Poor collection with capillary collects in infants can results in blood clotting in collection tubes leading to a spuriously low platelet count due to blood clotting in the tube. If clotting is visible likely to result in repeat collection which could come back normal.
- D69.3 Idiopathic thrombocytopenic purpura (ITP) is not in Table 16. Counties Manukau DHB receive referrals for around 1,000 patients with ITP per year.
- Indian ethnicity is included in the Asian ethnic group for this analysis.
- Thrombotic microangiopathy (TMA) includes disseminated intravascular coagulation (DIC), haemolytic uraemic syndrome, heparin induced thrombocytopenia (HIT), thrombotic thrombocytopenic purpura (TTP), and perhaps antiphospholipid syndrome.

5.1 Approach

Ethics and locality approvals were obtained in the same applications as for *Part A: Codes to cases*.

We requested a list of events where their laboratory confirmed a low platelet count (<150 x10^9/L) from eight DHBs. We asked them to assign these, where relevant, to a hospital admission or ED visit and provide a list that included platelet count, event identification (ID) number, *National Health Index* (NHI) number, patient demographics and ICD-10-AM discharge codes or SNOMED ED visit codes. Patients without an associated ED visit or admission were excluded, e.g., when blood was tested as part of an outpatient visit. No chart review will be done on these events.

The unit of analysis is an event that includes thrombocytopenia, using the first event for a given patient between 1 January 2008 and 31 December 2021. We describe the associated diagnostic codes.

A list of codes that may indicate thrombosis with thrombocytopenia syndrome (TTS) are reported in the *Results* section. It may be possible to test a set of codes for positive predictive value (PPV) for TTS, using the same process described in *Part A*. However, that was beyond the scope of this research.

5.1.1 Incomplete ED coding

Coding of ED attendances was very incomplete during this period. Coding started in 2019 with four DHBs to develop processes, with other DHBs starting at various times, and all being obligated to code from 1 July 2021.

5.1.2 Defining ED attendance and hospital admission

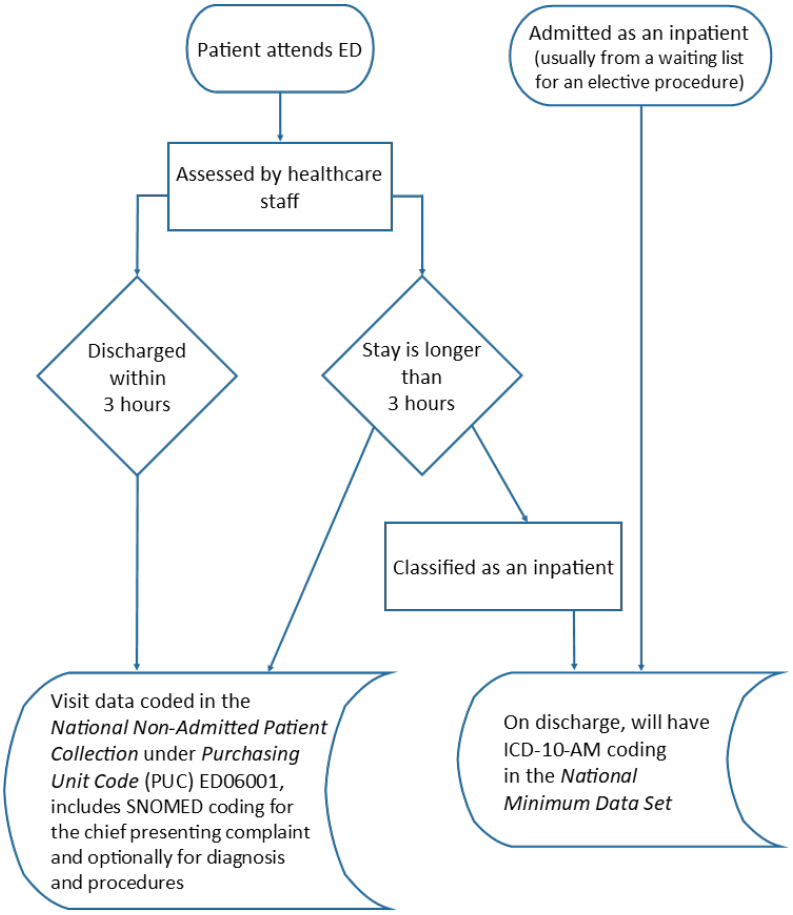
The *Ministry of Health* considers anyone who stays in ED for more than three hours to be classified as an inpatient. DHBs consider this a 'statistical admission' as the patient may not progress onto a true inpatient ward but could stay in ED or a medical assessment short stay unit before discharge. For data purposes there are three basic scenarios (illustrated in Figure 1.):

a) A patient attends ED, is seen and discharged within 3 hours; and classified as an ED 'outpatient'; data appears in *National Non-Admitted Patient Collection* (NNPAC) under *Purchasing Unit Code* (PUC) ED06001 and includes SNOMED coding for the chief presenting complaint and optionally for diagnosis and procedures.

b) A patient attends ED, is seen and stays longer than three hours; and classified as an 'inpatient'; data appears in NNPAC under PUC ED06001A; will have SNOMED coding as above; on discharge will additionally have ICD-10-AM coding in the *National Minimum Data Set* (NMDS).

c) A patient is admitted as an inpatient from a waiting list (usually elective procedures) and on discharge will have ICD-10-AM coding; data appears only in the NMDS.

Figure 1. ED attendance and hospital admission data scenarios



DHBs can electronically link the ED event with the inpatient event if they occur immediately consecutively, and this is considered as one event. A laboratory test can be linked to that one event where the test date falls within the ED presentation date and the inpatient end date. Discussions with DHB data analysts indicated that not all DHBs routinely linked these data, and linking logic and processes may vary, especially when the laboratory services are subcontracted to separate business units within the DHB or to an external agency.

Further background information and methods description can be found in the *Protocol for assessing accuracy of search strategies* for AESI in the Appendix 1.

5.2 Results

A total of 88,178 thrombocytopenia-associated hospital admissions, including only the first event per patient, were recorded between 1 January 2008 and 31 December 2019. Admissions in the first month after birth were excluded as these are a large group with their own physiology and will never be subject to COVID-19 vaccination. This left 77,647 admissions that are the subject of this report. Details on data collection and cleaning are described in Appendix 3. There were only two ED attendances, during this time, not associated with a hospital admission; they are not included in this report.

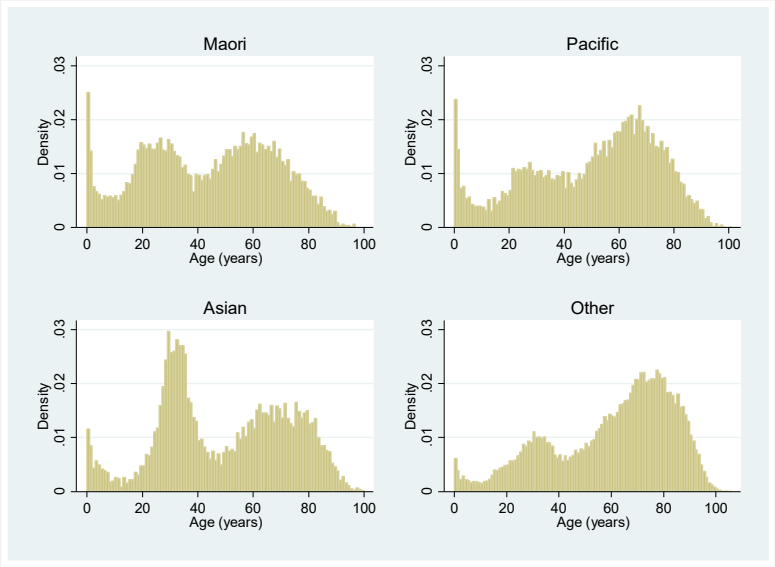
Table 1. Hospital admissions associated with thrombocytopenia

In eight DHBs, January 2008 to December 2019 by gender, ethnicity and first month after birth

		Admissions aged 1 month and over (subject of all further analyses)	Admissions in first month (excluded from further analyses)	Total admissions
Number		77,647 (88%)	10,531 (12%)	88,178
Gender	Female	36,589 (89%)	4,683 (11%)	41,272
	Male	41,058 (87%)	5,848 (13%)	46,906
Ethnicity	Māori	12,818 (87%)	1,979 (13%)	14,797
	Pacific	7,032 (94%)	468 (6%)	7,500
	Asian	8,868 (93%)	716 (7%)	9,584
	Other	48,929 (87%)	7,368 (13%)	56,297

Age distribution of hospital admissions is triphasic. Distributions after the first month are shown in Figure 2.

Figure 2. Hospital admissions by age, if aged 1 month and over, and ethnicity



There are only five ICD-10-AM codes that explicitly include thrombocytopenia codes, shown in Table 2. These codes were found in only 3% of admissions, similar across ethnicities. This means that no ICD-based search strategy is useful to screen for thrombocytopenia, and thus for TTS that requires thrombocytopenia as one component.

Table 2. Admissions with explicit thrombocytopenia code, aged 1 month and over

ICD10 Code	Admissions
D69.4 Other primary thrombocytopenia	7
D69.5 Secondary thrombocytopenia	461
D69.6 Thrombocytopenia, unspecified	2018
P61.0 Transient neonatal thrombocytopenia	6
Q87.26 Thrombocytopenia with absent radius syndrome	1

We examined the rank order of code frequency by ethnicity – rank one means the most frequently assigned code – shown in Table 3. These ranks suggest discrepancy in coding if underlying rates of the principal

reasons for admission do not differ for Māori versus non-Māori. Further investigation of selected principal reasons for admission and ethnic specific rates is needed to confirm this.

Three of the top-ranked codes relate to obstetrics, fitting with the middle peak seen in Figure 2 (these codes are for adults, separate from the high rate of thrombocytopenia seen in the first month after birth). The ethnic-specific rank that differed most from the overall population pattern was code O81 (Single delivery by forceps and vacuum extractor), rank 10 overall but rank 44 for Māori. It is known that the rate of forceps and vacuum extraction for Māori is about half that of New Zealand European women.[3]

Table 3. Frequency ranking for principal reason for admission

Top 10 in overall population by ethnicity, from a total of 4,105 distinct ICD-10-AM codes

ICD10 code	Overall Rank		Māori Rank	Pacific Rank	Asian Rank	Other Rank
O82 Single delivery by caesarean section	1		4	3	1	1
O80 Single spontaneous delivery	2		1	2	2	3
J18.9 Pneumonia, unspecified	3		2	5	5	2
I50.0 Congestive heart failure	4		3	1	11	6
N39.0 Urinary tract infection, site not specified	5		9	7	6	4
I21.4 Acute subendocardial myocardial infarction	6		16	9	7	5
J22 Unspecified acute lower respiratory infection	7		6	4	8	8
R07.4 Chest pain, unspecified	8		5	14	16	7
B34.9 Viral infection, unspecified	9		10	10	4	12
O81 Single delivery by forceps and vacuum extractor	10		44	20	3	16

We considered variation by ethnicity in a separate analysis that groups ICD-10 codes by disease chapter of the principal reason for admissions, sorted to calculate the smallest number of codes that account for 90% of admissions. We used the treemap visualisation technique in which the size of the rectangles is proportional to the number of admissions in each category[4] shown in Figure 3 and Figure 4. It is difficult to gauge differences thrombocytopenia coding without prior knowledge of underlying expected rates of the principal reason for admission. However, there are differences in rates of underlying admissions in each category which need more robust statistical investigation

Figure 3. Scaled rectangle diagram, proportion of admissions by ICD-10-AM code for principal diagnosis, Māori

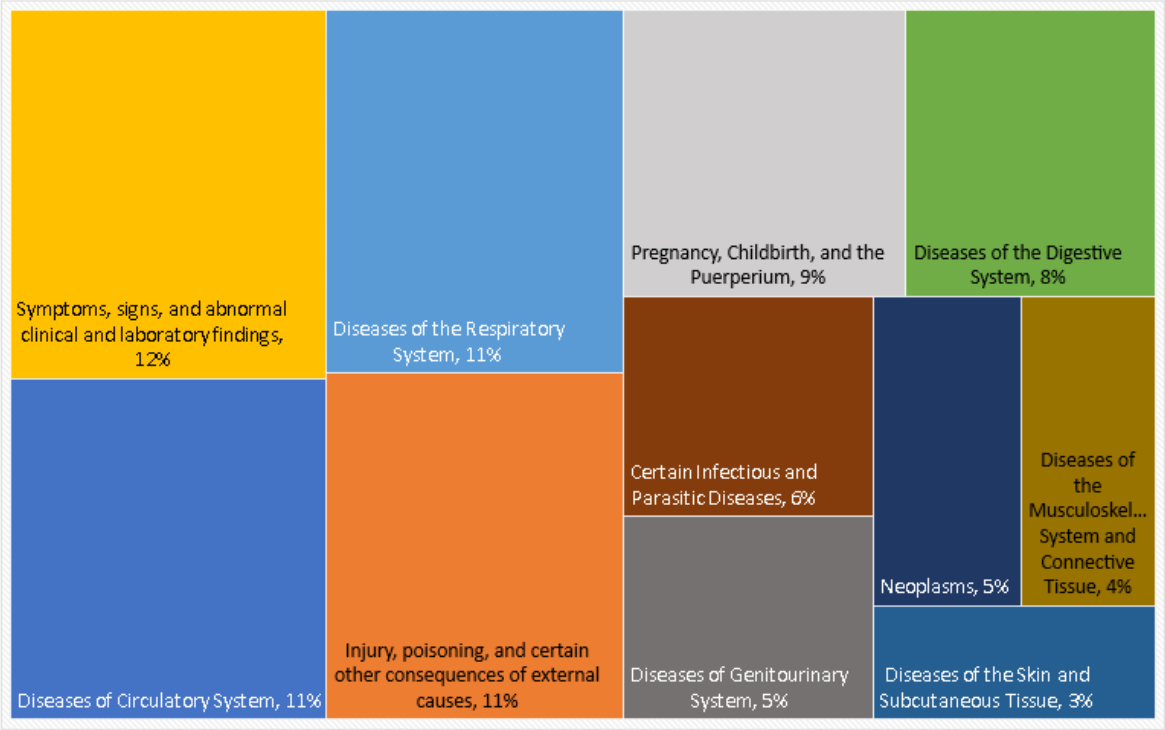
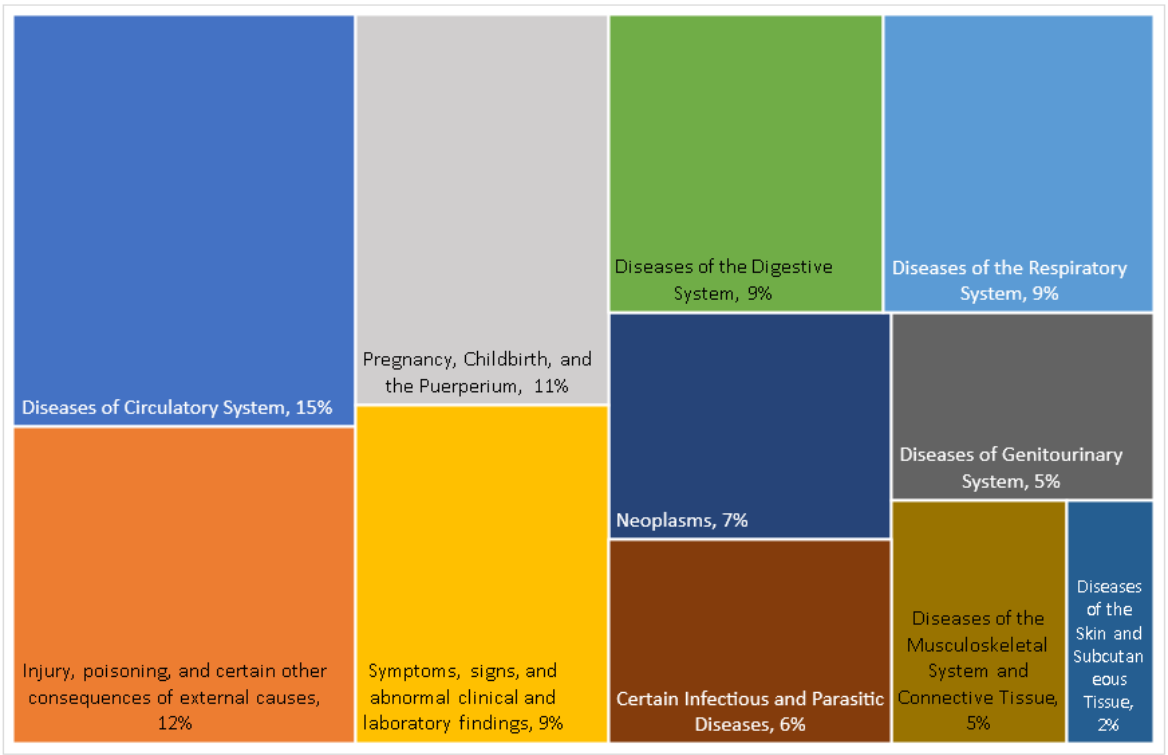


Figure 4. Scaled rectangle diagram, proportion of admissions by ICD-10-AM code for principal diagnosis, non-Māori



We considered frequency of all codes that may be assigned to a patient with TTS (Table 4). There were no apparent differences by ethnicity. Only one code (D69.6 - Thrombocytopenia, unspecified) reached more than 1% frequency either by ethnicity or in the overall population. Syndromes that might mimic TTS are

specific syndromes that can be distinguished from TTS, which is therefore not expected to change coding as such.

There are no ICD-10-AM 11th edition codes specific to disseminated intravascular coagulation (DIC) or deep vein thrombosis (DVT), which together may mimic TTS. Venous events are most likely to be coded differently in the presence of TTS and would point to clots post-vaccine even if no TTS was present.

The implications of this section of the work need further input from haematology and epidemiology specialists and others. We think the findings will inform a selection of codes to be applied in medical record reviews such as in *Part A* of this report, to identify a limited number of codes with a high PPV for TTS and other thrombotic conditions that may be an adverse event of special interest (AESI) with respect to vaccination for COVID-19.

Table 4. Patients with thrombocytopenia and hospital admission assigned an ICD code that may indicate an element of TTS

ICD10 code$^{\phi}$	Māori n=12,818	Pacific n=7,032	Asian n=8,868	Other n=48,929	Total n=77,647
Thrombocytopenia in classification					
D69.3 Idiopathic thrombocytopenic purpura	47	31	83	206	367
D69.4 Other primary thrombocytopenia	4	2	3	8	17
D69.5 Secondary thrombocytopenia	57	74	69	286	486
D69.6 Thrombocytopenia, unspecified	283	273	366	1,313	2,235
Syndromes that might mimic TTS					
D59.3 Haemolytic-uraemic syndrome	16	8	3	50	77
D59.4 Other nonautoimmune haemolytic anaemias	1	4	1	15	21
D59.5 Paroxysmal nocturnal haemoglobinuria [Marchiafava-Micheli syndrome]	0	0	0	2	2
D59.6 Haemoglobinuria due to haemolysis from other external causes	0	0	0	0	0
D59.8 Other acquired haemolytic anaemias	2	0	0	0	2
D59.9 Acquired haemolytic anaemia, unspecified	1	0	0	6	1
Cerebral infarction					
I63.0 Cerebral infarction due to thrombosis of precerebral arteries	3	1	4	4	12
I63.1 Cerebral infarction due to embolism of precerebral arteries	1	1	0	7	9
I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries	3	3	3	20	29
I63.3 Cerebral infarction due to thrombosis of cerebral arteries	14	3	12	57	86

ICD10 code[ϕ]	Māori n=12,818	Pacific n=7,032	Asian n=8,868	Other n=48,929	Total n=77,647
I63.4 Cerebral infarction due to embolism of cerebral arteries	20	25	25	133	203
I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries	8	15	13	52	88
*I63.6 Cerebral infarction due to cerebral venous thrombosis, non-pyogenic	3	0	0	0	3
I63.8 Other cerebral infarction	17	5	5	33	60
I63.9 Cerebral infarction, unspecified	84	51	51	517	703
Arterial clots					
I74.0 Embolism and thrombosis of abdominal aorta	0	1	1	10	12
I74.1 Embolism and thrombosis of other and unspecified parts of aorta	1	1	1	5	8
I74.2 Embolism and thrombosis of arteries of upper extremities	7	2	5	30	44
I74.3 Embolism and thrombosis of arteries of lower extremities	12	9	6	103	130
I74.4 Embolism and thrombosis of arteries of extremities, unspecified	0	0	0	4	4
I74.5 Embolism and thrombosis of iliac artery	7	2	5	27	41
I74.8 Embolism and thrombosis of other arteries	9	4	3	31	47
I74.9 Embolism and thrombosis of unspecified artery	0	0	0	4	4
Venous clots					
*I67.6 Non-pyogenic thrombosis of intracranial venous system	0	0	1	1	2
I81 Portal vein thrombosis	8	3	13	48	72
I82.0 Budd-Chiari syndrome	2	1	1	9	13
I82.2 Embolism and thrombosis of vena cava	5	6	2	10	23
I82.3 Embolism and thrombosis of renal vein	4	0	2	0	6
*I82.8 Embolism and thrombosis of other specified veins	32	33	18	145	228
*I82.9 Embolism and thrombosis of unspecified vein	0	0	1	6	7
Vascular					
K55.0 Acute vascular disorders of intestine	23	18	8	118	167
Causes					
Y57.8 Other drugs and medicaments causing adverse effects in therapeutic use	3	4	4	12	23

ICD10 code[ϕ]	Māori n=12,818	Pacific n=7,032	Asian n=8,868	Other n=48,929	Total n=77,647
Y57.9 Drug or medicament, unspecified causing adverse effects in therapeutic use	14	6	4	57	81
Y59.0 Viral vaccines causing adverse effects in therapeutic use	1	1	0	1	3
Y59.8 Other specified vaccines and biological substances causing adverse effects in therapeutic use	0	0	0	2	2
Y59.9 Vaccine or biological substance, unspecified causing adverse effects in therapeutic use	0	0	0	0	0

Notes

- [ϕ]ICD-10-AM code in any position, not only principal diagnosis.
- Patients aged 1 month and over, described by ethnicity.
- *Codes marked with an asterisk are considered the most likely to be used to code TTS.

5.2.1 Summary of *Cases to codes: Thrombocytopenia in depth* results

All people with thrombocytopenia attending a *District Health Board* (DHB) over a specified period were identified and described in terms of ethnicity and coding patterns.

- A total of 88,178 thrombocytopenia-associated hospital admissions, including only the first event per patient, were recorded between 1 January 2008 and 31 December 2019.
- Of these, only 3% (n=2493) had an associated ICD-10-AM code that specified thrombocytopenia. This proportion was similar across all ethnic groups however this represents a potential discrepancy in coding if the underlying rates of thrombocytopenia vary by ethnicity.
- Only one code (D69.6 – Thrombocytopenia, unspecified) reached more than 1% frequency either by ethnicity or in the overall population.

There are no ICD-10-AM 11th edition codes specific to disseminated intravascular coagulation (DIC) or deep vein thrombosis (DVT), both of which may mimic the newly identified TTS, and there are no specific ICD-10-AM or SNOMED codes that represent diagnosis of the syndrome.

6. References

1. Safety Platform for Emerging Vaccines, SPEAC. SO1-D2.0 Addendum to SO1-D2.2 & 2.3 Landscape analyses priority tiers for all CEPI vaccine development adverse events of special interest (AESI). Decatur, GA: Brighton Collaboration; 2020.
2. Stats NZ Tatauranga Aotearoa. Subnational population estimates (DHB, DHB constituency), by age and sex, at 30 June 1996-2021 (2021 boundaries) [Internet]. Wellington: Stats NZ Tatauranga Aotearoa; n.d. [updated 2021 June 30; cited 2021 July]. Available from: http://nzdotstat.stats.govt.nz/wbos/Index.aspx?DataSetCode=TABLECODE7509
3. Ratima M, Crengle S. Antenatal, labour, and delivery care for Māori: experiences, location within a lifecourse approach, and knowledge gaps. Pimatisiwin: A Journal of Aboriginal and Indigenous Community Health. 2013;10(3):353-66.
4. Johnson B, Shneiderman B. Treemaps: A space-filling approach to the visualization of hierarchical information structures. In: Shneiderman B, editor. Sparks of Innovation in Human-computer Interaction. Bristol: Intellect Ltd; 1993.

7. Appendices

Appendix 1

Protocol for assessing accuracy of search strategies for AESI

SAFE Project:

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

Protocol for assessing accuracy of search strategies for AESI

Prepared by

Timothy Kenealy

With input from Helen Petousis-Harris, Joan Ingram, Michael Tatley, Steven Black, Judith Hammond, Michael Browne, Richard Roxburgh, Gordon Royle, Hannah Chisholm, Tracy Thompson, Nelson Aguirre-Duarte

Version 16, 18 August 2021

CONTENTS

1 BACKGROUND

This protocol complements the document "The SAFE project: Background rates of Adverse Events of Special Interest (AESI) protocol" that describes the background, rationale, national and international context, and the data items used within the Integrated Data Infrastructure (IDI).

The Coalition for Epidemic Preparedness and Innovation (CEPI) has contracted with the Brighton Collaboration, through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project. SPEAC and the Brighton Collaboration has prioritized AESI into four tiers of importance,[1] the first tier being:

- Anaphylaxis
- Thrombocytopenia
- Generalised convulsion
- Aseptic meningitis
- Encephalitis
- Myelitis
- Acute disseminated encephalomyelitis
- Guillain Barré and Miller Fisher syndromes
- Peripheral facial nerve palsy

SPEAC and the Brighton Collaboration have been engaged in a long-term programme of establishing case definitions for AESIs, to support measuring baseline rates for these conditions in the absence of vaccinations. This information is essential for proper understanding of post-vaccine rates of the same conditions. This task has become urgent with the COVID-19 pandemic (Black et al, 2021). After international agreement on case definitions, the next step is to establish the accuracy of search strategies in identifying patient events that meet these case definitions. This is what we will do in our **Study Part A: Codes to Cases.** Searches as based on ICD and SNOMED codes assigned following hospital admissions or Emergency Department visits.

The New Zealand research team will validate codes for all the conditions listed above with the exception of anaphylaxis which generally occurs such a short time after vaccination that the connection is obvious. A Case Definition from the Brighton Collaboration is available for each of these conditions.
A recent and urgent concern is that the AstraZeneca vaccine and the Johnson and Johnson vaccine may, rarely, cause a syndrome still known by various names, referred to here as Vaccine Induced Thrombosis and Thrombocytopenia (VITT). The clinical syndrome is still being defined. Our contribution to this is our **Study Part B: Cases to Codes.** We will identify all cases of thrombocytopenia then describe the ICD and SNOMED codes associated and consider whether coding differs by ethnicity.

[1] Safety Platform for Emergency vACcines (SPEAC). SO1-D2.0 Addendum to SO1-D2.2 & 2.3 Landscape Analyses Priority Tiers for All CEPI Vaccine Development Adverse Events of Special Interest (AESI). V2.0-September 9, 2020. Table 4, page 9. https://brightoncollaboration.us/wp-content/uploads/2020/11/SPEAC_SO1_2.2_2.3-SO2-D2.0_Addendum_AESI-Priority-Tiers-Aug2020-v1.2.pdf (accessed 8 March 2021)

We seek clinical validation of hospital discharge codes which have been collected for administrative purposes that may differ from our research enquiry. We do not seek an exhaustive record of each of these events, which would require data collection from primary care, laboratories and directly from patients. No widespread, available, or consistent coding is available from primary care.

Hospital inpatient admissions are reported in ICD10-AM codes and are available from all DHBs. The national data are held in the National Minimum Dataset (NMDS). Up to 99 ICD10 diagnosis or procedure codes are allowed per admission, with the first-recorded being the primary reason for admission as determined by the DHB coder.

ED visits are reported in SNOMED codes and have been recorded from 2019 in four DHBs – Auckland, Bay of Plenty, Nelson Marlborough, and Canterbury. All other DBHs will start SNOMED coding by 1 July 2021. National Emergency Department (ED) data are held in the National Non-admitted Patients Collection (NNPAC). A single chief complaint is recorded – this is generally a patient symptom. Up to five diagnoses are allowed. These are entered by a clinician, with no explicit requirement that the first-entered is the principal reason for attendance. Up to 15 procedure codes are allowed.

1.1 ETHICS

Ethics approval is being sought from the Health and Disability Ethics Committees. The study includes DHBs outside the jurisdiction of the Auckland Health Research Ethics Committee, named patient medical records will be reviewed by researchers who are not the usual clinicians responsible for these patients, and some of those patients are likely to be children.

In the Study Part A: Codes to Cases, ethnicity will be recorded for patients whose charts are reviewed. This is for reporting the range of charts reviewed. No attempt will be made to stratify sampling by ethnicity as the focus is on coding validity against Case Definitions, not on condition rates which, however, will be an output from the IDI section of this project.

We are reviewing the notes for the sole purpose of validating codes and code combinations with respect to their accuracy in identifying a limited set of health conditions. If there appears to be an incorrect ICD or SNOMED code, we will notify the DHB coders.

1.2 ETHNICITY DATA

Ethnicity data will be taken from the NHI record. We are advised that this substantively under-counts Māori but is the best available for our purpose (Prof Sue Crengle). Where more than one ethnicity code is recorded, we will prioritise to Māori then Pacific then Asian then NZ European/Other as recommended by Stats NZ. Data will be reported in these four groups.

2 PURPOSE AND OUTCOME FROM PROJECT

2.1 STUDY PART A: CODES TO CASES

For each AESI we want to establish a small number of ICD10 or SNOMED codes that will point to that AESI as defined by our Case Definitions. We want to estimate the positive predictive value (PPV) of the chosen code/s for the target AESI. We will use the code/s with the highest PPV as input to the other arm of this study, which will use the chosen codes within the Integrated Data Infrastructure (IDI) to estimate population-level background rates of AESI prior to COVID vaccine rollout and later use them to examine trends in AESI over time.

We do not need a comprehensive list of codes that might indicate a target AESI. We are not attempting an exhaustive or complete catalogue of each AESI. To facilitate comparisons between COVID vaccine recipients and non-recipients and to allow evaluation of temporal trends it is essential to use consistent measurement methods over time.

The work described so far is not an audit of coding accuracy *per se*. Codes are assigned by professional coders according to clearly specified rules that include a requirement they code only diagnoses that are explicitly recorded by clinicians; they are prohibited from making their own clinical interpretation of data. (For example, even if they see a laboratory result showing low platelets, they cannot code as thrombocytopenia unless that diagnosis is explicitly noted in the clinical record.) In our case we need to clinically interpret the data to determine whether it meets our Case Definitions.

2.2 STUDY PART B: CASES TO CODES

Our Part A method will show, for each code, the number of true cases identified, and the number of false positive cases, but cannot detect false negatives, i.e., cases that, for whatever reason, were never coded as such. This requires an alternative method that will identify all cases then identify which of these are eventually coded as such. Thrombocytopenia is the only condition for which we have a method to identify all cases independent of coding.

We will identify all people with thrombocytopenia attending a DHB in a given time period, then describe this group in terms of ethnicity and coding patterns. This approach will address the possibility that coding, attendance at ED and admission rates vary by ethnicity. This approach was developed after discussions with Professor Sue Crengle from the Department of Preventive and Social Medicine, University of Otago, a senior Māori health researcher and a member of our Advisory Board. In addition, by describing coding patterns associated with thrombocytopenia we may contribute to the international effort to refine and develop search strategies for the emerging syndrome of VIPIT.

3 METHODS, STUDY PART A: CODES TO CASES

3.1 PRINCIPLE: CODE SELECTION FOR SPECIFICITY

We will select a limited set of codes for each condition, deemed to be relatively specific for the target AESI, based on expert advice and relevant literature.

Both our own experience and the literature (e.g., Mesfin et al 2011) indicate that there are often a large number of diagnosis and procedure codes that will each identify a small number of true cases of the target condition, but at the cost of identifying unhelpfully large numbers of non-cases. In other words, there are a number of codes with low specificity.

3.2 CODE EDITIONS

The ICD10 codes we use are the Australian Modification (ICD10-AM), 11th edition. The SNOMED-CT codes we use come from the New Zealand Emergency Diagnosis Reference Set 1 October 2020 Release.

3.3 CASE DEFINITIONS, LEVEL OF CERTAINTY

We will use Case Definitions from the Brighton Collaboration as the reference standard against which all cases will be determined to be classified as a confirmed, probable, or possible case, as stated but insufficient evidence, or as not a case. This is *not* a measure of severity of clinical illness but is an assessment of Level of Certainty that cases, identified by specific ICD or SNOMED codes, meet our Case Definition.

3.4 POWER CALCULATIONS

We have not conducted a formal power calculation. Furthermore, we found no study similar to our own which had undertaken power calculations.

However, in the study closest to our own, Mesfin et al (2011) reviewed records in a Melbourne ED, to validate three IDC10 codes chosen to identify cases of anaphylaxis from any cause and anaphylaxis post-vaccination. They used the Brighton Collaboration Case Definition of anaphylaxis. They reviewed 20, 23 and 26 charts for each of their three ICD codes, respectively. The code with 23 charts reviewed gave an estimated PPV of 95.6% (95% CI 78.1 to 99.9) for anaphylaxis from any cause. The two other codes gave lower PPVs. They also scanned a further 891 records identified by two more general codes without finding any further cases of anaphylaxis.

Given the high PPV achieved on one code over 23 charts, we decided that approximately 30 chart reviews per code would be sufficient. We seek to validate 15 codes across 10 AESIs, representing up to 480 chart reviews. These exact numbers are subject to change.

3.5 DHB SELECTION

Auckland, Bay of Plenty, Nelson Marlborough, and Canterbury DHBs have SNOMED (ED) codes available. We expect more people with Bell's palsy to be discharged from ED than from hospital admissions so decided to examine the Bell's palsy codes in both ED visits and hospital admissions in these DHBs. Auckland DHB, Counties Manukau, and Hutt Valley DHBs are known to have remote access available so are preferred for all case reviews.

The other DHBs listed are considered to give a broad sample of patient populations. We will approach other DHBs if those currently listed are unwilling or unable to work with us within the time frame and resources, we have available.

3.6 CODE SELECTION

The ICD10 and SNOMED codes used to define these conditions are listed below for each condition, along with case definitions and data collection guides. We have taken advice from the Brighton Collaboration for an initial list, Tracy Thompson (Senior Analyst, Classification and Terminology, National Collections and Reporting at the Ministry of Health), Associate Professor Richard Roxburgh (neurologist, Auckland DHB) and Dr Gordon Royle (haematologist, Counties Manukau DHB).

We are testing more than one search strategy in that for one condition (Bell's palsy) we are searching both hospital and ED records; for four neurological conditions we are searching on a single code that appears to be specific to the target condition; for two conditions (generalized convulsions and aseptic meningitis) we have included a second code and for one (thrombocytopenia) we have included four codes. The number of events correctly identified by the second, third and fourth codes may inform our future search strategies.

3.7 CODE SEQUENCE IN DHB & NATIONAL DATASETS

Events will be eligible if they are coded with one or more of the codes listed for each condition, in any sequence of the NMDS or NNAPC national datasets.

3.8 EVENT SELECTION, TIME PERIODS

We will ask each DHB to generate a list of events with specific ICD10 or SNOMED codes, in calendar years 2016 to 2019, and from these to randomly select 10 patients for each AESI. If more than one event is identified for a single patient, we will review only the first event.

ICD codes for hospital admissions are available back to 1988. They are available within the IDI from at least 2008. Year 2020 was considered an abnormal year due to COVID-19 incidence and associated lockdowns affecting rates of numerous health conditions, so we decided not to use year 2020 data for establishing baseline population rates of AESI. Because coding practice may change over time, we chose to examine the most recent years up to the end of 2019. If fewer than 10 patients are available with a specific AESI, we will extend the time period back to 2008.

SNOMED codes for ED visits are available only from 2019 and then only in 4 DHBs. People with some AESIs, e.g., Bell's palsy, are more likely to be seen in ED and discharged rather than be admitted to hospital. We chose to examine the SNOMED codes that are available in a limited number of DHBs and for a limited time, as SNOMED use will become widespread even within the time of this project.

Timeframes schematic

Study Part A: ICD discharge codes Bell's palsy, thrombocytopenia

January 2016 ---------- December 2019

Study Part A: SNOMED ED visit codes Bell's palsy, thrombocytopenia

Start of coding in 2019 ---------- March 2021

Study Part A: ICD discharge codes, all others

January 2016 ---------- December 2019

Study Part B: Laboratory data thrombocytopenia

January 2016 ---------- December 2019

3.9 CASE SELECTION FOR REVIEW

The DHB will provide a list of events for each code within the specified time period. Only the first event per patient is eligible.

For each ICD or SNOMED code there will be a list of eligible events. If there are more than the required number of events, we will randomly select a sample, as follows.

- Add a column in Excel, label "random number"
- Fill column with formula *rand()*
- Copy column, paste back to same column using Paste/values option
- Sort on this column, from highest value to lowest
- Select requisite number of events to review by counting down from the top of the column
- If replacement is required, select the next-highest value

3.10 CASE REVIEWS

The research auditor will require access to the clinical records, either on-site or remote (preferred). The auditor has previously used remote access to records at Auckland and Hutt Valley DHB. Based on preliminary discussions we are confident that we can meet the security requirements of the DHBs to use remote access where it is available. We will conduct initial reviews in remote-access DHBs as this will facilitate training and consensus development.

The first five reviews on each condition will be agreed between the auditor and researcher TK (general practitioner) or JI (infectious disease specialist) or RR (neurologist) or GR (haematologist). This will be repeated if needed until there is full agreement on five sequential records.

The code auditor will read through the event records to the extent needed to classify the event against our Case Definition. Data extraction form will be designed by the research auditor. Data to be collected is

specified under each AESI listed below. We require sufficient documentation to support the identification of Level of Certainty of classification of each event. Beyond that we will record age, gender, and ethnicity of the patient so we can describe the population included in the chart reviews.

3.11 OPTION TO ADAPT SEARCH CRITERIA

We may add a small number of conditions if they become of public or scientific concern during the course of this project. For example, venous thrombo-embolism has been a late addition, and it is possible that further childhood AESIs will become apparent as more children are vaccinated.
Similarly, we may find it useful or necessary to increase the number of cases reviewed for a specific code, or include searches for additional codes, if we have difficulty reaching consensus in data extraction, or if we find unexpected patterns in coding practice.

3.12 EVENT CLASSIFICATION

Each case review will result in the event being classified by Level of Certainty that the event meets the relevant Case Definition. Five outcomes are possible.
Event meets case definition

(1) Level 1: Criteria as specified in the [condition] Case Definition: “Confirmed”
(2) Level 2: Criteria as specified in the [condition] Case definition: “Probable”
(3) Level 3: Criteria as specified in the [condition] Case Definition: “Possible”

Event does not meet case definition

(4) Reported as having [condition] but there is insufficient evidence to meet the Case Definition
(5) Not a case of [condition]

3.13 DATA MANAGEMENT

The data collection form will identify the patient only by a unique study ID. The principal investigator (Assoc Prof Helen Petousis-Harris) and investigator TK will maintain a list, stored separately from the patient data, that includes the patient NHI and the study ID. This is in case we need to re-review the medical record for training or adjudication. This NHI / study ID list will be destroyed after the end-of-contract report has been accepted.
The de-identified data extracted for each patient will be entered into a master Excel sheet maintained by the research auditor and researcher TK on the University of Auckland Microsoft OneDrive which is one of the University preferred secure storage systems for research data.

3.14 REPORTING Y59 CODES

For all audits we will describe whether the following codes have been applied to the event:

Y590 Viral vaccines causing adverse effects in therapeutic use
Y598 Other specified vaccines and biological substances causing adverse effects in therapeutic use
Y599 Vaccine or biological substance, unspecified causing adverse effects in therapeutic use

3.15 THROMBOCYTOPENIA

ICD codes

D69.3 Idiopathic thrombocytopenic purpura (Evan's syndrome)

D69.4 Other primary thrombocytopenia

D69.6 Thrombocytopenia, unspecified

D69.5 Secondary thrombocytopenia (if vaccine related, identify vaccine)

The electronic file includes no lower-level codes.

SNOMED codes

32273002 Idiopathic thrombocytopenic purpura

Case Definition, data collection

The case definition is in:

Wise, R. P., Bonhoeffer, J., Beeler, J., Donato, H., Downie, P., Matthews, D., . . . Brighton Collaboration Thrombocytopenia Working, G. (2007). Thrombocytopenia: case definition and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine, 25(31), 5717-5724. 10.1016/j.vaccine.2007.02.067

This same document includes:

- Criteria to meet the Case Definition
- Criteria for Level of Certainty
- Text guidance on collecting and interpreting data

Our requirements for additional data are not as extensive as Wise et al recommend (to cover other purposes). Following their numbering sequence and subheadings, please note that only the following data are required.

Source of information / reporter

- Collect date and reviewer's name

Demographics

- Record unique study ID. Record NHI and study ID separately and report these separately from the case review data
- Age in years (months for infant), gender
- Ethnicity (prioritised to Māori; categories Māori, Pacific, Asian, NZ Euro/Other)

Details of immunisation

- Last immunisation, if any recorded – type of vaccine, number of days before admission

The adverse event

- Clinical description of signs and symptoms of thrombocytopenia; in particular, all criteria fulfilled to meet a case definition, and other signs and symptoms indicative for thrombocytopenia.

Miscellaneous / general

- Record if on chemotherapy

3.16 GENERALISED CONVULSION

ICD codes

G40.3 Generalised idiopathic epilepsy and epileptic syndromes; includes atonic, tonic-clonic

G40.5 Special epileptic syndromes; includes epileptic seizures related to drugs

The electronic file includes the following lower-level codes which will therefore be included using the codes above.

G4030 Generalised idiopathic epilepsy and epileptic syndromes, without mention of intractable epilepsy

G4031 Generalised idiopathic epilepsy and epileptic syndromes, with intractable epilepsy

G4050 Special epileptic syndromes, without mention of intractable epilepsy

G4051 Special epileptic syndromes, with intractable epilepsy

Case Definition, data collection

The case definition is in:

Bonhoeffer, J., Menkes, J., Gold, M. S., de Souza-Brito, G., Fisher, M. C., Halsey, N., . . . Brighton Collaboration Seizure Working, G. (2004). Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine, 22(5-6), 557-562. 10.1016/j.vaccine.2003.09.008

This same document includes:

- Criteria to meet the Case Definition
- Criteria for Level of Certainty
- Text guidance on collecting and interpreting data

Our requirements for additional data are not as extensive as Bonhoeffer et al recommend (to cover other purposes). Please note that only the following data are required. (Bonhoeffer et al do not have the same section headings as the other documents that include our Case Definitions.)

- Collect date and reviewer's name
- Record unique study ID. Record NHI and study ID separately and report these separately from the case review data
- Age in years (months for infant), gender
- Ethnicity (prioritised to Māori; categories Māori, Pacific, Asian, NZ Euro/Other)
- Last immunisation, if any recorded – type of vaccine, number of days before admission
- Clinical description of signs and symptoms of convulsion; in particular, all criteria fulfilled to meet a case definition, and other signs and symptoms indicative for convulsion.

3.17 ASEPTIC MENINGITIS

ICD codes

G03.0 Non-pyogenic meningitis; includes non-bacterial meningitis

G03.8 Meningitis from other specified causes

The electronic file includes no lower-level codes.

Case Definition, data collection

The case definition is in:

Tapiainen, T., Prevots, R., Izurieta, H. S., Abramson, J., Bilynsky, R., Bonhoeffer, J., . . . Brighton Collaboration Aseptic Meningitis Working Group. (2007). Aseptic meningitis: case definition and

guidelines for collection, analysis, and presentation of immunization safety data. Vaccine, 25(31),// 5793-5802. 10.1016/j.vaccine.2007.04.058

This same document includes:

- Criteria for Level of Certainty
- Criteria to meet the Case Definition
- Extensive text guidance on collecting

Our requirements for additional data are not as extensive as Tapiainen et al recommend (to cover other purposes). Following their numbering sequence and subheadings, please note that only the following data are required.

Source of information / reporter

- Collect date and reviewer's name

Vaccinee / control

- Record unique study ID. Record NHI and study ID separately and report these separately from the case review data
- Age in years (months for infant), gender
- Ethnicity

Details of immunisation

- Last immunisation, if any recorded – type of vaccine, number of days before admission

The adverse event

- Clinical description of signs and symptoms of aseptic meningitis, data on CSF examination to determine if criteria were fulfilled to meet the case definition and information about antimicrobial agent use before CSF sample collection.

Miscellaneous / general

- No data required

3.18 ENCEPHALITIS

ICD codes

G04.0 Acute disseminated encephalitis; excludes acute transverse myelitis; includes post immunisation encephalitis (separately identify the vaccine)

The electronic file includes no lower-level codes.

Case Definition, data collection

The case definition is in:

Sejvar, J. J., Kohl, K. S., Bilynsky, R., Blumberg, D., Cvetkovich, T., Galama, J., . . . Brighton Collaboration Encephalitis Working, G. (2007). Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine, 25(31), 5771-5792. 10.1016/j.vaccine.2007.04.060

This same document includes:

- Criteria for Level of Certainty
- Criteria to meet the Case Definition
- Extensive text guidance on collecting and interpreting data

Our requirements for additional data are not as extensive as Sejvar et al recommend. Following their numbering sequence and subheadings, please note that only the following data are required.

Source of information / reporter

- Collect date and reviewer's name

Demographics

- Record unique study ID. Record NHI and study ID separately and report these separately from the case review data
- Age in years (months for infant), gender
- Ethnicity

Details of immunisation

- Last immunisation, if any recorded – type of vaccine, number of days before admission

The adverse event

- Clinical description of signs and symptoms of neurologic events and results of neuroimaging, electrodiagnostic studies, CSF examination and histopathologic features as described in Sejvar et al.

Miscellaneous / general

- No data required

3.19 MYELITIS

ICD codes

G37.3 Acute transverse myelitis in demyelinating disease of central nervous system; includes acute transverse myelitis NOS. Excludes multiple sclerosis and neuromyelitis optica (Devic)
The electronic file includes no lower-level codes.

Case Definition, data collection

The case definition is in:
Sejvar, J. J., Kohl, K. S., Bilynsky, R., Blumberg, D., Cvetkovich, T., Galama, J., . . . Brighton Collaboration Encephalitis Working, G. (2007). Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine, 25(31), 5771-5792. 10.1016/j.vaccine.2007.04.060
This same document includes:

- Criteria for Level of Certainty
- Criteria to meet the Case Definition
- Extensive text guidance on collecting g and interpreting data

Our requirements for additional data are not as extensive as Sejvar et al recommend. Following their numbering sequence and subheadings, please note that only the following data are required.
Source of information / reporter

- Collect date and reviewer's name

Demographics

- Record unique study ID. Record NHI and study ID separately and report these separately from the case review data
- Age in years (months for infant), gender
- Ethnicity

Details of immunisation

- Last immunisation, if any recorded – type of vaccine, number of days before admission

The adverse event

- Clinical description of signs and symptoms of neurologic events and results of neuroimaging, CSF examination and histopathologic features as described in Sejvar et al.

Miscellaneous / general

- No data required

3.20 ACUTE DISSEMINATED ENCEPHALOMYELITIS

ICD codes

G04.0 Acute disseminated encephalitis; includes post immunisation encephalomyelitis (separately identify the vaccine)

The electronic file includes no lower-level codes.

Note that ICD-10-AM does not have separate subcodes for acute disseminated encephalitis and encephalomyelitis. ICD-CM has separate subcodes. This reflects a difference in approach between ICD-10-AM authors and the Brighton Collaboration Working group. Most neurologists who would see these as distinctly different pathological processes.

Case Definition, data collection

The case definition is in:

Sejvar, J. J., Kohl, K. S., Bilynsky, R., Blumberg, D., Cvetkovich, T., Galama, J., . . . Brighton Collaboration Encephalitis Working, G. (2007). Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine, 25(31), 5771-5792. 10.1016/j.vaccine.2007.04.060

This same document includes:

- Criteria for Level of Certainty
- Criteria to meet the Case Definition
- Extensive text guidance on collecting and interpreting data

Our requirements for additional data are not as extensive as Sejvar et al recommend. Following their numbering sequence and subheadings, please note that only the following data are required.

Source of information / reporter

- Collect date and reviewer's name

Demographics

- Record unique study ID. Record NHI and study ID separately and report these separately from the case review data
- Age in years (months for infant), gender
- Ethnicity

Details of immunisation

- Last immunisation, if any recorded – type of vaccine, number of days before admission

The adverse event

- Clinical description of signs and symptoms of neurologic events and results of neuroimaging, CSF examination and histopathologic features as described in Sejvar et al.

Miscellaneous / general

- No data required

3.21 GUILLAIN BARRÉ SYNDROME

ICD codes

G61.0 Guillain-Barre syndrome; includes acute (post-)infectious polyneuritis and Miller-Fisher syndrome

The electronic file includes no lower-level codes.

Case Definition, data collection

The case definition is in:

Sejvar, J. J., Kohl, K. S., Gidudu, J., Amato, A., Bakshi, N., Baxter, R., . . . Brighton Collaboration GBS Working Group. (2011). Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine, 29(3), 599-612. 10.1016/j.vaccine.2010.06.003

This same document includes:

- Criteria to meet the Case Definition, Guillain-Barré, Miller Fisher syndromes
- Criteria for Level of Certainty
- Extensive text guidance on collecting and interpreting data

Our requirements for additional data are not as extensive as Sejvar et al recommend (to cover other purposes). Following their numbering sequence and subheadings, please note that only the following data are required.

Source of information / reporter

- Collect date and reviewer's name

Demographics

- Record unique study ID. Record NHI and study ID separately and report these separately from the case review data
- Age in years (months for infant), gender
- Ethnicity (prioritised to Māori; categories Māori, Pacific, Asian, NZ Euro/Other)

Details of immunisation

- Last immunisation, if any recorded – type of vaccine, number of days before admission

The adverse event

- For all cases at any level of diagnostic certainty and for reported events with insufficient evidence, the criteria fulfilled to meet a case definition and other signs or symptoms indicative of GBS should be recorded

Miscellaneous / general

- No data required

3.22 BELL'S PALSY

ICD codes

G51.0 Bell's Palsy; includes facial palsy due to facial nerve disorder

The electronic file includes no lower-level codes.

SNOMED codes

193093009 Bell's Palsy

Case Definition, data collection

The case definition is in:

Rath, B., Gidudu, J. F., Anyoti, H., Bollweg, B., Caubel, P., Chen, Y. H., . . . Brighton Collaboration Bell's Palsy Working Group. (2017). Facial nerve palsy including Bell's palsy: Case definitions and guidelines for collection, analysis, and presentation of immunisation safety data. Vaccine, 35(15), 1972-1983. 10.1016/j.vaccine.2016.05.023

This same document includes:

- Criteria to meet the Case Definition Criteria for Level of Certainty
- Extensive text guidance on collecting and interpreting data

Our requirements for additional data are not as extensive as Sejvar et al recommend (to cover other purposes). Following their numbering sequence and subheadings, please note that only the following data are required.

Source of information / reporter

- Collect date and reviewer's name

Demographics

- Record unique study ID. Record NHI and study ID separately and report these separately from the case review data
- Age in years (months for infant), gender
- Ethnicity (prioritised to Māori; categories Māori, Pacific, Asian, NZ Euro/Other)

Details of immunisation

- Last immunisation, if any recorded – type of vaccine, number of days before admission

The adverse event

- Symptoms and signs meeting the criteria of the peripheral facial nerve palsy or Bell's palsy case

Miscellaneous / general

- No data required

3.23 MYOCARDITIS AND PERICARDITIS

ICD codes for myocarditis

Include any of the following

I401 Isolated myocarditis

I408 Other acute myocarditis

I409 Acute myocarditis, unspecified

I514 Myocarditis, unspecified

Exclude all of the following

I012 Acute rheumatic myocarditis

I020 Rheumatic chorea with heart involvement

I090 Rheumatic myocarditis

I400 Infective myocarditis

I410 Myocarditis in bacterial diseases classified elsewhere

I411 Myocarditis in viral diseases classified elsewhere

I412 Myocarditis in other infectious and parasitic diseases classified elsewhere

I418 Myocarditis in other diseases classified elsewhere

ICD codes for pericarditis

Include any of the following

I300 Acute nonspecific idiopathic pericarditis

I308 Other forms of acute pericarditis

I309 Acute pericarditis, unspecified

I319 Disease of pericardium, unspecified

Exclude all of the following

I010 Acute rheumatic pericarditis

I092 Chronic rheumatic pericarditis

I301 Infective pericarditis

I310 Chronic adhesive pericarditis

I311 Chronic constrictive pericarditis

I312 Haemopericardium, not elsewhere classified

I313 Pericardial effusion (noninflammatory)

I318 Other specified diseases of the pericardium

I320 Pericarditis in bacterial diseases classified elsewhere

I321 Pericarditis in other infectious and parasitic diseases classified elsewhere

I328 Pericarditis in other diseases classified elsewhere

Case Definition, data collection

The case definitions for both myocarditis and pericarditis are in:

https://brightoncollaboration.us/myocarditis-case-definition-update/

This same document includes:

- Flow diagrams to meet the Case Definition Criteria for Level of Certainty
- No additional text guidance on collecting and interpreting data

Please note that only the following additional data are required.

Source of information / reporter

- Collect date and reviewer's name

Demographics

- Record unique study ID. Record NHI and study ID separately and report these separately from the case review data
- Age in years (months for infant), gender
- Ethnicity (prioritised to Māori; categories Māori, Pacific, Asian, NZ Euro/Other)

Details of immunisation

- Last immunisation, if any recorded – type of vaccine, number of days before admission

4 METHODS, STUDY PART B: CASES TO CODES

We will request from eight DHBs a list of events where their laboratory confirmed a low platelet count (<150 x10^9/L). We will ask them to assign these, to a hospital admission or ED visit and provide us a list that includes platelet count, Event ID, NHI, patient demographics and ICD discharge codes or SNOMED ED visit codes. (Some patients may have blood tests taken as part of an outpatient visit and not attend ED or be admitted. These patients will not be included.) We will add a study ID and remove the NHI; investigator TK will keep a separate list of the NHI and Study ID. This latter list will be destroyed after the final contract report is accepted. Data transfer from the DHB will be via The University of Auckland Web Dropoff or an alternative process agreed with the DHB. No chart review will be done on these events.

4.1 THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME (TTS)

This syndrome requires two elements – thrombocytopenia and a clot – with exclusion when the cause is considered known. It should be noted that thrombocytopenia is usually associated with risk of excess bleeding rather than excess clotting, making the two elements of TTS a relatively rare event.
We ascertain thrombocytopenia from the laboratory, then seek TTS and clots under several categories.

Conditions that may be associated with thrombocytopenia and might mimic TTS

- Antiphospholipid syndrome
- Lupus anticoagulant
- Clots
- Miscarriage

Heparin induced thrombocytopenia (HIT)

- Associated TP by definition
- Usually about 10d after exposure
- Risk of clots in unusual places

Disseminated intravascular coagulation (DIC)

- Decreased platelets + clotting

Thrombotic thrombocytopenia purpura (TTP)

- Rare

Haemolytic uraemic syndrome

Chemotherapy

- Decreased platelets but clot not likely but possible

We identified the following code groups which will all be reported.

Syndromes that might mimic TTS

D593 Haemolytic-uraemic syndrome
D594 Other nonautoimmune haemolytic anaemias
D595 Paroxysmal nocturnal haemoglobinuria [Marchiafava-Micheli]
D596 Haemoglobinuria due to haemolysis from other external causes
D598 Other acquired haemolytic anaemias
D599 Acquired haemolytic anaemia, unspecified

Thrombocytopenia not classified in syndrome

D693 Idiopathic thrombocytopenic purpura

D694 Other primary thrombocytopenia

D695 Secondary thrombocytopenia

D696 Thrombocytopenia, unspecified

Cerebral infarction

I630 Cerebral infarction due to thrombosis of precerebral arteries

I631 Cerebral infarction due to embolism of precerebral arteries

I632 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries

I633 Cerebral infarction due to thrombosis of cerebral arteries

I634 Cerebral infarction due to embolism of cerebral arteries

I635 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries

I636 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic

I638 Other cerebral infarction

I639 Cerebral infarction, unspecified

Arterial clots

I740 Embolism and thrombosis of abdominal aorta

I741 Embolism and thrombosis of other and unspecified parts of aorta

I742 Embolism and thrombosis of arteries of upper extremities

I743 Embolism and thrombosis of arteries of lower extremities

I744 Embolism and thrombosis of arteries of extremities, unspecified

I745 Embolism and thrombosis of iliac artery

I748 Embolism and thrombosis of other arteries

I749 Embolism and thrombosis of unspecified artery

Venous clots

I676 Nonpyogenic thrombosis of intracranial venous system

I81 Portal vein thrombosis

I822 Embolism and thrombosis of vena cava

I823 Embolism and thrombosis of renal vein

I828 Embolism and thrombosis of other specified veins

I829 Embolism and thrombosis of unspecified vein

Causes

Y578 Other drugs and medicaments causing adverse effects in therapeutic use

Y579 Drug or medicament, unspecified causing adverse effects in therapeutic use

Y590 Viral vaccines causing adverse effects in therapeutic use

Y598 Other specified vaccines and biological substances causing adverse effects in therapeutic use

Y599 Vaccine or biological substance, unspecified causing adverse effects in therapeutic use

Malignancies

C00 to C96 malignancies

(D00 to D36 benign neoplasms)

D37 to D48 malignancies

Miscarriage codes remain to be specified**

5 ANALYSIS AND REPORTING

5.1 STUDY PART A: CODES TO CASES

The unit of analysis is an "event" as recorded in DHB and national databases, meaning one hospital admission or one ED visit. If an individual patient has more than one event for the same AESI within the observed time period, only the first will be the subject of chart review.

Analysis and reporting will follow the same pattern for each code:

- Number of events, number of patients identified for each code found
- Describing other codes applied to same event
- Number of codes listed as principal diagnosis
- Number of charts reviewed, number of charts excluded from review, with reason
- Number of events assigned to Level of Certainty 1, 2 or 3; or insufficient information; or not a case of target AESI Case Description
- Positive predictive value, sensitivity, and specificity (each with 95% confidence intervals) of each code (or combination of codes) with respect to Level of Certainty 1, 2 or 3 for target AESI Case Description
    - For overall codes audited
    - For subgroups by age, gender, ethnicity

5.2 STUDY PART B: CASES TO CODES

The unit of analysis is an event, using the first for a given patient within the time period studied. The initial analysis, primarily to identify differences in coding by ethnicity, follows the following table.

Population descriptors	Thrombocytopenia in DHB laboratory	ED visit (SNOMED)	Hospital admission (ICD10)
Age groups	N	N each SNOMED code	N each ICD code
Gender	N	N each SNOMED code	N each ICD code
Ethnicity	N	N each SNOMED code	N each ICD code

All events, by intention, will include thrombocytopenia. We will describe all the other diagnostic codes applied to these events. We will start with frequency counts of individual codes, described by age group, gender and ethnicity.

We are still considering how to analyze and present further analyses, but this is likely to include frequency counts for the top 10 more common combinations of codes but may also include a cluster analysis to identify patterns of cases that are alike in terms of their coding combinations. This may contribute to the search to define patterns of thrombocytopenia-related coding pre-COVID vaccination that might later be compared with thrombocytopenia-related coding post-COVID vaccination.

It may be possible to derive a new set of codes as a search-tool for thrombocytopenia-related syndromes of interest, using the same process as above in our Study Part A. However, at present that is beyond the scope of this study.

5.2.1 Thrombosis with Thrombocytopenia Syndrome

The following codes are of specific interest.

- I82.8 Embolism and thrombosis of other specified veins
- I82.9 Embolism and thrombosis of unspecified vein
- I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
- I67.6 Nonpyogenic thrombosis of intracranial venous system

In Part A – Codes to Cases – we will search for these codes but not audit charts. The purpose is to describe how many are and are not also coded with thrombocytopenia.
In Part B – Cases to Codes – we will specifically report these codes within the data collected following laboratory search for thrombocytopenia.

6 REQUESTS TO DHBS

We will request, from the data manager at each DHB, lists of events which meet the following criteria. The unit of analysis is a single event, not the whole record of a patient.

Checklist for internal use – columns are DHBs

	N	A	CM	BOP	HV	C&C	NM	C
Remote	?	x	x	?	x	?	?	?
ICD (Admissions)	x	x	x	x	x	x	x	x
SNOMED (ED)		x		x	x		x	
Laboratory TP	x	x	x	x	x	x	x	x

Checklist for internal use - Count of patient files to review, by AESI – columns are DHBs; based on approximately 30 chart reviews per code.

	N	**A**	**CM**	**BOP**	**HV**	**C&C**	**NM**	**C**	**Total**
Thrombocytopenia (admission, 4 codes)	16	16	16	16	16	16	16	16	128
Thrombocytopenia (ED, 2 codes)		16		16	16		16		64
Generalised convulsion (2 codes)	8	8	8	8	8	8	8	8	64
Aseptic meningitis (2 codes)	8	8	8	8	8	8	8	8	64
Encephalitis (1 code)	4	4	4	4	4	4	4	4	32
Myelitis (3 codes)	12	12	12	12	12	12	12	12	96

	N	A	CM	BOP	HV	C&C	NM	C	Total
Acute disseminated encephalomyelitis (3 codes, 2 overlap with myelitis)	4	4	4	4	4	4	4	4	32
Guillain Barre syndrome (1 code)	4	4	4	4	4	4	4	4	32
Bell's palsy (admission, 1 code)	4	4	4	4	4	4	4	4	32
Bell's palsy (ED, 1 code)		8		8	8		8		32
Totals	60	84	60	84	84	60	84	60	576

Northland, Counties Manukau, Capital and Coast, Canterbury DHBs

Study Part A: Codes to Cases; admission ICD codes, no ED SNOMED codes available

1. List all hospital discharge events with any of the ICD codes listed, discharged in calendar years 2016 to 2019 inclusive. Code set ICD10-AM 11th edition.
2. If there are fewer than 8 events for any code, extend the search period, for that code, back to 2008.
3. For each ICD code, report: event id, NHI, age, gender, ethnicity (prioritised to Māori then Pacific then Asian then NZ European / Other), primary ICD code, all other ICD codes (each in own cell across row)
4. Provide this list to us via agreed electronic transfer process
5. We will randomly select 8 charts per ICD code on our supplied list
6. We will audit these selected charts

Study Part B: Cases to Codes; all cases of thrombocytopenia

1. List all instances with bloods tested in the DHB laboratory having thrombocytopenia (platelet count < 150 x 10^9/L) in calendar years 2016 to 2019 inclusive.
2. For these instances, where possible, associate with either a hospital admission or ED event.
    a. Assume that a test done on the same day as an ED visit is associated with that visit.
    b. Assume that a test done on day of hospital admission, or discharge, or days between, is associated with that admission.
    c. Tests that cannot be linked to an ED visit or hospital admission can be excluded. This is likely to include, for example, blood tests collected at an outpatient visit.
3. For these instances, report:
    a. platelet count, whether confirmed on blood smear, date, NHI, age, gender, ethnicity (prioritised to Māori then Pacific then Asian then NZ European / Other), primary ICD code, all other ICD codes (each in own cell across row)
    b. associated admission or ED Event_ID
4. Provide these lists to us via agreed electronic transfer process
5. We will not audit charts of persons on the laboratory list with thrombocytopenia.

Auckland, Bay of Plenty, Hutt Valley, Nelson Marlborough DHBs

Study Part A: Codes to Cases; admission ICD codes and ED SNOMED codes available

1. List all hospital discharge events with any of the ICD codes listed, discharged in calendar years 2016 to 2019 inclusive. Code set ICD10-AM 11th edition.
2. If there are fewer than 8 events for any code, extend the search period, for that code, back to 2008.
3. List all ED events with any of the SNOMED codes listed, from start of SNOMED coding until end March 2021.
4. For each ICD and SNOMED code, report: event id, NHI, age, gender, ethnicity (prioritised to Māori then Pacific then Asian then NZ European / Other), primary ICD code, all other ICD codes (each in own cell across row)
5. Provide this list to us via agreed electronic transfer process
6. We will randomly select 8 charts per ICD and SNOMED code on our supplied list
7. We will audit these selected charts

Study Part B: Cases to Codes; all cases of thrombocytopenia

6. List all instances with bloods tested in the DHB laboratory having thrombocytopenia (platelet count < 150 x 10^9 / L) in calendar years 2016 to 2019 inclusive.
7. For these instances, where possible, associate with either a hospital admission or ED event.
    a. Assume that a test done on the same day as an ED visit is associated with that visit.
    b. Assume that a test done on day of hospital admission, or discharge, or days between, is associated with that admission.
    c. Tests that cannot be linked to an ED visit or hospital admission can be excluded. This is likely to include, for example, blood tests collected at an outpatient visit.
8. For these instances, report:
    a. platelet count, whether confirmed on blood smear, date, NHI, age, gender, ethnicity (prioritised to Māori then Pacific then Asian then NZ European / Other), primary ICD code, all other ICD codes (each in own cell across row)
    b. associated admission or ED Event_ID
9. Provide these lists to us via agreed electronic transfer process
10. We will not audit charts of persons on the laboratory list with thrombocytopenia.

Table. Code lists for data managers at DHBs

Condition	**ICD10 or SNOMED Codes**
Thrombocytopenia (ICD)	**D69.3** Idiopathic thrombocytopenic purpura (Evan's syndrome) **D69.4** Other primary thrombocytopenia **D69.5** Secondary thrombocytopenia **D69.6** Thrombocytopenia, unspecified
Thrombocytopenia (SNOMED)	**32273002** Idiopathic thrombocytopenic purpura **78129009** Thrombotic thrombocytopenic purpura
Thrombosis with Thrombocytopenia Syndrome (ICD)	**Part A – Codes to Cases.** *We will search for these codes but not audit charts. The purpose is to describe how many are and are not also coded with thrombocytopenia*. **I82.8** Embolism and thrombosis of other specified veins

Condition	ICD10 or SNOMED Codes
	I82.9 Embolism and thrombosis of unspecified vein **I63.6** Cerebral infarction due to cerebral venous thrombosis, nonpyogenic **I67.6** Nonpyogenic thrombosis of intracranial venous system **Part B - Cases to Codes.** *These codes will be specifically reported within the data collected following laboratory search for thrombocytopenia.*
Myocarditis	*Include any of the following (from DHB)* **I401** Isolated myocarditis **I408** Other acute myocarditis **I409** Acute myocarditis, unspecified **I514** Myocarditis, unspecified *Exclude all of the following (excluded by SAFE team)* **I012** Acute rheumatic myocarditis **I020** Rheumatic chorea with heart involvement **I090** Rheumatic myocarditis **I400** Infective myocarditis **I410** Myocarditis in bacterial diseases classified elsewhere **I411** Myocarditis in viral diseases classified elsewhere **I412** Myocarditis in other infectious and parasitic diseases classified elsewhere **I418** Myocarditis in other diseases classified elsewhere
Pericarditis	*Include any of the following (from DHB)* **I300** Acute nonspecific idiopathic pericarditis **I308** Other forms of acute pericarditis **I309** Acute pericarditis, unspecified **I319** Disease of pericardium, unspecified *Exclude all of the following (excluded by SAFE team)* **I010** Acute rheumatic pericarditis **I092** Chronic rheumatic pericarditis **I301** Infective pericarditis **I310** Chronic adhesive pericarditis **I311** Chronic constrictive pericarditis **I312** Haemopericardium, not elsewhere classified **I313** Pericardial effusion (noninflammatory) **I318** Other specified diseases of the pericardium **I320** Pericarditis in bacterial diseases classified elsewhere **I321** Pericarditis in other infectious and parasitic diseases classified elsewhere **I328** Pericarditis in other diseases classified elsewhere

Condition	ICD10 or SNOMED Codes
Generalised convulsion (ICD)	**G40.3** Generalised idiopathic epilepsy and epileptic syndromes; include G4030 without mention of intractable epilepsy; include G4031 with mention of intractable epilepsy **G40.5** Special epileptic syndromes; include G4050 without mention of intractable epilepsy; include G4051 with mention of intractable epilepsy
Aseptic meningitis (ICD)	**G03.0** Non-pyogenic meningitis **G03.8** Meningitis from other specified causes
Encephalitis (ICD)	**G04.0** Acute disseminated encephalitis
Myelitis (ICD)	**G37.3** Acute transverse myelitis in demyelinating disease of central nervous system **G04.8** Other encephalitis myelitis encephalomyelitis **G04.9** Encephalitis myelitis encephalomyelitis NOS
Acute disseminated encephalomyelitis (ICD)	**G04.0** Acute disseminated encephalitis **G04.8** Other encephalitis myelitis encephalomyelitis **G04.9** Encephalitis myelitis encephalomyelitis NOS
Guillain Barre syndrome (ICD)	**G61.0** Guillain-Barre syndrome
Bell's palsy (ICD10)	**G51.0** Bell's Palsy
Bell's palsy (SNOMED)	**193093009** Bell's Palsy

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Appendix 2

Table 1. Number of events reported by each DHB

DHB	Events raw data
Auckland	8,223
Bay of Plenty	1,944
Capital and Coast	3,878
Canterbury	5,474
Counties Manukau	3,166
Hutt Valley	2,028
Northland	1,269
Nelson Marlborough	1,176
Total	27,158

Raw data were cleaned to exclude events where; date of admission was invalid; age was invalid; gender was X (excluded due to small numbers and risk of re-identification); or events were a full duplicate. Nine persons with unknown ethnicity were included in 'Other' ethnicity. After retaining only the first event for a given patient, 19,402 events were available for analysis, shown in table 12.

Table 2. Data collection from which events were randomly selected for medical record review

Counts for myocarditis and pericarditis are before exclusions shown in Table 13.

Search code	Short description	Events (N)	First event per patient (N)	Code as principal diagnosis (N)
193093009	Bell's palsy (ED visit)	212	207	201
32273002	Idiopathic thrombocytopenic purpura (ED visit)	24	20	18
D69.3	Idiopathic thrombocytopenic purpura	1,919	1,061	566
D69.4	Other primary thrombocytopenia	173	98	23
D69.5	Secondary thrombocytopenia	1,823	1,349	103
D69.6	Thrombocytopenia, unspecified	10,849	7,400	362
G03.0	Non-pyogenic meningitis	129	103	63
G03.8	Meningitis due to other specified causes	82	59	21
G04.0	Acute disseminated encephalitis	219	70	58
G04.8	Other encephalitis, myelitis and encephalomyelitis	448	194	139
G04.9	Encephalitis, myelitis and encephalomyelitis, unspecified	471	329	170
G37.3	Acute transverse myelitis in demyelinating disease of central nervous system	179	114	91
G40.30	Generalised idiopathic epilepsy and epileptic syndromes, not intractable epilepsy	3,785	2,458	2,021
G40.31	Generalised idiopathic epilepsy and epileptic syndromes, with intractable epilepsy	360	215	148
G40.50	Special epileptic syndromes, not intractable epilepsy	114	98	53
G40.51	Special epileptic syndromes, with intractable epilepsy	4	3	3
G51.0	Bell's palsy	2,262	1,954	1,249
G61.0	Guillain-Barre syndrome	751	418	352
I40.1	Isolated myocarditis	4	4	4
I40.8	Other acute myocarditis	24	23	12
I40.9	Acute myocarditis, unspecified	57	51	38
I51.4	Myocarditis, unspecified	532	471	334
I30.0	Acute nonspecific idiopathic pericarditis	66	55	55
I30.8	Other forms of acute pericarditis	61	57	16
I30.9	Acute pericarditis, unspecified	402	382	239
I31.8	Other specified diseases of pericardium	44	42	14
I31.9	Disease of pericardium, unspecified	2,164	1,922	1,230

Table 3. Codes excluded from myocarditis and pericarditis events for medical record review

Code	Short description
I01.2	Acute rheumatic myocarditis
I02.0	Rheumatic chorea with heart involvement
I09.0	Rheumatic myocarditis
I40.0	Infective myocarditis
I41.0	Myocarditis in bacterial diseases classified elsewhere
I41.1	Myocarditis in viral diseases classified elsewhere
I41.2	Myocarditis in other infectious and parasitic diseases classified elsewhere
I41.8	Myocarditis in other diseases classified elsewhere
I01.0	Acute rheumatic pericarditis
I09.2	Chronic rheumatic pericarditis
I30.1	Infective pericarditis
I31.0	Chronic adhesive pericarditis
I31.1	Chronic constrictive pericarditis
I31.2	Haemopericardium, not elsewhere classified
I31.3	Pericardial effusion (non-inflammatory)
I31.8	Other specified diseases of the pericardium
I32.0	Pericarditis in bacterial diseases classified elsewhere
I32.1	Pericarditis in other infectious and parasitic diseases classified elsewhere
I32.8	Pericarditis in other diseases classified elsewhere

Table 4. Population whose medical records were reviewed for each code and level of diagnostic certainty that events met the case definition for each target condition

	Code	Age*		Gender*		Prioritised ethnicity*‡		Level of diagnostic certainty*¥	
Thrombocytopenia	32273002 (n=9)	≤15	2	M	7	A	2	1	5
		16–64	3	F	2	O	6	2	0
		≥65	4			M	0	3	0
						P	1	Stated	0
								Not case	0
								No data	4
	D69.3 (n=32)	≤15	5	M	13	A	4	1	29
		16–64	16	F	19	M	5	2	1
		≥65	11			O	19	3	0
						P	4	Stated	0
								Not case	2
	D69.4 (n=32)	≤15	16	M	17	A	3	1	26
		16–64	13	F	15	M	6	2	3
		≥65	3			O	19	3	3
						P	4	Stated	0
								Not case	0
	D69.5 (n=32)	≤15	1	M	21	A	4	1	31
		16–64	17	F	11	M	4	2	1
		≥65	14			O	19	3	0
						P	5	Stated	0
								Not case	0
	D69.6 (n=32)	≤15	4	M	19	A	3	1	31
		16–64	12	F	13	M	6	2	1
		≥65	16			O	21	3	0
						P	2	Stated	0
								Not case	0
Aseptic meningitis	G03.0 (n=32)	≤15	3	M	16	A	0	1	20
		16–64	24	F	16	M	3	2	5
		≥65	5			O	25	3	0
						P	4	Stated	1
								Not case	6
	G03.8 (n=27)	≤15	7	M	15	A	1	1	10
		16–64	11	F	12	M	6	2	2
		≥65	9			O	18	3	3
						P	2	Stated	0
								Not case	12
	G04.0 (n=30)	≤15	19	M	16	A	4	1	1
		16–64	6	F	14	M	12	2	11
		≥65	5			O	8	3	4

	Code	Age*		Gender*		Prioritised ethnicity*‡		Level of diagnostic certainty*¥	
						P	6	Stated	1
								Not case	13
Myelitis	G04.8 (n=28)	≤15	4	M	15	A	2	1	2
		16–64	11	F	13	M	3	2	3
		≥65	13			O	19	3	0
						P	4	Stated	0
								Not case	23
	G04.9 (n=28)	≤15	4	M	15	A	1	1	0
		16–64	16	F	13	M	11	2	1
		≥65	8			O	15	3	2
						P	1	Stated	0
								Not case	25
	G37.3 (n=28)	≤15	7	M	11	A	3	1	0
		16–64	14	F	17	M	5	2	15
		≥65	7			O	20	3	9
						P	0	Stated	0
								Not case	4
Acute disseminated encephalomyelitis	G04.8 (n=28)	≤15	4	M	15	A	2	1	3
		16–64	11	F	13	M	3	2	0
		≥65	13			O	19	3	3
						P	4	Stated	0
								Not case	22
	G04.9 (n=28)	≤15	4	M	15	A	1	1	1
		16–64	16	F	13	M	11	2	1
		≥65	8			O	15	3	8
						P	1	Stated	2
								Not case	16
	G04.0 (n=30)	≤15	19	M	16	A	4	1	16
		16–64	6	F	14	M	12	2	2
		≥65	5			O	8	3	0
						P	6	Stated	1
								Not case	11
Generalised Convulsion	G40.30 (n=24)	≤15	9	M	18	A	1	1	6
		16–64	19	F	14	M	12	2	18
		≥65	4			O	19	3	0
						P	0	Stated	2
								Not case	5
								No data	1
	G40.31 (n=32)	≤15	19	M	20	A	3	1	14
		16–64	13	F	12	M	7	2	15
		≥65	0			O	20	3	0
						P	2	Stated	1
								Not case	2

	Code	Age*		Gender*		Prioritised ethnicity*‡		Level of diagnostic certainty*¥	
	G40.50 (n=32)	≤15	1	M	25	A	1	1	3
		16–64	26	F	7	M	10	2	19
		≥65	5			O	20	3	0
						P	1	Stated	2
								Not case	8
	G40.51 (n=3)	≤15	0	M	2	A	0	1	1
		16–64	3	F	1	M	0	2	2
		≥65	0			O	3	3	0
						P	0	Stated	0
								Not case	0
Bell's palsy	G51.0 (n=32)	≤15	2	M	19	A	2	1	7
		16–64	15	F	13	M	1	2	2
		≥65	15			O	25	3	0
						P	4	Stated	1
								Not case	21
								No data	1
	193093009 (n=12)	≤15	1	M	6	A	3	1	1
		16–64	8	F	6	M	2	2	0
		≥65	3			O	6	3	0
						P	1	Stated	5
								Not case	3
								No data	3
Guillain-Barré syndrome	G61.0 (n=32)	≤15	2	M	9	A	3	1	6
		16–64	20	F	23	M	5	2	16
		≥65	10			O	21	3	4
						P	3	Stated	3
								Not case	3
Pericarditis	I30.0 (n=29)	≤15	1	M	19	A	2	1	3
		16–64	21	F	10	M	0	2	16
		≥65	7			O	23	3	0
						P	4	Stated	9
								Not case	1
	I30.8 (n=24)	≤15	2	M	20	A	0	1	1
		16–64	12	F	4	M	3	2	7
		≥65	10			O	18	3	0
						P	3	Stated	4
								Not case	12
	I30.9 (n=32)	≤15	1	M	20	A	1	1	0
		16–64	25	F	12	M	2	2	15
		≥65	6			O	24	3	0
						P	5	Stated	12
								Not case	5
		≤15	0	M	22	A	1	1	0

	Code	Age*		Gender*		Prioritised ethnicity*‡		Level of diagnostic certainty*¥	
	I31.9 (n=32)	16–64	24	F	10	M	5	2	13
		≥65	8			O	22	3	2
						P	3	Stated	8
								Not case	9
Myocarditis	I40.1 (n=4)	≤15	0	M	3	A	0	1	3
		16–64	4	F	1	M	0	2	1
		≥65	0			O	4	3	0
						P	0	Stated	0
								Not case	0
	I40.8 (n=18)	≤15	0	M	9	A	1	1	6
		16–64	16	F	10	M	4	2	1
		≥65	3			O	12	3	0
						P	2	Stated	0
								Not case	12
	I40.9 (n=27)	≤15	2	M	20	A	1	1	10
		16–64	23	F	8	M	3	2	14
		≥65	3			O	22	3	1
						P	2	Stated	2
								Not case	1
	I51.4 (n=32)	≤15	1	M	23	A	1	1	10
		16–64	29	F	9	M	6	2	17
		≥65	2			O	22	3	0
						P	3	Stated	0
								Not case	5

Notes

- *Data are counts.
- ‡Prioritised ethnicity
    - A = Asian.
    - M = Māori.
    - O = Other.
    - P = Pacific.
- ¥Level of diagnostic certainty
    - 1: Level 1 of diagnostic certainty.
    - 2: Level 2 of diagnostic certainty.
    - 3: Level 3 of diagnostic certainty.
    - Stated: Stated to be a case but insufficient evidence.

Not case: Confirmed as not being a case; or no data available.

Appendix 3

Data cleaning

Event date ranged from 26 May 2004 to 13 Jun 2021. Raw data counts, by DHB, are shown in Table 1.

Table 1. Number of events reported by each DHB

DHB	Events raw data
Auckland	46,785
Bay of Plenty	19,926
Capital and Coast	9,740
Canterbury	43,692
Counties Manukau	31,510
Hutt Valley	2,888
Northland	83,032
Nelson Marlborough	322
Total	237,895

Data were excluded if the event ID number was missing (12,950); both SNOMED and ICD-10-AM codes missing or invalid (16,961); gender unknown, "X" or missing (9); exclusion categories could overlap. This left 208,968 records that allowed multiple visits per patient. These were linked to 54,850 ED attendances; 208,757 hospital admissions; and 54,639 events of both ED attendance and hospital admission.