TARANAKI
District Health Board

PGY2 (Q2) PHU REPORT

ENTEROVIRAL MENINGITIS:

A PUBLIC HEALTH INVESTIGATION EXCERCISE

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ABSTRACT

This report summarizes the descriptive phase of an investigation to determine if the noticeable increase in paediatric enteroviral meningitis cases admitted under Taranaki District Health Board (TDHB) in April 2021 was representative of an outbreak. Data was collected through a literature review and using TDHB informatics on baseline levels of meningitis in the region and country. Further details from electronic clinical records of the 2021 enteroviral meningitis cases were collected and analysed to determine if there were any identifiable trends or patterns. All cerebrospinal (CSF) samples from cases that were part of the April 2021 cluster were sent to the Institute of Environmental Science and Research (ESR) for virus serotyping through reverse transcription polymerase chain reaction (RT-PCR) and Sanger sequencing. It was found that the proportion of viral meningitis cases at TDHB attributed to enterovirus (45%) was indeed higher than the presumed national baseline levels (27%).[1] Additionally, the majority of these cases (78%) were part of the April 2021 cluster, with Echovirus 25 being the most common serotype (57%). The 2021 case cluster consisted mainly of male New Zealand (NZ) European neonates who presented with lethargy or irritability, and had an uncomplicated hospital stay of an average of 4 days. The predominance of the echovirus 25 serotype possibly indicated a community outbreak, however the spontaneous drop in cases and lack of identifiable source meant no further investigation or control was needed. Inferences from this investigation can be made regarding methods for the prevention and investigation of similar outbreaks in the future.

INTRODUCTION

Enterovirus is the most common cause of viral meningitis.[2] It is a single stranded RNA virus and member of the Picornaviridae family.[3] The traditional subgenera include: echovirus, poliovirus, and Coxsackie virus (A and B).[3] Due to its lack of proof reading during genetic replication, enterovirus has a large amount of genetic variability with over 90 different serotypes identified.[4] An individual can

become infected through the inhalation of infected aerosols or faecal-oral route.[2] The type of infection depends on the target tissue, with replication of the virus in the meninges causing meningitis.[2] Diagnosis is through viral detection (via PCR) from throat swabs, stool specimens, or CSF.[2] Detection of enterovirus through PCR of CSF samples is the gold standard diagnostic test for enteroviral meningitis.[2]

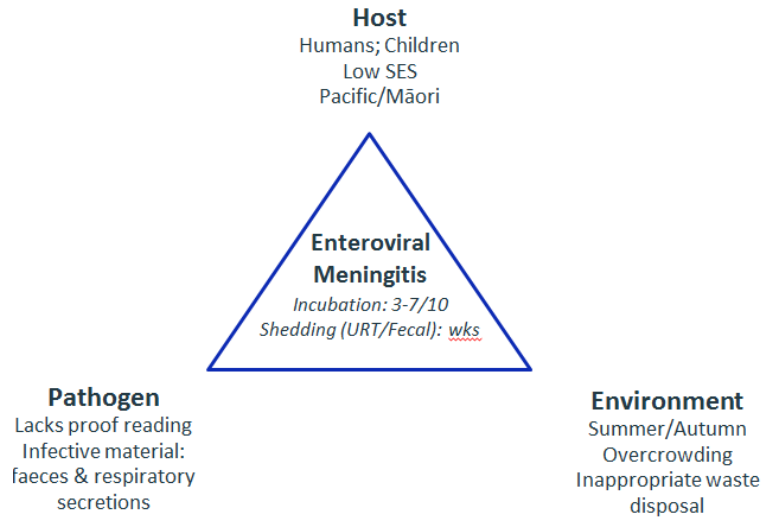
Enteroviral meningitis in adults is usually benign and self-resolving, however in infants it can result in more serious adverse health effects and even death.[2] Adults commonly get mild infections possibly due to the presence of partial cross-reactive immunity; something that infants lack.[4] When adults do get viral meningitis it is often manifests with features of meningism, whereas children have non-specific symptoms of lethargy and irritability.[2] Due to the delay in PCR results and lack of symptom specificity, infants often are treated with antibiotics initially on presentation as a septic screen is undergone.[2,5] Once diagnosis has been confirmed, supportive management (e.g. ensuring adequate feeding, oxygen supplementation if needed) is the mainstay of treatment.[3]

An outbreak is a localised increase in case number above expected in a population or group.[6] Enterovirus has been attributed to multiple meningitis outbreaks among infants.[4] For example, in a neonatal unit in Singapore echovirus 25 caused an outbreak of enteroviral meningitis.[7] From the data collected, it was determined the outbreak likely occurred within the unit by spread from contaminated staff, and following the implementation of infection control measures and case isolation it was able to be contained.[7] Outbreaks in the community have also been described, attributed to possibly the evolution of a new more virulent strain of enterovirus.[4]

The epidemiological triad (shown in figure 1) is a useful tool for considering how changes in host, environment, and pathogen factors can result in increased enteroviral meningitis.[8] Any identification of contributing factors helps in preventing the spread of infection.[8] This identification can be achieved through the descriptive phase of an outbreak investigation, where data is collected and analysed.[6] Measures to contain or control an enteroviral meningitis outbreak are imperative, particularly for infants due to the potential for serious disease.

In April 2021, the TDHB paediatric department contacted the public health unit with concerns regarding a noticeable increase in enteroviral meningitis cases admitted to TDHB. Our main aim outlined in this report was to determine if this increase was attributable to an outbreak. Firstly, we determined possible baseline levels of regional and national disease. We then collected information regarding the characteristics of the April 2021 case cluster to identify any commonalities. From this, conclusions were drawn regarding whether further investigation or control was needed.

Figure 1. The epidemiological triad for enteroviral meningitis in NZ.[1–4,8]



METHODS

To determine the baseline levels of enteroviral meningitis in the population, a literature review was conducted. Additionally data was collected to determine enteroviral meningitis levels in the Taranaki region. TDHB ICT services and coding used International Classification of Diseases, Tenth Revision, Australian Modification (ICD-10-AM) coding guidelines (appendix 1) to identify all meningitis cases (both paediatric and adult) discharged from TDHB over the past year (1/5/20-30/4/21).[9] This was used in combination with direct communication from the TDHB paediatric department to detect cases that constituted the April 2021 enteroviral meningitis cluster.

Electronic records obtained were used to collect demographic data and details regarding case presentation, investigative results, diagnosis and clinical course in hospital. All enteroviral meningitis cases that occurred in April 2021 had CSF samples arranged by collaboration with LabCare Base or Wellington SCL to be sent to ESR for viral serotyping. Several cases also had stool and/or throat swabs also sent to ESR for the same purpose. Viral serotyping was achieved through RT-PCR and Sanger sequencing. Results were then emailed directly to myself or LabCare Base and uploaded onto the clinical records of the patient.

FINDINGS

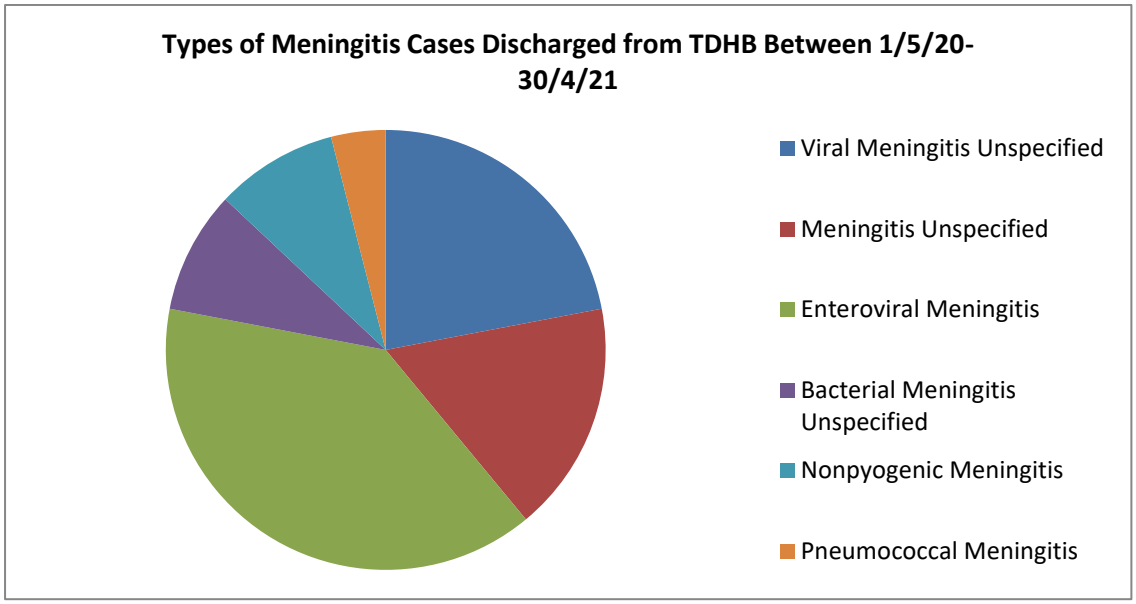
There was limited information in regards to the baseline regional and national levels of enteroviral meningitis. This was likely due in part to the fact that it isn't a notifiable disease, unless the presentation includes acute flaccid paralysis (suspicious for poliomyelitis).[10] A study conducted by McBride et al. (2020) analysed clinical records of NZ children hospitalized with aseptic meningitis over 27 years (1991-2017).[1] This analysis found that unspecified viral meningitis accounted for the majority of cases (69%), with enteroviral meningitis being the second most common cause (27%).[1] Rates of meningitis were higher in the northern parts of NZ, with patients more commonly being male, of pacific or NZ Māori ethnicity, and from areas of high deprivation.[1]

While McBride et al. didn't delineate enteroviral meningitis types, the most recent virology report released by ESR in 2017 indicated Coxsackie virus Group A type 6 was the most common serotyped enterovirus in NZ followed by Echovirus type 30.[11] Echovirus type 30 was isolated from faecal, respiratory, and CSF samples commonly in patients who had febrile illness and/or meningitis.[11] Similarly the national enteroviral surveillance program in Australia found that the most common serotype found in the 2017 viral meningitis cases studied was echovirus 30, followed by echovirus 6 and Coxsackie virus B type 5.[12] These results can be used to infer what would be the expected proportion of enteroviral meningitis cases in Taranaki, and the most common serotypes.

Based on background reading, the enteroviral meningitis case definition used was an individual who presents with clinical indications of meningitis (fever, irritability, meningism) and who has the presence of enterovirus confirmed through CSF PCR testing. Meningitis cases were defined as per their ICD-10-AM guideline code given.[9] From TDHB informatics, a total of 25 meningitis discharges were detected in the past year (1/5/20-30/4/21). Three duplicated cases were excluded and 1 case added that hadn't been detected through informatics but rather reported by the paediatric department, resulting in a total of 23 cases.

The most common type of meningitis was enteroviral (39%) followed by unspecified viral (22%) (figure 2). Enteroviral meningitis accounted for 45% of all viral meningitis cases. Half (56%) of the total meningitis cases were paediatric, with a mode age of 42 years, whereas the majority of enteroviral meningitis cases were paediatric (89%) with a mode age of 0 years. Information regarding case gender, ethnicity, and address were collected and compared between total enteroviral meningitis cases and all other meningitis cases (appendix 3). The differences between these two groups were largely unremarkable, apart from there being a higher proportion of males and lower proportion of Māori in the enteroviral case group.

Figure 2. Proportion of different types of meningitis admitted to TDHB over past year.



The number of both enteroviral and to a lesser extent other meningitis cases rose sharply in April 2021 (figure 3). In fact, the majority (8/9) of enteroviral meningitis cases occurred in 2021. Whilst the majority of these cases occurred in April, all cases that occurred in 2021 were included in a more detailed data collection and analysis, being referred to as the enteroviral meningitis case cluster.

Date of admission was used as a surrogate marker for date of illness onset. The epidemic curve (figure 4) outlines the temporal relationship between cases, showing that whilst no more than one case occurred in a day the majority occurred between April 10th-26th.

Figure 3. Meningitis case number by month of discharge from TDHB over past year

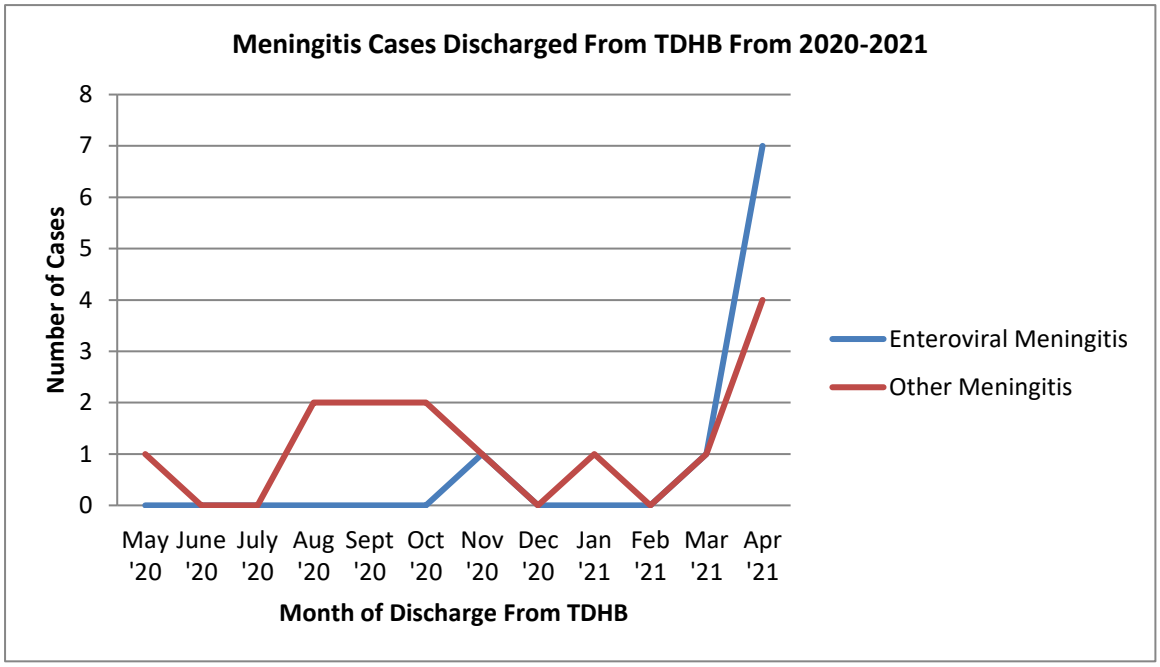
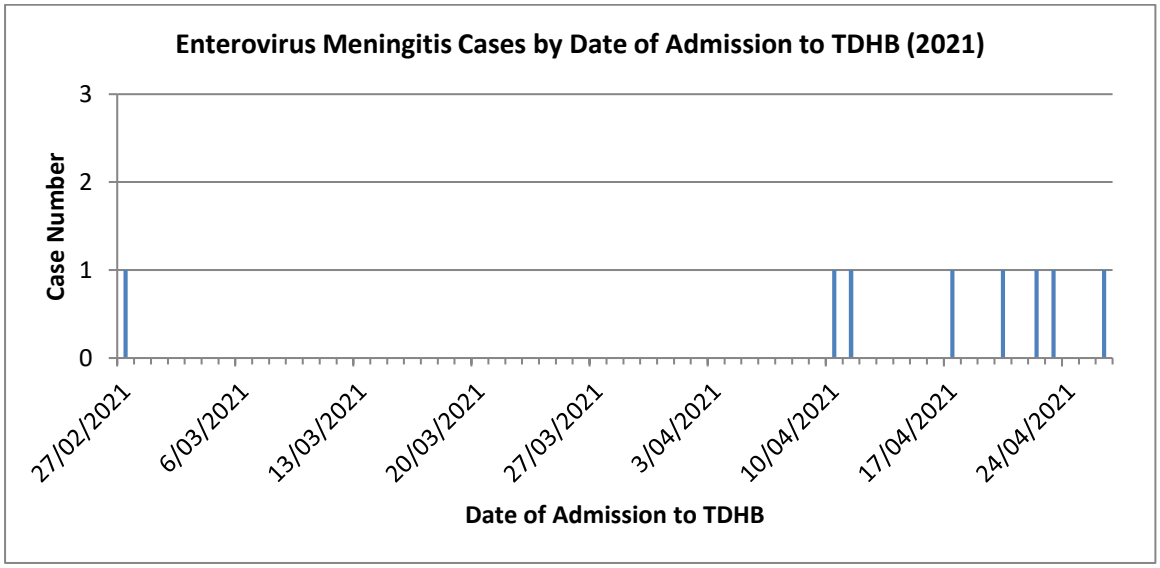
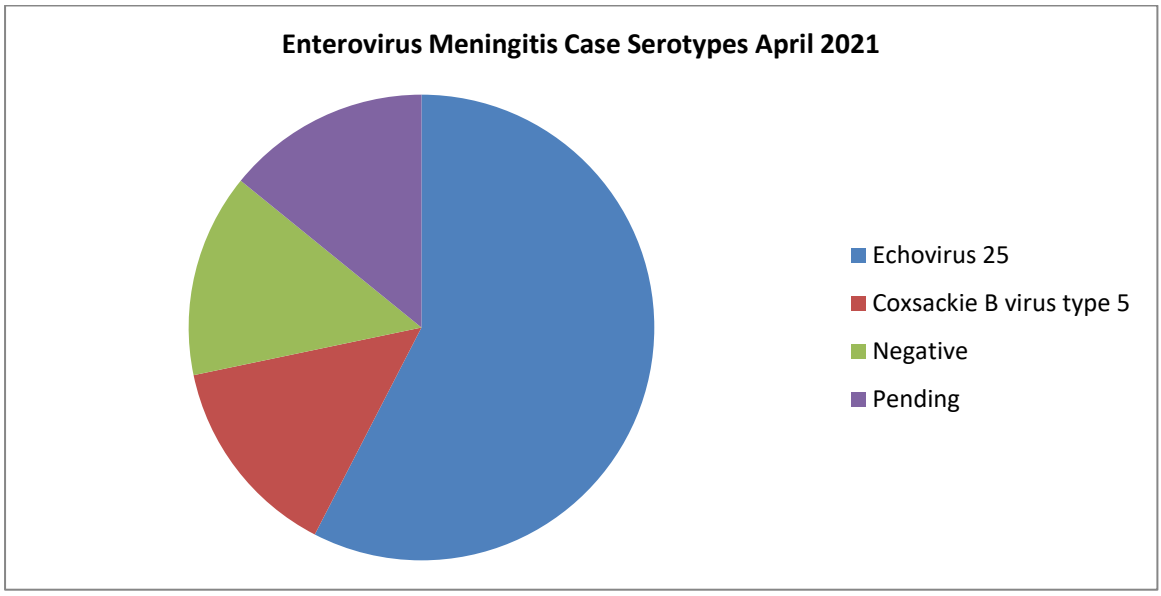


Figure 4. Epidemic curve for 2021 enteroviral meningitis case cluster.



Since Labcare base stores CSF samples for 2 months since collection, all April enteroviral meningitis cases CSF samples were available to be sent to ESR for serotyping via RT-PCR and Sanger sequencing. A stool specimen and throat swab were also arranged through collaboration with Labcare base and Wellington SCL to be sent to ESR for serotyping. The predominant serotype was echovirus 25 (4 cases), with the second most common serotype being Coxsackie B virus type 5 (1 case) (figure 5). To note, one serotype result was still being processed by ESR on writing this report. Labcare base confirmed that no change in testing methods of CSF or PCR have been made in the past year.

Figure 5. Serotype results from the 7 enteroviral meningitis cases occurring in April 2021



Case demographics, presentation, clinical course details, and investigative results were collected from electronic records and analysed for any possible trends (appendix 4). Of note, nil shared contacts or visited places were found in the recorded social history. The majority of cases were male, NZ European neonates (62%), residing in New Plymouth. All cases had fevers, with paediatric cases more commonly presenting with non-specific symptoms of lethargy and irritability. This prompted septic screening and initiation of IV antibiotics in the majority of cases (87%), with continuation until PCR results were received and/or clinical improvement. Most cases had an uncomplicated clinical course and stayed for an average of 4 days. All cases had CSF PCR positive for enterovirus, with half of the throat swabs taken (total of 4) also being positive for enterovirus and no positive stool specimens.

DISCUSSION

This investigation's main finding was that the increase in paediatric enteroviral meningitis cases in April 2021 may in fact represent an outbreak. From the literature review, no regional baseline levels could be determined. However, McBride et al.'s study indicated that enteroviral meningitis accounts for 27% of all viral meningitis cases in NZ.[1] From our data, this compares to enteroviral meningitis accounting for 45% of all viral meningitis cases admitted to TDHB in the past year. Additionally the majority (8/9) of these cases occurred in 2021. Therefore one could remark that the enteroviral meningitis cases in 2021 have risen from presumed baseline national levels. The fact that no change in testing methods was undergone indicates that the increase in case number was less likely a pseudo-outbreak and more likely representative of an outbreak.

From the collected data, the cause of the outbreak remains unclear. The majority of cases' serotypes were Echovirus 25. This virus serotype has been attributed to outbreaks in the past, such as the Singapore outbreak in the neonatal unit previously described.[7] However if the most recent ESR report and Australian national surveillance results are used as a reflection of current day common serotypes, echovirus 25 is not the expected most common cause of enteroviral meningitis in NZ.[11,12] The fact that it was the predominant serotype found amongst cases in this cluster indicates that

there could be a new and more virulent strain causing illness. There was no common exposures (people, places etc.) determined from case social history, but since all cases presented to hospital rather than occurred in hospital it can be presumed this new strain is likely circulating in the community.

With reference to the epidemiological triad for enteroviral meningitis (figure 1), the increase in cases could also be due to changes in the host or environment factors. For example, increases in crowded housing (more amenable environment) or birth rate (higher numbers of susceptible hosts) could also result in higher rates of infection. If we assume that the increase in enteroviral meningitis numbers is significant, then it could be attributed to several changes in the elements of this triad rather than one singular factor.

However this study had several limitations which put the reliability of the above statements in question. The lack of information regarding current regional baseline levels of enteroviral meningitis necessitated assumptions to be made based on national and Australian levels. In part, this is due to the fact that enteroviral meningitis is not a notifiable disease. If more time allowed, TDHB informatics could be used to gather information on enteroviral meningitis rates over more than just one year. This would allow more accurate conclusions to be made on whether the rise in enteroviral meningitis cases was truly a rise from baseline levels.

Additionally only information regarding admitted enteroviral meningitis cases were included. Whilst children are more likely to have serious disease with infection and thus are present to hospital, this means that we have no knowledge regarding community enteroviral infection levels. There could be a much larger cohort in the community who didn't present to hospital, and/or who had mild or asymptomatic enteroviral infections. If this was the case, then collecting information only on patients who were admitted to TDHB could result in an underestimation of enteroviral meningitis levels and size of the outbreak.

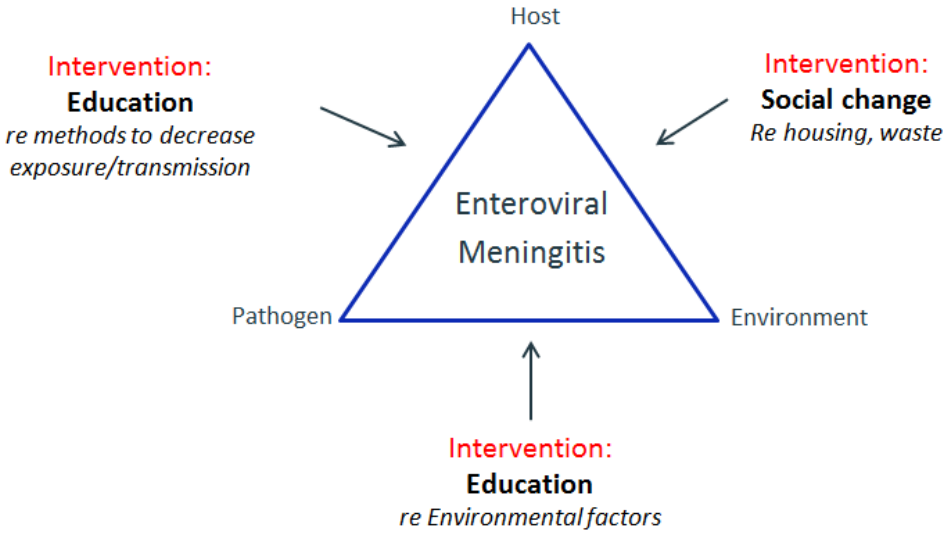
As a consequence of using admitted cases over only 1 year as the source of data regarding enteroviral meningitis infection levels, the number of cases collected was very small (total of 25 cases, 8 being enteroviral). This reduces the power of the descriptive investigation which will impact the statistical significance of any values (e.g. rates) obtained. Due to lack of available resources, no statistical analysis of results was done, so unfortunately this impact wasn't quantified.

A key strength of this study however is the fact that there has not been any recorded previous investigation of enteroviral meningitis outbreaks in the Taranaki region. Therefore the method used could be applied to the descriptive phase of investigations of future suspected outbreaks. Additionally this study was a useful learning tool in the process involved in the descriptive phase of an outbreak investigation, and how the application of an epidemiological triad can be used to develop hypotheses on causes of increased disease. Lastly the gap in knowledge regarding baseline rates of enteroviral meningitis in the region uncovered emphasizes an area of potential future research.

CONCLUSION

In conclusion, if we assume that the findings of this study are significant, the increase in enteroviral meningitis case number in 2021 could have been representative of an outbreak. However, on carrying out the information gathering and processing phase of this investigation, there were no further case of enteroviral meningitis beyond the last case at the end of April. This, in combination with the fact that no clear source or exposures were identified, was used to justify that no further investigation or specific control measures were needed. However general control measures to reduce the spread of disease should be encouraged. With specific reference to enteroviral meningitis, this could be by targeting the elements of the epidemiological triad, such as through simple hand hygiene methods or appropriate waste disposal of soiled nappies (figure 6).[4,8] The implementation of these measures will help to reduce the likelihood of future outbreaks.

Figure 6. Epidemiological triad for enteroviral meningitis showing ways to reduce disease spread.[4,8]



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APPENDIX

Appendix 1. ICD-10 –AM guideline codes used for informatics.[9]
Full list of codes: G00, G01, G02, G03, A87, A80 and their subsets + B00.3, B05.1, M26.1, B02.1, G04.2

Appendix 2. The case numbers as per type, represented in figure 2.

Types of Meningitis Cases Discharged From TDHB Between 1/5/20-30/4/21		
Meningitis Classification	**Number of cases**	**Proportion of all cases**
Viral meningitis unspecified	5	22%
Meningitis unspecified	4	17%
Enteroviral meningitis	9	39%
Bacterial meningitis unspecified	2	9%
Nonpyogenic meningitis	2	9%
Pneumococcal meningitis	1	4%

Appendix 3. The case demographic information collected, as per meningitis type.

Demographics of Meningitis Cases Discharged From TDHB Between 1/5/20-30/4/21				
Demographic	**All Meningitis Cases**	**Other Meningitis Cases***	**Total Enteroviral Meningitis Cases**	**Enteroviral Meningitis Case Cluster**
Total number of cases	23	14 (61%)	9 (39%)	8
Average age (years)**	22	33	6	7
Mode age (years)**	0	42	0	0
Paediatric (<16yo):	13 (56%)	5 (35%)	8 (89%)	7 (88%)
- Subset neonates (<4wks):	5 (21%)	0 (0%)	5 (21%)	5 (63%)
Adult (>16yo):	10 (43%)	9 (64%)	1 (11%)	1 (13%)
Gender: Male	13 (57%)	7 (50%)	6 (67%)	6 (75%)
Gender: Female	10 (43%)	7 (50%)	3 (33%)	2 (25%)
Ethnicity: NZ European***	18 (78%)	10 (71%)	8 (89%)	7 (87%)
Ethnicity: Maori	5 (22%)	4 (29%)	1 (11%)	1 (12%)
Ethnicity: Southeast Asian	1 (4%)	0 (0%)	1 (11%)	1 (12%)
Address: New Plymouth	14 (61%)	9 (64%)	5 (56%)	5 (62%)
Address: Hawera	4 (17%)	1 (7%)	3 (33%)	2 (25%)
Address: Stratford	2 (9%)	1 (7%)	1 (11%)	1 (12%)
Address: Other****	3 (13%)	3 (21%)	0 (0%)	0 (0%)

**Other Meningitis includes classifications: viral meningitis unspecified, bacterial meningitis unspecified, meningitis unspecified, nonpyogenic meningitis, pneumococcal meningitis*
***Age used is the age at presentation to hospital for that admission*
****1 case identified as Maori and NZ European, and was counted in both categories*
*****Other addresses includes Waitara, Inglewood, Eltham*

Appendix 4. Enteroviral meningitis case cluster demographic data and results

Demographics of Enteroviral Meningitis Case Cluster Discharged from TDHB in March-April 2021							
Case & Date of admission	**Age at Presentation**	**Gender**	**Ethnicity**	**Address**	**Clinical Presentation**	**Diagnostic Code (ICD-10)**	**Length of stay**
1 27/2/21	16d	F	NZ European	Hawera	Fever, poor feeding	A87.0	6
2 10/4/21	19d	F	NZ European	New Plymouth	Fever, irritability, poor feeding	A87.0	2
3 11/4/21	13y	M	NZ European	New Plymouth	Fevers, headaches, photophobia, vomiting	Not recorded	3
4 17/4/21	7d	M	NZ European, Maori	New Plymouth	Fever, lethargy	A87.0	5
5 20/4/21	141d	M	Southeast Asian	Stratford	Fever, poor feeding	A87.0	5
6 22/4/21	3d	M	NZ European	New Plymouth	Fever, irritability	A87.0	3
7 23/4/21	7d	M	NZ European	Hawera	Fever, irritability, lethargy	A87.0	5
8 26/4/21	41yo	M	NZ European	New Plymouth	Fever, headaches, neck stiffness	A87.0	2

Investigations of Enteroviral Meningitis Case Cluster Discharged from TDHB in March-April 2021							
Case	**Initial type of specimen**	**Initial specimen results (biochem)**	**CSF PCR**	**Throat swab**	**Stool spec**	**Type of specimen for serotype**	**Serotype Results**
1	CSF	Protein H, glucose N. Pleocytosis (neutrophilic). No growth. ++ RBC ?contaminated	Enterovirus +	Taken, not detected	Not taken	NA	NA
2	CSF	Protein H, glucose N. Low WCC. No growth	Enterovirus +	Taken, not detected	Not taken	CSF	Pending
3	CSF	Protein H, glucose N. Low WCC. No	Enterovirus +	Not taken	Not taken	CSF	Echovirus 25

		growth					
4	CSF	Protein H, glucose L. Low WCC. No growth.	Enterovirus +	Not taken	Not taken	CSF	Echovirus 25
5	CSF	Protein N, glucose N. Pleocytosis (lymphocyte). No growth.	Enterovirus +	Not taken	Not taken	CSF	Echovirus 25
6	CSF	Protein H, glucose N. Pleocytosis (neutrophilic). No growth. ++ RBC ?contaminated	Enterovirus +	Taken, enterovirus and rhinovirus detected	Taken, not detected	Fecal sample & CSF	Echovirus 25
7	CSF	Protein H, glucose N. Low WCC. No growth	Enterovirus +	Taken, enterovirus detected	Taken, not processed	Throat swab & CSF	Negative
8	CSF	Protein H, glucose N. Pleocytosis (lymphocyte). No growth.	Enterovirus +	Not taken	Not taken	CSF	Coxsackie B virus type 5