Original Article

Probable epidemic Mycoplasma pneumoniae disease activity in metropolitan Sydney, 2015: combining surveillance data to cross-validate signal detection

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Abstract

Introduction

Mycoplasma pneumoniae is a leading cause of community acquired pneumonia and well-recognised cause of encephalitis in children. Sentinel hospital surveillance identified a temporal cluster of children with suspected encephalitis associated with *M.pneumoniae* in NSW. We aimed to determine whether this cluster was associated with epidemic *M.pneumoniae* activity.

Methods

A multi-faceted investigation was undertaken using existing data sources including:

- Active clinical surveillance of suspected encephalitis (ACE study) associated with *M.pneumoniae* at the Children's Hospital at Westmead (CHW).
- Syndromic surveillance of Emergency Department presentations for pneumonia in children 0-16 years to 86 NSW hospitals.
- Laboratory sentinel surveillance of *M.pneumoniae* testing performed at CHW and the Institute for Clinical Pathology and Medical Research (ICPMR), Westmead.

Results

We detected an increased number of cases of hospitalised suspected encephalitis associated with *M. pneumoniae* in 2015 at the Sydney Childrens Hospital Network (SCHN), with a peak in July, that were predominantly in Western Sydney. Concurrently, monthly pneumonia presentations to 86 NSW emergency departments in children aged 0-16 years increased in 2015. This increase was greater in children aged 5-16 years compared to those aged 0-4 years and in metropolitan sites compared with rural hospitals. Laboratory data from sentinel laboratories showed increased frequency of testing, and of tests returned positive for *M.pneumoniae* in 2015 compared to preceding years. In aggregate, this information was considered suggestive of epidemic activity of *M.pneumoniae* in metropolitan Sydney in 2015.

Conclusions

Active surveillance for childhood encephalitis has the potential to provide sentinel surveillance data to identify epidemic infectious disease activity. Combining multiple sources of surveillance data affords opportunities to cross-validate epidemic signals. *M.pneumoniae* disease activity is challenging to measure, and may be a cause of significant disease burden in Australian children during epidemic years.

Keywords: *Mycoplasma pneumoniae*, surveillance, encephalitis, pneumonia, children, Australia

Introduction

Mycoplasma pneumoniae infection has well-recognised neurological complications that occur most commonly in children, the most severe form being encephalitis.[1, 2] *M.pneumoniae* most often causes respiratory tract infection and disease including atypical pneumonia, acute otitis media and coryzal illness.[3, 4] The importance of *M.pneumoniae* as a cause of childhood pneumonia was recently emphasised in a large study of hospitalised childhood community-acquired pneumonia (CAP) from the United States. In this study, *M.pneumoniae*, confirmed by polymerase chain reaction assay (PCR), was the most frequent bacterial cause of childhood pneumonia (20-35%) amongst children aged 5-17 years.[5] The epidemiology of *M.pneumoniae* disease is not well characterised, but it is considered to be a worldwide endemic infectious disease with superimposed epidemics every four to seven years.[3, 4] Major epidemics were reported from several European countries, and Israel between 2010 and 2013. [6-10]

M.pneumoniae has been reported to be one of the most frequently identified pathogens associated with encephalitis in children.[11, 12] However, the strength of its causal assocation remains controversial, because it is infrequently identified in cerebro-spinal fluid.[1, 13] A further challenge is the lack of available laboratory tests with high sensitivity and specificity.[14]

Here we report results from a collaborative investigation undertaken following identification of an increased frequency of suspected encephalitis associated with *M.pneumoniae* by childhood encephalitis surveillance (the Australian Childhood Encephalitis -ACE- study). This increase in cases suggested epidemic *M.pneumoniae* disease activity to ACE investigators and prompted reporting to Western Sydney Local Health District (WSLHD) Public Health Unit (PHU) followed by a subsequent joint investigation with the PHU and NSW Ministry of Health (NSW MoH) Rapid Surveillance team.

Methods

We sought to determine whether the temporal cluster of *M.pneumoniae* encephalitis was associated with evidence of epidemic *M.pneumoniae* activity in NSW by aggregating existing data sources in order to determine if further public health action was required.

1. Data sources

The Australian Childhood Encephalitis (ACE) study:

The ACE study utilises the Paediatric Active Enhanced Disease Surveillance (PAEDS) network to undertake active, sentinel site surveillance for childhood encephalitis at five tertiary paediatric hospitals across Australia. Surveillance commenced in 2013 at the Children's Hospital at Westmead (CHW), the NSW sentinel site and PAEDS coordinating centre. From 2014, surveillance extended to involve the national PAEDS network.[15] The ACE study methodology has been previously published.[16] Suspected encephalitis is defined as: a child aged 0 to 14 years AND hospitalised with acute encephalopathy AND has *one or more* of the following: fever, seizures, focal neurological findings, at least one abnormality of cerebrospinal fluid (CSF): age determined pleocytosis, or elevated protein ≥ 40mg/dl, or EEG/ neuroimaging findings consistent with encephalitis. An association with *M.pneumoniae* is defined as the presence of specific IgM antibodies in acute sera. All suspected encephalitis cases were reviewed by an expert panel of clinicians and designated as confirmed encephalitis or not encephalitis using published case definitions with higher specificity than the surveillance definition.[16-18]

Public Health Rapid Emergency Disease and Syndromic Surveillance (PHREDSS) system:

In 2003, NSW MoH implemented a syndromic surveillance system including administrative Emergency Department (ED) data.[19] The system, now called the Public Health Rapid Emergency Disease and Syndromic Surveillance (PHREDSS) system, combines near real-time

data directly from participating ED patient information management systems with cleaned, more complete Emergency Department Records for Epidemiology (EDRE) data sourced from the NSW Emergency Department Data Collection. The PHREDSS system automatically groups primary provisional ED diagnosis codes, assigned by treating clinicians, into acute illness and injury syndromes for monitoring. The diagnosis codes used include any of the Australian clinical implementations of the International Classification of Diseases (ICD) 9th revision, ICD-10th revision (ICD-10AM) or the Systematized Nomenclature of Medicine - Clinical Terminology (SNOMED-CT).[20, 21] Syndromes are monitored daily to detect unusual patterns that may signify an emerging outbreak or issue in the population. The PHREDSS 'pneumonia' syndrome includes provisional diagnoses of viral, bacterial, atypical or unspecified pneumonia, SARS and legionnaires disease, but excludes pneumonia with influenza, which is included in the 'influenza-like illness' syndrome.

Sentinel laboratory surveillance of *M. pneumoniae*:

Laboratatory testing for *M.pneumoniae* is usually undertaken with serology. At the Children's Hospital at Westmead (CHW), testing is performed for *M.pneumoniae* IgM using a commercial enzyme linked immunosorbent assay (ELISA:Diesse™ Chorus IgM); a positive is based on the product specified cut-off. At the Institute for Clinical Pathology and Medical Research (ICPMR), Westmead, *M.pneumoniae* serology is performed using complement fixation assay (CF: Virion\Serion™ reagents) and a commercial Immunofluoresence assay (IFA: Vircell™ IgM). Tests are reported positive where a CF titre of 64 or higher is measured, or IgM is identified based on the product specified cut-off. In addition at ICPMR, PCR for *M.pneumoniae* nucleic acid is performed as an 'in house' assay. CHW refers specimens to ICPMR for this test.

2. Investigation and analyses

ACE study:

ACE study surveillance continued at CHW with enhanced real-time review of cases. In addition, we contacted the Sydney Children's Hospital, Randwick infectious diseases department to identify additional cases.

Pneumonia syndromic surveillance:

A retrospective analysis of 'pneumonia' ED presentations in children aged 0-16 years was conducted. Data from EDRE were used to provide greater coverage of NSW EDs and included 86 NSW facilities that participated continuously from 2010-2015 and had diagnosis complete in 75% or more records. These data represented 85% of all NSW ED presentations in 2015. 'Pneumonia' ED presentations in children aged 0-16 years in 2015 were compared to the mean annual count for 2010-2014. The PHREDSS system uses an automated threshold for signalling of five standard deviations (SD) above the expected count to indicate a significant increase. The expected count is the mean count for the same period over the previous five years. We compared 'pneumonia' presentations by age group (0-4 years and 5-16 years), and geographical location (metropolitan and rural). The number of admissions and the proportion of presentations that were admitted were analysed. In addition, we sought to sub-categorise the 'pneumonia' syndrome to include a subset of ICD-9, ICD-10 and SNOMED-CT diagnosis codes more specific to atypical pneumonia (CS, PB & SB agreed the included codes).

Sentinel Laboratory surveillance:

We requested records of *M. pneumoniae* serology and PCR nucleic acid detection tests from ICPMR and CHW diagnostic laboratories. We examined number of tests ordered and the proportion that returned positive for 2014 and 2015.

Data were collated in Microsoft (WA, USA) Excel™ v14 (2010) , and statistical testing

performed using CDC Epi Info™ (GA, USA). Proportions were compared using two-tailed chi-square test with Yates correction.

This was a public health investigation conducted using provisions in the NSW *Public Health Act*, 2010 therefore ethical approval was not required. De-identified ED data were released for the purposes of this investigation by the Executive Director, Centre for Epidemiology and Evidence using provisions in the NSW *Health Administration Regulation*, 2015. The ACE study was approved by the Sydney Children's Hospitals Network human research ethics committee.

Results

Suspected encephalitis surveillance

Between January and October 2015 (10 months), *M.pneumoniae* was associated with 29% (13/45) of suspected encephalitis cases identified by the ACE study, including five in July alone (Table 1). Between May 2013 and December 2014 (20 months), the ACE study identified four cases of suspected encephalitis associated with *M. pneumoniae* at CHW, of 79 total cases (5%; two tailed chi square p-value <0.001 comparing 2015 to 2013/14). Of the 13 cases in 2015, median age was 10.1 years (range 3-11.7); ten were male. Seven cases resided in outer western Sydney. All cases presented with an altered level of consciousness. Other symptoms/signs included: fever (8/13), headache (9/13), focal neurological signs (7/13), seizure(s) (6/13), cerebrospinal fluid pleocytosis (7/11), and abnormal neuroimaging (6/13). Four of the thirteen children were admitted to intensive care. The median length of stay in hospital was 7 days (inter-quartile range 5.5, 15.5). Following review of these patients by the expert panel, two of the thirteen were deemed not to have encephalitis but other neurological syndromes; one with cerebral venous sinus thrombosis, and the other a non-specific seizure episode.

SCH-Randwick reported two cases of *M. pneumoniae* associated suspected encephalitis hospitalised in 2015; one in February and one in July (Table 1). This was considered to be in keeping with expected case numbers (A Bartlett, personal correspondence).

Table 1: Cases of suspected encephalitis* associated with Mycoplasma pneumoniae infection#^.

Sex	DOA	Age (yrs)	Geographic Statistical Sub-division (SSD)
Cases identified by PAEDS surveillance at the Children's Hospital at Westmead			
M	29/12/2014	5.7	Sydney-Inner Western SSD
M	15/03/2015	11.7	Sydney-Blacktown SSD
M	17/04/2015	11.5	Sydney -St George/Sutherland SSD
M	22/04/2015	10.8	Sydney-Central Western SSD
F	4/07/2015	5.7	Sydney-Central Western SSD
F	10/07/2015	3.0	Sydney-Blacktown SSD
M	16/07/2015	10.8	Sydney-Blacktown SSD
M	25/07/2015	10.1	Sydney-Blacktown SSD
F	25/07/2015	10.7	Sydney-Blacktown SSD
M	6/08/2015	8.2	Sydney-Blacktown SSD
M	23/09/2015	10.7	Central West-Lachlan SSD
M	30/09/2015	8.5	Sydney-Central Northern SSD
M	25/10/15	8.4	Sydney-Blacktown SSD
Additional cases identified by infectious diseases at Sydney Children's Hospital, Randwick			
M	03/02/2015	9.9	Sydney-St George-Sutherland SSD
M	22/07/2015	10.9	Sydney-Northern Beaches SSD

*Suspected encephalitis: Age 0 to 14 years AND Hospitalised with acute encephalopathy (defined by altered level of consciousness, lethargy and/or personality change lasting ≥24 hours) AND Has one or more of the following: fever, seizures, focal neurological findings, at least one abnormality of cerebrospinal fluid (CSF; age determined pleocytosis, or elevated protein ≥ 40mg/dl), or EEG/ neuroimaging findings consistent with infection-related encephalitis.
#Defined as the presence of positive *M.pneumoniae* specific IgM antibodies on acute sera.
^In three cases an additional possible infectious cause was identified (one enterovirus PCR positive on stool; one respiratory syncytial virus (RSV) PCR positive on naso-pharyngeal specimen; one RSV and human meta pneumovirus (hMPV) PCR positive on naso-pharyngeal specimen).
Abbreviations: DOA=date of admission; PAEDS=Paediatric Active Enhanced Disease Surveillance network; SSD=statistical sub-division

Pneumonia syndromic surveillance:

In 2015, among children aged 0-16 years there were 5,337 ED presentations to 86 NSW hos-

pitals, which was significantly greater (> 5 SD) than the mean number of annual presentations (3,824) during the previous five years (2010-2014). Monthly counts of "pneumonia" presentations were increased from March to September 2015, peaking in August with 663 "pneumonia" presentations (Figure 1).

In 2015 the increase in "pneumonia" ED presentations, compared to the mean number of annual presentations of the previous 5 years, was greater in children aged 5-16 years than in children aged 0-4 years (Figure 1) and in metropolitan hospitals compared to the rural hospitals (Figure 2).

Of the "pneumonia" presentations in 2015, 3,032 were admitted from ED to a ward (not critical care), which was significantly greater than the mean number of annual admissions (2,483) in the previous 5 years. However, the proportion of presentations that were admitted from ED in 2015 (57%) was lower than the mean proportion admitted between 2010 and 2014 (64%).

Of the pneumonia ED presentations in children aged 0-16 years in 2015, 81% had non-specific diagnosis codes assigned (Table 2).

Laboratory sentinel surveillance:

Analysis of diagnostic laboratory data obtained from CHW showed both an increased number of *M.pneumoniae* tests ordered and an increase in positive results in 2015 compared to 2014 (Figure 3a). From March to September, there was a significantly higher proportion of positive tests in 2015 compared to 2014 (35% vs 9%; two tailed chi square p-value <0.001). The proportion was similarly higher comparing full years (34% vs 12%; p-value <0.001).

Data from ICPMR showed that a greater number of *M.pneumoniae* serology tests were ordered in 2015 compared to 2014, and there was a peak in positive serology results (CFT or IgM) in August (Figure 3b). The proportion of positive tests (CFT and IgM) was not significantly higher in 2015 compared to 2014 for the whole year (10% vs 7%; p-value <0.2), but showed statistical significance when stratified to a 5-14 years age group (11% vs 3%; p-value <0.001) and approached significance for March to September (5% vs 2%; p-value 0.07). Additionally, a significantly higher proportion of *M.pneumoniae* PCR tests returned positive in 2015 relative to the preceding two years (Table 3).

Discussion

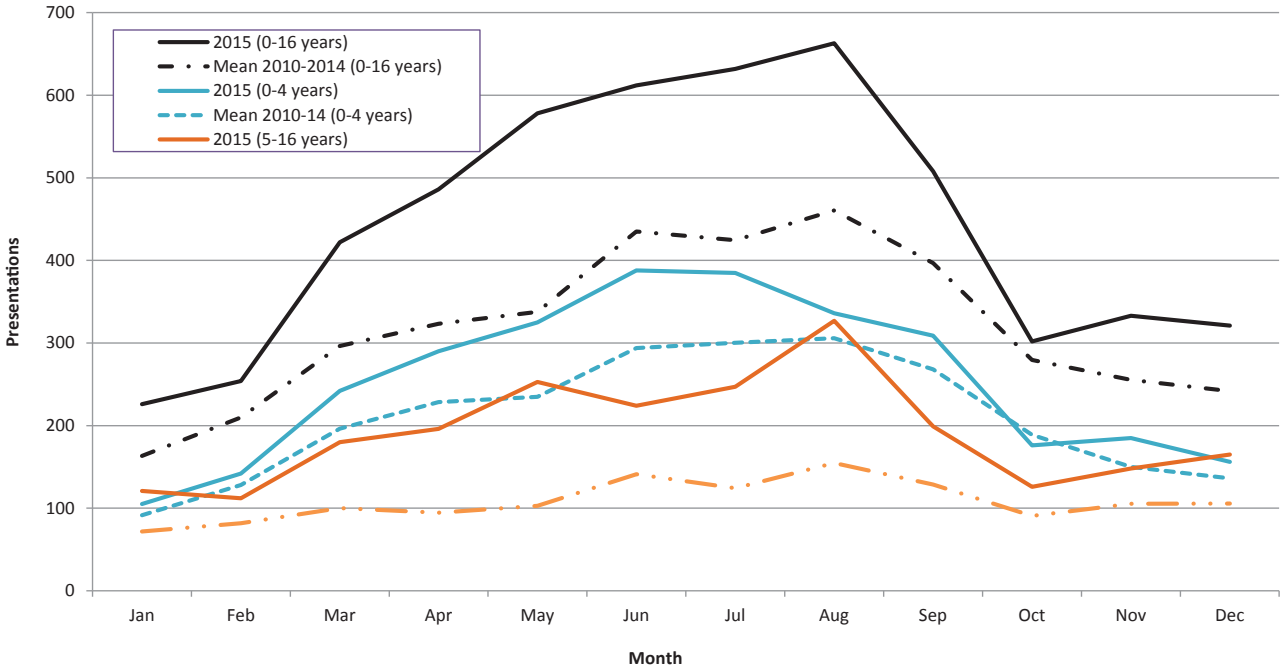
In 2015, active clinical surveillance for childhood encephalitis showed an increase in suspected encephalitis cases in NSW associated with *M.pneumoniae*. The cluster peaked in July in one geographic location, the Blacktown area. A similar increase in encephalitis cases was not observed, albeit passively, in Eastern Sydney (at SCHN-Randwick). In 2015, "pneumonia" ED presentations significantly increased in NSW in the age group in which *M.pneumoniae* is most common [5] (i.e. children aged 5-16 years) and in metropolitan locations. Laboratory surveillance showed increased frequency of testing, and tests returned positive for *M.pneumoniae* in 2015 compared with previous years at two sentinel referral laboratories. Together, this information was suggestive of epidemic *M.pneumoniae* activity in metropolitan Sydney in 2015. As this

Table 2: Frequency of top 5 diagnosis codes included in the PHREDSS "pneumonia" syndrome in 2015.

Diagnosis Code	Coding System*	Description	Frequency	Percentage
233604007	SNOMED-CT	Pneumonia (disorder)	2421	45%
J18.9	ICD-10AM	Diagnosis: Pneumonia, unspecified (Ed.1-Ed.9)	1135	21%
385093006	SNOMED-CT	Community acquired pneumonia (disorder)	540	10%
233606009	SNOMED-CT	Atypical pneumonia (disorder)	273	5%
53084003	SNOMED-CT	Bacterial pneumonia (disorder)	218	4%

*Abbreviations: SNOMED-CT = the Systematized Nomenclature of Medicine - Clinical Terminology; ICD-10AM = the Australian clinical implementations of the International Classification of Diseases ICD-10th revision.

Figure 1: Monthly counts of pneumonia Emergency Department presentations in children for 2015 (black solid lines), compared with each of the mean of the 5 previous 5 years (coloured dashed lines lines), persons aged 0-16 years, to 86 NSW hospitals in NSW, by age group



information was gathered, it was forwarded on to the WSLHD PHU and the Communicable Diseases Branch, Health Potection NSW. Clinicians (neurology, infectious diseases) at CHW and SCH-Randwick were made aware by email of the increased identification of *M. pneumoniae* associated encephalitis cases and to consider early testing and treatment. No further public health actions were undertaken.

We reported this cluster of *M.pneumoniae* associated encephalitis in Western Sydney and probable epidemic *M.pneumoniae* activity to demonstrate that active surveillance for childhood encephalitis has the potential to provide sentinel surveillance data to identify epidemic infectious disease activity. We have shown that combining surveillance data affords opportunities to cross-validate epidemic signals, and facilitate hypothesis testing. We have also shown that *M.pneumoniae* is likely an underappreciated cause of hospitalisation and acute morbidity in children in epidemic years.

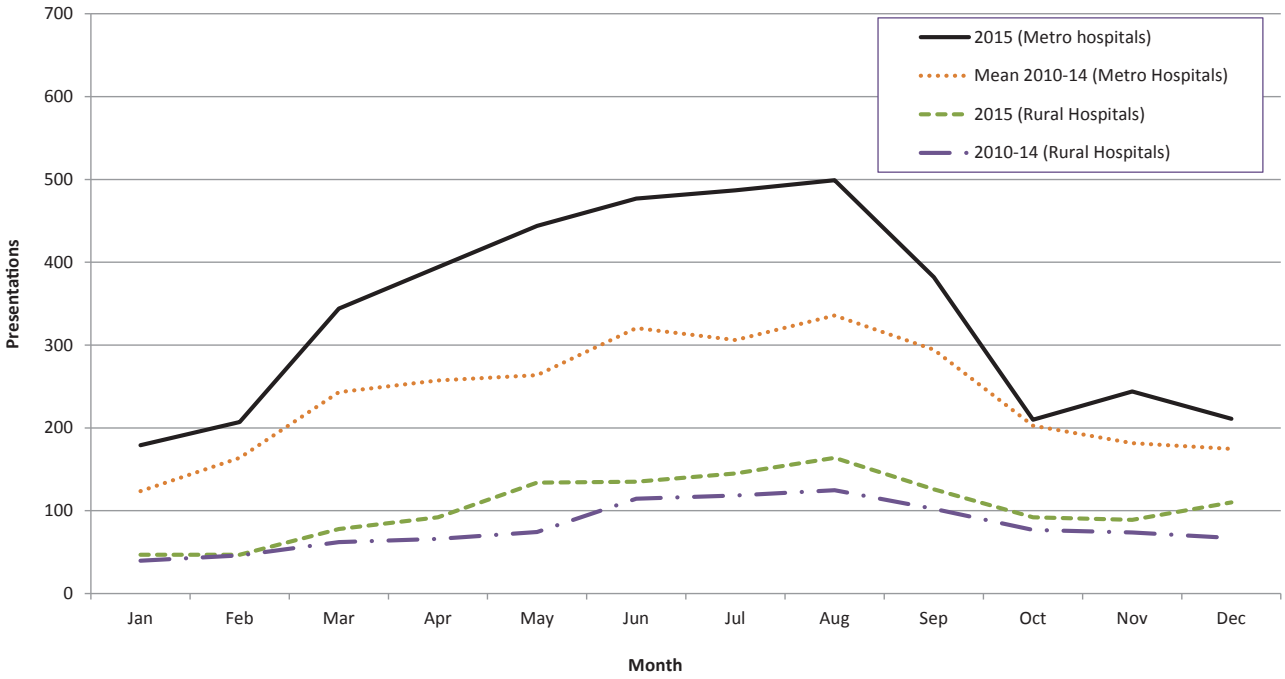
There are scarce published data describing the epidemiology of *M.pneumoniae* infection and disease from Australia. A recent molecular epidemiology study showed the circulation of diverse genotypes of *M.pneumoniae* in Sydney with a low prevalence of genetic markers of antibiotic resistance.[22] Furthermore, a clinical study from the Children's Hospital at Westmead showed *M.pneumoniae* infection to be most often associated with respiratory tract infection

Table 3: *Mycoplasma pneumoniae* polymerase chain reaction nucleic acid (PCR) testing performed at the Institute for Clinical Pathology and Medical Research (ICPMR) at Westmead, 2011 to 2015.

	2015	2014	2013	2012	2011
Total samples tested	617	501	409	401	211
Samples positive (%)	40 (6.5)	9 (1.8)	8 (2.0)	15 (3.7)	12 (5.7)
Two tailed Chi square p-value*		<0.001	<0.01	0.08	0.7

*compared with 2015. p-value <0.05 considered as statistically significant

Figure 2: Monthly counts of pneumonia Emergency Department presentations in children for for 2015 (solid lines), compared with the mean of the previous 5 years (dashed lines lines), to 86 NSW hospitals, by location



*Abbreviation: Metro = Metropolitan

Source (Figures 1-2): Emergency Department Records for Epidemiology (EDRE), held by the NSW Ministry of Health Secure Analyics for Population Health Research and Intelligence (SAPHaRI).

and children aged 5-9 years.[23] In this five year study, half of the cases occurred in a single 'epidemic' year (2001).[23] We could not identify any other contemporary published studies.

Epidemics of *M.pneumoniae* infection can result in a significant burden of disease. In 2015 there was a considerable increase in 'pneumonia' ED presentations amongst school aged children and an increase in admissions. A similar pattern was observed during an epidemic of *M.pneumoniae* in Scotland in 2010-11 where infection resulted in a high hospitalisation rate (59%) of cases with acute respiratory illness.[8] Furthermore, *M.pneumoniae* encephalitis results in one third to a half of cases suffering neurological morbidity (e.g. motor or cognitive dysfunction or seizures).[24-26] Given the significant increase in *M.pneumoniae* associated encephalitis that we observed in 2015, we are concerned about potential long-term morbidity arising from this epidemic year. We are undertaking a follow-up study that includes many of the cases described here that will further clarify neuro-psycological outcomes.

Monitoring *M.pneumoniae* disease activity is challenging for several reasons. Firstly, *M.pneumoniae* causes a variety of clinical syndromes, most commonly respiratory tract infections. Respiratory tract infections, including pneumonia, are among the most common reasons for children to present to primary care practitioners and emergency departments and are caused by a variety of pathogens.[5, 27] Furthermore, a Cochrane systematic review showed that *M. pneumoniae* cannot be reliably distinguished from other causes of pneumonia by clinicians on clinical grounds alone.[28] Despite these limitations, given the likely high proportion of pneumonia in school aged children caused by *M.pneumoniae,* we suggest that pneumonia when restricted to this age group is a potentially useful proxy for *M.pneumoniae* disease activity. The limitations of the laboratory diagnosis of *M. pneumoniae* infection preclude its use as a sole mechanism for disease surveillance. Serological diagnosis is hampered by cross-reactivity of IgM assays, limited sensitivity and specificity of single elevated titres of total antibody, and

Figure 3a: Mycoplasma pneumoniae IgM testing at the Children's Hospital at Westmead (CHW) 2014 – 2015.

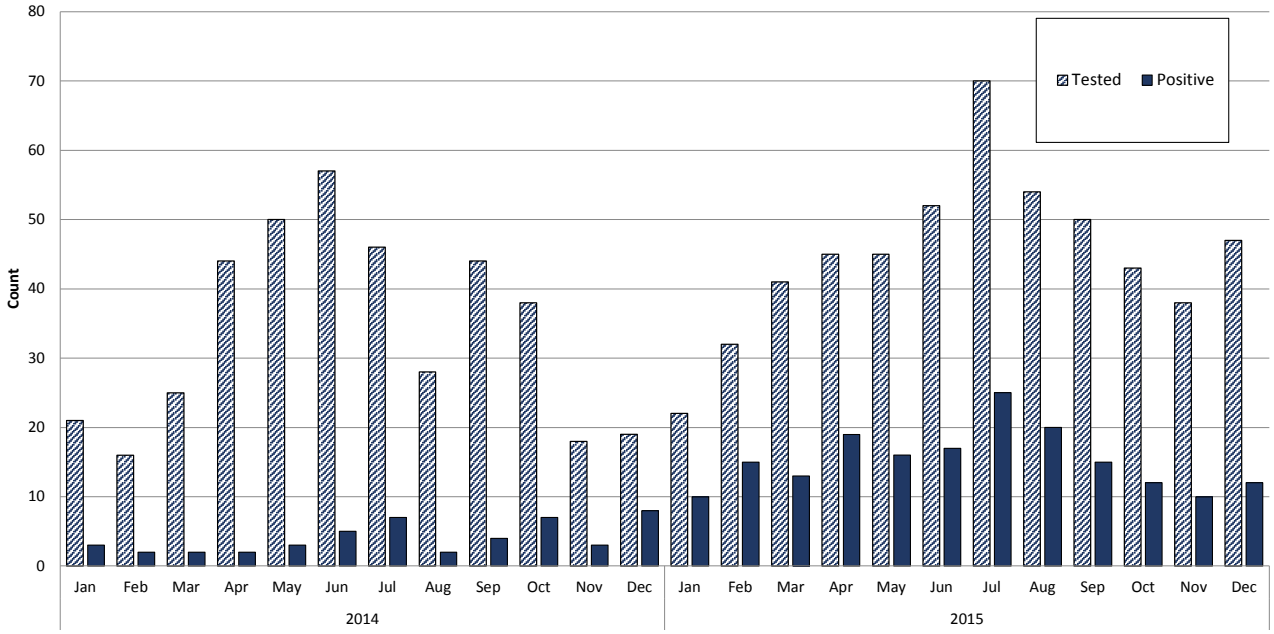
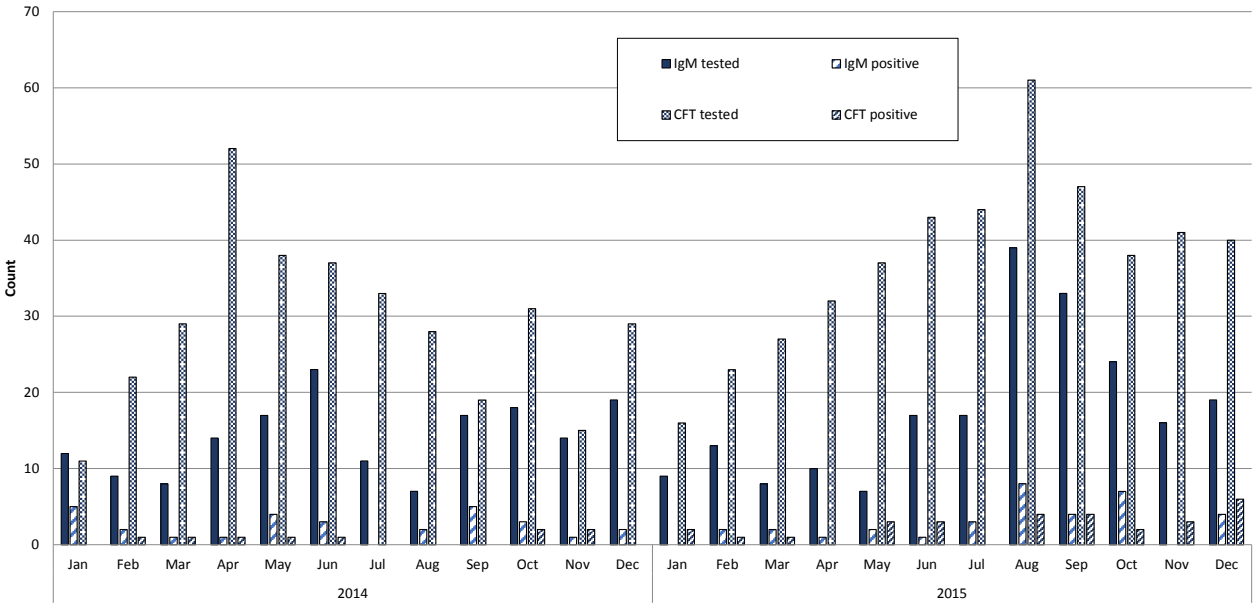


Figure 3b: Mycoplasma pneumoniae serology testing performed at the Institute for Clinical Pathology and Medical Research (ICPMR) at Westmead 2014 – 2015.



infrequent convalescent sampling required to demonstrate a fourfold rise in titres.[14, 29, 30] PCR is also limited by high rates of asymptomatic carriage in children.[4] As a result, cross validation of syndromic surveillance with laboratory surveillance, as performed in this outbreak investigation, is important in monitoring *M. pneumoniae* disease activity. This may still provide conflicting results, as shown in this investigation. In Norway, investigators have studied the possible monitoring of macrolide prescriptions at a population level, cross referenced with laboratory reports.[31] Further work is required to identify the best combination of tools for ongoing *M.pneumoniae* surveillance.

The Public Health response to infectious diseases outbreaks can be categorised into three core activities (i) monitoring and surveillance, (ii) communication and (iii) control of transmission. In this outbreak investigation, the PHU and Rapid Surveillance team undertook additional monitoring and surveillance of available data (PHREDSS) to identify the pattern of *M. pneumoniae* disease. Communication of the the evolving findings to children's hospital clinicians was facilitated through SCHN in August, 2015, to alert them to the possible epidemic period. Such alerting of clinicians supports earlier diagnosis and treatment, potentially reducing complications of severe illness, or exclusion of a diagnosis in critically ill patients. No specific community or healthcare transmission control measures were implemented in this situation. Here, our main goal was to cross validate surveillance mechanisms which proved complex and resulted in a delay in confidently identifying the epidemic. Community outbreaks remain largely undetected as *M.pneumoniae* surveillance is not routinely conducted.[32] As a result, this outbreak was a novel consideration for the PHU. These factors and the absence of clear nosocomial or institutional transmission resulted in the level of public health action being minimal. However, we note that *M. pneumoniae* outbreaks within healthcare facilities have been reported, with high attack rates and significant morbidity despite control measures.[14] The optimal public health response to community outbreaks of *M. pneumoniae* infection is unclear.[32] Given the likely community transmission, during future epidemics, additional public health actions for consideration include active communication with primary care practitioners to optimise testing and antimicrobial use, and with schools and child care facilities to emphasise preventive health behaviors. The possible need for direct communication with the public is emphasised by evidence that households may be central to amplifying transmission.[32]

We acknowledge a number of limitations with this analysis. Firstly, the use of a single positive IgM in the case definition for *M.pneumoniae* encephalitis lacks specificity; however this definition was unchanged across the surveillance period so should not affect trends. Secondly, we do not have an explanation for why the encephalitis cases were clustered in Western Sydney, despite evidence of an increase in pneumonia cases across metropolitan NSW. It is possible that cases at Sydney Children's Hospital, Randwick may have been missed given that case ascertainment at this site was based on clinician identification retrospectively rather than on established active surveillance. Furthermore, possible shared exposures were not explored directly with cases. Thirdly, ED provisional diagnoses are allocated at the end of the ED episode of care by a clinician (nurse or doctor) from a drop down list and there may be differences in ED provisional diagnosis coding practices across time and facility. Although we attempted to develop a more specific "atypical pneumonia" syndrome sub-category, the non-specific nature of ED diagnosis coding precluded this being useful. Fourthly, the assumption that up to a third of community acquired pneumonia in children aged 5-19 years is caused by *M.pneumoniae* is unproven in this study.[5] Finally, given the variability in the absolute number of laboratory tests performed at CHW and ICPMR for *M.pneumoniae* it is likely that testing is selective, and we do not know what additional factors apart from disease activity may have influenced this across the time period from which data were generated.

In conclusion, active, sentinel site surveillance for childhood encephalitis has the capacity to identify epidemic infectious diseases in children. Combining, and cross validating syndromic surveillance signals requires a collaborative approach and the combination of clinical, public health, and biostatistical expertise. We suggest that *M.pneumoniae* disease burden in Australia is currently inadequately measured, but that it may be considerable and should be the focus of future research.

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