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# BMJ Paediatrics Open

## **Pediatric critical respiratory illness associated with *Mycoplasma pneumoniae*: a single-centre, retrospective, cohort study**

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2020-000640
Article Type:	Original research
Date Submitted by the Author:	13-Jan-2020
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Keywords:	Infectious Diseases, Epidemiology

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3 **Pediatric critical respiratory illness associated with *Mycoplasma pneumoniae*: a single-**  
4 **centre, retrospective, cohort study**  
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37 Word count : 2493  
38  
39

40 Keywords: pneumonia, intensive care, respiratory tract infection, epidemiology, atypical  
41

42 Short title: Pediatric critical respiratory illness associated with *Mycoplasma pneumoniae*  
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45 Funding: This project was supported by a McMaster University Department of Pediatrics  
46 Resident Research Grant. JMP was supported by a Hamilton Health Sciences Early Career  
47 Award. There are no conflicts of interest.  
48

49 Presentation: Poster presentation, Association of Medical Microbiology and Infectious Disease  
50 Canada annual conference, 2018.  
51  
52

53 Acknowledgements: The authors would like to acknowledge the assistance of Samir Patel who  
54 oversaw the Mycoplasma resistance testing.  
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## Abstract

**Objectives.** To measure the prevalence of *Mycoplasma pneumoniae* infection in critically ill children with respiratory infections and to determine if children in whom *M. pneumoniae* is detected differ systematically from those that are not.

**Study design.** A retrospective, single-centre, cohort study. All children aged 2 months – 18 years with presumed respiratory infection who were admitted to the McMaster Children's Hospital pediatric intensive care unit between September 2015-October 2016 were eligible. Participants were grouped by clinical syndrome (viral respiratory infection, asthma exacerbation, undifferentiated/uncomplicated pneumonia, pneumonia complicated by effusion/empyema, and 'other'). Testing for *M. pneumoniae* from nasopharyngeal specimens was done using a lab-developed PCR assay.

**Results.** There were 227 participants; the median age was 3.1 y, 43% were female, and 79% had medical comorbidities. Those with any pneumonia were significantly less likely to have a respiratory virus identified in their NPS and had significantly higher C-reactive protein values than those in the viral infection and asthma groups. There were 10 participants in whom *M. pneumoniae* was detected (4.4%, 95%CI 2.1-8.0%). *Mycoplasma*-positive children were older (difference 3.5 y, 95%CI 0.54 – 6.4 y) and had fewer viral co-infections (30% compared to 68%,  $p=0.02$ ). The prevalence of *Mycoplasma* infection in children aged > 5 y with any pneumonia was 12.5% (95%CI 4-27%).

**Conclusions.** *M. pneumoniae* infection was not rare in a cohort of children admitted to the PICU with critical respiratory infection. Rapid diagnostic testing and targeted treatment should be considered in an effort to avert morbidity and mortality from respiratory infection.

### What is known about this topic?

*Mycoplasma pneumoniae* is commonly detected in children with non-severe pneumonia.

Guidelines for the management of community-acquired pneumonia in children do not advocate empiric treatment with antibiotics active against *Mycoplasma* nor routine testing for this pathogen.

### What this study adds:

*Mycoplasma pneumoniae* was detected in 12.5% of school-aged children with critically severe community-acquired pneumonia.

Systematic screening of school-aged children with pneumonia in the intensive care unit should be considered.

## BACKGROUND

Community-acquired pneumonia (CAP) is a leading cause of pediatric hospitalization in North America (1). Children with respiratory disease severe enough to warrant admission to a paediatric intensive care unit (PICU) represent a minority of pneumonia-related hospitalizations (2) but infection-related morbidity and mortality is higher in this subgroup (3).

*Streptococcus pneumoniae* has long been considered the most important bacterial pathogen causing severe CAP (4,5). *Mycoplasma pneumoniae*, in contrast, is thought of as a less virulent pathogen, possibly due to how often *M. pneumoniae* infection self-resolves (6). Neither the American, Canadian, nor British guidelines recommend antimicrobials with activity against *M. pneumoniae* as first-line empiric treatment for pediatric CAP (7-9). However, this pathogen is a common cause of CAP, especially in school-aged children; *M. pneumoniae* was the most commonly identified bacterial pathogen in American children hospitalized with CAP, being detected in 8% of the overall cohort and in an astonishing 19% of school-aged children (2). A subsequent analysis of this data demonstrated that the children with *M. pneumoniae* infection could not be distinguished reliably on a clinical basis from those without and that, in contrast to dogma (8,9), single lobar infiltrates and pleural effusions were common on chest radiography (32% and 26% of those infected, respectively) (10). Furthermore, 12% of those with *M. pneumoniae* infection required intensive care (10). Clearly, the epidemiology of this common respiratory pathogen – and its effect on the clinical course and prognosis for children with severe CAP – should be evaluated further. The objective of our study was to describe children

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3 admitted to the PICU of McMaster Children's Hospital (MCH) with respiratory infection and  
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5 explore the epidemiology of *M. pneumoniae* infection in this population.  
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## 10 **METHODS**

### 11 **Design**

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17 A single center, retrospective cohort study. Eligible children were those aged 2 months to 18  
18 years admitted to the MCH PICU from September 2015 to October 2016 with a presumptive  
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20 respiratory infection, as defined by a discharge diagnosis of any lower respiratory tract  
21  
22 infection; we attempted to capture all those with possible infection, to minimize bias. Children  
23  
24 aged less than two months were not included due to the very different epidemiology of  
25  
26 respiratory infection in that age group. Furthermore, all eligible participants must have had a  
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28 nasopharyngeal swab (NPS) taken and a respiratory symptom or sign, including at least one of  
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30 the following: 1) tachypnoea as per age-specific norms (35); 2) cough; 3) increased work of  
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32 breathing on exam, or 4) auscultatory findings such as crackles, wheeze, or rhonchi. The study  
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34 was approved by the Hamilton Integrated Research Ethics Board. Patients or the public were  
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36 not involved in study design. No formal sample size calculation was done.  
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### 47 **Data collection**

48  
49 Information was obtained by retrospective chart review using a standardized data collection  
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51 form. To group study participants by infection syndrome, the diagnoses of the clinical team  
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53 were categorized as follows: viral infection without pneumonia (including bronchiolitis and  
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3 croup), undifferentiated/uncomplicated pneumonia, pneumonia complicated by  
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5 effusion/empyema, asthma, and 'other.' If the clinical team recorded multiple diagnoses from  
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7 the list above, they were classified using the following rules:  
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- 10 1. Participants marked as having both viral infection and pneumonia were classified as  
11 having 'pneumonia' if the chest radiograph was read by the radiologist as consistent  
12 with pneumonia and as 'viral infection' (without pneumonia) if not.  
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- 15 2. Participants marked as having both asthma and pneumonia were classified as having  
16 'pneumonia' if the chest radiograph was read by the radiologist as consistent with  
17 pneumonia and as 'asthma' if not.  
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- 20 3. Participants marked as having both viral infection and asthma were classified as having  
21 'asthma' if they were older than 1 y of age and had a history of atopy; if not, they were  
22 classified as 'viral infection.'  
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### 35 **Laboratory testing**

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37 All children hospitalized with a potentially infectious respiratory illness at MCH have an NPS  
38 performed routinely to identify respiratory viruses. NPSs are assayed using a lab-developed  
39 multiplex respiratory virus panel that detects RSV A/B, human metapneumovirus, influenza  
40 A/B, parainfluenza I-III, adenovirus, and rhinovirus/enterovirus. NPS specimens from eligible  
41 participants were identified and stored. After the surveillance period, NPSs from participants  
42 were batch-tested (ie. test results were not available to treating clinicians) using an HRLMP lab-  
43 developed multiplex PCR assay to detect *M. pneumoniae* and *Chlamydia pneumoniae*.  
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3 Any MP testing ordered prospectively by treating clinicians in the course of routine care was  
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5 not processed using the lab-developed PCR assay but at Public Health Ontario Laboratories  
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7 using a commercial multiplex real-time assay (ProPneumo-1 Assay; Gen-Probe Inc., San Diego,  
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9 CA, USA), which also tests for *Chlamydia pneumoniae*. Samples that tested positive for MP  
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11 underwent further testing at Public Health Ontario laboratories; nested PCR amplification and  
12  
13 DNA sequencing of domain V of the partial 23S rRNA gene were performed to detect mutations  
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15 at nucleotide positions 2063 and 2064, which are associated with macrolide resistance (11,12).  
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23 'Confirmed invasive bacterial infections' were defined as those children with a sterile-site  
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25 culture (eg. blood, pleural fluid) positive for a pathogen (eg. *S. pneumoniae*, *S. pyogenes*, *S.*  
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27 *aureus*). Cultures positive for coagulase-negative staphylococci were categorized as  
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29 contaminants.  
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### 35 **Statistical analysis**

36  
37 Descriptive statistics to describe the baseline characteristics were reported as count (percent)  
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39 for categorical variables, and mean (standard deviation) or median (first quartile-third quartile,  
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41 labeled as interquartile range [IQR]) for continuous variables depending on the distribution.  
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43 Linear regression or ANOVA was used to compare normally-distributed continuous variables  
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45 and Kruskal-Wallis testing was used when the distribution of the variable differed greatly from  
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47 the normal distribution. Chi-square or Fisher exact testing was used to compare categorical  
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49 variables between groups. No imputation of missing data was done.  
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## 55 **RESULTS**

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3 In the study period there were 740 children admitted to the PICU; of these, 227 participants  
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5 (31%) had a diagnosis of acute respiratory illness, an NPS, and at least one respiratory tract  
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7 symptom or sign (Table 1). The median age was 3.1 y (IQR 1.4-6.2 y) and 43% were female. The  
8  
9 majority of participants (79%) had comorbidities, with 58 (26%) having a neurodevelopmental  
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11 problem or difficulty handling secretions, 28 (12%) having a cardiac problem, 89 (39%) having  
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13 atopic disease/asthma, 24 (11%) having another pulmonary issue, 28 (12%) having a genetic  
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15 disorder, and 21 (9%) being ex-premature infants. There were 13 participants (6%) that had a  
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17 tracheostomy, 7 (3%) that were receiving home ventilation, 6 (3%) that were receiving home  
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19 non-invasive ventilation, and 9 (4%) on home oxygen therapy. There were three deaths (1.3%)  
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21 in the cohort and all had comorbidities. Sixteen participants (7%) were not up-to-date with  
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23 DPTaP-Hib or PCV13 vaccine and 26 (11%) had not received the influenza vaccine.  
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32 In the PICU, the majority of participants (n=143, 63%) received high-flow oxygen support, 52  
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34 (29%) received CPAP/BiPAP, 41 (18%) required conventional mechanical ventilation, and 3  
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36 (1.3%) were treated with high-frequency oscillatory ventilation. Viral detections were common,  
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38 with 80 (35%) participants positive for rhinovirus/enterovirus, 38 (17%) positive for RSV, and 24  
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40 (11%) positive for parainfluenza; only 76 (33%) tested negative for respiratory viruses. There  
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42 were 8 participants with confirmed invasive bacterial infections. The median length of stay in  
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44 the PICU was 3 days (IQR 2-5 d) and the medial length of stay in-hospital was 4 days (IQR 3-10  
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3 Of the 227 participants, 51 (22%) were categorized as having had viral infection without  
4 pneumonia, 82 (36%) as uncomplicated pneumonia, 13 (5.8%) as pneumonia complicated by  
5 effusion/empyema, 63 (27%) as an asthma exacerbation, and 18 (7.9%) as 'other.' There was  
6 considerable overlap in the white blood cell (WBC) distributions between categories. C-reactive  
7 protein measurements were clearly different between groups; those with pneumonia (median  
8 45.5 mg/L) had significantly higher median CRP values than those in the viral infection (median  
9 12.6 mg/L) and asthma (median 7.0 mg/L) groups, whereas those with pneumonia complicated  
10 by effusion/empyema (median CRP 222.3 mg/L) had significantly higher CRP values than all  
11 other groups (Table 2). There were clear differences in the proportions of participants in each  
12 group with respect to viral NPS testing; 90% of the viral infection group and 71% of the asthma  
13 group had a respiratory virus detected, while only 60% of the uncomplicated pneumonia group  
14 and 23% of the complicated pneumonia group did ( $p < 0.001$ ). All of the participants in the  
15 uncomplicated and complicated pneumonia groups were treated with antibiotics, compared to  
16 94% of the 'other' group, 73% of the viral-infection group, and 35% of the asthma group  
17 ( $p < 0.0001$ ). The duration of antibacterial treatment was also significantly shorter in the viral  
18 infection and asthma groups than all other groups ( $p < 0.0001$ ), as well as significantly longer in  
19 the complicated pneumonia group than in the uncomplicated pneumonia group ( $p = 0.02$ ).

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47 There were 3 participants who tested positive, of 10 who had specimens tested, for *M.*  
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*pneumoniae* through testing that was ordered prospectively by clinicians in the course of  
routine care (one sputum, one NPS, and one bronchoalveolar lavage [BAL]). There were an  
additional 7 participants that were found to have an NPS positive for *M. pneumoniae* via

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3 retrospective study testing. The overall prevalence of *M. pneumoniae*-associated respiratory  
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5 illness in the study cohort was therefore 10/227 (4.4%, 95%CI 2.1-8.0%). *Mycoplasma*-positive  
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7 participants were significantly older than *Mycoplasma*-negative children (difference 3.5 y, 95%  
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9 CI 0.54-6.4 y,  $p=0.02$ )(Table 3). The overall prevalence of *Mycoplasma* infection in participants  
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11 aged > 5 years with any type of pneumonia was 12.5% (4 of 34 in the uncomplicated  
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13 pneumonia group and 1 of 6 in the complicated pneumonia group, 95% CI 4-27%). In this older  
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15 subset, there were zero *Mycoplasma*-positive participants in the viral infection or asthma  
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17 groups.  
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25 None of the *Mycoplasma*-positive group had invasive bacterial infections. Three (30%) of the  
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27 *Mycoplasma*-positive group had a respiratory viral pathogen detected as compared to 148  
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29 (68%) of the *Mycoplasma*-negative group ( $p=0.02$ ). Antimicrobials were prescribed for  
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31 significantly longer from the time of admission in the *Mycoplasma*-positives (median 11 days,  
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33 IQR 7-17 d) as compared to the *Mycoplasma*-negatives (median 5 d, IQR 0-8 d,  $p=0.02$ ); this  
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35 difference remained significant when the analysis was restricted to only those participants with  
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37 uncomplicated pneumonia (median 12 d as compared to median 7 d,  $p=0.004$ ).  
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45 Of the 10 *Mycoplasma* isolates, 5 were macrolide-sensitive and 1 harboured the G2063  
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47 mutation in the 23S rRNA gene (overall prevalence 17%, 95%CI 0.4-64%); 3 isolates were low-  
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49 level positives, and so could not be sequenced. One isolate was not retained. Only half of the  
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51 participants with *Mycoplasma* infection were prescribed macrolide or fluoroquinolone  
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53 antibacterials.  
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No study participants had *Chlamydia pneumoniae* detected in their NPS.

## DISCUSSION

In this retrospective single-centre study, we found that 4% of all children with acute respiratory illness admitted to the PICU, the majority of whom had comorbidities, had *M. pneumoniae* detected in respiratory specimens. More importantly, 12.5% (95%CI 4-27%) of children diagnosed with pneumonia who were at least 5 years of age were positive for *M. pneumoniae*. Children that were *Mycoplasma*-positive were older, had fewer respiratory virus co-infections, were more often treated with antibacterials before admission, and received a longer course of antibacterials in-hospital than *Mycoplasma*-negative children. Half of the *Mycoplasma*-positive children did not receive antibacterials active against *Mycoplasma*. One of the six *Mycoplasma* isolates that could be sequenced harboured a macrolide resistance gene.

The fact that *Mycoplasma* was commonly detected in critically ill children would argue that routine surveillance for this pathogen should be considered, as others have suggested (13). Our results are consistent with the findings of the EPIC study, which also demonstrated that *M. pneumoniae* is found commonly in school-aged children with CAP (2), including children admitted to the intensive care unit (10). A recent retrospective cohort study of all children admitted to two PICUs in Australia over a 6-year period revealed 30 cases identified by testing done as part of routine clinical care among 3005 “nonelective infection-related admissions”, for a prevalence of ~1% (14). Those authors stated “*M. pneumoniae* infections in critically ill

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3 children are uncommon” and noted that outcomes were comparable to those children without  
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5 *Mycoplasma* detected. However, there is considerable variability in what constitutes an  
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8 “infection-related admission” (14); furthermore, given the range of presenting symptoms/signs  
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10 associated with this pathogen (10,15,16), one questions whether these clinicians would have  
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12 been able to reliably identify which children merited testing, and so the true prevalence of  
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14 *Mycoplasma* infection in this cohort could be much higher. The incidence of *M. pneumoniae*  
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16 infection does vary widely by location and season (10,17) and so we cannot exclude the  
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18 possibility that the prevalence observed in our study was higher than in years before or after.  
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25 An older iteration of the Canadian Paediatric Society guidelines for the management of CAP  
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27 (circa 2011) recommended routine use of azithromycin for all children with ‘severe’ pneumonia  
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29 because of the possibility of ‘atypical infection’, though diagnostic testing to identify atypical  
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31 pathogens was not suggested or even mentioned (18). At that time, we thought that this  
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33 practice would not represent appropriate antimicrobial stewardship, given that the majority of  
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35 severe pediatric CAP is likely to be caused by *S. pneumoniae*. The CPS guidelines were later  
36  
37 revised in 2015 and no longer recommend routine treatment with macrolides (8). They state  
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39 that atypical pneumonia should be suspected in children with ‘subacute, nonsevere  
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41 pneumonia, presenting with features such as prominent cough, minimal leukocytosis, and a  
42  
43 nonlobar infiltrate’ and that azithromycin is recommended ‘for suspected or proven  
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45 *Mycoplasma* or *Chlamydia pneumoniae*’ (8). Unfortunately, it has been repeatedly  
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47 demonstrated that these symptoms and signs cannot reliably identify atypical pneumonia  
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49 (10,15,16); it seems likely that many clinicians may not consider the possibility that *M.*  
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3 *pneumoniae* may play a significant role in the pathogenesis of critically ill children with  
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5 respiratory compromise. Based on our data, we would suggest that clinicians be aware that a  
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7 reasonable proportion of school-aged children with CAP admitted to the PICU may have an  
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9 active *M. pneumoniae* infection and recommend empiric treatment with anti-*Mycoplasma*  
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11 agents (eg. macrolides, doxycycline, fluoroquinolones) until diagnostic (molecular) testing  
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13 results are available.  
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20 One obvious issue is that we cannot be certain of the therapeutic benefit of antibacterials (such  
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22 as macrolides or doxycycline) for pediatric CAP presumed to be caused at least in part by *M.*  
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24 *pneumoniae*. (We suspect that almost all clinicians would treat suspected or presumed  
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26 *Legionella* CAP with antibacterials, but this pathogen is rare in pediatrics (19).) Furthermore,  
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28 the detection of *Mycoplasma* in the respiratory tract does not prove causation, as coinfections  
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30 have been shown to be common (10) and some investigators have documented high rates of  
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32 PCR-positivity in control persons (20) (although others have not (10,21)). We would agree with  
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34 other authors who have suggested that specific anti-*Mycoplasma* treatment might yield  
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36 significant benefit, especially for those with severe disease, and have called for the execution of  
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38 a randomized treatment trial (10,13). However, until results of a definitive treatment trial are  
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40 available, we feel that the potential benefit of treating critically ill children with *Mycoplasma*  
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42 detected in respiratory symptoms outweighs the potential antimicrobial stewardship harms of  
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44 this strategy.  
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3 In conclusion, we found that *Mycoplasma pneumoniae* was detected in 12.5% of children aged  
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5 5 years and older admitted with CAP to the PICU of a children's hospital over a 13-month  
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7 period. Consideration should be given to empiric anti-*Mycoplasma* antimicrobial therapy  
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9 pending the result of rapid molecular diagnostic testing in this subset of critically ill children.  
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#### 15 Contributorship Statement

16  
17 HA designed the study, wrote the protocol, did the chart reviews, wrote the abstract, and  
18  
19 revised the manuscript critically. JMP conceived the study question, provided input on study  
20  
21 design, performed statistical analyses, and wrote the manuscript. KL and MS provided input on  
22  
23 microbiologic methods, revised the protocol, did testing to identify *M. pneumoniae*, and revised  
24  
25 the manuscript critically. AE and JBG provided input on microbiologic methods, did testing to  
26  
27 identify resistance genes, and revised the manuscript critically.  
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Table 1. Whole-cohort characteristics.

Median age (IQR)	3.14 y (1.39 – 6.15 y)
# Female (%)	98 (43%)
Fever recorded (%)	124 (56%)
Median duration of fever (IQR)	3 d (2 – 6.5 d)
Symptoms	
Cough	195 (30%)
Increased work of breathing	206 (91%)
Stridor	13 (5.8%)
Wheeze	112 (50%)
Chest pain	4 (1.8%)
Antibiotics given before presentation?	
Yes	45 (20%)
Amoxicillin	18
Amoxicillin/clavulanate	2
Cephalosporins	11
Macrolides	10
Other	11
Comorbid medical conditions	179 (79%)
neurologic/neurodevelopmental	58
tracheostomy	13
prematurity	44
chronic lung disease/bronchopulmonary dysplasia	20
asthma	89
cystic fibrosis	1
other pulmonary disease	24
genetic disease	28
cardiac disease	28
chronic liver disease	1
chronic kidney disease	7
endocrine disorders	14
malignancy	4
immunodeficiency	3
haemoglobinopathies	5
other	26
Home ventilation/oxygenation	16 (7%)
Mechanical ventilation	7
Noninvasive ventilation	6
Oxygen therapy without ventilation	3
Highest level of respiratory support given in PICU	
High frequency oscillatory ventilation	3 (1.3%)
Conventional mechanical ventilation	38 (17%)
BiPAP/CPAP	34 (15%)

High flow oxygen by nasal cannula	98 (43%)
Low flow oxygen (FiO <sub>2</sub> > 0.4)	10 (4.4%)
Antibiotics given in PICU	171 (75%)
ampicillin	14
ceftriaxone	154
vancomycin	33
clarithromycin	3
azithromycin	37
ciprofloxacin	1
levofloxacin	11
tetracyclines	0

Table 2. Differences between diagnostic categories.

	Viral infection	Asthma	Pneumonia (uncomplicated/undifferentiated)	Pneumonia (complicated by effusion)	Other
Count	51 (22%)	63 (27%)	82 (36%)	13 (5.8%)	18 (7.9%)
mean WBC (SD)	12.2 (4.3)	13.6 (5.0)	12.9 (8.1)	17.5 (11.8)	11.8 (7.3)
median CRP, mg/L (IQR)	12.6 (3.5-28.6)	7.0 (3.6-16.4)	45.5 <sup>1</sup> (15.2-103)	222.3 <sup>2</sup> (177.6-259.1)	25.7 (15.0-82.6)
No respiratory virus detected	5 (9.8%)	18 (29%)	33 (40%)	10 (77%)	10 (56%)
median duration of antibiotics, days (IQR)	2 <sup>3</sup> (0-4)	0 <sup>3</sup> (0-1)	7 (7-10)	23 <sup>4</sup> (14-27)	10 (7-14)

<sup>1</sup>median of pneumonia group significantly greater than that of viral infection group (p=0.007) and asthma group (p=0.0009) but significantly lower than that of complicated pneumonia group (p=0.009)

<sup>2</sup>median of complicated pneumonia group significantly greater than viral infection and asthma groups (p<0.0001), other group (p=0.01), and pneumonia group (p=0.009)

<sup>3</sup>median of viral infection and asthma groups significantly smaller than all other groups (p<0.0001)

<sup>4</sup>median of complicated pneumonia group also significantly higher than pneumonia group (p=0.02)

Table 3. Comparison of *Mycoplasma*-positive and *Mycoplasma*-negative participants.

	<i>Mycoplasma</i> -positive	<i>Mycoplasma</i> -negative	p
Count	10	217	n/a
mean age, y(SD)	8.1 (6.1)	4.7 (4.5)	0.02
# with viral infection or asthma diagnosis (%)	3 (30%)	111 (51%)	0.2

(restricted to participants > 5 y)	0	30 (41%)	0.08
# with no detectable respiratory virus in NPS	7 (70%)	69 (32%)	0.02
(restricted to participants > 5 y)	5 (83%)	36 (49%)	0.2
median duration of antibiotic treatment, d (IQR)	11 (7-17)	5 (0-8)	0.02
(restricted to participants with uncomplicated pneumonia)	12 (10-13)	7 (7-10)	0.004
Median length of stay in PICU, d (IQR)	4.5 (2-8)	3 (2-5)	0.1
(restricted to participants with uncomplicated pneumonia)	7 (2-8)	4 (2-7)	0.7
Median length of stay in hospital, d (IQR)	10 (5-13)	4 (3-9)	0.04
(restricted to participants with uncomplicated pneumonia)	13 (7-14)	7 (3-14)	0.3

# BMJ Paediatrics Open

## Pediatric critical respiratory illness: a single-centre, retrospective, cohort study

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2020-000640.R1
Article Type:	Original research
Date Submitted by the Author:	06-Mar-2020
Complete List of Authors:	Alfaraidi, Haifa; McMaster University, Department of Pediatrics Luinstra, Kathy; Saint Joseph's Healthcare Hamilton Charlton Campus, Laboratory Medicine Eshaghi, Alireza; Public Health Ontario Laboratory Services Smieja, Marek; McMaster University, Department of Pathology and Molecular Medicine Gubbay, Jonathan; Public Health Ontario Laboratory Services Pernica, Jeffrey; McMaster University, Department of Pediatrics - RINGGOLD INSTITUTION 3710
Keywords:	Infectious Diseases, Epidemiology

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## **Pediatric critical respiratory illness: a single-centre, retrospective, cohort study**

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Word count : 2777

Keywords: pneumonia, intensive care, respiratory tract infection, epidemiology, atypical

Short title: Pediatric critical respiratory illness: a retrospective study

Funding: This project was supported by a McMaster University Department of Pediatrics Resident Research Grant. JMP was supported by a Hamilton Health Sciences Early Career Award. There are no conflicts of interest.

Presentation: Poster presentation, Association of Medical Microbiology and Infectious Disease Canada annual conference, 2018.

Acknowledgements: The authors would like to acknowledge the assistance of Samir Patel who oversaw the Mycoplasma resistance testing.



## Abstract

**Objectives.** To describe children admitted with respiratory infections to a paediatric intensive care unit (PICU), classify them by infection syndrome type, and determine the prevalence of *Mycoplasma pneumoniae* infection.

**Study design.** A retrospective, single-centre, cohort study. All children aged 2 months – 18 years with presumed respiratory infection who were admitted to the McMaster Children's Hospital PICU between September 2015–October 2016 were eligible. Subjects were grouped by clinical syndrome (viral respiratory infection, asthma exacerbation, undifferentiated/uncomplicated pneumonia, pneumonia complicated by effusion/empyema, and 'other'). Testing for *M. pneumoniae* from nasopharyngeal specimens was done using a lab-developed PCR assay.

**Results.** There were 221 subjects; the median age was 3.1 y, 44% were female, and 78% had medical comorbidities. Those with any pneumonia were significantly less likely to have a respiratory virus identified in their nasopharynxes and had significantly higher C-reactive protein (CRP) values than those in the viral infection and asthma groups. There were 10 subjects in whom *M. pneumoniae* was detected (4.5%, 95%CI 2.2–8.2%). *Mycoplasma*-positive children were older (difference 3.5 y, 95%CI 0.66 – 6.4 y) and had fewer viral co-infections (30% compared to 69%,  $p=0.02$ ). The prevalence of *Mycoplasma* infection in children aged > 5 y with any pneumonia was 13.2% (95%CI 4.4–28%).

**Conclusions.** There were differences in CRP and viral prevalence observed between children with different infection syndrome types. *M. pneumoniae* infection was not rare in school-aged children with pneumonia admitted to the PICU. Rapid diagnostic testing for *Mycoplasma* and targeted treatment in older, critically ill children should be considered in an effort to avert morbidity and mortality from respiratory infection.

## What is known about this topic?

*Mycoplasma pneumoniae* is commonly detected in children with non-severe pneumonia.

Guidelines for the management of community-acquired pneumonia in children do not advocate first-line empiric treatment with antibiotics active against *Mycoplasma* nor routine testing for this pathogen.

## What this study adds:

There are clear biochemical (eg. CRP) and microbiologic (eg. respiratory virus prevalence) differences between critically ill children with different respiratory infection syndromes.

*Mycoplasma pneumoniae* was detected in 13.2% of school-aged critically ill children with severe community-acquired pneumonia.

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## BACKGROUND

Community-acquired pneumonia (CAP) is a leading cause of pediatric hospitalization in North America (1). Children with respiratory disease severe enough to warrant admission to a paediatric intensive care unit (PICU) represent a minority (~20%) of pneumonia-related hospitalizations (2) but infection-related morbidity and mortality is higher in this subgroup (3).

*Streptococcus pneumoniae* has long been considered the most important bacterial pathogen causing severe CAP (4,5). *Mycoplasma pneumoniae*, in contrast, is thought of as a less virulent pathogen, possibly due to the fact that *M. pneumoniae* infection often self-resolves (6). Neither the American, Canadian, nor British guidelines recommend antimicrobials with activity against *M. pneumoniae* as first-line empiric treatment for pediatric CAP (7-9). However, this pathogen is a common cause of CAP, especially in school-aged children; *M. pneumoniae* was the most commonly identified bacterial pathogen in American children hospitalized with CAP, being detected in 8% of the overall cohort and in 19% of school-aged children (2). A subsequent analysis of this data demonstrated that the children with *M. pneumoniae* infection could not be distinguished reliably on a clinical basis from those without and that, in contrast to dogma (8,9), single lobar infiltrates and pleural effusions were common on chest radiography (32% and 26% of those infected, respectively) (10). Furthermore, 12% of those with *M. pneumoniae* infection required intensive care (10). Clearly, the epidemiology of this common respiratory pathogen – and its effect on the clinical course and prognosis for children with severe CAP – should be evaluated further. The objective of our study was to describe children admitted to the PICU of

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3 McMaster Children's Hospital (MCH) with respiratory infection and determine the prevalence  
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5 of *M. pneumoniae* infection in this population.  
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## 10 **METHODS**

### 11 **Setting**

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18 MCH is a tertiary care centre serving a population of approximately 2.3 million residents. At the  
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20 time of the study, the centre had 159 beds (12 PICU beds) and, on a yearly basis, admitted  
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22 approximately 6500 children, with over 40 000 emergency department visits.  
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### 27 **Design**

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30 A single center, retrospective cohort study. Eligible children were those aged 2 months to 18  
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32 years admitted to the MCH PICU from September 2015 to October 2016 with a presumptive  
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34 respiratory infection, as defined by a discharge diagnosis of any lower respiratory tract  
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36 infection. Discharge diagnoses for all patients leaving the PICU were reviewed on a biweekly  
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38 basis by the principal investigator (HA); we attempted to capture all those with possible  
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40 respiratory infection, to minimize bias. Children aged less than two months were not included  
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42 due to the very different epidemiology of respiratory infection in that age group. Furthermore,  
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44 all eligible subjects must have had a nasopharyngeal swab (NPS) taken less than a week after  
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46 admission to hospital and a respiratory symptom or sign, including at least one of the following:  
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52 1) tachypnoea as per age-specific norms (35); 2) cough; 3) increased work of breathing on  
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54 exam, or 4) auscultatory findings such as crackles, wheeze, or rhonchi. The study was approved  
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3 by the Hamilton Integrated Research Ethics Board, who waived the requirement for consent in  
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5 this retrospective study. Patients or the public were not involved in study design. No formal  
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7 sample size calculation was done.  
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### 10 11 12 13 **Data collection**

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15 Information was obtained by retrospective chart review using a standardized data collection  
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17 form. To group study subjects by infection syndrome, the discharge diagnoses of the clinical  
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19 team were categorized as follows: viral infection without pneumonia (including bronchiolitis  
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21 and croup), undifferentiated/uncomplicated pneumonia, pneumonia complicated by  
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23 effusion/empyema, asthma, and 'other.' If the clinical team recorded multiple diagnoses from  
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25 the list above, they were classified using the following rules:  
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30 1. Subjects marked as having both viral infection and pneumonia were classified as having  
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32 'pneumonia' if the chest radiograph was read by the radiologist as consistent with  
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34 pneumonia and as 'viral infection' (without pneumonia) if not.  
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38 2. Subjects marked as having both asthma and pneumonia were classified as having  
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40 'pneumonia' if the chest radiograph was read by the radiologist as consistent with  
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42 pneumonia and as 'asthma' if not.  
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- 45  
46 3. Subjects marked as having both viral infection and asthma were classified as having  
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48 'asthma' if they were older than 1 y of age and had a history of atopy; if not, they were  
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50 classified as 'viral infection.'  
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### 54 55 **Laboratory testing**

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3 All children hospitalized with a potentially infectious respiratory illness at MCH have an NPS  
4 performed routinely to identify respiratory viruses, as per the institutional Acute Respiratory  
5 Infection Surveillance Protocol. NPSs are assayed using a lab-developed multiplex respiratory  
6 virus panel (11) that detects RSV A/B, human metapneumovirus, influenza A/B, parainfluenza I-  
7 III, adenovirus, and rhinovirus/enterovirus. NPS specimens from eligible subjects were  
8 identified and stored. After the surveillance period, NPSs from subjects were batch-tested (ie.  
9 test results were not available to treating clinicians) using an Hamilton Regional Laboratory  
10 Medicine Program lab-developed multiplex PCR assay to detect *M. pneumoniae* and *Chlamydia*  
11 *pneumoniae* that was validated against sequencing and external quality control materials.  
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28 Any MP testing ordered prospectively by treating clinicians in the course of routine care was  
29 not processed using the lab-developed PCR assay but at Public Health Ontario Laboratories  
30 using a commercial multiplex real-time assay (ProPneumo-1 Assay; Gen-Probe Inc., San Diego,  
31 CA, USA), which also tests for *Chlamydia pneumoniae*. Samples that tested positive for MP  
32 underwent further testing at Public Health Ontario laboratories; nested PCR amplification and  
33 DNA sequencing of domain V of the partial 23S rRNA gene were performed to detect mutations  
34 at nucleotide positions 2063 and 2064, which are associated with macrolide resistance (12,13).  
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47 'Confirmed invasive bacterial infections' were defined as those children with a sterile-site  
48 culture (ie. blood, pleural fluid) positive for a recognized pathogen. Cultures positive for  
49 coagulase-negative staphylococci were categorized as contaminants.  
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## Statistical analysis

Descriptive statistics to describe the baseline characteristics were reported as count (percent) for categorical variables, and mean (standard deviation) or median (first quartile-third quartile, labeled as interquartile range [IQR]) for continuous variables depending on the distribution. Normality was assessed visually. T-tests or linear regression were used to compare normally-distributed continuous variables. Kruskal-Wallis testing was used when the distribution of the variable differed greatly from the normal distribution. If Kruskal-Wallis testing identified significant differences, nonparametric pairwise multiple comparisons of the groups using Dunn's test with Bonferroni adjustment were done. Chi-square or Fisher exact testing was used to compare categorical variables between groups. Alpha was set at 0.05, with no adjustments for multiple comparisons in this exploratory study. No imputation of missing data was done. Analyses were conducted using Stata v11.2 (College Station, TX).

## RESULTS

In the study period there were 740 children admitted to the PICU; of these, 221 subjects (31%) had a diagnosis of acute respiratory illness, an NPS taken less than a week after admission, and at least one respiratory tract symptom or sign (Table 1). The median age was 3.1 y (IQR 1.4-6.0 y) and 44% were female. The majority of subjects (78%) had comorbidities (see Table 1). There were 13 subjects (6%) that had a tracheostomy, 7 (3%) that were receiving home ventilation, 6 (3%) that were receiving home non-invasive ventilation, and 9 (4%) on home oxygen therapy. There were three deaths (1.3%) in the cohort and all had comorbidities. Fourteen subjects (6%) were not up-to-date with DPTaP-Hib or PCV13 vaccine.

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3 In the PICU, the majority of subjects (n=139, 63%) received high-flow oxygen support, 49 (22%)  
4 received CPAP/BiPAP, 38 (17%) required conventional mechanical ventilation, and 1 (0.45%)  
5 were treated with high-frequency oscillatory ventilation (see Table 2). Viral detections were  
6 common, with 79 (36%) subjects positive for rhinovirus/enterovirus, 37 (17%) positive for RSV,  
7 and 24 (11%) positive for parainfluenza; only 72 (33%) tested negative for respiratory viruses  
8 (see Table 3). There were 7 subjects with confirmed invasive bacterial infections. The median  
9 length of stay in the PICU was 3 days (IQR 2-5 d) and the medial length of stay in-hospital was 4  
10 days (IQR 3-8 d).  
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25 Of the 221 subjects, 50 (23%) were categorized as having had viral infection without  
26 pneumonia, 81 (37%) as uncomplicated pneumonia, 12 (5.4%) as pneumonia complicated by  
27 effusion/empyema, 63 (29%) as an asthma exacerbation, and 15 (6.8%) as 'other.' There was  
28 considerable overlap in the white blood cell (WBC) distributions between categories (see Table;  
29 4). C-reactive protein measurements were clearly different between groups; those with  
30 pneumonia (median 45.5 mg/L) had significantly higher median CRP values than those in the  
31 viral infection (median 12.6 mg/L) and asthma (median 7.0 mg/L) groups, whereas those with  
32 pneumonia complicated by effusion/empyema (median CRP 203.8 mg/L) had significantly  
33 higher CRP values than all other groups. There were clear differences in the proportions of  
34 subjects in each group with respect to viral NPS testing; 90% of the viral infection group and  
35 72% of the asthma group had a respiratory virus detected, while only 60% of the uncomplicated  
36 pneumonia group and 25% of the complicated pneumonia group did ( $p < 0.0001$ ). All of the  
37 subjects in the uncomplicated and complicated pneumonia groups were treated with  
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3 antibiotics, compared to 93% of the 'other' group, 74% of the viral-infection group, and 35% of  
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5 the asthma group ( $p<0.0001$ ). The duration of antibacterial treatment was also significantly  
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7 shorter in the viral infection and asthma groups than all other groups ( $p<0.0001$ ), as well as  
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9 significantly longer in the complicated pneumonia group than in the uncomplicated pneumonia  
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11 group ( $p=0.02$ ).  
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18 There were 3 subjects who tested positive, of 10 who had specimens tested, for *M.*  
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20 *pneumoniae* through testing that was ordered prospectively by clinicians in the course of  
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22 routine care (one sputum, one NPS, and one bronchoalveolar lavage [BAL]). There were an  
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24 additional 7 subjects that were found to have an NPS positive for *M. pneumoniae* via  
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26 retrospective study testing. The overall prevalence of *M. pneumoniae*-associated respiratory  
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28 illness in the study cohort was therefore 10/221 (4.5%, 95%CI 2.2-8.2%). *Mycoplasma*-positive  
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30 subjects were significantly older than *Mycoplasma*-negative children (difference 3.5 y, 95% CI  
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32 0.66-6.4 y,  $p=0.02$ )(Table 4). The overall prevalence of *Mycoplasma* infection in subjects aged >  
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34 5 years with any type of pneumonia was 13.2% (4 of 33 in the uncomplicated pneumonia group  
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36 and 1 of 5 in the complicated pneumonia group, 95% CI 4.4-28%). In this older subset, there  
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38 were zero *Mycoplasma*-positive subjects in the viral infection or asthma groups.  
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47 None of the *Mycoplasma*-positive group had invasive bacterial infections. Three (30%) of the  
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49 *Mycoplasma*-positive group had a respiratory viral pathogen detected as compared to 146  
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51 (69%) of the *Mycoplasma*-negative group ( $p=0.02$ , see Table 5). Antimicrobials were prescribed  
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53 for significantly longer from the time of admission in the *Mycoplasma*-positives (median 11  
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3 days, IQR 7-17 d) as compared to the *Mycoplasma*- negatives (median 5 d, IQR 0-8 d,  $p=0.02$ );  
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5 this difference remained significant when the analysis was restricted to only those subjects with  
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7 uncomplicated pneumonia (median 12 d as compared to median 7 d,  $p=0.004$ ).  
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11  
12 Of the 10 *Mycoplasma* isolates, 5 were macrolide-sensitive and 1 harboured the G2063  
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14 mutation in the 23S rRNA gene (overall prevalence 17%, 95%CI 0.4-64%); 3 isolates were low-  
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16 level positives, and so could not be sequenced. One isolate was not retained. Only half of the  
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18 subjects with *Mycoplasma* infection were prescribed macrolide or fluoroquinolone  
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23 antibacterials.  
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28 No study subjects had *Chlamydia pneumoniae* detected in their NPS.  
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## 32 **DISCUSSION**

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35 In this retrospective single-centre study, we found that 4.5% of all children with acute  
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37 respiratory illness admitted to the PICU, the majority of whom had comorbidities, had *M.*  
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39 *pneumoniae* detected in respiratory specimens. More importantly, 13.2% (95%CI 4.4-28%) of  
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41 children diagnosed with pneumonia who were at least 5 years of age were positive for *M.*  
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43 *pneumoniae*. Children that were *Mycoplasma*-positive were older, had fewer respiratory virus  
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45 co-infections, were more often treated with antibacterials before admission, and received a  
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47 longer course of antibacterials in-hospital than *Mycoplasma*-negative children. Half of the  
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52 *Mycoplasma*-positive children did not receive antibacterials active against *Mycoplasma*. One of  
53  
54 the six *Mycoplasma* isolates that could be sequenced harboured a macrolide resistance gene.  
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6 Our results would argue that routine surveillance for this pathogen should be considered, as  
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8 others have suggested (14), although infection was more rare in infants or preschool-aged  
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10 children. Our results are consistent with the findings of the EPIC study, which also  
11  
12 demonstrated that *M. pneumoniae* is found commonly in school-aged children with CAP (2),  
13  
14 including children admitted to the intensive care unit (10). A recent retrospective cohort study  
15  
16 of all children admitted to two PICUs in Australia over a 6-year period revealed 30 cases  
17  
18 identified by testing done as part of routine clinical care among 3005 “nonelective infection-  
19  
20 related admissions”, for a prevalence of ~1% (15). Those authors stated “*M. pneumoniae*  
21  
22 infections in critically ill children are uncommon” and noted that outcomes were comparable to  
23  
24 those children without *Mycoplasma* detected. However, there is considerable variability in  
25  
26 what constitutes an “infection-related admission” (15); furthermore, given the range of  
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28 presenting symptoms/signs associated with this pathogen (10,16,17), one questions whether  
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30 these clinicians would have been able to reliably identify which children merited testing, and so  
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32 the true prevalence of *Mycoplasma* infection in this cohort could be much higher. The  
33  
34 incidence of *M. pneumoniae* infection does vary widely by location and season (10,18) and so  
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36 we cannot exclude the possibility that the prevalence observed in our study was higher than in  
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38 years before or after.  
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50 An older iteration of the Canadian Paediatric Society guidelines for the management of CAP  
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52 (circa 2011) recommended routine use of azithromycin for all children with ‘severe’ pneumonia  
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54 because of the possibility of ‘atypical infection’, though diagnostic testing to identify atypical  
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3 pathogens was not suggested or even mentioned (19). One might question whether this  
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5 practice would represent appropriate antimicrobial stewardship, given that the majority of  
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7 severe pediatric CAP is likely to be caused by *S. pneumoniae*. The CPS guidelines were later  
8  
9 revised in 2015 and no longer recommend routine treatment with macrolides (8). They state  
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11 that atypical pneumonia should be suspected in children with 'subacute, nonsevere  
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13 pneumonia, presenting with features such as prominent cough, minimal leukocytosis, and a  
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15 nonlobar infiltrate' and that azithromycin is recommended 'for suspected or proven  
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17 *Mycoplasma* or *Chlamydia pneumoniae*' (8). Unfortunately, it has been repeatedly  
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19 demonstrated that these symptoms and signs cannot reliably identify atypical pneumonia  
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21 (10,16,17); it seems likely that many clinicians may not consider the possibility that *M.*  
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23 *pneumoniae* may play a significant role in the pathogenesis of critically ill children with  
24  
25 respiratory compromise. Based on our data, we would suggest that clinicians be aware that a  
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27 reasonable proportion of school-aged children with CAP admitted to the PICU may have an  
28  
29 active *M. pneumoniae* infection and recommend empiric treatment with anti-*Mycoplasma*  
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31 agents (eg. macrolides, doxycycline, fluoroquinolones) until diagnostic (molecular) testing  
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33 results are available.  
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45 There were obvious limitations to our study. As noted previously, this was a retrospective  
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47 design and included only a single centre over a 13-month period; as outbreaks with this  
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49 pathogen have been frequently described (20), we cannot be certain that the prevalence of  
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51 infection documented in this study is an accurate estimate of children hospitalized with critical  
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53 respiratory illness in our region of Canada. It is also quite possible that hospital clinicians may  
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3 not have strictly followed hospital infection control policy and failed to sample the  
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5 nasopharynges of some patients who otherwise would have been eligible. The study cohort  
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7 only comprised 221 children and there were only 10 found to be positive for *M. pneumoniae*;  
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9 consequently, 95% confidence intervals around our point estimates are wide. Having said that,  
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11 the prevalence of *Mycoplasma* infection found in this small study was similar to that found in a  
12  
13 much larger study conducted recently in the United States (2).  
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20 One obvious issue is that we cannot be certain of the therapeutic benefit of antibacterials (such  
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22 as macrolides or doxycycline) for pediatric CAP presumed to be caused at least in part by *M.*  
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24 *pneumoniae*; one systematic review found no clear difference in outcomes between children  
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26 treated with *Mycoplasma*-active agents and those without (21). Furthermore, the detection of  
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28 *Mycoplasma* in the respiratory tract does not prove causation, as coinfections have been shown  
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30 to be common (10) and some investigators have documented high rates of PCR-positivity in  
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32 control persons (22) (although others have not (10,23)); some investigators have identified  
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34 novel serologic tests that can confirm active infection (24). We would agree with other authors  
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36 who have suggested that specific anti-*Mycoplasma* treatment might yield significant benefit,  
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38 especially for those with severe disease, and have called for the execution of a randomized  
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40 treatment trial (10,14). However, until results of a definitive treatment trial are available, we  
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42 feel that the potential benefit of treating critically ill children with *Mycoplasma* detected in  
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44 respiratory symptoms outweighs the potential antimicrobial stewardship harms of this strategy.  
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3 In conclusion, we found that *Mycoplasma pneumoniae* was detected in 12.5% of children aged  
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5 5 years and older admitted with CAP to the PICU of a children's hospital over a 13-month  
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7 period. Consideration should be given to empiric anti-*Mycoplasma* antimicrobial therapy  
8  
9 pending the result of rapid molecular diagnostic testing in this subset of critically ill children.  
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#### 15 Contributorship Statement

16  
17 HA designed the study, wrote the protocol, did the chart reviews, wrote the abstract, and  
18  
19 revised the manuscript critically. JMP conceived the study question, provided input on study  
20  
21 design, performed statistical analyses, and wrote the manuscript. KL and MS provided input on  
22  
23 microbiologic methods, revised the protocol, did testing to identify *M. pneumoniae*, and revised  
24  
25 the manuscript critically. AE and JBG provided input on microbiologic methods, did testing to  
26  
27 identify resistance genes, and revised the manuscript critically.  
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Table 1. Whole-cohort baseline characteristics.

Median age (IQR)	3.11 y (1.39 – 6.02 y)
Age	
< 1 y	36 (16%)
1-2 y	45 (20%)
2-5 y	63 (29%)
5-10 y	45 (20%)
10-15 y	32 (14%)
# Female (%)	96 (44%)
Fever recorded (%)	120 (55%)
Median duration of fever (IQR)	3 d (2 – 6 d)
Symptoms	
Cough	191 (87%)
Increased work of breathing	202 (91%)
Stridor	13 (5.9%)
Wheeze	112 (51%)
Chest pain	4 (1.8%)
Antibiotics given before presentation?	
Yes	44 (20%)
Amoxicillin	18
Amoxicillin/clavulanate	2
Cephalosporins	10
Macrolides	10
Other	11
Comorbid medical conditions	174 (78%)
neurologic/neurodevelopmental	52
tracheostomy	13
other lung disease (including bronchopulmonary dysplasia)	36
asthma	89
cystic fibrosis	1
genetic disease	26
cardiac disease	26
chronic liver disease	1
chronic kidney disease	7
endocrine disorders	13
malignancy	3
immunodeficiency/immunosuppressant drugs	5
haemoglobinopathies	5
other	27
Home ventilation/oxygenation	16 (7%)
Mechanical ventilation	7
Noninvasive ventilation	6
Oxygen therapy without ventilation	3

Highest level of respiratory support given in PICU	
High frequency oscillatory ventilation	1 (0.45%)
Conventional mechanical ventilation	37 (17%)
BiPAP/CPAP	34 (15%)
High flow oxygen by nasal cannula	96 (43%)
Low flow oxygen (FiO <sub>2</sub> > 0.4)	10 (4.4%)
Antibiotics given in PICU	
ampicillin	14
ceftriaxone	149
piperacillin-tazobactam	12
carbapenems	3
vancomycin	29
clindamycin	25
clarithromycin	3
azithromycin	35
levofloxacin	11
tetracyclines	0

Table 2. Whole-cohort clinical course in the PICU

Median length of stay in PICU (IQR)	3 d (2-5 d)
Highest level of respiratory support given in PICU	
High frequency oscillatory ventilation	1 (0.45%)
Conventional mechanical ventilation	37 (17%)
BiPAP/CPAP	34 (15%)
High flow oxygen by nasal cannula	96 (43%)
Low flow oxygen (FiO <sub>2</sub> > 0.4)	10 (4.4%)
Antibiotics given in PICU	
ampicillin	14
ceftriaxone	149
piperacillin-tazobactam	12
carbapenems	3
vancomycin	29
clindamycin	25
clarithromycin	3
azithromycin	35
levofloxacin	11
tetracyclines	0

Table 3. Whole-cohort microbiology

Mucosal testing	
RSV	37 (17%)
Influenza	6 (3%)
Metapneumovirus	7 (3%)

Adenovirus	5 (2%)
Parainfluenza	24 (11%)
Rhino/enterovirus	79 (36%)
<i>Mycoplasma</i>	10 (5%)
Pleural fluid testing	
group A Streptococcus	2
<i>Streptococcus anginosus</i>	1
Blood culture testing	
<i>Streptococcus pneumoniae</i>	1
<i>Haemophilus influenzae</i>	1
<i>Escherichia coli</i>	1
<i>Enterococcus faecalis</i>	1

Table 4. Differences between diagnostic categories.

	Viral infection	Asthma	Pneumonia (uncomplicated/undifferentiated)	Pneumonia (complicated by effusion)	Other
Count (%)	50 (22%)	63 (29%)	81 (37%)	12 (5.4%)	15 (6.8%)
mean WBC (SD)	12.1 (4.3)	13.6 (5.0)	13.0 (8.1)	19.0 <sup>1</sup> (11.0)	12.8 (7.5)
missing	1	1	1	0	0
median CRP, mg/L (IQR)	12.6 (3.5-28.6)	7.0 (3.6-16.4)	45.5 <sup>2</sup> (15.2-103)	203.8 <sup>3</sup> (146.8-274.7)	23.6 (14.6-80.2)
missing	28	47	31	4	2
No respiratory virus detected	5 (10%)	18 (29%)	32 (40%)	9 (75%)	8 (53%)
missing	0	0	0	0	0
median duration of antibiotics, days (IQR)	2 <sup>4</sup> (0-4)	0 <sup>4</sup> (0-1)	7 (7-10)	23 <sup>5</sup> (14-27)	10 (7-14)
missing	0	0	0	0	0

<sup>1</sup>mean of complicated pneumonia group significantly greater than the others (p=0.002).

<sup>2</sup>median of pneumonia group significantly greater than that of viral infection group (p=0.007) and asthma group (p=0.0009) but significantly lower than that of complicated pneumonia group (p=0.02)

<sup>3</sup>median of complicated pneumonia group significantly greater than viral infection and asthma groups (p<0.0001) and pneumonia group (p=0.009)

<sup>4</sup>median of viral infection and asthma groups significantly smaller than all other groups (p<0.0001)

<sup>5</sup>median of complicated pneumonia group also significantly higher than pneumonia group (p=0.02)

Table 5. Comparison of *Mycoplasma*-positive and *Mycoplasma*-negative subjects.

	<i>Mycoplasma</i> -positive	<i>Mycoplasma</i> -negative	p
Count	10	211	n/a
age, years			0.02
mean (SD)	8.1 (6.1)	4.6 (4.4)	
median (IQR)	7.2 (2.0 – 16)	3.0 (1.3 – 6.0)	
% greater than 5 y	60%	34%	
# with viral infection or asthma diagnosis (%)	3 (30%)	110 (51%)	0.2
(restricted to subjects > 5 y)	0	30 (42%)	0.08
# with no detectable respiratory virus in NPS	7 (70%)	65 (31%)	0.02
(restricted to subjects > 5 y)	5 (83%)	33 (46%)	0.1
median duration of antibiotic treatment, d (IQR)	11 (7-17)	5 (0-8)	0.02
(restricted to subjects with uncomplicated pneumonia)	12 (10-13)	7 (7-10)	0.004
Median length of stay in PICU, d (IQR)	4.5 (2-8)	3 (2-5)	0.1
(restricted to subjects with uncomplicated pneumonia)	7 (2-8)	4 (2-7)	0.7
Median length of stay in hospital, d (IQR)	10 (5-13)	4 (3-8)	0.03
(restricted to subjects with uncomplicated pneumonia)	13 (7-14)	7 (3-14)	0.3

# BMJ Paediatrics Open

## **Pediatric critical illness associated with respiratory infection: a single-centre, retrospective, cohort study**

Journal:	<i>BMJ Paediatrics Open</i>
Manuscript ID	bmjpo-2020-000640.R2
Article Type:	Original research
Date Submitted by the Author:	30-Mar-2020
Complete List of Authors:	Alfaraidi, Haifa; McMaster University, Department of Pediatrics Luinstra, Kathy; Saint Joseph's Healthcare Hamilton Charlton Campus, Laboratory Medicine Eshaghi, Alireza; Public Health Ontario Laboratory Services Smieja, Marek; McMaster University, Department of Pathology and Molecular Medicine Gubbay, Jonathan; Public Health Ontario Laboratory Services Pernica, Jeffrey; McMaster University, Department of Pediatrics - RINGGOLD INSTITUTION 3710
Keywords:	Infectious Diseases, Epidemiology

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3 **Pediatric critical illness associated with respiratory infection: a single-centre, retrospective,**  
4 **cohort study**  
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37  
38 Word count : 2974  
39

40  
41 Keywords: pneumonia, intensive care, respiratory tract infection, epidemiology, Mycoplasma  
42

43  
44 Short title: Pediatric critical respiratory illness: a retrospective study  
45

46  
47 Funding: This project was supported by a McMaster University Department of Pediatrics  
48 Resident Research Grant. JMP was supported by a Hamilton Health Sciences Early Career  
49 Award. There are no conflicts of interest.  
50

51  
52 Presentation: Poster presentation, Association of Medical Microbiology and Infectious Disease  
53 Canada annual conference, 2018.  
54

55  
56 Acknowledgements: The authors would like to acknowledge the assistance of Samir Patel who  
57 oversaw the Mycoplasma resistance testing.  
58  
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60

## Abstract

**Objectives.** To describe critically ill children with respiratory infections, classify them by infection syndrome type, and determine the prevalence of *Mycoplasma pneumoniae* detection.

**Study design.** A retrospective, single-centre, cohort study. All children aged 2 months – 18 years with presumed respiratory infection who were admitted to a tertiary hospital paediatric intensive care unit between September 2015-October 2016 were eligible. Subjects were grouped by clinical syndrome (viral respiratory infection, asthma exacerbation, undifferentiated/uncomplicated pneumonia, pneumonia complicated by effusion/empyema, and 'other'). All subjects had nasopharyngeal swabs tested for respiratory viruses, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

**Results.** There were 221 subjects; the median age was 3.1 y, 44% were female, and 78% had medical comorbidities. A majority (75%) was treated with antibiotics, most often ceftriaxone (90% of treated children). Those with any pneumonia were significantly less likely to have a respiratory virus identified in their nasopharynxes and had significantly higher C-reactive protein (CRP) values than those in the viral infection and asthma groups. There were 10 subjects in whom *M. pneumoniae* was detected (4.5%, 95%CI 2.2-8.2%). *Mycoplasma*-positive children were older (difference 3.5 y, 95%CI 0.66 – 6.4 y) and had fewer viral co-infections (30% compared to 69%,  $p=0.02$ ). The prevalence of *Mycoplasma* infection in children aged > 5 y with any pneumonia was 13.2% (95%CI 4.4-28%).

**Conclusions.** The majority of participants had respiratory viruses detected and were treated with broad-spectrum antibiotics. Differences in CRP and viral prevalence were observed between children with different infection syndrome types. *M. pneumoniae* infection was not rare in school-aged children with pneumonia admitted to the PICU. Attention to antibiotic treatment and rapid diagnostic testing for *Mycoplasma* in older, critically ill children should be considered to optimize management and avert morbidity and mortality from respiratory infection.

### What is known about this topic?

Respiratory viruses and *Mycoplasma pneumoniae* are commonly detected in children with non-severe pneumonia.

Guidelines for the management of community-acquired pneumonia in children do not advocate first-line empiric treatment with antibiotics active against *Mycoplasma* nor routine testing for this pathogen.

### What this study adds:

There are clear biochemical (eg. CRP) and microbiologic (eg. respiratory virus prevalence) differences between critically ill children with different respiratory infection syndromes.



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4 Respiratory viruses were detected in 67% of the entire study cohort and *Mycoplasma*  
5 *pneumoniae* was detected in 13.2% of school-aged critically ill children with severe community-  
6 acquired pneumonia.  
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Confidential: For Review Only

## BACKGROUND

Community-acquired pneumonia (CAP) is a leading cause of pediatric hospitalization in North America (1). Children with respiratory disease severe enough to warrant admission to a paediatric intensive care unit (PICU) represent a minority (~20%) of pneumonia-related hospitalizations (2) but infection-related morbidity and mortality is higher in this subgroup (3).

*Streptococcus pneumoniae* has long been considered the most important bacterial pathogen causing severe CAP (4,5). *Mycoplasma pneumoniae*, in contrast, is thought of as a less virulent pathogen, possibly due to the fact that *M. pneumoniae* infection often self-resolves (6). Neither the American, Canadian, nor British guidelines recommend antimicrobials with activity against *M. pneumoniae* as first-line empiric treatment for pediatric CAP (7-9). However, this pathogen is a common cause of CAP, especially in school-aged children; *M. pneumoniae* was the most commonly identified bacterial pathogen in American children hospitalized with CAP, being detected in 8% of the overall cohort and in 19% of school-aged children (2). A subsequent analysis of this data demonstrated that the children with *M. pneumoniae* infection could not be distinguished reliably on a clinical basis from those without and that, in contrast to dogma (8,9), single lobar infiltrates and pleural effusions were common on chest radiography (32% and 26% of those infected, respectively) (10). Furthermore, 12% of those with *M. pneumoniae* infection required intensive care (10). Clearly, the epidemiology of this common respiratory pathogen – and its effect on the clinical course and prognosis for children with severe CAP – should be evaluated further. The objective of our study was to describe children admitted to the PICU of

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3 McMaster Children's Hospital (MCH) with respiratory infection and determine the prevalence  
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5 of *M. pneumoniae* detection in this population.  
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## 10 **METHODS**

### 11 **Setting**

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16 MCH is a tertiary care centre serving a population of approximately 2.3 million residents. At the  
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18 time of the study, the centre had 159 beds (12 PICU beds) and, on a yearly basis, admitted  
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20 approximately 6500 children, with over 40 000 emergency department visits.  
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### 27 **Design**

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30 A single center, retrospective cohort study. Eligible children were those aged 2 months to 18  
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32 years admitted to the MCH PICU from September 2015 to October 2016 with a presumptive  
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34 respiratory infection, as defined by a discharge diagnosis of any lower respiratory tract  
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36 infection. Discharge diagnoses for all patients leaving the PICU were reviewed on a biweekly  
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38 basis by an investigator (HA); we attempted to capture all those with possible respiratory  
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40 infection, to minimize bias. Children aged less than two months were not included due to the  
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42 different epidemiology of respiratory infection in that age group. Furthermore, all eligible  
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44 subjects had to have had a nasopharyngeal swab (NPS) taken less than a week after admission  
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46 to hospital and a respiratory symptom or sign, including at least one of the following: 1)  
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48 tachypnoea as per age-specific norms (35); 2) cough; 3) increased work of breathing on exam,  
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50 or 4) auscultatory findings such as crackles, wheeze, or rhonchi. The study was approved by the  
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Hamilton Integrated Research Ethics Board, who waived the requirement for consent in this retrospective study. Patients or the public were not involved in study design. No formal sample size calculation was done.

### Data collection

Information was obtained by retrospective chart review using a standardized data collection form. To group study subjects by infection syndrome, the discharge diagnoses of the clinical team were categorized as follows: viral infection without pneumonia (including bronchiolitis and croup), undifferentiated/uncomplicated pneumonia, pneumonia complicated by effusion/empyema, asthma, and 'other.' If the clinical team recorded multiple diagnoses from the list above, they were classified using the following rules:

1. Subjects marked as having both viral infection and pneumonia were classified as having 'pneumonia' if the chest radiograph was read by the radiologist as consistent with pneumonia and as 'viral infection' (without pneumonia) if not.
2. Subjects marked as having both asthma and pneumonia were classified as having 'pneumonia' if the chest radiograph was read by the radiologist as consistent with pneumonia and as 'asthma' if not.
3. Subjects marked as having both viral infection and asthma were classified as having 'asthma' if they were older than 1 y of age and had a history of atopy; if not, they were classified as 'viral infection.'

### Laboratory testing

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3 All children hospitalized with a potentially infectious respiratory illness at MCH have an NPS  
4 performed routinely to identify respiratory viruses, as per the institutional Acute Respiratory  
5 Infection Surveillance Protocol. NPSs are assayed using a lab-developed multiplex respiratory  
6 virus panel (11) that detects respiratory syncytial virus (RSV) A/B, human metapneumovirus,  
7 influenza A/B, parainfluenza I-III, adenovirus, and rhinovirus/enterovirus. NPS specimens from  
8 eligible subjects were identified and stored. After the surveillance period, NPSs from subjects  
9 were batch-tested (ie. test results were not available to treating clinicians) using an Hamilton  
10 Regional Laboratory Medicine Program lab-developed multiplex PCR assay to detect *M.*  
11 *pneumoniae* and *Chlamydia pneumoniae* that was validated against sequencing and external  
12 quality control materials.  
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30 Any MP testing ordered prospectively by treating clinicians in the course of routine care was  
31 not processed using the lab-developed PCR assay but at Public Health Ontario Laboratories  
32 using a commercial multiplex real-time assay (ProPneumo-1 Assay; Gen-Probe Inc., San Diego,  
33 CA, USA), which also tests for *Chlamydia pneumoniae*. Samples that tested positive for MP  
34 underwent further testing at Public Health Ontario laboratories; nested PCR amplification and  
35 DNA sequencing of domain V of the partial 23S rRNA gene were performed to detect mutations  
36 at nucleotide positions 2063 and 2064, which are associated with macrolide resistance (12,13).  
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50 'Confirmed invasive bacterial infections' were defined as those children with a sterile-site  
51 culture (ie. blood, pleural fluid) positive for a recognized pathogen. Cultures positive for  
52 coagulase-negative staphylococci were categorized as contaminants.  
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## Statistical analysis

Descriptive statistics to describe the baseline characteristics were reported as count (percent) for categorical variables, and mean (standard deviation) or median (first quartile-third quartile, labeled as interquartile range [IQR]) for continuous variables depending on the distribution.

Normality was assessed visually. T-tests or linear regression were used to compare normally-distributed continuous variables. Kruskal-Wallis testing was used when the distribution of the variable differed greatly from the normal distribution. If Kruskal-Wallis testing identified significant differences, nonparametric pairwise multiple comparisons of the groups using Dunn's test with Bonferroni adjustment were done. Chi-square or Fisher exact testing was used to compare categorical variables between groups. Alpha was set at 0.05, with no adjustments for multiple comparisons in this exploratory study. No imputation of missing data was done.

Analyses were conducted using Stata v11.2 (College Station, TX).

## RESULTS

In the study period there were 740 children admitted to the PICU; of these, 221 subjects (31%) had a diagnosis of acute respiratory illness, an NPS taken less than a week after admission, and at least one respiratory tract symptom or sign (Table 1). The median age was 3.1 y (IQR 1.4-6.0 y) and 44% were female. The majority of subjects (78%) had comorbidities (see Table 1). There were 13 subjects (6%) that had a tracheostomy, 7 (3%) that were receiving home ventilation, 6 (3%) that were receiving home non-invasive ventilation, and 9 (4%) on home oxygen therapy.

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3 There were three deaths (1.3%) in the cohort and all had comorbidities. Fourteen subjects (6%)  
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5 were not up-to-date with DPTaP-Hib or PCV13 vaccine.  
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10 In the PICU, the majority of subjects (n=139, 63%) received high-flow oxygen support, 49 (22%)  
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12 received CPAP/BiPAP, 38 (17%) required conventional mechanical ventilation, and 1 (0.45%)  
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14 were treated with high-frequency oscillatory ventilation (see Table 2). Viral detections were  
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16 common, with 79 (36%) subjects positive for rhinovirus/enterovirus, 37 (17%) positive for RSV,  
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18 and 24 (11%) positive for parainfluenza; only 72 (33%) tested negative for respiratory viruses  
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20 (see Table 3). There were 7 subjects with confirmed invasive bacterial infections. The median  
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22 length of stay in the PICU was 3 days (IQR 2-5 d) and the medial length of stay in-hospital was 4  
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24 days (IQR 3-8 d).  
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32 Of the 221 subjects, 50 (23%) were categorized as having had viral infection without  
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34 pneumonia, 81 (37%) as uncomplicated pneumonia, 12 (5.4%) as pneumonia complicated by  
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36 effusion/empyema, 63 (29%) as an asthma exacerbation, and 15 (6.8%) as 'other.' There was  
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38 considerable overlap in the white blood cell (WBC) distributions between categories (see Table  
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40 4). C-reactive protein measurements were clearly different between groups; those with  
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42 pneumonia (median 45.5 mg/L) had significantly higher median CRP values than those in the  
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44 viral infection (median 12.6 mg/L) and asthma (median 7.0 mg/L) groups, whereas those with  
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46 pneumonia complicated by effusion/empyema (median CRP 203.8 mg/L) had significantly  
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48 higher CRP values than all other groups. There were clear differences in the proportions of  
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50 subjects in each group with respect to viral NPS testing; 90% of the viral infection group and  
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3 72% of the asthma group had a respiratory virus detected, while only 60% of the uncomplicated  
4 pneumonia group and 25% of the complicated pneumonia group did ( $p<0.0001$ ). All of the  
5 subjects in the uncomplicated and complicated pneumonia groups were treated with  
6 antibiotics, compared to 93% of the 'other' group, 74% of the viral-infection group, and 35% of  
7 the asthma group ( $p<0.0001$ ). The duration of antibacterial treatment was also significantly  
8 shorter in the viral infection and asthma groups than all other groups ( $p<0.0001$ ), as well as  
9 significantly longer in the complicated pneumonia group than in the uncomplicated pneumonia  
10 group ( $p=0.02$ ).  
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25 There were 3 subjects who tested positive, of 10 who had specimens tested, for *M.*  
26 *pneumoniae* through testing that was ordered prospectively by clinicians in the course of  
27 routine care (one sputum, one NPS, and one bronchoalveolar lavage [BAL]). There were an  
28 additional 7 subjects that were found to have an NPS positive for *M. pneumoniae* via  
29 retrospective study testing. The overall prevalence of *M. pneumoniae*-associated respiratory  
30 illness in the study cohort was therefore 10/221 (4.5%, 95%CI 2.2-8.2%). *Mycoplasma*-positive  
31 subjects were significantly older than *Mycoplasma*-negative children (difference 3.5 y, 95% CI  
32 0.66-6.4 y,  $p=0.02$ )(Table 4). The overall prevalence of *Mycoplasma* detection in subjects aged >  
33 5 years with any type of pneumonia was 13.2% (4 of 33 in the uncomplicated pneumonia group  
34 and 1 of 5 in the complicated pneumonia group, 95% CI 4.4-28%). In this older subset, there  
35 were zero *Mycoplasma*-positive subjects in the viral infection or asthma groups.  
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3 None of the *Mycoplasma*-positive group had invasive bacterial infections. Three (30%) of the  
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6 *Mycoplasma*-positive group had a respiratory viral pathogen detected as compared to 146  
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8 (69%) of the *Mycoplasma*-negative group ( $p=0.02$ , see Table 5). Antimicrobials were prescribed  
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10 for significantly longer from the time of admission in the *Mycoplasma*-positives (median 11  
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12 days, IQR 7-17 d) as compared to the *Mycoplasma*- negatives (median 5 d, IQR 0-8 d,  $p=0.02$ );  
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14 this difference remained significant when the analysis was restricted to only those subjects with  
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16 uncomplicated pneumonia (median 12 d as compared to median 7 d,  $p=0.004$ ).  
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23 Of the 10 *Mycoplasma* isolates, 5 were macrolide-sensitive and 1 harboured the G2063  
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25 mutation in the 23S rRNA gene (overall prevalence 17%, 95%CI 0.4-64%); 3 isolates were low-  
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27 level positives, and so could not be sequenced. One isolate was not retained. Only half of the  
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29 subjects with *Mycoplasma* infection were prescribed macrolide or fluoroquinolone  
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31 antibacterials.  
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38 No study subjects had *Chlamydia pneumoniae* detected in their NPS.  
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## 42 DISCUSSION

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44 In this retrospective single-centre study, we found that children with acute respiratory illness  
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46 admitted to the PICU were predominantly preschool-aged, often had medical comorbidities,  
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48 and frequently had viral pathogens detected in their nasopharynges. A minority had *M.*  
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50 *pneumoniae* detected in respiratory secretions and even fewer had documented invasive  
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52 bacterial infections. Despite this, 75% of the cohort was treated with antibacterials, most  
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3 commonly ceftriaxone (90% of treated children). Children diagnosed with asthma or viral  
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5 infections were found to differ microbiologically (more viral pathogens detected) and  
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7 biochemically (lower CRP values) from children diagnosed with pneumonia. Interestingly, 13.2%  
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9 (95%CI 4.4-28%) of children diagnosed with pneumonia who were at least 5 years of age were  
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11 positive for *M. pneumoniae*. Children that were *Mycoplasma*-positive were older, had fewer  
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13 respiratory virus co-infections, were more often treated with antibacterials before admission,  
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15 and received a longer course of antibacterials in-hospital than *Mycoplasma*-negative children.  
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18 Half of the *Mycoplasma*-positive children did not receive antibacterials active against  
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27 The fact that respiratory viruses were frequently detected in critically ill paediatric patients with  
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29 respiratory illness is not surprising, given the epidemiology of respiratory infection in children.  
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32 Respiratory viruses have been long known to be important causes of paediatric pulmonary  
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34 disease; for example, it has been estimated that there are at least 50 000 RSV-associated  
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36 hospitalizations per year in the United States, with more than a quarter requiring intensive care  
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38 (14). One large recent cohort study enrolling over two thousand children hospitalized for  
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40 pneumonia (21% of whom required PICU admission) at three American hospitals detected  
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42 respiratory viral pathogens in 73% (2). Viral coinfections may be even more common in children  
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44 with critical illness, given that paediatric patients with bacterial pneumonia with confirmed viral  
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46 coinfection have been found to have worse outcomes than those without (15).  
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3 It is unfortunate that almost three-quarters of all patients thought to have a purely viral  
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5 syndrome received treatment with antibacterials. Needless to say, neither the Canadian,  
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7 American, nor British guidelines recommend antibiotic treatment for viral lower respiratory  
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9 tract infections (16-18). Furthermore, the vast majority of treated patients received ceftriaxone,  
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11 which would be appropriate for some children with pneumonia (eg. immunocompromised  
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13 patients) but not for others (eg. group A streptococcal empyema). It is difficult to make  
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15 definitive statements about appropriateness given that we did not examine the precise  
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17 sequence of antibiotic administration in each patient in relation to the timing of microbiologic  
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19 results. However, the fact that the vast majority of CAP in children is caused by pneumococcus  
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21 or group A streptococcus, coupled with the observation that only 14 children (6%) received  
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23 ampicillin, is very suggestive that antimicrobial stewardship was sub-optimal in the PICU during  
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25 the study period.  
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35 Our results would argue that routine surveillance for *Mycoplasma* in school-aged children  
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37 should be considered, as others have suggested (19). Our findings are consistent with other  
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39 studies that demonstrated that *M. pneumoniae* is found commonly in school-aged children with  
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41 CAP (2), including children admitted to the intensive care unit (10). The incidence of *M.*  
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43 *pneumoniae* infection does vary widely by location and season (10,20) and so we cannot  
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45 exclude the possibility that the prevalence observed in our study was higher than in years  
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47 before or after. An older iteration of the Canadian Paediatric Society guidelines for the  
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49 management of CAP (circa 2011) recommended routine use of azithromycin for all children  
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51 with 'severe' pneumonia because of the possibility of 'atypical infection', though diagnostic  
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3 testing to identify atypical pathogens was not suggested or even mentioned (21). One might  
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5 question whether this practice would represent appropriate antimicrobial stewardship, given  
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7 that the majority of severe pediatric CAP is likely to be caused by *S. pneumoniae*. The CPS  
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9 guidelines were later revised in 2015 and no longer recommend routine treatment with  
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11 macrolides (8). They state that atypical pneumonia should be suspected in children with  
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13 'subacute, nonsevere pneumonia, presenting with features such as prominent cough, minimal  
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15 leukocytosis, and a nonlobar infiltrate' and that azithromycin is recommended 'for suspected or  
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17 proven *Mycoplasma* or *Chlamydia pneumoniae*' (8). Unfortunately, it has been repeatedly  
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19 demonstrated that these symptoms and signs cannot reliably identify atypical pneumonia  
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21 (10,22,23); it seems likely that many clinicians may not consider the possibility that *M.*  
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23 *pneumoniae* may play a significant role in the pathogenesis of critically ill children with  
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25 respiratory compromise. Based on our data, we would suggest that clinicians be aware that a  
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27 reasonable proportion of school-aged children with CAP admitted to the PICU may have an  
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29 active *M. pneumoniae* infection and recommend empiric treatment with anti-*Mycoplasma*  
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31 agents (eg. macrolides, doxycycline, fluoroquinolones) until diagnostic (molecular) testing  
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33 results are available. Of course, we cannot be certain of the therapeutic benefit of  
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35 antibacterials targeting *M. pneumoniae*; one systematic review found no clear difference in  
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37 outcomes between children treated with *Mycoplasma*-active agents and those without (24).  
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39 Furthermore, the detection of *Mycoplasma* in the respiratory tract does not prove causation, as  
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41 coinfections have been shown to be common (10) and some investigators have documented  
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43 high rates of PCR-positivity in control persons (25) (although others have not (10,26)); some  
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45 investigators have identified novel serologic tests that can confirm active infection (27). We  
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3 would agree with other authors who have suggested that specific anti-*Mycoplasma* treatment  
4 might yield significant benefit, especially for those with severe disease, and have called for the  
5 execution of a randomized treatment trial (10,19). However, until results of a definitive  
6 treatment trial are available, we feel that the potential benefit of treating critically ill children  
7 with *Mycoplasma* detected in respiratory symptoms outweighs the potential antimicrobial  
8 stewardship harms of this strategy.  
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20 There were obvious limitations to our study. As noted previously, this was a retrospective  
21 design and included only a single centre over a 13-month period; as outbreaks with this  
22 pathogen have been frequently described (28), we cannot be certain that the prevalence of  
23 infection documented in this study is an accurate estimate of children hospitalized with critical  
24 respiratory illness in our region of Canada. It is also quite possible that hospital clinicians may  
25 not have strictly followed hospital infection control policy and failed to sample the  
26 nasopharynges of some patients who otherwise would have been eligible. The study cohort  
27 only comprised 221 children and there were only 10 found to be positive for *M. pneumoniae*;  
28 consequently, 95% confidence intervals around our point estimates are wide. Having said that,  
29 the prevalence of viral and *Mycoplasma* detection found in this small study was similar to other  
30 estimates (2).  
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50 In conclusion, we found that the majority of children admitted to the PICU with respiratory  
51 illness over a 13-month period were positive for respiratory viruses and potentially  
52 inappropriate antibiotic treatment was common. *Mycoplasma pneumoniae* was detected in  
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3 13.2% of children aged 5 years and older diagnosed with CAP. Effort should be made to  
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5 distinguish those with plausible bacterial infections from those without and consideration  
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7 should be given to empiric anti-*Mycoplasma* antimicrobial therapy pending the result of rapid  
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9 molecular diagnostic testing in a subset of critically ill children.  
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#### 15 Contributorship Statement

16  
17 HA designed the study, wrote the protocol, did the chart reviews, wrote the abstract, and  
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19 revised the manuscript critically. JMP conceived the study question, provided input on study  
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21 design, performed statistical analyses, and wrote the manuscript. KL and MS provided input on  
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23 microbiologic methods, revised the protocol, did testing to identify *M. pneumoniae*, and revised  
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25 the manuscript critically. AE and JBG provided input on microbiologic methods, did testing to  
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27 identify resistance genes, and revised the manuscript critically.  
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Table 1. Whole-cohort baseline characteristics.

Median age (IQR)	3.11 y (1.39 – 6.02 y)
Age	
< 1 y	36 (16%)
1-2 y	45 (20%)
2-5 y	63 (29%)
5-10 y	45 (20%)
10-15 y	32 (14%)
# Female (%)	96 (44%)
Fever recorded (%)	120 (55%)
Median duration of fever (IQR)	3 d (2 – 6 d)
Symptoms	
Increased work of breathing	202 (91%)
Cough	191 (87%)
Wheeze	112 (51%)
Stridor	13 (5.9%)
Chest pain	4 (1.8%)
Antibiotics given before presentation?	
Yes	44 (20%)
Amoxicillin	18
Amoxicillin/clavulanate	2
Cephalosporins	10
Macrolides	10
Other	11
Comorbid medical conditions	174 (78%)
asthma	89
other lung disease (including bronchopulmonary dysplasia)	36
neurologic/neurodevelopmental	52
genetic disease	26
cardiac disease	26
endocrine disorders	13
tracheostomy	13
chronic kidney disease	7
immunodeficiency/immunosuppressant drugs	5
haemoglobinopathies	5
malignancy	3
chronic liver disease	1
other	27
Home ventilation/oxygenation	16 (7%)
Mechanical ventilation	7
Noninvasive ventilation	6
Oxygen therapy without ventilation	3
Antibiotics given in PICU	166 (75%)

ampicillin	14
ceftriaxone	149
piperacillin-tazobactam	12
carbapenems	3
vancomycin	29
clindamycin	25
clarithromycin	3
azithromycin	35
levofloxacin	11
tetracyclines	0

Table 2. Whole-cohort clinical course in the PICU

Median length of stay in PICU (IQR)	3 d (2-5 d)
Highest level of respiratory support given in PICU	
High frequency oscillatory ventilation	1 (0.45%)
Conventional mechanical ventilation	37 (17%)
BiPAP/CPAP	34 (15%)
High flow oxygen by nasal cannula	96 (43%)
Low flow oxygen (FiO <sub>2</sub> > 0.4)	10 (4.4%)
Antibiotics given in PICU	166 (75%)
ceftriaxone	149
azithromycin	35
vancomycin	29
clindamycin	25
ampicillin	14
piperacillin-tazobactam	12
levofloxacin	11
carbapenems	3
clarithromycin	3

Table 3. Whole-cohort microbiology

Mucosal testing	positive in 156 (71%)
Rhino/enterovirus	79 (36%)
RSV	37 (17%)
Parainfluenza	24 (11%)
<i>Mycoplasma</i>	10 (5%)
Metapneumovirus	7 (3%)
Influenza	6 (3%)
Adenovirus	5 (2%)
Pleural fluid testing	
group A Streptococcus	2
<i>Streptococcus anginosus</i>	1
Blood culture testing	

<i>Streptococcus pneumoniae</i>	1
<i>Haemophilus influenzae</i>	1
<i>Escherichia coli</i>	1
<i>Enterococcus faecalis</i>	1

Table 4. Differences between diagnostic categories.

	Viral infection	Asthma	Pneumonia (uncomplicated/undifferentiated)	Pneumonia (complicated by effusion)	Other
Count (%)	50 (22%)	63 (29%)	81 (37%)	12 (5.4%)	15 (6.8%)
mean WBC (SD)	12.1 (4.3)	13.6 (5.0)	13.0 (8.1)	19.0 <sup>1</sup> (11.0)	12.8 (7.5)
missing	1	1	1	0	0
median CRP, mg/L (IQR)	12.6 (3.5-28.6)	7.0 (3.6-16.4)	45.5 <sup>2</sup> (15.2-103)	203.8 <sup>3</sup> (146.8-274.7)	23.6 (14.6-80.2)
missing	28	47	31	4	2
No respiratory virus detected	5 (10%)	18 (29%)	32 (40%)	9 (75%)	8 (53%)
missing	0	0	0	0	0
median duration of antibiotics, days (IQR)	2 <sup>4</sup> (0-4)	0 <sup>4</sup> (0-1)	7 (7-10)	23 <sup>5</sup> (14-27)	10 (7-14)
missing	0	0	0	0	0

<sup>1</sup>mean of complicated pneumonia group significantly greater than the others (p=0.002).

<sup>2</sup>median of pneumonia group significantly greater than that of viral infection group (p=0.007) and asthma group (p=0.0009) but significantly lower than that of complicated pneumonia group (p=0.02)

<sup>3</sup>median of complicated pneumonia group significantly greater than viral infection and asthma groups (p<0.0001) and pneumonia group (p=0.009)

<sup>4</sup>median of viral infection and asthma groups significantly smaller than all other groups (p<0.0001)

<sup>5</sup>median of complicated pneumonia group also significantly higher than pneumonia group (p=0.02)

Table 5. Comparison of *Mycoplasma*-positive and *Mycoplasma*-negative subjects.

	<i>Mycoplasma</i> -positive	<i>Mycoplasma</i> -negative	p
Count	10	211	n/a
age, years			0.02
mean (SD)	8.1 (6.1)	4.6 (4.4)	
median (IQR)	7.2 (2.0 – 16)	3.0 (1.3 – 6.0)	
% greater than 5 y	60%	34%	

# with viral infection or asthma diagnosis (%)	3 (30%)	110 (51%)	0.2
(restricted to subjects > 5 y)	0	30 (42%)	0.08
# with no detectable respiratory virus in NPS	7 (70%)	65 (31%)	0.02
(restricted to subjects > 5 y)	5 (83%)	33 (46%)	0.1
median duration of antibiotic treatment, d (IQR)	11 (7-17)	5 (0-8)	0.02
(restricted to subjects with uncomplicated pneumonia)	12 (10-13)	7 (7-10)	0.004
Median length of stay in PICU, d (IQR)	4.5 (2-8)	3 (2-5)	0.1
(restricted to subjects with uncomplicated pneumonia)	7 (2-8)	4 (2-7)	0.7
Median length of stay in hospital, d (IQR)	10 (5-13)	4 (3-8)	0.03
(restricted to subjects with uncomplicated pneumonia)	13 (7-14)	7 (3-14)	0.3