The emerging role of community sentinel surveillance in the understanding of the clinical features and epidemiology of acute *Mycoplasma pneumoniae* infection

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Abstract

Retrospective analysis of 3984 test results for the detection of *Mycoplasma pneumoniae* performed between 2009 and 2013 in Wales was undertaken. Analysis of the clinical presentation of positive cases suggested that mild respiratory infection was common in the community and appeared to coincide with increased hospitalizations. Symptomatic infection was more prevalent in men, with a median age of 22.6 years (range <1–88 years), and 40% of hospitalized cases presented with pneumonia. Inclusion of *M. pneumonia* nucleic acid amplification tests (NAATs) into routine respiratory NAAT screens will increase the understanding of the epidemiology and clinical spectrum of acute infections in the wider population.

Keywords: community-acquired pneumonia, *M. pneumoniae* NAAT, molecular diagnostics, *Mycoplasma pneumoniae*, sentinel surveillance

Original Submission: 13 August 2013; **Revised Submission:** 3 December 2013; **Accepted:** 9 December 2013

Editor: D. Raoult

Article published online: 8 January 2014

Clin Microbiol Infect 2014; **20:** O489–O492

10.1111/1469-0691.12499

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Introduction

Mycoplasma pneumoniae is a significant cause of community-acquired pneumonia (CAP) and is associated with chronic respiratory illness and extrapulmonary complications such as Steven-Johnson syndrome [1–6]. An *M. pneumoniae* epidemic occurred in northern Europe from 2010 to 2012 [7–11].

An accurate diagnosis of acute *M. pneumoniae* infection based on clinical symptoms alone is difficult and laboratory confirmation should be used to confirm an infection prior to prescribing antibiotics [12–17]. Serology is the method of choice in most centres but the requirement of acute and convalescent sera to demonstrate an increase in antibody titre delays time to results and thus antibiotics may be prescribed inappropriately or not at all [12,14–16]. IgM results should be interpreted with caution due to non-specific reactions, including cross-reactivity between other *Mycoplasma* species, and false-negative results can occur as a result of infection in a background of immunosuppression [16]. Conventional laboratory methods used to diagnosis acute *M. pneumoniae* infection are applied in a non-standardized way and a recognized reference standard method is needed [15]. Although specific *M. pneumoniae* nucleic acid amplification tests (NAATs) have been described, their widespread use is limited by the lack of standardized quality control material and validated algorithms, and a paucity of good quality studies combining laboratory diagnosis with clinical features. Laboratory confirmation of *M. pneumoniae* therefore remains a challenge. [13,15].

In Wales, an *M. pneumoniae* NAAT was introduced in October 2011, this study aims to describe how its introduction led to improved diagnosis and understanding of the presenting features of acute infection in both hospital and community settings.

A laboratory data search was undertaken to identify all samples where an *M. pneumoniae* test was performed by serology, NAAT or a combination of both between January 2009 and June 2013.

The frontline serological screen used for acute infection was the SERODIA-MYCO II particle agglutination (PA) kit (Fujirebio Inc., Tokyo, Japan). This was performed following the manufacturer's instructions, but with a titre of 1:160 considered significant. A qualitative *M. pneumoniae* NAAT targeting the conserved region of the P1 adhesin gene [18] was optimized for use with the ABI 7500 FAST and the 4X ABI FAST Virus mix using previously described amplification parameters [19,20].

Local validation of the NAAT was performed using the *M. pneumoniae* 2011 QCMD panel and known positive samples. Validation was performed on both upper and lower respiratory tract samples. Nucleic acid was extracted with the NucliSens EasyMag extractor (BioMérieux, Marseille, France), using previously described methods [19,20]. The *M. pneumoniae* NAAT was incorporated into the routine respiratory screen and human RNaseP was used as a control for both nucleic acid extraction and amplification as previously described [19].

Data from 3984 patients were included in the final analysis. Where applicable, variables were compared using Fisher's exact test and proportions were compared using the Z test with a p value of <0.05 considered significant.

Acute serological testing was undertaken for a total of 566 samples over the time period, whereas NAAT testing was performed for 3464 samples from October 2011 until June 2013 (positivity rates 3.4%, 2011; 1.2%, 2012; 0.7%, 2013). Of those tested by both PA and NAAT with a significant titre by PA, 45/46 (92%) were found to be negative by NAAT, suggesting previous rather than acute infection. One case was positive in two successive samples by NAAT and showed an increase in PA titre from <40 to >1280.

Clinical data were obtained for 110 laboratory-confirmed *M. pneumoniae* cases. Of these, 53 were NAAT positive and 57 were positive by serology. Ages ranged from <1 year to 88 years old (median age 22.6 years) (Fig. 1). The median age of hospitalized cases was 17.5 years, which was younger than the median age for confirmed community cases (27.3 years), although this was not statistically significant (Table 1).

Confirmed *M. pneumoniae* infection was more likely in men (p 0.004 community cases, p 0.009 hospitalized cases and p 0.03 critical care cases). Community cases were more likely to present with a mild upper respiratory tract infection than hospitalized cases (p <0.05). A significantly higher proportion of hospitalized cases (40%) presented with pneumonia (p <0.05); this is at the higher end of previous estimates [5].

Extrapulmonary symptoms were found in hospitalized cases, but in this study Steven-Johnson syndrome was significantly more likely in confirmed cases in hospital (p 0.03). Only 2/16 cases presenting with extrapulmonary symptoms were confirmed by NAAT. In addition, a male aged 19 with underlying asthma died in the community following a respiratory illness. *M. pneumoniae* DNA was detected in lower respiratory tract samples collected at the post-mortem.

Over the study period, 19/144 (13%) samples received through the sentinel surveillance scheme were positive for

TABLE 1. Characteristics of laboratory-confirmed *M. pneumoniae* cases

	Community (*n* = 36)	Hospital (*n* = 58)	Critical care (*n* = 16)
Age (mean years)	27.3	17.5	31
Gender			
Male	24	36	11
Female	12	22	5
Symptoms			
Upper respiratory tract			
Cough	15	10	0
Sore throat	2	1	0
Influenza-like illness[a]	15	1	0
Lower respiratory tract			
Pneumonia	3	28	13
Bronchiolitis	0	2	1
Extrapulmonary			
Rash	1	1	0
Neurological symptoms	0	3	0
Jaundice	0	1	0
Hepatosplenamegaly	0	1	0
Renal failure	0	1	0
Sepsis	0	1	2
Sickle cell crisis	0	1	0
Immunological			
Steven-Johnson syndrome	0	7	0

[a]Influenza-like illness is defined in Wales as being an illness of sudden onset typified by a pyrexia of >38°C and at least two other symptoms including cough, sore throat, myalgia, fatigue, rigors and headache.

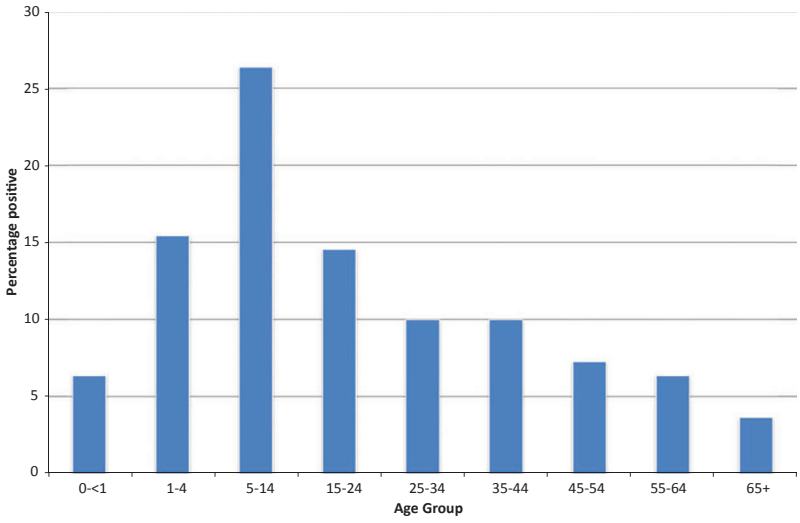

FIG. 1. Ages of those confirmed as *M. pneumoniae* positive by serology and/or NAAT. The peak incidence occurred in the 5–14-year-old age group, although the average age of both patients in the community and patients admitted to critical care was higher than that seen in those admitted to general wards in the hospital. The cluster of cases that occurred in the community in south-east Wales predominantly affected people in the age range 45–64 with one admission to critical care; this is higher than the age ranges normally associated with *M. pneumoniae* infection.