HHS Public Access

Author manuscript

Pediatr Infect Dis J. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Pediatr Infect Dis J. 2017 June ; 36(6): 564–571. doi:10.1097/INF.0000000000001476.

Epidemiology and Molecular Characteristics of *Mycoplasma pneumoniae* During an Outbreak of *M. pneumoniae*-associated Stevens-Johnson Syndrome

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Abstract

Background—An increase in *Mycoplasma pneumoniae*-associated Stevens-Johnson syndrome (SJS) cases at a Colorado pediatric hospital led to an outbreak investigation. We describe the epidemiologic and molecular characteristics of *M. pneumoniae* among SJS case-patients and surrounding community members during the outbreak.

Methods—*M. pneumoniae* polymerase chain reaction-positive respiratory specimens from 5 Colorado hospitals and 4 referral laboratories underwent confirmatory polymerase chain reaction testing; positive specimens then underwent multilocus variable-number tandem-repeat analysis (MLVA) and macrolide resistance testing. Three SJS-*M. pneumoniae* case-patient households were

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Preliminary results from this study were presented at the IDWeek conference; Philadelphia, PA; October 8–12, 2014.

All remaining authors have declared no conflicts of interest.

surveyed using a standardized questionnaire, and nasopharyngeal/oropharyngeal swabs were obtained from all consenting/assenting household contacts. International Classification of Diseases, 9th revision codes were used to identify pneumonia cases among Colorado patients 5–21 years of age from January 2009 to March 2014.

Results—Three different *M. pneumoniae* MLVA types were identified among the 5 SJS case-patients with confirmed infection; MLVA type 3-X-6-2 was seen more commonly in SJS case-patients (60%) than in 69 non-SJS community specimens (29%). Macrolide resistance was identified in 7% of community specimens but not among SJS case-patients. Of 15 household contacts, 5 (33%) were *M. pneumoniae* positive; all MLVA types were identical to those of the corresponding SJS case-patient, although the specimen from 1 contact was macrolide resistant. Overall pneumonia cases as well as those caused by *M. pneumoniae* specifically peaked in October 2013, coinciding with the SJS outbreak.

Conclusions—The outbreak of *M. pneumoniae*-associated SJS may have been associated with a community outbreak of *M. pneumoniae*; clinicians should be aware of the *M. pneumoniae*–SJS relationship. Household transmission of *M. pneumoniae* was common within the households investigated.

Keywords

disease transmission; infectious macrolide susceptibility; multilocus variable-number tandem-repeat analysis; *Mycoplasma pneumoniae*; outbreak; pneumonia; mycoplasma; pneumonia; bacterial; Stevens-Johnson syndrome

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Mycoplasma pneumoniae is a leading bacterial cause of community-acquired pneumonia (CAP) in school-age children and adolescents in the United States,[1–3] although a majority of children with *M. pneumoniae* infections may experience only upper respiratory congestion, pharyngitis or tracheobronchitis.[4,5] Although most children with *M. pneumoniae* infections are managed as outpatients, some cases may be severe enough to warrant hospitalization.[4] Preferred antimicrobial therapy for CAP caused by *M. pneumoniae* in children is a macrolide antibiotic such as azithromycin.[6]

Children often serve as the primary reservoir of disease,[7] and transmission of *M. pneumoniae* may occur through close personal contact within households.[8–10] Focal outbreaks of *M. pneumoniae* tend to occur in schools or other institutions fostering close contact between residents.[8,11,12] Large-scale community outbreaks are rarely reported and likely under-recognized, in part because *M. pneumoniae* is not a notifiable condition in the United States and microbiologic testing is not routinely performed.

Stevens-Johnson syndrome (SJS) is an immune-mediated blistering disorder of the skin and mucous membranes; complications include blindness, urethral strictures, sepsis and death.[13,14] *M. pneumoniae* has been recognized as the leading infectious trigger of SJS in children and adolescents since the 1960s.[15] Children with *M. pneumoniae*-associated SJS often have prominent mucositis and limited skin involvement.[16]

In November 2013, clinicians at Children's Hospital Colorado (CHCO) noted an unusual number of children diagnosed with SJS. An investigation into this cluster of cases revealed

that of the 8 SJS case-patients (8–16 years of age) identified between September 1 and November 30, 2013, 5 had confirmed [*M. pneumoniae* polymerase chain reaction (PCR) positive] and 3 had possible (concurrent radiographic pneumonia or fever plus cough, shortness of breath or hypoxia) infection with *M. pneumoniae*, making this one of the largest reported outbreaks of *M. pneumoniae*-associated SJS to date.[17]

In this article, we discuss the epidemiologic and molecular characteristics of *M. pneumoniae* in the community at the time of the *M. pneumoniae*-associated SJS outbreak. To better understand why the outbreak occurred, we evaluated our 2 leading hypotheses: first, a small but significant number of children experienced SJS in the context of a larger *M. pneumoniae* outbreak; and second, a unique *M. pneumoniae* strain type contributed to the development of SJS. We also describe the intra-household transmission of *M. pneumoniae* among a small subset of case-patients.

METHODS

Outbreak Setting

The CHCO is the primary children's referral hospital for the state of Colorado, with a catchment population of more than 1.2 million children. Children with severe illness requiring specialty care (such as SJS) are commonly referred from smaller hospitals throughout Colorado and the surrounding states. In the 5 years prior to September 1, 2013, CHCO treated an average of 7.5 children with SJS per year, of whom 32% had confirmed or probable *M. pneumoniae* infection on chart review.[17] Therefore, the 8 cases that occurred between September 1 and November 30, 2013 represented a significant rise above the expected number of cases by cumulative sum analysis,[17] prompting further investigation into the possible reasons for this increase.

Pneumonia Case Finding

A case of pneumonia was defined as a pneumonia diagnosis indicated by an International Classification of Diseases, 9th revision (ICD-9) code of 483.0 (pneumonia caused by *M. pneumoniae*), 482.9 (bacterial pneumonia, unspecified) or 486 (pneumonia, unspecified organism) in a patient 5–21 years of age from January 1, 2009 to March 31, 2014. We selected this age range to reflect the population of children and young adults most at risk for developing *M. pneumoniae* pneumonia (and subsequent SJS) as well as to exclude infants and young children in whom pneumonia is both more common and more likely to be because of a viral etiology.[1,18,19] Only the first occurrence of pneumonia within a 12-month period was included. We selected the time period to parallel the time for which independent ICD-9 codes were available for SJS.

We contacted 5 hospitals in the Denver metropolitan area, 1 regional Colorado health management organization, the Colorado Hospital Association (CHA) and the schools and day-care facilities of *M. pneumoniae*-associated SJS case-patients and their household contacts 21 years of age or younger to assess the trend in pneumonia cases among children 5–21 years of age. Here, we report data from the most complete and relevant data sources: CHCO, the largest children's hospital in Colorado, and the CHA hospital discharge dataset,

which contains patient demographics and discharge diagnoses from approximately 85 hospitals in the state of Colorado. Pneumonia cases at CHCO were identified from the hospital-wide network, including inpatient, emergency department and outpatient visits. Cases from the CHA discharge database are for inpatients only.

Laboratory Investigation

We requested frozen residuals of *M. pneumoniae* PCR-positive respiratory specimens collected from Colorado residents between January 1 and December 10, 2013 from the 5 hospitals and their 4 affiliated referral laboratories. These specimens were shipped to the Pneumonia Response and Surveillance Laboratory at the Centers for Disease Control and Prevention (CDC) for further analysis. We collected all *M. pneumoniae* PCR-positive specimens prospectively identified by CHCO and its affiliated referral laboratory from December 10, 2013 to January 31, 2014. All accessible specimens were accepted for testing, including those from patients 5 years of age or younger or 21 years of age or older.

All specimens received at CDC were re-tested for *M. pneumoniae* in triplicate using a validated multiplex real-time PCR assay as previously described.[20] Culture was attempted on all PCR-positive specimens using previously described methods[8,21] to obtain isolates for further molecular characterization. All isolates were confirmed by *M. pneumoniae*-specific PCR.

Multilocus variable-number tandem-repeat analysis (MLVA) was performed on nucleic acid extracted from all PCR-positive specimens and isolates as previously described.[22,23]Typing of the major adhesion molecule P1 was performed on all isolates using a high-resolution melt assay for determination of types 1 and 2 and identification of genetic variants.[24] Classification as types 1, 2 or variant was based upon comparison of melting profiles to reference strains M129 (type 1) and FH (type 2) included in each run.

All PCR-positive specimens were assessed for macrolide susceptibility using an high-resolution melt assay to detect single base transitions (A to G) at position 2063 or 2064 within the 23S rRNA gene, which are known to confer resistance to macrolide antibiotics.[25] Specimens were classified as susceptible or resistant based upon comparison of melting profiles to reference strains as previously described.[26] In some cases, sequencing of the 23S rRNA gene was also performed to confirm results or identify the specific mutation present.

Household Contact Survey to Assess *M. pneumoniae* Transmission

Households of 3 SJS case-patients with confirmed *M. pneumoniae* infection were considered eligible for survey, as these case-patients were diagnosed within 6 weeks of the onset of the outbreak investigation.[17] We surveyed household contacts, defined as any person living in the same residential unit as an SJS case-patient with confirmed *M. pneumoniae* infection, for each of these 3 case-patients. Consenting adults and assenting children were interviewed about the presence and timing of respiratory or skin symptoms as well as any clinic visits, hospitalizations, diagnoses of pneumonia or medication use over the preceding 2 months. Parents were asked to respond to all interview questions on behalf of children 6 years of age or younger and to participate in interviews of children 7 years of age or older to assist with recall. Combined nasopharyngeal/oropharyngeal (NP/OP) swabs were obtained from all

consenting/assenting household contacts and submitted to CDC for *M. pneumoniae* PCR testing, culture, MLVA typing, P1 typing and macrolide susceptibility testing as previously described. The potential incubation period for *M. pneumoniae* was considered to be 1–4 weeks.[27]

Data Analysis

We analyzed trends in pneumonia case counts over time from the CHCO hospital network (inpatient and outpatient) and the Colorado state CHA hospital discharge dataset (inpatient only). To facilitate comparison of the 2013–2014 *M. pneumoniae* season to prior years, we averaged cases by month from the previous 3 years (we did not include the season between 2009 and 2010 because of the difficulty in adjusting for the rise in pneumonia cases caused by H1N1 during that season). We compared the MLVA types, P1 types and macrolide resistance of the *M. pneumoniae* strains from patients with and without SJS, and from SJS case-patients and their household contacts. All analyses were performed using Microsoft Excel and SAS version 9.3.

Outbreak Response and Ethical Review

This investigation was conducted as a collaborative effort between hospital staff at CHCO, the Colorado Department of Public Health and Environment and the CDC. Investigation methods were reviewed by the CDC and determined to be nonresearch because this investigation was part of a public health outbreak response. For the household contact survey, written consent for the interview and collection of an NP/OP specimen were obtained from parents/guardians for their participation and that of all children 18 years of age or younger; in addition, written assent was obtained from all children 7 years of age or older.

RESULTS

M. pneumoniae Surveillance

Between April 2013 and March 2014, the number of pneumonia cases remained close to baseline (monthly average of the previous 3 years) until September 2013, when it rose and remained elevated through March 2014 (Fig. 1). In the CHCO network, this increase was observed for both inpatients and outpatients and for pneumonia cases without a specified etiology, but was most pronounced among *M. pneumoniae*-specific cases (Fig. 1). Statewide discharge data from the CHA (inpatient only) showed a similar increase in both pneumonia cases and *M. pneumoniae*-specific pneumonia cases beginning in September 2013 and persisting through March 2014.

Molecular Characteristics of *M. pneumoniae*-positive Specimens

Positive PCR results for *M. pneumoniae* were confirmed in 5 specimens from SJS patients and 69 specimens from non-SJS patients (Table 1). The 5 children with SJS came from 5 different counties in Colorado (3 in the Denver metropolitan area and 2 from nonadjacent counties in the west and southwest), and no epidemiologic connections between these children could be established. MLVA typing revealed 3 different strain profiles among SJS patients (3-5-6-2, 3-6-6-2 and 4-5-7-2); 3 SJS patients (60%) had closely related strain types

with the pattern 3-X-6-2, compared with 20 (29%) of non-SJS patients. Figure 2 shows the results of MLVA typing over time; the majority of 3-X-6-2 patterns occurred during the SJS outbreak period. Isolates were obtained from all 5 SJS patients and from 45 (65%) non-SJS patients, and P1 typing results showed 3 isolates (60%) from SJS patients were type 2 or 2 variant, compared with 14 isolates (31%) from non-SJS patients. Overall, 5 (7%) specimens contained macrolide-resistant *M. pneumoniae* (all from non-SJS patients).

Household Contact Survey and Transmission

The households of 3 patients with *M. pneumoniae*-associated SJS were visited between 4 and 8 weeks after SJS patient symptom onset. A total of 15 household contacts were available at the time of the visits (Fig. 3; Table 2); all consented/assented to both interview and collection of NP/OP swab for *M. pneumoniae* testing. The 3 SJS case-patients were also interviewed. Overall, 13 of 15 (87%) household contacts reported respiratory symptoms during the 2 months before the interview, 4 of 13 (31%) received antibiotics and 2 of 13 (15%) of the ill contacts reported that they were diagnosed with pneumonia. Five household contacts (33%) tested PCR positive for *M. pneumoniae*, including 4 of the 8 (50%) household contacts 21 years of age or younger. Of the household contacts who tested positive for *M. pneumoniae*, MLVA types were identical to those of the case-patient; however, although all SJS patient *M. pneumoniae* strains were susceptible to macrolide, the strain of 1 household contact was resistant. Of note, the contact with the resistant strain had been treated with azithromycin almost a month before the *M. pneumoniae*-positive specimen was obtained.

The timing of symptom onset was carefully evaluated within households to assess potential patterns of transmission between household contacts. Figure 4 shows each household member's date of symptom onset and potential incubation period for *M. pneumoniae*. Symptom onset dates within households were generally spaced out over several weeks, consistent with the prolonged contact period required for transmission and the long incubation period of 1–4 weeks typically associated with *M. pneumoniae*.

DISCUSSION

This investigation was among the first to involve real-time molecular typing of *M. pneumoniae* by P1 and MLVA during an outbreak, providing a unique opportunity to correlate laboratory and epidemiologic findings. The results of our epidemiologic investigation suggest that an epidemic of *M. pneumoniae* occurred in Colorado among children 5–21 years of age from September of 2013 to March of 2014. Furthermore, the onset of this epidemic coincided both with the onset of *M. pneumoniae*-associated SJS cases and with the introduction of secondary *M. pneumoniae* strains of MLVA type 3-X-6-2, joining the dominant circulating strain, MLVA type 4-5-7-2. The use of MLVA typing also established molecular evidence for intra-household transmission of *M. pneumoniae*.

We believe that the unusually heavy burden of *M. pneumoniae* in Colorado during the fall of 2013 likely contributed to the concurrent increase in *M. pneumoniae*-associated SJS cases. However, no cases of SJS were observed at CHCO during either December 2013 or January 2014, despite the fact that concentrations of *M. pneumoniae* remained elevated above

baseline and active surveillance for SJS cases was continued during this time (Active surveillance for SJS cases at CHCO was continued through January 31, 2014 and consisted of screening for SJS cases by ICD-9 code [695.13 (SJS), 695.14 (SJS-toxic epidermal necrolysis, or SJS-TEN) and 695.15 (TEN)] and monitoring for cases by specialist services typically called to consult on patients with SJS (including pediatric infectious disease, ophthalmology and critical care services); pediatric hospitalists were also notified of the investigation and asked to report cases). Therefore, we considered whether a certain *M. pneumoniae* strain (distinguished by MLVA type) may have been more likely to trigger SJS in children. We observed a trend toward MLVA type 3-X-6-2 among SJS case-patients (60% vs. 29% of patients with pneumonia only) and a decrease in MLVA type 3-X-6-2 among pneumonia cases in January 2014, the last month for which data were collected. This decrease roughly paralleled the drop off in SJS cases. However, the different MLVA types observed among SJS cases and the fact that cases with similar MLVA types were not closely clustered geographically suggest that MLVA type may not be related to SJS. Ultimately, the numbers were too small to draw conclusions about the impact of MLVA type on development of SJS. It is possible that more advanced techniques such as whole genome sequencing could identify relevant differences between strains; alternatively, other host features (genetics, co-infections, concurrent medications), which were not evaluated in this investigation, may play a role in determining which children with *M. pneumoniae* are more likely to develop SJS.

M. pneumoniae case counts in Colorado reached a 5-year peak between 2013 and 2014. Such “epidemic seasons” of *M. pneumoniae* have been observed to occur at 4- to 7-year intervals and may reflect shifts in herd immunity as the population is exposed to different strains over time.[28–30] The presence of multiple MLVA types in epidemic seasons of *M. pneumoniae*, observed in this investigation, has been previously documented.[23,31,32]

Our investigation found an overall prevalence of macrolide resistance of 7%, which is consistent with recent estimates elsewhere in the United States.[31] While rising global rates of macrolide resistance, particularly in Asia,[33–36] have sparked discussion about best first-line antimicrobial treatment for *M. pneumoniae* disease in children, our findings support continued use of azithromycin or an alternative macrolide as first-line antimicrobial agents in the United States.[6] However, macrolide use may result in the rapid development of resistance[34,37] and its efficacy in the treatment of lower respiratory infections in children has been questioned.[38]

The household survey represents a rare opportunity to examine molecular characteristics of *M. pneumoniae* strains transmitted within a household and highlights several notable findings. First, the majority of household contacts (87%) reported respiratory symptoms, and one-third tested positive for *M. pneumoniae* despite a time lapse of several weeks between symptoms and specimen collection in most cases. P1 and MLVA types between the case patient and associated household contacts were identical in all cases. The *M. pneumoniae*-positive specimen obtained from the 20-year-old sibling of the second case-patient showed a macrolide-resistant genotype, while the specimen from the case-patient was found to be susceptible. Interestingly, the sibling had been diagnosed with pneumonia and was treated with a 5-day course of azithromycin roughly 1 month before we obtained the sample, raising

the possibility that the sibling's recent exposure to azithromycin may have induced resistance.[39,40] The original specimen from the case-patient was obtained before she received any treatment. The potentially long incubation period of *M. pneumoniae* and the lack of symptom specificity make it difficult to accurately trace transmission within households, but the timing of the PCR-positive cases' symptom onset is consistent with transmission either from 1 household member to another or with infection from a common source (as might be suspected in household 1, where the 2 PCR-positive household members had symptom onset on the same day). Together, these findings support previous studies documenting children as the primary reservoir of *M. pneumoniae*,[7] a long incubation period of up to 4 weeks,[9,10,41,42] asymptomatic carriage for several weeks following infection[43,44] and the easy spread of *M. pneumoniae* within households.[8–10]

This investigation calls attention to the fact that our knowledge of the epidemiology of *M. pneumoniae* remains rudimentary. This probable epidemic of *M. pneumoniae*, which potentially affected a large number of individuals in Colorado, went undetected until the unusual occurrence of this cluster of SJS cases prompted further exploration. In addition, it is unlikely that this epidemic was limited to 1 state. The ability to detect epidemic *M. pneumoniae* has implications for public health interventions such as timely outreach to clinicians, health-care facilities and schools; despite controversy over efficacy of macrolide therapy in an individual child, treatment with azithromycin during an epidemic may help to disrupt transmission to others,[45] and in rare instances, targeted prophylaxis may be indicated.[8] There are also important clinical implications for the early detection of epidemic *M. pneumoniae*, including ensuring appropriate treatment for children with CAP, limiting inappropriate antibiotic use, which may lead to resistance, and alerting clinicians to the possibility of *M. pneumoniae*-associated sequelae. Currently, children with CAP are likely to receive amoxicillin as first-line empiric therapy, which is ineffective against *M. pneumoniae*,[6] particularly if their symptoms are not compatible with the common clinical perception of "walking pneumonia."

A major obstacle to detecting *M. pneumoniae* epidemics is the lack of routine testing for this organism. Several factors contribute to low rates of diagnostic testing. First, current guidelines instruct clinicians to order diagnostic testing for children only when signs and symptoms suspicious for *M. pneumoniae* are present.[6] However, emerging evidence suggests that CAP caused by *M. pneumoniae* may be clinically indistinguishable from that because of other etiologies.[1,46] Furthermore, in many settings, PCR-based testing is preferred over serology for its superior specificity and lack of required paired specimens[44,47]; however, PCR is costly, may have slow turnaround time and may be unavailable to clinicians. Finally, because children may test PCR positive for several weeks after an infection,[43,44] positive results may not reflect acute infection, complicating the clinical interpretation and contributing to clinician dissatisfaction with *M. pneumoniae* testing. Increased adoption by clinical labs of new Food and Drug Administration-cleared multipathogen molecular technology, which includes *M. pneumoniae* in addition to other common bacterial and viral respiratory pathogens,[48] will address some of these issues. Indeed, rapid detection of increasing numbers of *M. pneumoniae*-positive respiratory specimens by such a panel at CHCO heralded the onset of the outbreak and quickly established the association between this organism and SJS.

There are several limitations to this investigation. In assessing the community trends in *M. pneumoniae* infection over time, we were unable to rely on laboratory-confirmed cases of *M. pneumoniae* because of inconsistent diagnostic testing in this population. Instead, we used ICD-9 codes for pneumonia (including unspecified etiology) as proxy variables for *M. pneumoniae* infection, which may have been less specific, and missed cases of *M. pneumoniae*, which resulted in a presentation besides pneumonia. Furthermore, it is controversial whether *M. pneumoniae* may be carried in the nasopharynx of a child without causing illness. A recent study[43] suggested that detection rates of *M. pneumoniae* were almost equivalent between asymptomatic children and those with respiratory symptoms, while other studies have found little to no carriage in healthy children[1,49,50]; colonization with *M. pneumoniae* in the children studied could lead to overestimation of *M. pneumoniae*-associated disease. In assessing the molecular features of *M. pneumoniae* in cases of *M. pneumoniae*-associated SJS, we are limited by the small number of PCR-positive *M. pneumoniae* specimens available. Because the molecular characteristics of *M. pneumoniae* in SJS have not been previously reported, we are unable to correlate our findings with prior studies. In addition, current molecular typing methods (MLVA and P1) are limited in their ability to distinguish strains and may miss important variation. Finally, the number of household contacts surveyed is small and may not reflect trends in the broader population.

In summary, this investigation into one of the largest documented outbreaks of *M. pneumoniae*-associated SJS revealed an epidemic of *M. pneumoniae* pneumonia. Household transmission of *M. pneumoniae* was common within the households investigated, and the novel use of MLVA and P1 typing revealed that molecular characteristics were conserved among household contacts of case-patients. Improved availability and affordability of reliable and rapid *M. pneumoniae* diagnostic testing are needed to increase testing rates in the pediatric population. This will allow for better appreciation of the incidence and spectrum of *M. pneumoniae* infections as well as facilitate appropriate treatment and earlier detection of epidemics. Whole genome sequencing may yield superior strain characterization and provide further insight into the clinical implications of strain features. Human genetic analysis may also be needed to reveal the biologic reasons for the development of *M. pneumoniae*-associated SJS.

Acknowledgments

We gratefully acknowledge Corey R. Butler (CDC, Denver, CO), Teresa Foo (University of Colorado, Denver, CO; Colorado Department of Public Health and Environment, Denver, CO), Katelyn Hall (Colorado Department of Public Health and Environment, Denver, CO), Max Kiefer (CDC, Denver, CO), Ursula Lauper (University of Colorado, Denver, CO), Kristin Pretty (Children's Hospital Colorado, Aurora, CO), Brent Seaton (Focus Diagnostics Reference Laboratory, San Juan Capistrano, CA), Kelly West (Children's Hospital Colorado, Aurora, CO) and Melanie Whittington (University of Colorado, Denver, CO).

M.P.G. is a member of the Data Safety Monitoring Board for Pfizer with regard to a vaccine under development. The vaccine has no relationship to the findings presented in this study; however, Pfizer manufactures an antibiotic (azithromycin), which is sometimes used to treat *M. pneumoniae* infections. D.O. has a grant for a vaccine-related study through June 2016, which has no bearing on the research presented in this article. He was also paid by Takeda to attend a dengue virus vaccine discussion panel as a consultant at the ASTHM conference in October 2014.

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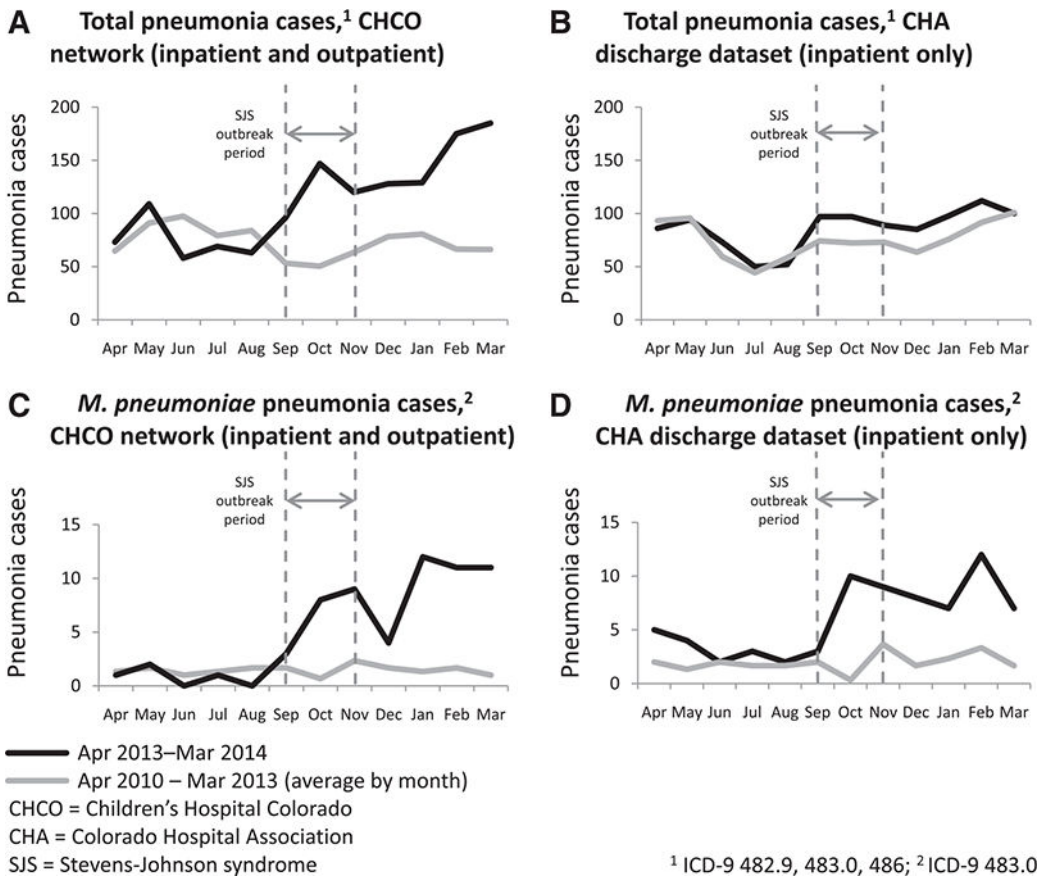


FIGURE 1.

Pediatric pneumonia cases (5–21 years of age) by month, outbreak year (April 2013–March 2014) versus baseline (average by month, April 2010–March 2013).

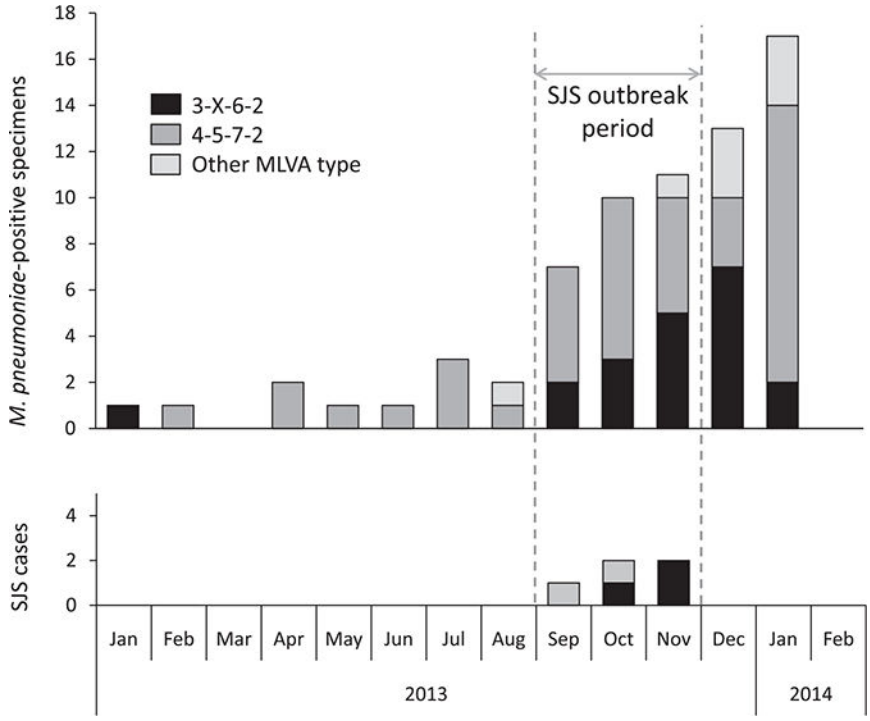


FIGURE 2.

MLVA types in total and SJS *M. pneumoniae*-positive specimens— Colorado, January 2013–January 2014. Other MLVA types include 3-5-7-2 (n = 1), 4-4-7-2 (n = 1), 4-6-7-2 (n = 3) and undetermined (n = 4).

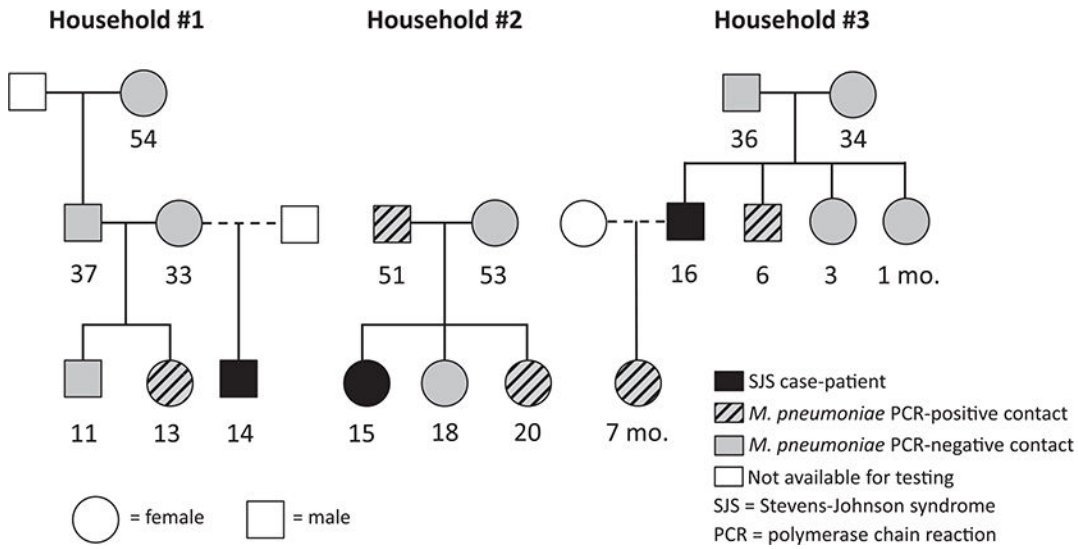
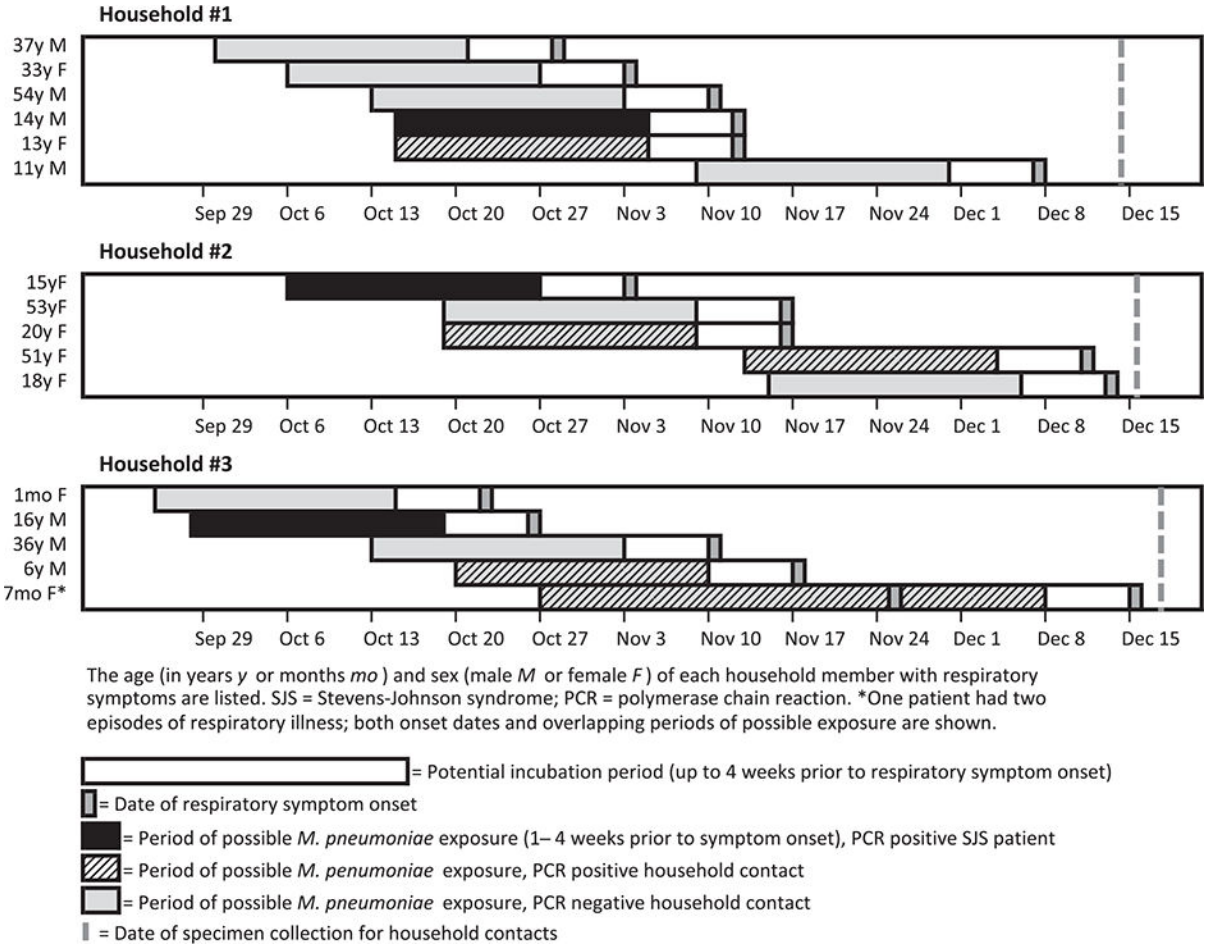


FIGURE 3.

Genograms depicting households of 3 *M. pneumoniae*-associated SJS patients showing PCR results of household contacts. Ages of each surveyed contact are shown (age given in years unless otherwise specified). Solid lines indicate relationships between household members. Dotted lines represent relationships with nonhousehold members (unavailable for testing).



The age (in years *y* or months *mo*) and sex (male *M* or female *F*) of each household member with respiratory symptoms are listed. SJS = Stevens-Johnson syndrome; PCR = polymerase chain reaction. *One patient had two episodes of respiratory illness; both onset dates and overlapping periods of possible exposure are shown.

FIGURE 4.

Timing of respiratory symptom onset and period of possible exposure to *M. pneumoniae* for SJS patients and their household contacts by household, fall 2013.

TABLE 1

Molecular Characteristics of *Mycoplasma pneumoniae* PCR-positive Specimens From SJS and Non-SJS Patients in Colorado

	SJS Patients, n = 5	Non-SJS Patients, n = 69
Laboratory Characteristics	**n (%)**	**n (%)**
Dates of collection	September–November, 2013	January 2013–January 2014
Isolates generated	5 (100)	45 (65)
MLVA typing		
3-5-6-2	1 (20)	15 (22)
3-6-6-2	2 (40)	5 (7)
4-5-7-2	2 (40)	40 (58)
Other/indeterminate	0	9 (13)
Macrolide susceptibility testing		
Susceptible	5 (100)	62 (90)
Resistant	0	5 (7)
Indeterminate	0	2 (3)
P1 typing *	n = 5	n = 45
Type 1	2 (40)	31 (69)
Type 2	1 (20)	10 (22)
Type 2 variant	2 (40)	4 (9)

* P1 typing was performed only on isolates, not total specimens; percentages reflect the percentage of total isolates available for testing.

TABLE 2

Clinical and Laboratory Characteristics of Household Contacts of 3 *Mycoplasma pneumoniae*-associated SJS Patients

Household Member (age*)	Respiratory Symptoms†	Symptom Onset	Antibiotic Use (Start Date)‡	*M. pneumoniae* PCR Test Result	MLVA Type	Macrolide Susceptibility
Household #1				Visit 12/14/13		
SJS case: male (14)	**Yes§**	**November 12, 2013**	**Az ithromycin (November 18, 2013)**	**Positive¶**	**3-6-6-2**	**Susceptible**
Grandmother (54)	Yes	November 10, 2013	—	Negative	—	—
Stepfather (37)	Yes§	October 28, 2013	Azithromycin (November 11, 2013)	Negative	—	—
Mother (33)	Yes	November 3, 2013	—	Negative	—	—
Sister (13)	Yes	November 12, 2013	Amoxicillin (November 14, 2013)	Positive	3-6-6-2	Susceptible
Brother (11)	Yes	December 7, 2013	—	Negative	—	—
Household #2				Visit 12/15/13		
SJS case: female (15)	**Yes§**	**November 3, 2013**	**Azithromycin (November 10, 2013)**	**Positive‖**	**3-5-6-2**	**Susceptible**
Father (51)	Yes	December 11, 2013	—	Positive	3-5-6-2	Susceptible
Mother (53)	Yes	November 16, 2013	—	Negative	—	—
Sister (20)	Yes§	November 16, 2013	Azithromycin (November 19, 2013)	Positive	3-5-6-2	Resistant
Sister (18)	Yes	December 13, 2013	—	Negative	—	—
Household #3				Visit 12/17/13		
SJS case: male (16)	**Yes§**	**October 26, 2013**	**Azithromycin (October 30, 2013)**	**Positive****	**4-5-7-2**	**Susceptible**
Father (36)	Yes	November 10, 2013	—	Negative	—	—
Mother (34)	No	—	—	Negative	—	—
Brother (6)	Yes	November 17, 2013	—	Positive	4-5-7-2	Susceptible
Sister (3)	No	—	—	Negative	—	—
Sister (1 mo)	Yes	October 22, 2013	—	Negative	—	—
Daughter (7 mo)	Yes	November 26, 2013; December 15, 2013††	Unknown (November 26, 2013) ##	Positive	4-5-7-2	Susceptible
Summary	n (%)		n (%)	n (%)		n (%)
Household contacts (n = 15)	Symptoms13 (87%)		Antibiotic use 4 (27%)	PCR positive 5 (33%)		Susceptible 4 (80%)

Boldface text indicates the SJS patient within each household.

[*] Age at the time of specimen collection, in years unless otherwise noted (mo = months).

[†] Respiratory symptoms include 1 or more of fever, cough, "cold," congestion, sore throat, shortness of breath and wheezing.

[‡] SJS symptoms developed before the initiation of treatment with azithromycin in all 3 case-patients.

[§] Symptoms resulted in clinician diagnosis of pneumonia.

[¶] *M. pneumoniae*-positive specimen collected on November 18, 2013.

[‖] *M. pneumoniae*-positive specimen collected on November 14, 2013.

[**] *M. pneumoniae*-positive specimen collected on October 30, 2013.

[††] Contact had 2 episodes of respiratory illness, between which she fully recovered.

[‡‡] Family did not recall the name of the antibiotic prescribed; child was diagnosed with an ear infection and prescribed antibiotics for treatment.