

## Enhanced Control of an Outbreak of *Mycoplasma pneumoniae* Pneumonia with Azithromycin Prophylaxis

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There are currently no recommended epidemic-control measures for *Mycoplasma pneumoniae* pneumonia outbreaks in closed communities. Previous studies have suggested the usefulness of chemoprophylaxis administered to close contacts of case-patients. To evaluate the effectiveness of various epidemic-control measures during an institutional outbreak, an observational study was undertaken during a very large outbreak of *M. pneumoniae* pneumonia at a facility for developmentally disabled residents ( $n = 142$  cases). Control measures evaluated included no control, standard epidemic-control measures, and targeted azithromycin prophylaxis (500 mg on day 1, 250 mg/day on days 2–5) plus standard epidemic-control measures. The combined use of azithromycin prophylaxis and standard epidemic-control measures was associated with a significant reduction in the secondary attack rate. This study suggests that the addition of antibiotic prophylaxis to standard epidemic-control measures can be useful during institutional outbreaks of *M. pneumoniae* pneumonia.

*Mycoplasma pneumoniae* is an important cause of upper and lower respiratory tract infections and is the most common cause of pneumonia during the summer months. It has been implicated in several institutional outbreaks of pneumonia, some of which lasted as long as 6 months [1–7]. Secondary attack rates have ranged from 10% to 50% in closed populations of mentally disabled patients, institutionalized boys, military recruits, children at summer camp, and families [1, 2, 8–13]. Although *M. pneumoniae* infection is rarely fatal, long-term sequelae can include neurologic, dermatologic, and hematologic complications [14].

Transmission occurs via respiratory droplets, requiring close contact with an infected person. The incubation period is usually 14–21 days [15]. Recommendations for infection control in patients hospitalized with *Mycoplasma* infection include the use of both standard and droplet precautions [16]. Currently, however, there are no specific recommendations for control of *Mycoplasma* epidemics in a closed community [17]; in fact, antibiotic prophylaxis of close contacts of infected persons has been discouraged [18].

Two placebo-controlled studies have suggested that the use of antibiotics by susceptible persons during an outbreak can reduce the rate of secondary transmission of *M. pneumoniae*. During a community outbreak of *M. pneumoniae* pneumonia, household contacts receiving oxytetracycline had a reduced rate of clinical disease [19], and during a hospital-associated

*M. pneumoniae* outbreak, hospital staff receiving tetracycline had a reduced rate of illness [20]. Here we describe the largest reported institutional outbreak of *M. pneumoniae* pneumonia to our knowledge and our evaluation of the effectiveness of various epidemic-control measures in reducing the secondary attack rate of pneumonia.

### Methods

**Background.** Facility A is a very large long-term-care hospital for the developmentally and mentally disabled. About 800 residents are grouped by diagnosis and functional status and live in 33 closed residential units. Unit residents spend most of their time together, dining and participating in rehabilitation activities, separate from residents of other units, but on occasion unit residents mix with residents from other units at the check-dispensing office or at the hospital canteen.

From mid-June through early August 1995, clinicians at facility A noted an increase in the number of patients admitted to the on-site acute-care hospital because of pneumonia. On 4 August, infection-control measures were implemented for hospitalized patients by use of standard precautions (which included universal precautions and body substance isolation) and droplet precautions (i.e., placing patients into private rooms and wearing masks when appropriate) [16]. Epidemic-control measures for units in which these patients resided included cohorting staff and residents and promoting hand washing. On 15 August, because of the continuing number of cases and the lack of identification of an etiologic agent, the facility requested assistance from the California Department of Health Services.

Preliminary analyses suggested that a high proportion of cases of pneumonia were occurring within the same housing unit and the epidemic was only slowly progressing from one unit to another. In an effort to reduce secondary transmission of pneumonia within units, the facility staff elected to add chemoprophylaxis to the existing epidemic-control measures. Starting 25 August, oral

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azithromycin (500 mg on day 1 and 250 mg on days 2–5) was administered to all unit residents and offered to staff working on a particular unit the day a newly involved unit identified its first case. Azithromycin (a macrolide) was chosen because it has a long half-life and can be administered once a day; it has few adverse effects or drug interactions and was provided by the manufacturer at no cost to the facility.

*Initial investigation and case-finding.* To confirm the presence of an outbreak, admission records to the facility's acute-care hospital were reviewed. The number of cases of pneumonia in June and July 1995 were compared with the average number of cases of pneumonia in June and July during the previous 5 years. Because this was a summertime epidemic of pneumonia, *M. pneumoniae* was suspected as the etiologic agent. Sera from convalescent patients were sent to the Centers for Disease Control and Prevention (CDC; Atlanta), and tested by using an antibody test system for *M. pneumoniae* IgG and IgM antibody (Remel, Lenexa, KS) [21].

After the outbreak was confirmed as being caused by *M. pneumoniae*, a facility-wide surveillance system for new cases was implemented by taking daily oral or rectal temperatures of all residents and referring either febrile residents (temperature  $\geq 37.8^{\circ}\text{C}$ ) or residents with cough for further evaluation and chest radiography. Ill staff members were requested to report to the employee health clinic. A case of pneumonia in a resident or staff member was defined as both the presence of an infiltrate on chest radiograph and a fever or cough, with onset of illness during 13 June to 6 October 1995.

During the first 9 weeks of the outbreak, convalescent sera from residents who had pneumonia were sent to a private laboratory for *M. pneumoniae* IgG testing by indirect fluorescent antibody (Zeus Scientific, Raritan, NJ). In addition, sera were obtained and tested from residents with pneumonia between 1 January and 12 June 1995. Laboratory confirmation of *M. pneumoniae* pneumonia was defined as a 4-fold rise or fall in titer or a single convalescent titer  $\geq 1:64$ . Paired sera from a convenience sample of cases were also tested by use of a complement fixation assay for antibody to *M. pneumoniae* (Viral and Rickettsial Disease Laboratory, California Department of Health Services, Berkeley) and were defined as positive if there was a 4-fold rise or fall in titer or a single titer of  $\geq 1:32$  [22]. *M. pneumoniae* was also isolated from some patients by culture of the throat or nasopharyngeal swabs in SP4 medium [23]. Presence of *M. pneumoniae* DNA was detected by polymerase chain reaction (PCR) in swab specimens with use of species-specific primers [24]. Case-patient information was obtained from medical records. Resident's Diagnostic Statistical Manual-IV (DSM-IV) axis 5 score was used as a measure of global function. Unit census and demographic information were obtained for each unit at the time of diagnosis of the first unit case.

*Observational study.* We reviewed the effectiveness of the different epidemic-control measures that were instituted sequentially during the outbreak period. Once epidemic-control measures were instituted in a particular unit, these measures did not change during the outbreak period. We defined "standard epidemic-control" measures as active surveillance, use of standard and droplet precautions in hospitalized case-patients, cohorting of residents and staff, and promoting hand washing in units where case-patients resided. To compare the effectiveness of epidemic-control measures in reducing the unit secondary attack rate, we categorized units in which case-patients resided into the following 3 groups based on the

epidemic-control measure in place at the time the first case-patient was diagnosed: group 1, no standard epidemic-control measures (13 June–3 August 1995); group 2, standard epidemic-control measures (4–24 August 1995); and group 3, standard epidemic-control measures plus azithromycin prophylaxis (25 August–6 October 1995). A primary case was defined as the first diagnosed case among residents in a unit or a case occurring in another resident in the same unit within the first 2 weeks after the initial case was diagnosed, given an incubation period for this disease of  $\geq 14$  days. A secondary case was defined as a case occurring 2–9 weeks after the initial case was diagnosed in the unit.

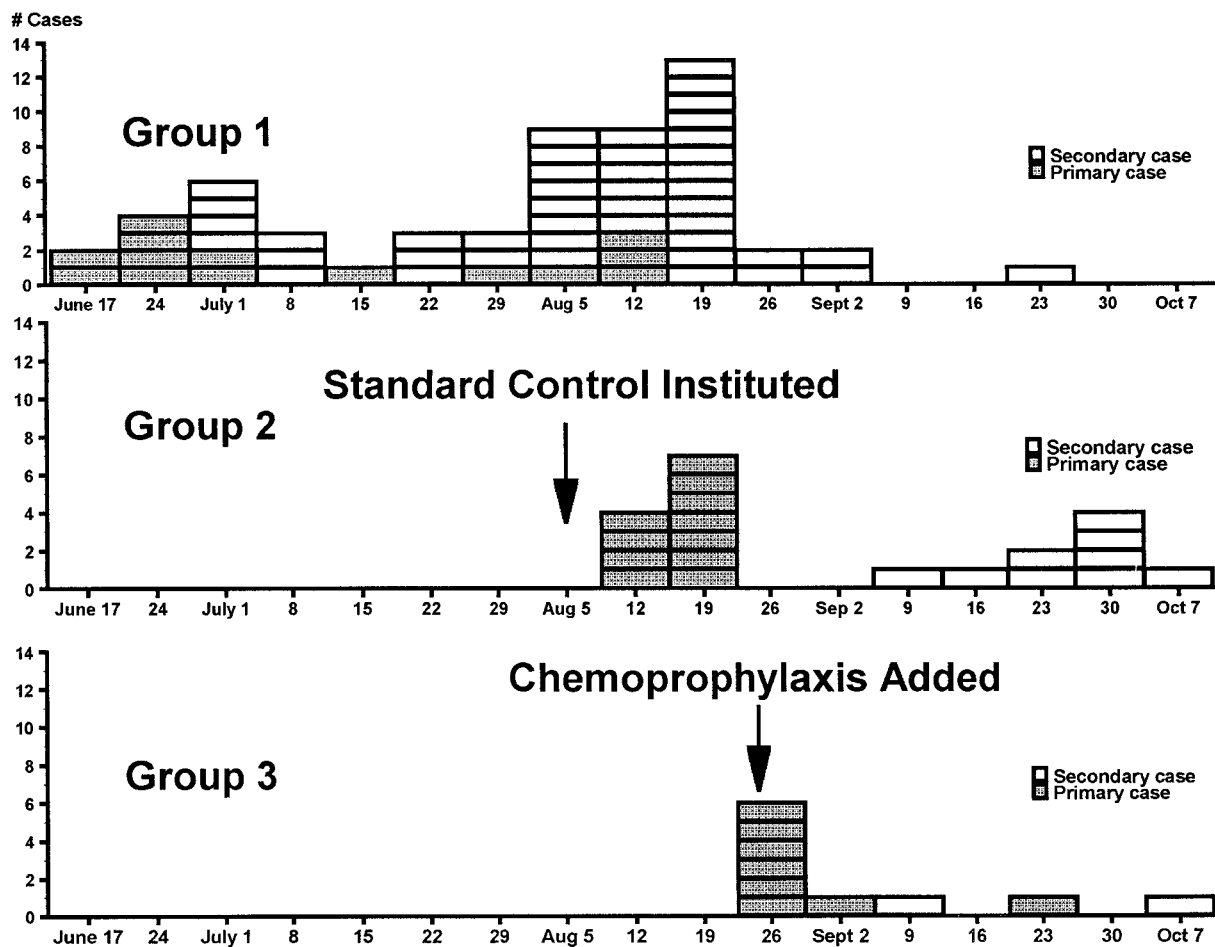
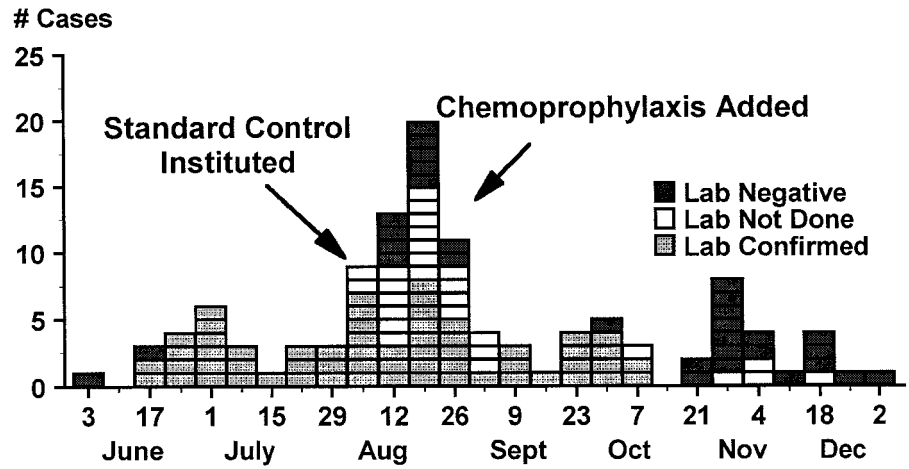
To evaluate the role of previous infection with *M. pneumoniae* in determining effectiveness of epidemic-control measures and to identify subclinical infection, we obtained baseline sera for *M. pneumoniae* IgG antibody from residents of group 3 units within 1 week after the identification of the initial unit case and follow-up sera at least 3 weeks later. Residents were defined as previously infected if they had a baseline complement fixation IgG titer of  $\geq 1:32$ . Residents were defined as recently infected if there was a 4-fold rise or fall in titer or a follow-up titer of  $\geq 1:32$  [22].

Secondary attack rates for the residents in each housing unit were calculated by dividing the number of secondary cases by the number of susceptible residents within the housing unit. The number of susceptible residents was equal to the number of residents in the housing unit minus the number of primary cases minus the number of previously infected residents. This secondary attack rate was adjusted by dividing by the number of primary cases in each unit to account for "transmission pressure" (i.e., the increased likelihood of secondary transmission in housing units with more than one primary case). Crude and adjusted housing unit secondary attack rates were compared by use of Kruskal-Wallis analysis of variance for nonparametric data. The  $\chi^2$  test was used to compare proportions. All *P* values were two-tailed, and *P*  $\leq .05$  was significant.

## Results

*Initial investigation and case-finding.* During June and July 1995, 23 cases of pneumonia were identified in facility A residents, versus on average only 5 cases in June and July during the previous 5 years. During the outbreak period, from 13 June to 6 October 1995, we identified 95 cases of pneumonia among residents (figure 1), for a 16-week cumulative incidence of 11.9% (95/795). Seventy-two (76%) of these 95 patients were tested for evidence of recent *M. pneumoniae* infection; of these, 60 (83%) were positive. Convalescent sera were obtained from the 22 residents who had pneumonia with onset from 13 June to 31 July 1995, and all of these were seropositive for acute *M. pneumoniae* infection by the Remel test. *M. pneumoniae* was cultured from 5 (29%) of 17 cases and was identified in 7 (41%) of 17 cases by PCR. Culture isolates were confirmed by PCR as *M. pneumoniae*. None of the residents tested who had pneumonia from 1 January to 12 June 1995 (*n* = 16) or from 7 October to 17 November 1995 (*n* = 15) had laboratory evidence of *M. pneumoniae* infection. In addition, during the outbreak period, 47 cases of radiographically confirmed pneumonia among staff members were reported to the facility's employee

**Figure 1.** Cases of pneumonia among residents of long-term-care facility during outbreak of *M. pneumoniae* pneumonia, California, by week of onset—June–December 1995. Standard epidemic-control measures were implemented week of 5 August 1995, and chemoprophylaxis was added to standard epidemic-control measures week of 26 August 1995.



**Figure 2.** Primary and secondary cases of pneumonia among facility A residents by week of onset and by epidemic-control group. Group 1, no standard epidemic-control measures (13 June–3 August 1995); group 2, standard epidemic-control measures (4–24 August 1995); group 3, standard epidemic-control measures plus azithromycin prophylaxis (25 August–6 October 1995).

health clinic, for a total of 142 radiographically confirmed cases of pneumonia among the 1940 residents and staff at the facility.

Clinical signs and symptoms among residents who had pneumonia included cough (80%), fever  $\geq 38.0^{\circ}\text{C}$  (63%), sore throat (40%), congestion or coryza (34%), and chest or back pain (25%). Seventy (74%) of the ill residents were male. Ill residents had a mean age ( $\pm\text{SD}$ ) of  $40 \pm 15$  years. Sex and age were similar to the general resident population (74% male; mean age,  $35 \pm 11$  years). The mean IQ for ill residents was  $33 \pm 22$  (range, 6–80) and mean global function score (DSM-IV, axis 5) was  $22 \pm 14$  (range, 2–90); these values were lower but not significantly different from the respective mean unit scores for non-ill residents (IQ,  $41 \pm 18$ ; global function score,  $30 \pm 10$ ). Units in which developmentally disabled persons (those with disorders of psychological development) resided were more likely to have cases (15/19) than units in which only mentally disabled persons (those with psychiatric illness) resided (2/14) ( $P < .001$ ).

**Observational study.** The epidemic involved 17 of the 33 housing units. The number of secondary and subsequent cases ( $n = 62$ ) was almost twice the number of primary cases ( $n = 33$ ). There were 14 primary and 44 secondary cases in group 1 units, 11 primary and 9 secondary cases in group 2 units, and 8 primary and 2 secondary cases in group 3 units (figure 2). Throughout the outbreak, the number of primary cases for each unit ranged from 1 to 5 (median, 1) and was relatively constant over the course of the epidemic (data not shown).

The overall baseline anti-*M. pneumoniae* IgG prevalence among residents who did not become ill (i.e., the non-case residents) was 16 (3.7%) of 427. In the 11 units in which most residents were tested, the baseline IgG prevalence by unit ranged from 0 to 10% (median, 0). Only 4 (3.1%) of 129 residents had recent infection among the group 3 unit residents tested.

**Table 1.** Baseline characteristics of housing units with resident-cases of *M. pneumoniae* pneumonia at facility A, by epidemic-control group.

	Epidemic-control measure			<i>P</i>
	None (group 1)	Standard* (group 2)	Standard plus chemoprophylaxis† (group 3)	
No. of units	5	7	5	
Census	$32 \pm 4$	$23 \pm 10$	$33 \pm 4$	.08
% male	$85 \pm 15$	$75 \pm 18$	$65 \pm 25$	NS
Age, years	$41 \pm 11$	$31 \pm 15$	$35 \pm 3$	NS
IQ	$29 \pm 18$	$40 \pm 21$	$53 \pm 10$	NS
Global function score	$19 \pm 3$	$32 \pm 9$	$39 \pm 8$	.02

NOTE. Data are mean  $\pm$  SD. NS, not significant.

\* Active surveillance, use of standard and droplet precautions in hospitalized case-patients, and in units in which case-patients resided, cohorting residents and staff and promoting hand washing.

† Oral azithromycin 500 mg on day 1 and 250 mg/day on days 2–5 administered to all unit residents and offered to all unit staff after first case diagnosed in unit.

**Table 2.** Findings among residents of housing units with resident-cases of *M. pneumoniae* pneumonia at facility A, by epidemic-control group.

	Epidemic-control measure		
	None (group 1)	Standard (group 2)	Standard plus chemoprophylaxis (group 3)
No. of units	5	7	5
Primary cases per unit	2 (1–5)	1 (1–3)	1 (1–4)
Secondary cases per unit	8 (6–14)	0 (0–6)	0 (0–1)
Crude unit secondary attack rate, %	$31.0 \pm 12.1$	$7.5 \pm 12.7$	$1.3 \pm 1.7^*$
Adjusted unit secondary attack rate, %	$17.6 \pm 18.6$	$7.5 \pm 12.7$	$0.9 \pm 1.6^{\dagger}$

NOTE. Data are median (range) or mean  $\pm$  SD.

\*  $P = .02$ , Wilcoxon rank sum test, comparing group 1 crude unit secondary attack rate with group 2 crude unit secondary attack rate. Group 2 and group 3 crude unit secondary attack rates were not significantly different ( $P > .05$ ). Group 3 crude unit secondary attack rate was significantly lower than that of group 1 ( $P = .008$ ).

†  $P = .008$ , Wilcoxon rank sum test, comparing group 1 adjusted unit secondary attack rate with group 3 adjusted unit secondary attack rate. Group 2 adjusted unit secondary attack rate was not significantly different from those of group 1 or group 3 ( $P > .05$ ).

The baseline characteristics of the units in the 3 epidemic-control groups were similar (table 1). There were no significant differences among the epidemic-control groups by unit census, sex, age, or IQ. Epidemic-control group 1 had a lower mean level of global functioning ( $P = .02$ ), but global functioning was not significantly correlated with the unit secondary attack rate within any of the 3 epidemic-control groups or among the individual units ( $r = -.42$ ,  $P = .09$ ). Additionally, IQ was not correlated with the unit secondary attack rate ( $r = -.03$ ,  $P = .92$ ). Within each group, there was no correlation between unit secondary attack rate and duration of the outbreak.

Table 2 shows the number of primary and secondary cases per unit and the crude and adjusted unit secondary attack rates by the different methods of epidemic control. Comparing crude unit secondary attack rates by group showed that group 2 units had a large and statistically significant reduction in secondary attack rates compared with group 1 units ( $P = .02$ ), which was further reduced in group 3 units (but not statistically significantly so). Comparing adjusted unit secondary attack rates by group showed that group 2 unit adjusted secondary attack rates were also substantially reduced, but this reduction did not reach statistical significance ( $P = .11$ ). Both crude and adjusted secondary attack rates were significantly lower for group 3 units compared with group 1 units ( $P = .008$  for both comparisons).

## Discussion

Our study documents the largest outbreak to our knowledge of *M. pneumoniae* pneumonia in a closed institutional setting

[1–13, 25]. A total of 142 cases of pneumonia in residents and staff at facility A were identified by chest radiographs during the 16-week outbreak period from 13 June to 6 October 1995.

The attack rate (11.9%) for pneumonia among residents was higher than previously reported attack rates in similar populations [1, 2] (Cochi SL, personal communication). This might be explained by the low prevalence of detectable antibody in this relatively isolated population, suggesting a lack of recent exposure, which resulted in increased susceptibility to infection, especially pneumonia. A second factor that might have contributed to the high proportion of pneumonia in this outbreak was the low functional status of the residents. Developmentally disabled patients have experienced increased attack rates of *Mycoplasma pneumoniae* during outbreaks [1] (Cochi SL, personal communication), and, in our study, cases were significantly more likely to occur in units housing developmentally disabled patients than in units housing mentally disabled patients.

Another major finding in our investigation was the reduction in the unit secondary attack rates by using standard epidemic-control measures and a further reduction in the unit secondary attack rates with the addition of targeted azithromycin chemoprophylaxis. With an increase in intensity of epidemic-control measure by group, there was a qualitative change in each group's epidemic curve and a decrease in secondary transmission.

Transmission in this facility occurred primarily within units and not between units. There was infrequent contact between different unit residents, and units were distant from each other. The slow progressive involvement of additional units and the low prevalence of anti-*Mycoplasma* antibody in group 3 units further supported the notion that there was little exposure between units. Therefore, an effective control strategy could be developed that targeted each unit only when a case first appeared in any such unit. By relocating case-patients, cohorting contacts of case-patients, and administering chemoprophylaxis to contacts of case-patients, secondary transmission within units was significantly reduced.

Our analysis of the effectiveness of the various epidemic-control measures used in this outbreak was limited by several factors. The most important limitation was that we could not perform a randomized study and thus we compared different groups at different times during the outbreak. We did, however, explore what confounding factors (i.e., age, sex, unit census, IQ score, and functional level) might exist in the different epidemic-control groups and found either that these factors were not different among epidemic-control groups or that they were not associated with the unit secondary attack rates.

The most common reason for a decrease in the secondary attack rate during an outbreak is "exhaustion of susceptibles" due to exposure to the infectious agent. To evaluate prior exposure to *M. pneumoniae*, we obtained sera from all residents within group 3 units. Few showed evidence of recent exposure (4/129). We subsequently controlled for decreased susceptibil-

ity in our analysis by removing these seropositive residents from the unit susceptible population. Additionally, to account for differences in the force of transmission by exposure of contacts to multiple primary cases, we adjusted the secondary attack rates and were still able to demonstrate a reduction in the secondary attack rate between group 1 and group 3 units.

Our study is consistent with two previous studies [19, 20] demonstrating the efficacy of chemoprophylaxis in reducing the secondary transmission of *M. pneumoniae* pneumonia. Adding azithromycin chemoprophylaxis to standard epidemic-control measures in this large institutional outbreak of *M. pneumoniae* further reduced unit secondary attack rates. Until it is possible to conduct a randomized controlled trial, the addition of targeted chemoprophylaxis to standard epidemic-control measures should be considered in the control of institutional outbreaks of *M. pneumoniae*.

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