Identification of Risk Factors for Infection in an Outbreak of *Mycoplasma pneumoniae* Respiratory Tract Disease

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(See the editorial commentary by Johnson on page 1246)

**Background.** *Mycoplasma pneumoniae* is one of the most common pathogens that causes community-acquired respiratory tract infection. Outbreaks are well known, and all age groups are susceptible. An outbreak in an army training unit afforded an opportunity to identify possible risk factors for morbidity.

**Methods.** An outbreak of respiratory illness that occurred in a unit comprising 91 trainees was investigated and analyzed as a cohort study. *M. pneumoniae* infection was suspected on clinical grounds and was confirmed by polymerase chain reaction, culture, and serologic testing. Data regarding medical history, symptoms, signs, and laboratory tests were collected.

**Results.** During a period of 12 days, 41 soldiers (45.1%) had respiratory illnesses, of which 10 (11.0%) were pneumonia. Comparison of symptomatic and asymptomatic individuals revealed that smoking was associated with higher rates of disease (risk ratio, 2.1; 95% confidence interval [CI], 1.3–3.2; *P* < .005) and seroconversion (risk ratio, 2; 95% CI, 1.2–3.4; *P* < .005) and smoking (adjusted odds ratio, 5.6; 95% CI, 1.5–20.4; *P* < .005) were associated with symptomatic infection; stratification according to smoking status revealed that immunoglobulin G levels among nonsmokers were protective. Patients who had pneumonia had lower lymphocyte counts (vs. cells/µL; *P* < .001)

**Conclusions.** Smoking and lower preexisting immunoglobulin G levels were strongly associated with *M. pneumoniae* respiratory infection. These findings emphasize the importance of immunity and cessation of smoking for the prevention of disease. The high attack rate emphasizes the extent of infection transmission among healthy persons living in close contact.

*Mycoplasma pneumoniae* is a common respiratory pathogen that affects both the upper and lower respiratory tracts in all age groups [1–3]. This agent is estimated to be responsible for ~15%–20% of all cases of community-acquired pneumonia (CAP) and for up to 40% of cases of CAP among children [3–5]. Thus, it is 1 of the 2 most prevalent pathogens (with *Streptococcus pneumoniae*) that causes CAP. Two studies have shown that *M. pneumoniae* is considered to be responsible for up to 32.5% of hospitalizations for CAP and is second only to *S. pneumoniae* in cases of CAP among elderly, hospitalized patients [5, 6].

Previous epidemiological studies have suggested that...
M. pneumoniae infection can be found worldwide, with peaks occurring every 3–5 years [4, 7]. Outbreaks have been described in closed-community settings [8–11]. Most outbreaks evolve gradually [12]; however, point source acute outbreaks in which many people are infected simultaneously occur in closed or semiclosed settings. In this study, we describe an acute M. pneumoniae outbreak that occurred in an army unit of basic trainees. Comparison of healthy individuals with patients who have respiratory illness enabled us to identify risk factors for acquiring infection.

METHODS

Outbreak Description

On 19 September 2004, a report of an unusual cluster of respiratory tract illness in 11 soldiers was received at the Army Health Branch of the Israeli Defense Force Medical Corps (Ramat-Gan, Israel). An epidemiologic investigation, started the following day, revealed that morbidity was confined to a single unit in a training camp. This unit numbered 91 male soldiers aged 18–21 years (75 of whom were 18–19-year-old recruits and 16 of whom were command staff). All were otherwise healthy. The trainees lived in confined quarters and slept in close proximity to each other. Acute urine and serum samples were obtained from 72 soldiers. Throat and nasopharyngeal specimens were obtained from soldiers who complained of any signs of respiratory illness and who had an oral temperature of at least 37.3°C in the preceding 48 h (n = 38). All symptomatic soldiers were treated with azithromycin (500 mg/day for 7 days) within 1 week after the first visit by the investigative team. At the second visit 2 weeks later, convalescent-phase serum samples were obtained from 42 of the original 72 soldiers and from an additional 6 soldiers. The distribution of samples by clinical definition is given in table 1. On both visits, soldiers completed questionnaires regarding current morbidity, time of disease onset, and risk factors such as number and age of siblings, military function (i.e., command staff or trainee), and smoking habits. Soldiers who reported smoking at least 1 cigarette a day at the time of the outbreak were defined as smokers.

The number of cigarettes per day per smoker ranged from 1 to 15 (mean ± SD, 6.7 ± 4.2). Soldiers were asked to subjectively grade their various clinical signs (except sputum production and rhinorrhea) as “mild” or “moderate.”

Case definition. Symptomatic soldiers were categorized as follows: (1) respiratory tract infection (RTI), defined as an oral temperature of at least 37.3°C accompanied by ≥1 of the following symptoms: sore throat, cough, rhinorrhea, or headache (41 patients); (2) febrile RTI, defined as an infection with the same symptoms as RTI, but with an oral temperature of at least 37.8°C (29 patients from within the RTI category); and (3) pneumonia, determined by a diagnosis of pneumonia by chest radiography (10 patients from within the RTI category). These soldiers were compared with a control group of 50 soldiers from the same unit who were present at the time of the outbreak but who did not have respiratory symptoms or who had an oral temperature <37.3°C.

Serologic controls. A collection of 40 paired serum samples obtained 1–3 months apart from soldiers not related to the outbreak [13] was used to determine cutoffs for seroconversion (see the section Serologic Testing below). Twenty of these samples were collected from soldiers who had performed their basic training in the same camp 2 years previously, and the other 20 samples were obtained from recruits at another basic training camp approximately during the time of the outbreak.

Laboratory Methods

Duplicate throat samples were obtained from 38 available patients, of whom 25 had an oral temperature of at least 37.3°C. One sample from each subject was inoculated on blood agar for detection of Streptococcus pyogenes. The other was transferred to 4 mL of SP4 medium and used for M. pneumoniae culture and molecular detection [14]. Molecular detection was performed by an in-house specific nested PCR (PCR1), as previously described [15, 16]. This test was shown in our laboratory to have a detection limit of ~20 CFU/mL when using the type strain M129 (ATCC 29342) and a clinical isolate dating from before this outbreak. A real-time PCR assay specific for

<table>
<thead>
<tr>
<th>Patient group</th>
<th>PCR</th>
<th>Culture</th>
<th>Acute-phase serum</th>
<th>Convalescent-phase serum</th>
<th>Acute-phase blood cell counts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with pneumonia (n = 10)</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>6 (5 paired)</td>
<td>7</td>
</tr>
<tr>
<td>Patients with RTI without pneumonia (n = 31)</td>
<td>17</td>
<td>17</td>
<td>28</td>
<td>18 (16 paired)</td>
<td>21</td>
</tr>
<tr>
<td>Control subjects (n = 47)</td>
<td>13</td>
<td>13</td>
<td>36</td>
<td>24 (21 paired)</td>
<td>12</td>
</tr>
<tr>
<td>Serologic controlsb</td>
<td></td>
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<td></td>
<td></td>
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</tbody>
</table>

NOTE. RTI, respiratory tract infection with an oral temperature of at least 37.3°C.

a Control subjects did not have RTI.
b No data were available for 3 control subjects.
c Serologic controls were obtained from other unrelated military units not experiencing outbreaks.
Risk Factors for *M. pneumoniae* Infection

Figure 1. Epidemic curve depicting dates of disease onset for patients with febrile respiratory tract infection (temperature, $\geq 37.8^\circ$C; black columns) and nonfebrile respiratory tract infection (temperature, $\geq 37.3^\circ$C or $< 37.8^\circ$C; grey columns). Precise time of disease onset was available for only 36 of 41 patients with febrile respiratory tract infection.

*M. pneumoniae* was performed at the Centers for Disease Control and Prevention (Atlanta, GA) to confirm the PCR1 results. The real-time PCR assay can detect $< 5$ genome copies of the *M. pneumoniae* ATPase gene [17]—thus, the real-time PCR assay was, at a minimum, 4 times more sensitive than PCR1. Molecular subtyping of the epidemic strain was performed as recently described [18].

**Detection of Legionella and Chlamydiophila species.** Nine urine samples were tested for the presence of *Legionella pneumophila* serogroup 1 antigen (NOW Legionella Urinary Immunochromatographic Antigen Test; Binax). All swabs were tested for *Chlamydiophila pneumoniae* DNA as described by Black et al. [19].

**Virus detection.** Nasopharyngeal swabs (Virocult; MW&E) were examined for the presence of respiratory syncytial virus, influenza A and B viruses, parainfluenza viruses, and adenovirus by direct immunofluorescence assay using commercial monoclonal antibodies (Chemicon International) and by tissue culture. PCR and RT-PCR were used as previously described [20–22] to test for the presence of adenovirus, influenza viruses, and human metapneumovirus by real-time PCR.

**Serologic Testing.** Acute-phase serum samples (defined as having been obtained at the first visit) and convalescent-phase serum samples (defined as having been obtained at the second visit 2 weeks later) were tested for specific anti-*M. pneumoniae* IgA, IgG, and IgM antibodies using SeroMP ELISA kits (IgG, IgM, and IgA; Savyon Diagnostics). Results were then calculated for each serum sample as arbitrary binding units (BU) per mL, according to a calibration curve. Seroconversion was determined if the increase in IgA, IgM, or IgG levels between the convalescent- and acute-phase serum samples was higher than the mean increase plus 2 SDs of the serologic control group, and only if the absolute IgA, IgM, or IgG level was higher in convalescent-phase serum samples than the mean of the serologic control group plus 2 SDs.

**Data Analysis.** Statistical significance for the differences in antibody levels was tested using the nonparametric Mann-Whitney U test when the independent variable had 2 levels and using the Kruskal-Wallis H test when it had $\geq 3$ levels. Comparison of categorical variables was performed by the $\chi^2$ test or Fisher’s exact test for small samples. Analysis of acute IgG levels in association with clinical and laboratory findings was further performed after stratifying for smoking status. Effectiveness of protection by specific IgG levels among nonsmokers was calculated as $1 - risk ratio$. Multivariate analysis was performed using a logistic regression model that included smoking status, level of specific anti-*M. pneumoniae* IgG, and military function (basic trainees or command staff). Data analysis was performed using SPSS, version 12.0 for Windows (SPSS).

**RESULTS.** Febrile morbidity began in the unit on 10 September 2004 and peaked on 19 and 20 September 2004 (figure 1). Forty-one (45.1%) of 91 individuals had RTI, 29 (31.9%) of whom had FRTI and 10 (11.0%) of whom had radiologically confirmed pneumonia. Clinical symptoms and signs are summarized in figure 2.

**Diagnostic tests.** Blood cell counts obtained from 28 of the patients with RTI (of whom 7 had pneumonia) were within the normal range. Patients who had pneumonia ($n = 7$) had lower absolute lymphocyte counts (still within normal limits) than the remaining 21 patients with RTI ($1400 \pm 258$ vs. $2000 \pm 465$ cells/μL, respectively; $P = .001$).

All patients were negative for respiratory syncytial virus, influenza viruses, parainfluenza viruses, adenoviruses, human metapneumovirus, *C. pneumoniae*, and *L. pneumophila*. Twenty-eight
(73.7%) of 38 individuals tested were positive for *M. pneumoniae* by real-time PCR, whereas 17 (44.7%) tested positive by PCR1. The frequency of patients positive by PCR1 was highest among the patients with pneumonia (6 [75%] of 8 patients), lower in other patients with RTI (9 [52.9%] of 17 patients), and lowest in individuals who did not meet the clinical definition of RTI (2 [15.4%] of 13 patients; *P* = .02). For real-time PCR, the figures were 5 (62.5%) of 8 patients, 16 (94.1%) of 17 patients, and 7 (53.8%) of 13 patients, respectively (*P* = .03). Patients who had pneumonia were most frequently positive by culture (5 [71.4%] of 7 patients), followed by trainees who did not have RTI (4 [28.6%] of 13 patients) and other patients with RTI (2 [11.8%] of 17 patients; *P* = .015).

Seroconversion for any of the tested IgGs was observed in all patients with pneumonia and in 75% of the other patients with RTI (5 of 12 of 16 patients, respectively), but in only 5 (22.7%) of 21 trainees whose conditions did not meet the definition of RTI (*P* = .001). In 5 of the 8 samples that were tested, typing PCR succeeded and confirmed an outbreak with *M. pneumoniae* subtype 2.

**Risk factors for *M. pneumoniae* infection.** The number and age of siblings as well as an individual’s military function were not associated with an elevated risk of symptomatic *M. pneumoniae* infection (data not shown). However, an association between smoking and *M. pneumoniae* infection was confirmed (table 2). Incidence of RTI was 2.1 times more frequent among smokers than nonsmokers (95% CI, 1.3–3.2). This association was strengthened in multivariate analysis when military function and acute IgG levels were included (adjusted odds ratio [OR], 5.6; 95% CI, 1.5–20.4; table 3). Smokers had higher rates of positivity by both PCR1 (risk ratio [RR], 2.2; 95% CI, 1.1–4.3) and real-time PCR (RR, 1.4; 95% CI, 1–2) and higher seroconversion rates (RR, 2; 95% CI, 1.2–3.4), primarily by IgM (RR, 4.5; 95% CI, 1.3–15.9). Interestingly, there was no correlation between the number of cigarettes smoked per day and disease severity, symptoms and signs, or positivity by any diagnostic assay (data not shown). Moreover, the incidence of pneumonia and the frequency of positive cultures were similar among smokers and nonsmokers.

**Interaction between smoking and immunoglobulin levels.** Acute anti–*M. pneumoniae* IgG levels were lower in patients who had RTI than in patients who did not have RTI (23.2 ± 20.9 vs. 32.1 ± 19.4 BU/mL; *P* = .043). Similarly, IgG levels were significantly lower in individuals who seroconverted with IgA (17.6 ± 15.2 vs. 33.9 ± 20.9 BU/mL; *P* = .01) or IgM (10.5 ± 17.6 vs. 32.3 ± 18.7 BU/mL; *P* = .003). Furthermore, stratification by smoking status revealed that a preexisting, anti–*M. pneumoniae* IgG was protective only in nonsmokers, with an attack rate of 29.5% in immune (i.e., individuals who tested positive for specific anti–*M. pneumoniae* IgG) nonsmokers, whereas in the others (immune smokers, nonimmune nonsmokers, and nonimmune smokers), attack rates were 76.9%–85.7% (table 4). IgM seroconversion was, as might be expected, positively associated with low acute IgG levels in both smokers and nonsmokers.

**DISCUSSION**

*M. pneumoniae* outbreaks are well documented in the medical literature [3, 8–11, 23, 24]. However, many outbreaks are associated with relatively low numbers of concurrent cases and persist for months, whereas relatively few occur in short time periods, such as this one [12]. The explosive nature of this outbreak and the very early collection of samples enabled us to conduct a cohort study to assess the effect of prior immune status to *M. pneumoniae* and smoking habits of participants on the risk for morbidity, with minimal possible confounding.

That more trainees who did not have RTI tested positive for

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage of smokers (ratio)</th>
<th>Percentage of nonsmokers (ratio)</th>
<th>RR (95% CI)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical definition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All RTI</td>
<td>71.4 (15/21)</td>
<td>34.5 (20/58)</td>
<td>2.1 (1.3–3.2)</td>
<td>.005</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>14.3 (3/21)</td>
<td>10.3 (6/58)</td>
<td>1.4 (0.4–5)</td>
<td>.69</td>
</tr>
<tr>
<td>Laboratory definition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR1</td>
<td>69.2 (9/13)</td>
<td>32 (5/25)</td>
<td>2.2 (1.1–4.3)</td>
<td>.042</td>
</tr>
<tr>
<td>Real time PCR</td>
<td>92.8 (12/13)</td>
<td>64 (16/25)</td>
<td>1.4 (1.2–2.1)</td>
<td>.12</td>
</tr>
<tr>
<td>Culture</td>
<td>23.1 (3/13)</td>
<td>33.3 (8/24)</td>
<td>0.7 (0.2–2.2)</td>
<td>.7</td>
</tr>
<tr>
<td>Seroconversion (IgA, IgM or IgG)</td>
<td>81.8 (9/11)</td>
<td>40 (12/30)</td>
<td>2 (1.2–3.4)</td>
<td>.03</td>
</tr>
<tr>
<td>IgA seroconversion</td>
<td>63.6 (7/11)</td>
<td>26.7 (8/30)</td>
<td>2.4 (1.1–5)</td>
<td>.06</td>
</tr>
<tr>
<td>IgG seroconversion</td>
<td>54.5 (6/11)</td>
<td>26.7 (8/30)</td>
<td>2 (0.9–4.6)</td>
<td>.14</td>
</tr>
<tr>
<td>IgM seroconversion</td>
<td>45.5 (5/11)</td>
<td>10 (3/30)</td>
<td>4.5 (1.3–15.9)</td>
<td>.02</td>
</tr>
</tbody>
</table>

**NOTE.** RR, risk ratio; RTI, respiratory tract infection.
M. pneumoniae by the more sensitive real-time PCR compared with PCR1 might suggest that the M. pneumoniae bacterial load is lower in persons with milder infections or in asymptomatic individuals. This is in agreement with previous findings [25]. Asymptomatic children who are temporary carriers have been implicated as silent spreaders of the disease [26]. This suggests that a carrier state might exist in adults as well.

The low lymphocyte counts observed in the patients with pneumonia, although within normal limits, represent (to our knowledge) a new finding. Whether this is a result of the disease itself or whether it represents a preexisting state cannot be determined. Lower preexisting lymphocyte counts might be associated with greater susceptibility to infection and more severe morbidity, whereas M. pneumoniae infection contracted by individuals with higher lymphocyte counts may have a lower probability of progressing to pneumonia.

The unique scenario of this epidemic allowed us to investigate a few coexisting conditions that have been considered to influence M. pneumoniae infection. No significant association was observed between M. pneumoniae infection and the number and age of siblings or military function. We confirmed that smoking was significantly associated with a higher risk for respiratory infection with M. pneumoniae, as was suggested a few years ago [8] in a large, clinically defined outbreak of M. pneumoniae infection at a federal service training academy. The association of morbidity due to this pathogen with smoking is a relatively new observation. One possible explanation relates to M. pneumoniae pathogenesis; the attachment of M. pneumoniae to the respiratory epithelium is a prerequisite for later events that lead to disease onset [3]. Cigarette smoke is well known for its harmful effect on the mucociliary epithelium [27], which plays an important role in protection against M. pneumoniae infection. Therefore, it is plausible that defective clearance of the organism from the upper respiratory tract as a result of the effects of smoking may contribute to the pathogenesis of this infection. Moreover, smoking is a well-established risk factor for respiratory tract infection caused by other pathogens [28].

Another important observation is that acute IgG levels were inversely associated with morbidity and with seroconversion of both IgM and IgA. Considering IgG as a marker of previous exposure to M. pneumoniae, this finding suggests that a significant protective immunity is elicited by previous exposure to M. pneumoniae. Indeed, a recent study revealed that at least 80% of healthy individuals in the 18–21-year-old age group were found to be seropositive by IgG assay, confirming previous exposure to M. pneumoniae [29]. McCormick et al. [30] observed that preexisting antibodies to M. pneumoniae measured by complement fixation conferred protection against both mild and severe disease that required hospitalization. However, antibodies found by complement fixation may represent recent exposure to M. pneumoniae, whereas our results demonstrate protective immunity that is not necessarily recent. According to our results, this protection only benefits nonsmokers. This novel finding is evidenced by the attack rate of RTI in 29.5% of immune nonsmokers, compared with 76.9%–85.7% in immune smokers and nonimmune individuals (table 4). The similar findings for IgM seroconversion—but not for PCR—further support the roles of smoking and low IgG levels as risk factors.

These findings may shed light on some of the reasons why M. pneumoniae vaccine studies conducted during the 1960s and 1970s showed variable results [31–33]. In these trials, the vaccine efficacy in M. pneumoniae–specific pneumonia ranged from 27% to 67%, depending on the method of M. pneumoniae detection; the variance for protection against M. pneumoniae–specific bronchitis was even higher, ranging from no efficacy to 87%. All the vaccines were tested in army-based facilities in

**Table 3. Multivariate model of risk factors for Mycoplasma pneumoniae–associated clinical respiratory tract infection.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>5.6 (1.5–20.4)</td>
<td>.01</td>
</tr>
<tr>
<td>Absence of specific IgG</td>
<td>7.8 (1.4–42.5)</td>
<td>.018</td>
</tr>
<tr>
<td>Military function (command staff vs. basic trainees)</td>
<td>0.37 (0.07–2)</td>
<td>.28</td>
</tr>
</tbody>
</table>

**Table 4. Association of preexisting Mycoplasma pneumoniae–specific IgG levels with pneumonia, respiratory tract infection, IgM seroconversion, and PCR positivity, stratified for smokers and nonsmokers.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Nonsmokers</th>
<th>Smokers</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No IgG</td>
<td>IgG</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3/7 (42.9)</td>
<td>2/44 (4.5)</td>
<td>.015</td>
</tr>
<tr>
<td>RTI</td>
<td>6/7 (85.7)</td>
<td>13/44 (29.5)</td>
<td>.008</td>
</tr>
<tr>
<td>IgM seroconversion</td>
<td>2/3 (66.7)</td>
<td>1/27 (3.7)</td>
<td>.02</td>
</tr>
<tr>
<td>PCR1 positive</td>
<td>2/5 (40)</td>
<td>6/20 (30)</td>
<td>1</td>
</tr>
<tr>
<td>Real-time PCR positive</td>
<td>3/5 (60)</td>
<td>13/20 (65)</td>
<td>1</td>
</tr>
</tbody>
</table>

**NOTE.** Data are n/N (%), unless otherwise indicated. RTI, respiratory tract infection.
which the prevalence of smoking exceeded 50% at the time [34], which may have contributed to the lack of vaccine efficacy. This implies that vaccination might be effective in nonsmokers. From our data, the protective effect of positive prior IgG levels in nonsmokers can be calculated to be 65.5% (95% CI, 40%–80%), suggesting that vaccination may have a protective role in this group.

The outbreak on which we reported again emphasized the significant morbidity of an infection that is considered by most to be characterized by a mild course. Our study also defined another harmful consequence of smoking and illustrated the association of IgG levels and resistance to infection in nonsmokers. Furthermore, our analysis implied that the goal of finding an effective vaccine for protection against M. pneumoniae might be achievable. Further studies are thus warranted to reduce the burden of this ubiquitous pathogen.

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