Serological Study of Responses to Selected Pathogens Causing Respiratory Tract Infection in the Institutionalized Elderly


In a prospective 2-year study, serological responses to selected pathogens were analyzed in 224 episodes of fever attributable to respiratory tract infection (51.8%) or of unknown source (48.2%) in 131 residents of two long-term-care facilities. A serological response was identified in 45 episodes (20.1%): Chlamydia pneumoniae (14 episodes), Haemophilus influenzae type b (1), influenza virus type A (14), respiratory syncytial virus (RSV; 2), parainfluenza virus type 3 (7), C. pneumoniae and H. influenzae (3), C. pneumoniae and influenza virus type A (2), C. pneumoniae and RSV (1), and C. pneumoniae and parainfluenza virus type 3 (1). No serological responses to Chlamydia psittaci, Chlamydia trachomatis, parainfluenza virus types 1 and 2, influenza virus type B, or Mycoplasma pneumoniae were seen. Vaccination did not affect the duration of fever in those residents with serologically confirmed influenza A. Serologically confirmed C. pneumoniae infection was detected in 9.4% of all febrile episodes. Serological responses to a second agent were detected in 33% of the patients with C. pneumoniae infections, and these dual infections were associated with an underlying malignancy (P = .02). C. pneumoniae should be recognized as a potential pathogen when choosing empirical antimicrobial therapy for respiratory tract infection in residents of long-term-care facilities.

Respiratory tract infection is a significant cause of morbidity and mortality in the institutionalized elderly. In prospective studies of long-term-care facilities [1–4], 13%–35% of febrile episodes in residents were attributable to infection of the respiratory tract. Risk factors for infection in this population include the effects of aging and underlying disease on mucosal and systemic immunity as well as therapeutic interventions and environmental conditions that promote transmission of nosocomial pathogens within institutions.

Studies of respiratory infection in long-term-care facilities have been hampered by variations in the clinical presentation of this illness in the elderly as well as by limitations in the availability and use of diagnostic resources. In a prospective study, we identified episodes of febrile respiratory tract infection or fever of unknown source in residents of two long-term-care facilities by using a case definition developed specifically for this population. The clinical and serological features of these episodes are presented.

Patients and Methods

From 1 January 1989 to 31 December 1990, residents of two long-term-care facilities in Winnipeg, Manitoba, Canada, were enrolled in a prospective study of febrile episodes. Through active surveillance at both institutions, 187 residents with 372 episodes of fever were enrolled in the study. The study design, methodology, and results, which estimate the contribution of invasive urinary tract infection to febrile morbidity in the cohort, have been previously published [5].

Acute-phase and convalescent-phase serum samples were obtained from all subjects enrolled in the study, and antibodies to selected pathogens were analyzed in those subjects with febrile respiratory tract infection or fever of unknown source. The acute-phase serum sample was obtained on the day of study enrollment, and the convalescent-phase serum sample was obtained 21–28 days later. Fever surveillance protocols and patient enrollment criteria have been previously described [5]. Informed consent from the patient or guardian was obtained for all study patients. The study was noninterventional. Study investigators were not involved in the examination, investigation, or management of the patients. Data on clinical symptoms and signs, laboratory and radiological investigations, and outcome were collected.

Facility 1 is a former veterans hospital with 258 beds and a male-to-female ratio of 3:1. The institution has on-site radiological and diagnostic laboratory facilities, and there is a house medical officer on duty 24 hours a day. Facility 2 is a personal care home with 316 long-term-care beds and a male-to-female ratio of 1:2. Medical care is provided by private practitioners who visit once weekly or as necessary. A physician is not on duty 24 hours a day, and clinical specimens are sent to an outside laboratory. Most residents at both facilities are older than 65 years of age. A small number of young individuals with chronic neurologic disabilities who require permanent institutional care are also residents.
Definitions of infection for surveillance in long-term-care facilities that were reported by McGeer et al. [6] were used in the clinical diagnosis of fever. For episodes of respiratory tract infections, the common cold syndrome or pharyngitis was defined by the new onset, in the absence of allergies, of two or more of the following: runny nose or sneezing, nasal congestion, sore throat, dry cough, and cervical lymphadenopathy. The diagnosis of influenza-like illness required a temperature of \( \geq 38^\circ C \) (any site) during the influenza season with three or more of the following: chills, new headaches or eye pain, myalgias, malaise or anorexia, sore throat, and new or increased dry cough. Bronchitis or tracheobronchitis was defined by the presence of three or more of the following: new or increased cough, new or increased sputum production, fever (temperature of \( \geq 38^\circ C \)), pleuritic chest pain, new or increased physical findings (rales, rhonchi, wheezes, and/or bronchial breathing) during chest examination, and new or increased shortness of breath, a respiratory rate of \( > 25 \), or worsening mental and/or functional status.

Residents with two or more of the signs or symptoms described for bronchitis and radiographic evidence of pneumonia for whom noninfectious causes of their symptoms were ruled out were said to have pneumonia. The source of fever was considered unknown if the episode failed to meet the criteria of McGeer et al. [6] for infection at a specific site or if the information was consistent with more than one potential site of infection.

Paired serum samples were analyzed by the CF test for evidence of infection due to adenovirus, parainfluenza virus types 1, 2, and 3, and influenza virus types A and B (Virion, Morristown, NJ) as well as respiratory syncytial virus (RSV) and Mycoplasma pneumoniae (Microbix Biosystems, Etobicoke, Ontario, Canada). Positive tests were defined by a fourfold rise or fall in titer, with a peak titer of \( \geq 1:32 \).

The samples were also tested in twofold dilutions, starting at 1:16, for antibodies to purified elementary bodies of Chlamydia trachomatis serovars A–K, Chlamydia psittaci (avian strain 6BC), and Chlamydia pneumoniae (TW-183 strain) by microimmunofluorescence [7]. A positive result for \( C. pneumoniae \) was defined by an IgM titer of \( \geq 1:16 \), an IgG titer of \( \geq 512 \), or a fourfold rise in IgG titer [8]. A positive test for \( C. psittaci \) or \( C. trachomatis \) was defined by an IgM titer of \( \geq 1:16 \) or a fourfold rise in IgG titer.

Serum antibodies to the outer-membrane protein of Haemophilus influenzae type b were detected by ELISA [9]; a positive result was defined by a threefold rise in the ratio of optical density to control, determined during the period between the acute phase and the convalescent phase, in convalescent-phase serum samples with a ratio of \( \geq 5.0 \).

Sputum and blood specimens for cultures were obtained by attending physicians as part of the routine care of the patient in only 28 (12.5%) and 22 (9.8%), respectively, of the 224 febrile episodes. Throat swab specimens for bacterial and viral cultures were obtained in only 15 febrile episodes (6.7%).

### Table 1. Demographic characteristics of 131 elderly residents of long-term-care facilities who had fever due to respiratory tract infection or fever of unknown origin.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD) in y</td>
<td>76.4 (12.3)</td>
</tr>
<tr>
<td>No. of males/no. of females</td>
<td>76/55</td>
</tr>
<tr>
<td>Mean duration (SD) in the facility in mo</td>
<td>36.8 (48.3)</td>
</tr>
<tr>
<td>Mean no. (SD) of underlying chronic diseases</td>
<td>3.7 (1.4)</td>
</tr>
<tr>
<td>No. (%) with underlying chronic illness Neurological</td>
<td>109 (83.2)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>68 (51.9)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>34 (26.0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>26 (19.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (11.5)</td>
</tr>
<tr>
<td>No. (%) with functional status</td>
<td></td>
</tr>
<tr>
<td>Impaired mental status*</td>
<td>68 (51.9)</td>
</tr>
<tr>
<td>Impaired mobility†</td>
<td>114 (87.0)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>73 (55.7)</td>
</tr>
<tr>
<td>Indwelling urinary catheter</td>
<td>14 (10.7)</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>48 (36.6)</td>
</tr>
</tbody>
</table>

* Demented, confused, obtunded, or comatose.
† Chair or bed bound or required assistance to move.

These investigations were performed at the discretion of the attending physicians, and their results are not reported here because of the small number of specimens obtained and the resulting potential for testing bias.

The unpaired \( t \) test was used to compare means for continuous data. The Kruskal-Wallis nonparametric test was used to compare means for continuous data that did not follow a normal distribution. Comparison of proportions was by the \( X^2 \) test or Fisher's exact test for small expected values.

### Results

During the 24-month study period, 131 residents with 224 episodes of febrile respiratory tract infection or fever of unknown origin were enrolled in the study. Eighty-two residents (62.6%) had 1 febrile episode, 27 residents (20.6%) had 2 febrile episodes, and 22 residents (16.8%) had \( \geq 3 \) febrile episodes. Fifty-four residents (41.2%) were from facility 1, and 77 (58.8%) were from facility 2. The demographic characteristics of the residents are shown in table 1. Subjects were elderly, had multiple associated illnesses, and were highly functionally impaired.

Of the 224 febrile episodes, 116 (51.8%) were due to respiratory tract infection, and 108 (48.2%) were of unknown origin. The mean duration of fever \( \pm \) SD was 3.4 \( \pm \) 3.8 days, and antibiotics were administered in 180 episodes (80.4%). Of the episodes of presumed respiratory tract infection, 4 (3.4%) were diagnosed as the common cold syndrome or pharyngitis; 67 (57.8%), as bronchitis; 30 (25.9%), as pneumonia; and 15 (12.9%), as influenza-like illness. Chest radiographs were obtained in 82 episodes (36.6%), and these films showed a pneu-
monic process in 30 episodes (13.4%). Thirty (54.5%) of the 55 chest radiographs of residents with clinical respiratory tract infection showed evidence of pneumonia; the 27 radiographs of those residents with an unknown source of fever did not show infiltrates consistent with pneumonia.

Urine specimens for cultures were obtained in all 224 febrile episodes (100%), and these cultures were positive in 97 cases (43.3%). They were more likely (P = .0001) to be positive in febrile episodes of unknown origin (61 of 108) than in febrile episodes attributed to respiratory tract infection (36 of 116). The febrile episodes of unknown origin in this study did not meet the criteria of McGeer et al. [6] for the diagnosis of urinary tract infection, and the positive urine cultures were attributed to asymptomatic bacteriuria, which is prevalent in the institutionalized elderly.

A serological response to C. pneumoniae, H. influenzae type b, RSV, parainfluenza virus type 3, and/or influenza virus type A occurred in 45 (20.1%) of the 224 febrile episodes and 43 (32.8%) of the 131 residents (table 2). The seroconversion results in the 45 episodes were as follows: C. pneumoniae, 14 episodes; H. influenzae type b, 1; influenza virus type A, 14; RSV, 2; parainfluenza virus type 3, 7; and C. pneumoniae and a second agent (H. influenzae type b [3], influenza virus type A [2], RSV [1], and parainfluenza virus type 3 [1]), 7. No serological responses to C. trachomatis, C. psittaci, parainfluenza virus types 1 and 2, influenza virus B, or M. pneumoniae were seen.

At the time of presentation, of the 45 febrile episodes associated with positive serological responses, 32 (71.1%) were attributed to respiratory tract infection by the attending physician, and 13 (28.9%) were of unknown origin. Of the episodes of respiratory tract infection that were clinically diagnosed, serological responses were observed in 1 (25%) of the 4 attributed to the common cold syndrome or pharyngitis, 19 (28.4%) of the 67 attributed to bronchitis, 7 (23.3%) of the 30 attributed to pneumonia, and 5 (33.3%) of the 15 attributed to influenza-like illness. The diagnosis of influenza-like illness was made before the results of serological testing were received, and all five seroconversions were to influenza virus type A.

Residents with a positive serological response to the agents tested were more likely than those with a negative serological response to have impaired mobility (41 of 43 vs. 73 of 88, respectively; P = .04) and either urinary incontinence or an indwelling urinary catheter (35 of 43 vs. 52 of 88, respectively; P = .01). There was no significant difference between these two groups in terms of age, sex, facility, underlying chronic disease, number of medications, bowel function, or mental status. Febrile episodes associated with a positive serological response were more likely to be clinically diagnosed as respiratory tract infection than were febrile episodes associated with a negative serological response (32 of 45 vs. 84 of 179, respectively; P = .003). There was no significant difference between residents with a positive serological response and those with a negative serological response in terms of the duration of fever (3.5 ± 2.8 days vs. 3.2 ± 4.0 days, respectively; P = .12) or the presence of a pneumonia process on chest radiographs (7 of 18 vs. 23 of 63, respectively; P = .8).

In December 1989, an outbreak of influenza A occurred in Winnipeg. During that month, four of eight residents at facility 1 and 10 of 23 residents at facility 2 who had either febrile respiratory tract infection or fever of unknown origin had positive serological responses to influenza virus type A alone, and two patients, one from each facility, had dual serological responses to both influenza virus type A and C. pneumoniae.

<table>
<thead>
<tr>
<th>Pathogen(s)</th>
<th>Common cold or pharyngitis (n = 4)</th>
<th>Acute bronchitis (n = 67)</th>
<th>Pneumonia (n = 30)</th>
<th>Influenza-like illness (n = 15)</th>
<th>Unknown source (n = 108)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. pneumoniae</td>
<td>1</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Haemophilus influenzae type b</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>RSV</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Influenza virus type A</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Parainfluenza virus type 3</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>C. pneumoniae and H. influenzae type b</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>C. pneumoniae and influenza virus type A</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>C. pneumoniae and RSV</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C. pneumoniae and parainfluenza virus type 3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>19</td>
<td>7</td>
<td>5</td>
<td>13</td>
<td>45</td>
</tr>
</tbody>
</table>

NOTE. RSV = respiratory syncytial virus.

Table 2. Number of febrile episodes in institutionalized elderly individuals that were characterized by a positive serological response to selected pathogens according to the source of fever.
A viral culture of a throat swab specimen from one resident at facility 2 yielded influenza virus type A Shanghai 11/87 H3N3; this patient also had a serological response to influenza virus type A. There was no significant difference between residents with and without a serological response to influenza virus type A in terms of age, sex, underlying chronic disease, number of medications, or functional status. Influenza virus vaccine containing type A Taiwan 1/86 H1N1, type A Shanghai 11/87 H3N3, and type B Yamagata 16/88 antigens was administered to 59 of the 131 study subjects as part of their routine preventive care in the fall of 1989. The duration of fever in the 16 subjects who had serologically confirmed influenza A was not significantly different ($P = .06$) for those who did or did not receive vaccine.

A positive serological response to C. pneumoniae occurred in 21 (9.4%) of the 224 febrile episodes: 14 (12.1%) of 116 respiratory tract infections and seven (6.5%) of 108 infections of unknown origin. In residents with clinically diagnosed respiratory tract infection, serological responses to C. pneumoniae occurred in 1 (25%) of 4 with the common cold syndrome or pharyngitis, 8 (11.9%) of 67 with bronchitis, and 5 (16.7%) of 30 with pneumonia. A seasonal variation in the occurrence of C. pneumoniae infection was not observed.

The duration of fever did not differ between those residents with serologically confirmed C. pneumoniae infection and those with a negative serological response to C. pneumoniae or those with a positive serological response to other agents. Residents with positive serological responses to C. pneumoniae were more likely than other residents to have urinary incontinence (16 of 21 vs. 56 of 110, respectively; $P = .01$), fecal incontinence (13 of 21 vs. 33 of 110, respectively; $P = .005$), and impaired mental status (15 of 21 vs. 53 of 110, respectively; $P = .05$); there were no differences between these two groups in terms of age, sex, number or type of underlying chronic diseases, or number of medications.

Of the 21 episodes meeting the criteria for acute C. pneumoniae infection, 10 (47.6%) were diagnosed on the basis of a fourfold rise in IgG titer; 5 (23.8%), an IgG titer of $>512$; 4 (19.1%), an IgM titer alone; and 2 (9.5%), a fourfold rise in IgG titer and elevated IgM titers. In these serologically confirmed cases, there was no significant difference between those residents who did or did not have IgM responses in terms of age, sex, functional status, number or type of underlying chronic diseases, number of medications, source of fever, presence or absence of pneumonia, or duration of fever.

A positive serological response to two pathogens was identified in seven febrile episodes (table 2). These cases were characterized by seroconversion to C. pneumoniae as well as to RSV (1 case), influenza virus type A (2), parainfluenza virus type 3 (1), and H. influenzae type b (3). Those residents with a dual serological response were more likely than those who seroconverted to a single agent to have an underlying malignancy (2 of 7 vs. 0 of 36, respectively; $P = .02$). There was no significant difference between these two groups in terms of age, sex, facility, number of underlying chronic diseases, number of medications, functional status, or duration of fever.

### Discussion

After admission, respiratory tract, urinary tract, and soft-tissue infections are the most common newly diagnosed conditions in residents of long-term-care facilities. Risk factors for respiratory tract infection in this population include chronic obstructive lung disease, neurogenic oropharyngeal dysphagia, tube feedings, tracheostomy, and impaired mobility [10]. In these institutions, the reported incidence of respiratory tract infection varies from 0.3 to 4.7 infections per 1,000 resident days, and the prevalence varies from 0.3% to 5.8% [3, 4, 11–20]. Variations in these rates may be ascribed to differences in clinical definitions, patient populations, and surveillance methods. Fever, cough, sputum production, and localized chest findings may be absent in cases of pneumonia in the elderly [10]. Sputum specimens for gram staining and cultures are usually not obtained, and when results of these tests are available, they are frequently difficult to interpret.

Oropharyngeal contamination of specimens results in problems distinguishing between colonization and infection. Invasive procedures such as transtracheal aspiration or bronchoscopy are not appropriate for institutionalized elderly patients [19]. Although in one report [21] cultures of blood from five (23%) of 22 elderly patients with pneumonia were positive, in practice, these specimens are infrequently obtained in long-term-care facilities. Efficient access to laboratory and radiological facilities is frequently limited, thus creating further diagnostic difficulties.

The noninterventional descriptive design of this study was chosen to realistically reflect the nature of patient care and diagnostic resources in long-term-care facilities. Therefore, it is not surprising that sputum, blood, and throat swab specimens for cultures were obtained in a minority of febrile episodes. In the absence of systematic collection of microbiological specimens in studies such as ours, reporting of culture results risks compromising the internal validity because of possible testing bias that favors increased investigation of more ill individuals or those from whom specimens are easier to obtain. Alternatively, studies in which systematic collection of specimens is performed must preserve the external validity, or generalizability, of their conclusions for facilities at which such intensive investigation may not routinely be possible.

The addition of serology, primarily in the context of research studies, to microbiological investigations for pneumonia has enhanced our understanding of the etiology and epidemiology of this condition in adult populations. A serological study of antibody responses to the major outer-membrane protein of Escherichia coli (an antigen shared among Enterobacteriaceae) [5] suggested that these organisms are infrequent causes of respiratory tract infection in the institutionalized elderly. Microimmunoassay has been used to detect species-specific antibody to C. pneumoniae in elderly populations; the sensitivity of this technique has been 60%–88% [22, 23]. Enzyme immunoassays for serum antibody to H. influenzae and
Moraxella catarrhalis have been shown to be highly specific diagnostic tests in studies of adults hospitalized because of pneumonia, but the sensitivity of these tests has been shown to be lower than those of blood culture and transtracheal aspiration [24, 25].

In North American and European studies [26–30], C. pneumoniae has accounted for 4%–34% of cases of community-acquired pneumonia and 2%–5% of cases of pharyngitis, sinusitis, or bronchitis in adults. Although the incidence of C. pneumoniae infection in the elderly is unknown, this rate is more frequent among older age groups [26]. Serological evidence of infection with this organism was seen in 9.4% of all febrile episodes in this study. This finding may represent an underestimate of the true frequency of C. pneumoniae infection in the study population, because serodiagnosis for the elderly may be compromised by the presence of rheumatoid factor or immune senescence [31, 32]. Appropriate antibiotic therapy early in the course of infection may also prevent the formation of antibodies [33].

It is likely that most serologically confirmed febrile episodes in this study represent reinfection with C. pneumoniae, because an IgM response was seen in only 28.6% of cases. Primary infections with C. pneumoniae usually occur in childhood and adolescence. Reinfections are thought to be common in adults and are usually associated with a fourfold rise in IgG titer, or boosting of a preexisting IgG level, without an associated IgM response [22]. Previous studies [27, 34, 35] have suggested that compared with individuals with primary infection due to C. pneumoniae, those with C. pneumoniae reinfection may have milder disease, may be older in age, and are more likely to be male. These findings were not observed in the present study, although the small number of C. pneumoniae infections detected precludes conclusions regarding differences within this subgroup.

Seven (33%) of the 21 patients with positive serological responses to C. pneumoniae in this study had evidence of concurrent infection with a second agent. Streptococcus pneumoniae, M. pneumoniae, Neisseria meningitidis, Legionella pneumophila, H. influenzae, adenovirus, parainfluenza virus, and RSV infections were identified in 25%–56% of cases of community-acquired pneumonia in adults for whom acute C. pneumoniae infection was diagnosed [28–30, 36, 37].

Initial upper respiratory tract infection with C. pneumoniae may predispose patients to subsequent pneumonia due to a second agent [38]. Mixed infections have been associated with a greater severity of illness and more underlying chronic diseases than have infections due to C. pneumoniae alone [38]. In a study of adults hospitalized because of community-acquired pneumonia during an epidemic of C. pneumoniae pneumonia, Kauppinen et al. [39] demonstrated that those with dual infection due to C. pneumoniae and S. pneumoniae were significantly more likely to be older in age, have a greater number of preexisting chronic diseases, and have a productive cough than were those with infection due to C. pneumoniae alone.

In our study, the presence of an underlying malignancy was associated with dual infection, possibly through immunosuppression secondary to the neoplastic process or subsequent therapeutic interventions.

Serology remains a useful research tool for clarifying the etiology and epidemiology of infection in residents of long-term-care facilities. However, for the clinician, timely and specific diagnoses await the development of a suitable diagnostic test, such as a molecular detection method, for the most common causes of pneumonia. In the interim, physicians should remain cognizant of the frequency of C. pneumoniae disease with or without concurrent infection when choosing empirical antimicrobial therapy for respiratory tract infection in residents of long-term-care facilities.

References


