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Upper respiratory tract infection and serum antibody responses in nursing home patients

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Residents of a Veterans Administration nursing home care unit (NHCU) were observed for the development of upper respiratory tract infection (URI) during 12 consecutive months to determine the frequency of sporadic cases or outbreaks of URI and to characterize them clinically and by laboratory means. Fifty-nine episodes of URI occurred in 56 residents during the study period. Serologic testing or virus isolation proved or suggested an etiologic agent on 22 occasions. URI was more common in late Fall and Winter and was caused by various agents, including influenza, *Mycoplasma pneumoniae*, respiratory syncytial virus, and parainfluenza viruses. A minor outbreak of influenza B in February 1986 contrasted with previous cases of URI in that the patients had a higher mean temperature and abnormal breath sounds, and they were clinically sicker. This suggests that clinical and epidemiologic surveillance during the influenza season may allow the early recognition of influenza in elderly nursing home residents. Over a 4-year period 147 serum antibody responses after influenza infection or influenza vaccination were compiled. Antibody responses to individual influenza vaccine components were measured 75 to 90 days after vaccination. The geometric mean titer (GMT) and the percentage of samples with antibody levels ≥1:40 were determined for each of the three antigenic subtypes on 3 consecutive years. The GMT to individual vaccine components was consistently greater than 1:40, except to influenza B/Singapore in 1984 and A/Chile and B/U.S.S.R. in 1985, when these subtypes were first included in the vaccine, suggesting the NHCU residents responded less vigorously to unfamiliar vaccine subtypes. In 1984 the GMT to A/Philippines of unvaccinated NHCU residents without URI was surprisingly no different from the corresponding GMT of their vaccinated counterparts, raising the possibility that an influenza A/Philippines outbreak in 1983 conferred herd immunity. (AM J INFECT CONTROL 1988;16:152-8)

Nursing home patients are at risk of developing serious infections from influenza viruses and other respiratory tract pathogens.\(^1\) Because of the closed, frequently crowded, and shared living conditions in nursing homes, respiratory viral infections, particularly influenza, can spread swiftly from patient to patient and from employee to patient.\(^4\) The ability of elderly patients to combat such infections may be impaired by underlying illnesses and waning immunity\(^7\) and, in the case of influenza, by lack of vaccination\(^8\) or suboptimal antibody response to the vaccine.\(^9\)\(^10\) In practice, the diagnosis of influenza depends on careful clinical assessment because rapid diagnostic tests are not
available in nursing homes and, in the best of circumstances, virus isolation may take 4 to 7 days from the time the sample is obtained. Other factors, however, can hamper early recognition of influenza illness in nursing homes. For example, oral temperatures in the elderly are unreliable, and elderly patients may not develop appropriate temperature elevations in response to infection. Furthermore, recognition of illness may be delayed in patients unable to express themselves or in patients with decreased levels of consciousness. Failure to check or record vital signs regularly is yet another dilatory factor in nursing homes. It is not possible to tell if a patient has fever by observation alone. On a different plane, recognition of an influenza outbreak may be delayed if the outbreak occurs early in the influenza season or if no influenza activity has yet been reported in the community.

Because influenza illness is of variable severity and, in the individual patient, may be clinically indistinguishable from other viral upper respiratory infections (URI) a prospective evaluation of the residents (patients) of the Dorn Veterans Administration nursing home care unit (NHCU) with URI was initiated. The goals of the study were to determine the frequency of URI in NHCU residents over a 12-month period and to attempt to distinguish influenza from other URI on laboratory and clinical grounds. Influenza antibody levels measured for 4 consecutive years in NHCU residents also are reported.

**MATERIAL AND METHODS**

The NHCU is a 120-bed, self-contained two-storied building connected to the main hospital by an underground corridor. The NHCU has its own kitchen, a dining room on the second floor, and two congregate baths in addition to individual bathrooms. Each Fall influenza vaccine is offered to NHCU residents and employees. The vaccine is administered intramuscularly in the deltoid region. In 1985 91 residents, but only three employees, were vaccinated. The daily census during the study period ranged from 114 to 120 patients.

The same examiner (J.C.A.) evaluated all NHCU residents within 4 days (usually within 48 hours) of the acute onset of two or more of the following symptoms: sneezing, runny nose, sore throat, hoarseness, cough, and fever higher than 99° F orally or 100° F rectally. The presence or absence of headache, myalgia, and fatigue (unusual tiredness) was also ascertained. The NHCU staff was instructed to report any patient suspected of having URI. In addition, two nurse specialists assigned to the NHCU were actively involved in early identification of URI cases on the basis of these criteria.

Acute and convalescent or postvaccine sera were tested against a battery of respiratory pathogens at the Veterans Administration Reference Laboratory in Lexington, Kentucky, including influenza, parainfluenza, respiratory syncytial virus, adenovirus, measles, herpes simplex, chlamydia, Coxiella burnetti, and Mycoplasma pneumoniae. Antibody levels also were measured in randomly selected, asymptomatic NHCU residents. Influenza virus antibody levels were determined by hemagglutination inhibition (HI) and by complement fixation. A fourfold or greater increase in convalescent antibody titer was considered diagnostic. Throat gargles were obtained sporadically from clinically ill residents and submitted to the South Carolina Department of Health and Environmental Control, Bureau of Laboratories, for virus isolation. Isolates were typed at the Centers for Disease Control in Atlanta, Georgia. In the results that follow, chi-square was computed to ascertain the significance of differences in proportions of pro-
Table 1. Summary of serum antibody responses that supported an etiologic diagnosis

| Organism                | No. of paired responses | Acute | Convalescent |
|-------------------------|-------------------------|-------|-------------|
| Influenza A             | 2                       | 13    | 160         |
| Respiratory syncytial   | 5                       | 1.2   | 74          |
| virus                   |                         |       |             |
| Parainfluenza           | 2                       | 1.3   | 45          |
| Mycoplasma pneumonia†   | 10                      | 2     | 37          |
| Influenza B             | 6                       | 29    | 184         |
| Chlamydia‡             | 1                       | 0     | 128         |

*Reciprocal values.
†Seven patients had concomitant fourfold antibody rises to other agents: 1 to influenza A, 2 to parainfluenza, 2 to influenza B, 1 to respiratory syncytial virus, and 1 to chlamydia.
‡This patient also had fourfold increments in antibody to mycoplasma and parainfluenza.

Protective titers. Student's *t* test was used to evaluate the significance of protective antibody levels after linear transformation of the titers (Log, [titer]).

RESULTS

From June 1985 through May 1986, 59 episodes of URI were detected in 54 male and 2 female NHCU residents (Fig. 1), whose mean age was 66.4 years. All levels of care were represented. The number of major underlying illnesses in residents with URI ranged from one to eight, with a mean of 2.9. Chronic obstructive lung disease, cerebrovascular accident, and hypertension were present in 34%, 34%, and 30% of residents, respectively. Organic heart disease, diabetes mellitus, peripheral vascular disease, and dementia occurred in decreasing frequency. Only four patients had neoplastic disorders. Underlying illnesses were not compared in residents with and without URI. Although sporadic cases of URI occurred from June through September, the number increased steadily from 5 in October to 13 in December. No cases were detected in January or April, but there were 11 cases in February and 8 cases in May.

Antibody assays of paired sera yielded either diagnostic results or suggested a diagnosis in 21 (55%) of 38 patients tested. Patient refusal, death, discharge, or failure to draw blood accounted for incomplete studies in the other 27 episodes. Of nine specimens submitted for virus isolation, influenza B was recovered from only two (during February). The two isolates were later identified as B/Ann Arbor by the Centers for Disease Control. Six influenza B cases were confirmed serologically or by virus isolation during February and March. Four of the six had been vaccinated in the Fall. Of interest, one vaccinated patient with culture-proved influenza B had a seemingly protective baseline HI antibody level (1:40) but no significant rise in properly timed convalescent titer (1:80). The HI antibody titers in the other culture-proved case of influenza B increase from 1:10 to 1:640. One ill, unvaccinated patient was tested 1 week late; although his “acute” HI antibody titer was already 1:80, his complement-fixing type-specific antibody rose from 1:8 to 1:128. In all, the six patients with influenza B had an acute HI geometric mean titer (GMT) of 1:29 and a convalescent GMT of 1:184 (Table 1). Twenty-four vaccinated NHCU residents who were not ill had a baseline GMT to influenza B of 1:46, significantly higher than the corresponding acute GMT of the six patients with influenza B (comparison of titers converted to linear form: *t* = 2.05, df = 28, *p* = 0.05). Other probable causes of URI included influenza/A Philippines, respiratory syncytial virus, parainfluenza, and Mycoplasma pneumoniae. Serum antibody responses are summarized in Table 1.

A comparison of signs and symptoms was made by dividing the 59 episodes into four seasonal groups according to peaks of URI activity during the 12-month period (Table 2). The percentage of patients with fever was highest in February, cough occurred at about the same rate throughout, and runny nose was more common in May. The six patients with influenza were analyzed separately and all had cough and fever. Their mean number of symptoms was 4.6. In this subgroup the mean temperature was 1.3° F higher than in the other groups. Additional differences were that these patients on examination appeared clinically sicker and all had diffuse, raspy bronchovesicular breath sounds. One patient was transferred to the hospital. Chest films, however, did not disclose...
Table 2. Clinical features of nursing home patients with upper respiratory infections (URI) during a 12-month period

| Variable              | June-Oct. 1985 | Nov.-Dec. 1985 | Feb.-March 1985 | May-June 1986 |
|-----------------------|----------------|----------------|-----------------|---------------|
| No. ill               | 15             | 22             | 14*             | 8             |
| Mean No. symptoms     | 4.2            | 4.6            | 3.9             | 3.0           |
| Fever† (mean temperature (F)) | 43 (100.7°) | 32 (100.4°) | 79 (100.7°) | 50 (99.7°) |
| Cough†                | 79             | 82             | 86              | 75            |
| Runny nose†           | 57             | 73             | 50              | 88            |
| Sore throat†          | 57             | 32             | 21              | 13            |
| Sneezing†             | 57             | 64             | 36              | 63            |
| Hoarseness†           | 50             | 27             | 7               | 25            |
| Headache†             | 43             | 23             | 14              | 0             |
| Myalgia†              | 21             | 23             | 20              | 0             |
| Fatigue               | 7              | 14             | 21              | 0             |

*Six of the 14 patients had laboratory evidence of influenza B infection and were analyzed separately (see text).
†The numbers for these conditions are given in percentages.

Pneumonic infiltrates in any of them. Other symptoms were less consistently elicited.

It is generally believed that antibody titers ≥1:40 are protective against serious influenza infection.6,14,15 Since patients may be exposed to influenza several months after vaccination, we measured HI antibodies in NHCU residents without URI 75 to 90 days after vaccination, on 3 consecutive years, to determine the prevalence of antibody titers ≥1:40. These results are shown in Table 3. The H3N2 vaccine component (A/Philippines/2/82) did not change during this 3-year period, and the percentage of vaccinees with titers ≥1:40 did not differ significantly. However, the number of patients with antibody titers ≥1:40 to A/Chile (H1N1 vaccine component) was significantly lower in 1985 as compared with 1986 (χ² = 7.02, df = 1, p < 0.01). A similar analysis for influenza B showed that the difference in protective titers approached but did not reach significance (χ² = 2.75, df = 1, 0.05 < p < 0.10).

As expected, the percentage of titers to influenza A (H1N1) and influenza B ≥1:40 was significantly lower in unvaccinated NHCU residents sampled in 1983 and 1984 (Table 4) compared to their vaccinated counterparts (Table 3): χ² = 6.7, df = 1, p < 0.01 for influenza A (H1N1); χ² = 9.7, df = 1, p < 0.005 for influenza B). However, antibody titers to influenza A (H3N2) in unvaccinated and vaccinated residents were not significantly different. Protective antibody levels in unvaccinated residents in 1984 were similar to those measured in vaccinees both in 1984 and 1985. This reflects, perhaps, residual immunity in this population after an influenza A (H3N2) outbreak in 1983 caused by A/Philippines/2/82.16 That unvaccinated residents in 1983 had significantly higher antibody titers to influenza A (H3N2), as compared to healthy unvaccinated residents in 1984 (t = 2.403, df = 42, p < 0.025), is further confirmatory evidence of an influenza outbreak.

Simultaneous bacterial infections were documented or suspected in 11 of the 56 patients with URI. Urinary tract infections were diagnosed in five, bacteremia in one, sinusitis in four, and bronchitis in one. Three of 11 chest radiographs revealed infiltrates whose etiology remained uncertain. There were four additional patients evaluated who did not fit the criteria for URI. The diagnoses in these four were tracheitis, bronchopneumonia, exacerbation of chronic bronchitis, and chronic obstructive lung disease.

DISCUSSION

To document the incidence of URI in a nursing home, residents with symptoms were systematically identified and evaluated over a 12-month period. Fifty-nine URI cases were clinically identified. An etiologic diagnosis was suggested or established in 22 of 38 residents tested serologically or by virus isolation, or
Table 3. Serum hemagglutination-inhibiting antibody levels in nursing home residents 75 to 90 days after influenza vaccination

| Vaccination year and vaccine strains | No. vaccines tested | Percentage titer ≥ 1:40 | GMT |
|-------------------------------------|---------------------|-------------------------|-----|
| 1983                                |                     |                         |     |
| A/Philippines/2/82                   | 23                  | 67                      | 1.67|
| A/Brazil/78                          |                     | 70                      | 1.52|
| B/Singapore/79                       |                     | 35                      | 1.22|
| 1984                                |                     |                         |     |
| A/Philippines/2/82                   | 29                  | 83                      | 1.44|
| A/Chile/1/83                         |                     | 48                      | 1.29|
| B/USSR/100/83                        |                     | 48                      | 1.28|
| 1985                                |                     |                         |     |
| A/Philippines/2/82                   | 24                  | 71                      | 1.50|
| A/Chile/1/83                         |                     | 63                      | 1.57|
| B/USSR/100/83                        |                     | 71                      | 1.46|

*Antibody titers were determined in January 1984, 1985, and 1986.

About half of the patients because of either incomplete testing or perhaps inefficient antibody responses in some. It is possible that a number of cases were due to rhinoviruses or coronaviruses,20 yet routine serologic tests do not include these agents. The eight URI cases seen in May may have been caused by one of these viruses.

The majority of URI episodes were benign. There were no deaths and only two patients were transferred to the hospital, one with influenza B and the other with pneumonia (a May case). A larger influenza B outbreak was probably averted because of the high proportion of vaccinated NHCU residents, the prevailing GMT of 1:46, and the fact that the circulating strain and the vaccine strain matched. In contrast, the six influenza cases (four of whom had been vaccinated) had an acute GMT of 1:29 to influenza B, suggesting a lower degree of vaccine protection and therefore greater predisposition to infection. In 3 consecutive years serum HI antibody levels were measured in NHCU residents without URI 75 to 90 days after influenza vaccination. Assuming that the composition of the patient population in our NHCU did not vary significantly during the study period (and indeed many are long-term residents), comparison of antibody responses obtained longitudinally seems justified. Another justification is
that in 1983, 1984, and 1985 the H3N2 vaccine component was the same, and all 3 components were the same in 1984 and 1985. It is notable therefore that antibody responses to some vaccine components differed significantly from year to year, whereas responses to others did not. The percentage of NHCU residents with protective levels of antibody to A/Philippines/2/82 and to B/U.S.S.R./100/83 was significantly lower in 1985 compared to 1986, whereas protective levels to A/Philippines/2/82 did not differ significantly during the 3-year period. An influenza A/Philippines/2/82 outbreak in 1983\textsuperscript{16} may have contributed to herd immunity. If verified, these results may raise questions about the ability of elderly NHCU residents to respond to unfamiliar antigenic subtypes in the influenza vaccine.

Clusters of URI during late Fall and Winter arouse the specter of influenza. We found that other respiratory viruses preceded and numerically mimicked influenza in the NHCU. The explosive nature of an influenza outbreak and the severity of illness of the patients as a group should help to distinguish influenza from other diseases.\textsuperscript{21}

Other interesting but previously described aspects of influenza were noted in our study. These include the failure of some patients with influenza to develop an antibody response\textsuperscript{22}; the cocirculation of other respiratory pathogens during influenza epidemics,\textsuperscript{23} which may cause overestimation of clinically diagnosed cases and underestimation of amantadine and vaccine efficacy; and the variable antibody responses of elderly patients to influenza vaccine.\textsuperscript{24} It remains unclear, even at this stage of better purified vaccines,\textsuperscript{25} whether the immunogenicity of vaccine subtypes differs from year to year or if antibody responses are more dependent on the complex interplay of individual host factors such as prior immunologic experience, intercurrent illnesses, and aging host defenses.\textsuperscript{26} Finally, even if patients are vaccinated and develop appropriate antibody titers, little can be done against unexpected antigenic variations of influenza viruses.\textsuperscript{25}

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