Detection and Control of Influenza Outbreaks in Well-Vaccinated Nursing Home Populations

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Background. Influenza outbreaks continue to occur in nursing homes despite high vaccination coverage among residents. Recommendations for outbreak control in institutions such as nursing homes advises use of antiviral drugs to reduce influenza transmission.

Methods. Influenza surveillance was performed among elderly residents of nursing homes in Michigan during 2 influenza seasons. The antiviral drug oseltamivir was used for outbreak control at the discretion of nursing home staff once influenza transmission was confirmed by virus isolation or rapid antigen detection.

Results. During 2000–2001, influenza was not confirmed in any of the 28 participating homes, despite transmission of types A (H1N1) and B in the community. During 2001–2002, influenza type A (H3N2) transmission was confirmed in 8 (26%) of 31 participating homes; influenza vaccine coverage among residents was 57%–98% in outbreak-associated homes. Oseltamivir was used in all homes with influenza transmission; outbreak control varied according to the rapidity of outbreak recognition and the extent of antiviral use. Reported adverse events were primarily gastrointestinal reactions and rashes. Analysis of the usefulness of rapid antigen detection tests for outbreak recognition indicated a sensitivity of only 77% (specificity, 92%).

Conclusions. Oseltamivir was reasonably well tolerated, and its use, along with continued promotion of vaccination coverage among nursing home residents and staff, should be a valuable addition to institutional outbreak-control strategies.

Influenza outbreaks in nursing homes are recognized as preventable causes of severe disease and often death [1, 2]. The cornerstone of the prevention strategy is promoting the vaccination of nursing home residents [3]. Higher overall vaccination coverage might reduce the likelihood of outbreaks through production of indirect or herd immunity [4]. Such a positive outcome has not as yet been demonstrated, and influenza outbreaks in nursing homes continue to be reported.

Vaccination is known to be efficacious in independently living older individuals. However, in elderly nursing home residents, there is evidence that it is not as protective, possibly as a result of immune senescence [5, 6]. The Advisory Committee on Immunization Practices (ACIP) provides recommendations on vaccine use and for influenza outbreak control in institutions such as nursing homes [3]. These measures include droplet precautions, cohorting of symptomatic residents, and restricting contact between ill staff or visitors and residents. An additional key component of the recommendation advises use of antiviral drugs, should an influenza outbreak occur.

Four licensed influenza antiviral agents are now available: the M2 inhibitors amantadine and rimantadine, which are active against influenza type A only, and the more recently developed neuraminidase inhibitors, zanamivir and oseltamivir, which are active against influenza types A and B [7–9]. Antiviral resistance and side-effect issues have complicated the use of M2 inhibitors, particularly amantadine, and have limited their usefulness [3, 10, 11]. In contrast, the neuraminidase inhibitors are generally well tolerated, and resistance is rarely seen, although their cost is higher than that of the M2 inhibitors [12, 13].

Effective use of antivirals for outbreak control requires an organized approach to recognition of influ-
enza activity plus rapid administration of medications used for treatment and prophylaxis. We report here a 2-year observational study of the occurrence of influenza outbreaks in well-vaccinated nursing home populations, the application of measures to detect influenza, and the use of the antiviral drug oseltamivir to limit transmission.

**MATERIALS AND METHODS**

**Nursing home recruitment.** Before the influenza seasons of 2000–2001 and 2001–2002, nursing homes in southern lower Michigan were invited to participate in a study identifying cases of influenza-like illness (ILI) among residents, using virological techniques to determine the cause of the illnesses and applying outbreak-control measures, including use of oseltamivir. Participation was voluntary and unrestricted. Participating homes were visited, influenza education was offered, and specimen collection was demonstrated. Participating homes were asked to provide information on the number of residents and the percentage of vaccinated residents and to estimate the level of staff vaccination. Throughout the study, medical decisions were made by the staff at the facilities, and the study was intended to observe events as they occurred. This study was reviewed and approved by the medical institutional review board at the University of Michigan (Ann Arbor).

**Surveillance activities.** Surveillance during each season began in November and continued through April. Nursing home staff members were asked to collect throat swab specimens whenever a resident exhibited symptoms of ILI, specifically cough and temperature of at least 37.5°C (99.5°F) [14]. Duplicate throat swab specimens were collected from individual residents, and 1 Dacron swab was placed in viral transport media. Specimens were sent from participating homes to the virology laboratory at the University of Michigan School of Public Health by express courier. Specimens were processed for influenza identification by rapid antigen detection tests and by virus isolation in cell culture and, in some cases, were also tested for influenza viral RNA using RT-PCR. Positive results of diagnostic tests were communicated promptly to affected facilities so decisions on antiviral use could be made. Additional local community surveillance was performed to assist in defining periods of influenza activity and determining circulating influenza types.

**Antiviral use for outbreak control.** When 2 cases of laboratory-confirmed influenza illness were detected in a nursing home within 5 days, it was recommended that outbreak-control measures be initiated, including administering antivirals to residents to prevent further transmission. Participating homes made their own decisions in consultation with their medical staff on how to proceed in managing the outbreak. Further occurrence of ILI among residents was recognized by date and treatment status and by specimen collection. Data were collected on adverse events experienced by residents receiving antivirals. Oseltamivir was made available at no charge to homes with documented outbreaks through commercial pharmacies. The recommended dosage was 75 mg twice daily for 5 days for those with influenza-like illness and 75 mg daily for 15 days for all others, with dose reduction for residents with reduced kidney function.

**Processing of specimens for virus identification.** The principal method of identifying influenza infection throughout the study was virus isolation in cell culture of material collected by throat swab and shipped in viral transport media, with isolate typing by means of the hemagglutination-inhibition assay [15]. In an effort to speed the detection of influenza virus, commercially available rapid antigen detection tests—including the QuickVue (Quidel) and Flu OIA (Biostar) tests, which were used in season 1, and the Directigen A + B test (Becton Dickinson Diagnostic Systems), which was used in season 2—were also employed for influenza diagnosis. Specimens used in rapid tests were from throat swabs and were collected without use of viral transport media, and processing was performed in the virology laboratory. RT-PCR was used to amplify and identify subtype-specific influenza viral RNA directly from the material shipped in viral transport media; these assays were performed in batches and were not used in decisions about outbreak recognition [16].

**RESULTS**

**2000–2001 Influenza Season**

**Characteristics of nursing homes.** For the 2000–2001 influenza season, 28 nursing homes agreed to participate. The mean size of participating homes was 134 residents, and the mean proportion of vaccinated residents was 79%; for 16 homes (57%), resident vaccine coverage was >80% (table 1). Although most homes reported providing vaccine to staff members at no cost, only 42% of staff members overall were vaccinated; only...
8 homes (30%) reported at least 50% vaccine coverage among staff members.

**Outbreak recognition and response.** Both influenza types A (H1N1) and B viruses circulated in the community and nationally during the 2000–2001 season [17]. Respiratory illnesses meeting the ILI case definition were observed among residents in 10 nursing homes, and 54 specimens were collected. The results of rapid diagnostic tests (QuickVue and Biostar) for influenza were positive for 2 specimens collected within 5 days from each of 3 homes. As a result, 194 residents (nearly 100% in 2 homes but only 9% in the third home) of these homes initiated antiviral therapy with oseltamivir; 25 residents were treated, and 169 were given prophylaxis. However, despite repeated attempts, no influenza viruses were isolated from any of the specimens collected from residents, nor did any specimens test positive with RT-PCR. Thus, despite transmission of types A (H1N1) and B viruses in the community, no influenza transmission could be documented in the 28 participating homes. In all 3 homes using oseltamivir for outbreak control, ILI activity continued among residents.

**2001–2002 Influenza Season**

**Characteristics of nursing homes.** For the 2001–2002 influenza season, 31 nursing homes agreed to participate (34% had participated previously). The mean size of participating homes was 136 residents, and, overall, 76% of residents were vaccinated; for 19 homes (61%), resident vaccine coverage was >80% (table 1). The mean staff vaccine coverage was 32%; only 8 homes (26%) reported at least 50% vaccine coverage among staff members.

**Influenza activity and characteristics of outbreak-associated homes.** During the 2001–2002 influenza season, type A (H3N2) circulated in the community and nationally from mid- November through late March [18]. Respiratory illnesses meeting the ILI case definition were observed among residents in 20 participating nursing homes, and 94 specimens were collected. Influenza transmission meeting the study outbreak definition of at least 2 cases within 5 days was documented in 8 homes (26%); the first outbreak occurred in late January and the last in March. Homes with outbreaks were slightly larger than homes without outbreaks (median size, 134 vs. 89 residents). However, the median proportion of residents’ vaccinated in homes with (84%: range, 57%–98%) and without outbreaks (83%) were nearly identical. Median staff vaccination coverage was higher in homes with outbreaks (42%), compared with those without outbreaks (24%). None of these comparisons were significantly different ($P > .05$).

**Outbreak response: antiviral use.** As in the first season, it was recommended that residents in homes with confirmed influenza begin to receive antiviral therapy for outbreak control. Treatment decisions were made by nursing home medical staff. Surveillance, recognition of influenza activity, and outbreak response varied among the 8 outbreak-associated homes.

Five (63%) of the 8 homes were able to rapidly recognize influenza activity and initiate outbreak-control measures. In these 5 homes, ILI attack rates before the initiation of antiviral therapy ranged from 1% (2 residents) to 20% (13 residents). In all 5 homes, use of oseltamivir in at least some residents was initiated within 24 h after virological confirmation of influenza among cases of ILI and within 3 days after initial recognition of ILI activity among residents. One home prescribed oseltamivir, which was used as treatment or prophylaxis, to nearly the entire facility population, whereas the other 4 limited antiviral therapy to residents of affected units only. In 2 homes, no additional cases were identified once therapy was begun. In the other 3 homes, additional cases occurred among treated ($n = 4$) and untreated ($n = 5$) residents (<2% of all residents in each of the 3 homes). Overall, 432 residents (17%–92% of residents per home) of these 5 homes initiated antiviral therapy with oseltamivir, of whom 34 were treated and 398 received prophylaxis.

Outbreak recognition and response in the 3 remaining homes did not proceed as successfully. In 1 of these 3 facilities, initiation of antiviral therapy was delayed for 8 days after the first case of ILI was recognized and for 3 days after confirmation of the ILI as being influenza. Although the ILI attack rate was 23% among the 107 residents before initiation of antiviral therapy, once therapy was started, no additional cases of ILI were identified. In another facility, which had 219 residents, a continuing outbreak affecting 21% of residents was not recognized or confirmed as influenza for nearly 1 month. Because ILI was still noted to be occurring at that time, antiviral therapy with oseltamivir was initiated in residents of a single unit. No additional cases of ILI were seen on the treated unit; however, 4 residents of other units developed ILI. In the last of the 8 outbreak-associated homes, confirmation of influenza activity among residents was delayed for 5 days. This home initiated nonantiviral outbreak-control measures and elected to treat residents with ILI, but only 2 residents were provided with oseltamivir as prophylaxis. Cases of ILI continued to occur after outbreak recognition and response; 40% of residents ($n = 57$) in this small home were affected by ILI. Overall, 121 residents (19%–71% of residents per home) of these 3 homes initiated antiviral therapy with oseltamivir, of whom 22 were treated and 99 were given prophylaxis.

In all 8 outbreak homes combined, ILI occurred in 4 (0.8%) of 497 individuals ≥2 days after starting prophylaxis. Among those who did not receive prophylaxis (some of whom had not been directly exposed to patients with ILI), 12 (1.8%) of 667 developed ILI ($P > .05$).

**Adverse events among residents prescribed antiviral therapy.** During 2000–2001, data on adverse events were col-
lected in a review of residents’ medical records by study personnel; during 2001–2002, data were collected and reported by nursing home staff. In 2000–2001, gastrointestinal symptoms, including nausea, vomiting, and diarrhea, were reported in 26 residents (13%) receiving oseltamivir, and neurological reactions, including tremor, muscle spasm, fall, and seizure, were reported in 5 residents (3%). Rash or skin irritation was reported in 9 residents (5%), including 1 with a severe allergic rash requiring hospitalization. Antiviral therapy was discontinued in 11 residents (6%), mainly because of gastrointestinal distress. In the 2001–2002 influenza season, gastrointestinal symptoms were reported in 9 residents (2%), and gait disturbance was reported in 1 (<1%); rash was not reported. Medication was discontinued in 6 residents (1%).

**Tests used to detect influenza.** During the 2000–2001 season, 2 different rapid antigen detection tests (QuickVue and Flu OIA) were used to detect the presence of influenza in collected specimens. Results of rapid tests of 6 throat culture specimens from residents with ILI were positive for influenza. However, these results could not be confirmed by cell culture or by RT-PCR.

In 2001–2002, the Directigen A + B rapid diagnostic test was used. This assay had reasonable concordance with results from virus isolation in cell culture (table 2). The rapid test was 77% sensitive and 92% specific, using cell culture as a gold standard.

In 2001–2002, specimens from residents at participating homes were also tested using the sensitive RT-PCR technique. This assay is more technically difficult and is still a research procedure (table 3). More than 60% of specimens positive by RT-PCR were missed by cell culture techniques (sensitivity 39%). However, all culture-positive specimens were also determined to be positive by RT-PCR (specificity, 100%). All specimens that tested positive using RT-PCR were collected from residents at nursing homes in which influenza transmission was confirmed by positive results of cell cultures.

**DISCUSSION**

Influenza outbreaks in nursing homes were thought to be associated with low vaccination coverage among residents. Thus, in a previous study, it was possible to demonstrate that, in a major year of influenza type A (H3N2) virus infection, more than one-half of the nursing homes in which <80% of residents were vaccinated had outbreaks and that, in those in which a greater proportion of residents were vaccinated, the outbreak frequency was reduced to 20% [19]. It is therefore disappointing that, in 2001–2002, when vaccine coverage overall was higher than that demonstrated >10 years before, the proportion of vaccinated residents in homes with and homes without outbreaks were similar. Influenza transmission was documented in facilities in which up to 98% of residents were vaccinated. Additionally, vaccine-based and circulating strains of influenza virus were well matched. The conclusion must be that, with current vaccines in years with influenza type A (H3N2) virus in circulation, vaccination of most or all residents will not necessarily prevent outbreaks [20]. More immunogenic vaccines would be useful, but their development is still ongoing.

Staff vaccination has been suggested to be as at least as important as resident vaccination in preventing outbreaks [3, 21, 22]. The rationale is that such an approach would help to prevent introduction of influenza into the nursing home environment. In the present study, the percentage of staff who had been vaccinated was low in nearly all homes. Providing vaccine free to staff members would increase this percentage; providing paid sick time and encouraging sick staff members to stay home would also reduce the risk of introducing influenza to residents [20].

Institutional illness surveillance is essential to identifying influenza activity and managing outbreaks. Respiratory-illness logs can assist in this process and should be maintained, especially during the influenza season, because illnesses may be widely scattered among residents of large facilities. However, as observed in 2000–2001, ILI can sometimes be caused by something other than influenza virus [23]. Before antivirals are used for outbreak control, transmission of influenza should at least be demonstrated (if not among residents, at least among staff or in the community). In the past, clusters of ILI during a period of documented influenza transmission in the community have been considered to be sufficient to initiate medication in residents of nursing homes for outbreak control. This approach may still be appropriate, especially in view of the greater safety of the newer antivirals. Certainly, it is not possible in most circumstances to wait for results of virus isolation tests. There are now rapid diagnostic tests that are Clinical Laboratory Improvement Amendments (CLIA)–waived and can be performed on-site in any facility with a CLIA waiver. These and other rapid antigen detection tests are simple to use and have

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<tr>
<th>Results of Directigen rapid diagnostic test</th>
<th>Results of virus isolation in cell culture</th>
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<tr>
<td>Positive</td>
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<td>Positive</td>
<td>13</td>
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<td>Negative</td>
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**NOTE.** Data are limited to the subset of specimens tested using both assays. Sensitivity, 76.5% ([13/17] × 100); specificity, 92.3% ([60/66] × 100).

* Becton Dickinson Diagnostic Systems.
a role in outbreak control, but sensitivity and specificity issues need to be considered [16, 24].

In the present study, oseltamivir was made available to nursing homes and was recommended for use when ≥2 cases of influenza were detected. These recommendations were consistent with ACIP guidelines [3]. In the 2001–2002 season, oseltamivir was used in all homes in which influenza transmission was occurring, and outbreak control varied according to the rapidity of outbreak recognition and the extent of antiviral use. Our data suggest that early intervention results in better outbreak control. These results are consistent with those of another study in which institutional outbreak control was examined [25].

Our data are limited by the small numbers of participating homes with outbreak activity. In addition, outbreaks may have resolved at the same time, even without antiviral intervention. It is obvious that controlled studies to test this strategy cannot be performed once influenza transmission occurs in homes, but success when antivirals are used and continuation of outbreaks when they are not indicates that the recommendations are correct. This has been demonstrated in the past with amantadine and rimantadine therapy. Oseltamivir was reasonably well tolerated, unlike the situation with amantadine, and therefore should be a valuable addition to institutional outbreak-control strategies [25].

Reported adverse events—primarily gastrointestinal reactions and rashes—were observed in residents receiving oseltamivir as treatment or prophylaxis. The frequency of reported adverse events decreased dramatically between the first year, when study personnel reviewed residents’ medical records, and the second year, when influenza transmission may still occur. The results of RT-PCR indicate that infections in affected homes are likely to be more widespread than was indicated by virus isolation testing, which supports the concept that antiviral use should begin when illness clusters are detected. The consequences of influenza in these frail populations is well documented, and early use of safe antiviral therapy would seem to be less risky than allowing an outbreak to proceed while waiting for positive test results.

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