Effect of Timing of Amantadine Chemoprophylaxis on Severity of Outbreaks of Influenza A in Adult Long-Term Care Facilities

Marcie S. Rubin, Beth Nivin, and Joel Ackelsberg

1Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, and 2Bureau of Communicable Diseases, New York City Department of Health and Mental Hygiene, New York, New York

Background. Long-term care facilities (LTCFs) are vulnerable to outbreaks of influenza. There are limited data on the impact of antiviral chemoprophylaxis on the duration of outbreaks of influenza. We investigated the association of timely initiation of amantadine chemoprophylaxis on the duration and severity of outbreaks of influenza A in LTCFs in New York, New York.

Methods. Outbreaks of influenza A occurring from October through May each year during the period 2001–2004 in LTCFs in New York were defined as a single laboratory-confirmed case or a cluster of ≥2 cases of influenza-like illness on a unit of an LTCF. For those facilities that provided amantadine chemoprophylaxis, we examined the association between the time to initiation of chemoprophylaxis after outbreak onset and duration of outbreak, incidence rate, and case-fatality proportion using simple t tests, multivariate analyses of covariance, and linear regression modeling.

Results. Adjusting for influenza season year, facility bed capacity, and the proportion of residents who were vaccinated against influenza, LTCFs that initiated chemoprophylaxis >5 days after outbreak onset (25 facilities) had significantly longer duration of outbreaks (18.3 vs. 6.7 days; P < .001), higher incidence rates (10.5 cases per 100 residents vs. 6.2 cases per 100 residents; P < .023), and higher case-fatality rates (3.3 deaths per 100 residents with influenza A vs. 0.45 deaths per 100 residents with influenza A; P < .005) than did LTCFs that initiated chemoprophylaxis ≤5 days after outbreak onset (27 facilities).

Conclusions. LTCFs that initiated chemoprophylaxis >5 days after initiation of outbreaks of influenza A had significantly longer outbreaks, significantly higher incidence rates, and significantly higher case-fatality rates. These data support prompt initiation of amantadine chemoprophylaxis after identification of influenza A in LTCFs.
which antiviral medication is administered after the occurrence of a case of influenza in an LTCF, has not been comprehensively studied. Several descriptive studies of single facilities in which amantadine or rimantadine chemoprophylaxis was initiated at varying times after the onset of an influenza A outbreak found a decreased influenza attack rate during the chemoprophylaxis period, compared with during the prechemoprophylaxis period [7–11]. There are data that support the effectiveness of oseltamivir and zanamivir, neuraminidase inhibitors that are licensed for chemoprophylaxis, in controlling outbreaks in LTCFs [12–19], including a study in which prophylaxis with zanamivir was more effective than prophylaxis with rimantadine [16]. Although some studies reported the time between the onset of the first case of influenza and/or influenza-like illness and initiation of chemoprophylaxis, none had sufficient data to determine whether prompt administration of prophylaxis with any of the 4 agents reduced the duration or severity of the outbreak [7–13, 15, 16, 18, 19].

Although there have not been randomized, placebo-controlled studies of the adamantane derivatives for secondary chemoprophylaxis of influenza A in LTCFs with elderly resident populations, the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices recommends that chemoprophylaxis be initiated as soon as possible when a confirmed or suspected outbreak of influenza occurs in an institution with residents at high risk for infection, such as an LTCF [5]. This analysis is designed to assess the impact of timing of secondary chemoprophylaxis with amantadine on outbreaks of influenza A in multiple LTCFs over several influenza seasons.

METHODS

Ascertainment of outbreaks of influenza. Respiratory infection outbreaks occurring between October and May each year during the period 2001–2004 in LTCFs in New York, New York, were identified by the New York City Department of Health and Mental Hygiene (DOHMH) through: (1) nosocomial outbreak reports from LTCFs and (2) active surveillance by DOHMH personnel of major diagnostic laboratories for reports of samples positive for influenza. LTCFs in New York State are required by law (New York State Sanitary Code) to report each laboratory-confirmed case of influenza and each cluster of ≥2 cases of influenza-like illness on a unit of an LTCF. The information requested includes facility name and address, bed capacity, date of onset of symptoms in index resident, causative agent, number of people initially ill, predominant symptoms and duration of illness, control measures taken by the facility, type of laboratory specimens collected, and type of laboratory tests performed [20]. Additional information, solicited by telephone calls by DOHMH personnel during the outbreak, included percentage of residents vaccinated against influenza, number and date of illness onset for additional residents and staff with influenza A, duration of illness, number of hospitalizations, number of deaths, total number of staff, infection-control measures employed, type of antiviral chemoprophylaxis used (if any), extent of use of antiviral chemoprophylaxis (unit-wide vs. facility-wide administration), time to initiation of antiviral chemoprophylaxis after onset of outbreak, and updated information regarding laboratory testing and results. LTCFs with influenza A outbreaks identified by DOHMH personnel through active laboratory surveillance were contacted by DOHMH personnel, who instructed the facilities to submit the report and solicited the aforementioned information.

Inclusion criteria. Outbreaks included in this analysis met the following criteria: (1) they occurred in a facility with an adult resident population; (2) they consisted of at least 1 laboratory-confirmed case of influenza A or ≥2 cases of an influenza-like illness on a unit within a facility, with subsequent laboratory confirmation of influenza A; and (3) amantadine chemoprophylaxis was administered to residents on a single unit or throughout the facility.

Definitions. Onset of an influenza A outbreak was defined as the first day on which symptoms were present in an index case that was subsequently confirmed by laboratory testing to be influenza A. Time to initiation of amantadine chemoprophylaxis was defined as the number of days between onset of an outbreak and initiation of amantadine chemoprophylaxis. Duration of outbreak was defined as the number of days between onset of symptoms in the index case and onset of symptoms in the last case. Resident incidence rate was estimated as the number of residents with influenza A divided by the total number of beds. Case-hospitalization rate was defined as the number of residents hospitalized with cases of influenza A divided by the total number of residents with influenza A. Case-fatality rate was defined as the number of deaths due to influenza divided by the total number of residents with influenza A. Time between initiation of chemoprophylaxis and the end of an outbreak was defined as the time interval in days between

![Figure 1](cid2008470948f1.png)

**Figure 1.** Timing of amantadine chemoprophylaxis in long-term care facilities with influenza A outbreaks, by days after outbreak onset, 2001–2004.
the initiation of chemoprophylaxis and the onset of symptoms in the last case in an outbreak. Influenza season year was defined as the season year in which the outbreak occurred (2001–2002, 2002–2003, or 2003–2004). Facility bed capacity was defined as the total number of beds in a facility when at maximum capacity. Proportion of residents vaccinated against influenza was defined as the number of residents who received the influenza vaccine divided by the facility bed capacity.

Statistical methods. We examined whether mean duration of outbreaks, incidence rates, case-fatality rates, hospitalization rates, and other factors differed according to whether facilities initiated chemoprophylaxis ≤5 days or >5 days after outbreak onset using Student’s t tests for continuous data and χ² tests for categorical data. Time between outbreak onset and initiation of chemoprophylaxis was dichotomized at 5 days, because that was the median number of days between outbreak onset and the initiation of chemoprophylaxis in our sample. Another reason that this cutoff value was chosen was because it seems to be clinically reasonable to recognize that a resident may have influenza, obtain specimens and send them to the laboratory, obtain the laboratory results, and initiate treatment and chemoprophylaxis within a 5-day period. We evaluated these associations—controlling for factors that have been shown to be important in previous studies (such as influenza season year, facility bed capacity, and proportion of residents vaccinated against influenza)—using multivariate analysis of covariance. Facility bed capacity and proportion of residents vaccinated against influenza were treated as continuous variables. We determined the incremental effect of each additional day of delayed initiation of chemoprophylaxis controlling for the same potential confounders and using linear regression, after ensuring that the assumptions for linear regression were met. Outliers in the data set were examined by looking at Cook’s distance, a measure of influence of a case in the regression equation. Fox’s recommendation of using a cutoff value for detecting influential cases—values of D > 4/(n – k – 1), where n is the number of cases and k is the number of predictor variables—was used to determine if any outliers were significantly influencing the regression equation [21]. All statistical analyses were conducted using SPSS, version 14.0 (SPSS).

RESULTS

Over 3 winter seasons, there were 89 identified outbreaks of respiratory illness in 59 of 180 LTCFs, with 21 facilities reporting multiple outbreaks. Influenza A virus was identified as the causative agent by laboratory testing in 69 of these outbreaks (29, 6, and 34 outbreaks during influenza seasons 2001–2002, 2002–2003, and 2003–2004, respectively). Amantadine chemoprophylaxis was initiated in 56 of these outbreaks, and data were sufficiently complete for analysis in 52 (93%). Amantadine chemoprophylaxis was initiated facility-wide in 40 (77%) of the outbreaks and was limited to the affected unit in the remaining 16 outbreaks. The time between onset of influenza A outbreak and initiation of chemoprophylaxis ranged from 0 to 34 days (median duration, 5 days; figure 1).

Chemoprophylaxis was initiated within 5 days after outbreak onset in 27 (52%) of the outbreaks analyzed (table 1). The 3 influenza season years did not differ in a statistically significant way with respect to the percentage of outbreaks reported in which chemoprophylaxis was initiated ≤5 days or >5 days after outbreak onset (P = .913). Chemoprophylaxis was administered facility-wide in 21 (78%) of the outbreaks in which chemoprophylaxis was initiated ≤5 days after outbreak onset and

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interval between outbreak and initiation of chemoprophylaxis</th>
<th>≤5 days</th>
<th>&gt;5 days</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion (%) of outbreaks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>27/52</td>
<td>25/52</td>
<td>.59</td>
</tr>
<tr>
<td>By influenza season year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001–2002</td>
<td></td>
<td>9/17</td>
<td>8/17</td>
<td>.47</td>
</tr>
<tr>
<td>2002–2003</td>
<td></td>
<td>3/5</td>
<td>2/5</td>
<td>.40</td>
</tr>
<tr>
<td>2003–2004</td>
<td></td>
<td>15/30</td>
<td>15/30</td>
<td>.50</td>
</tr>
<tr>
<td>Facility bed capacity, mean no. of beds ± SD</td>
<td></td>
<td>360 ± 206</td>
<td>404 ± 370</td>
<td>.59</td>
</tr>
<tr>
<td>Percentage of residents vaccinated, mean % ± SD</td>
<td></td>
<td>93 ± 4</td>
<td>91 ± 6.8</td>
<td>.24</td>
</tr>
<tr>
<td>Duration of outbreak, mean days ± SD</td>
<td></td>
<td>6.6 ± 4.9</td>
<td>18.4 ± 13.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Incidence rate, mean no. of cases per 100 residents ± SD</td>
<td></td>
<td>6.4 ± 5.9</td>
<td>10.4 ± 7.6</td>
<td>.037</td>
</tr>
<tr>
<td>Case-hospitalization rate, mean no. of hospitalizations per 100 residents ± SD</td>
<td></td>
<td>9.2 ± 19.9</td>
<td>11.6 ± 16.4</td>
<td>.64</td>
</tr>
<tr>
<td>Case-fatality rate, mean no. of deaths per 100 residents ± SD</td>
<td></td>
<td>0.6 ± 1.9</td>
<td>3.2 ± 4.5</td>
<td>.011</td>
</tr>
<tr>
<td>Time between initiation of chemoprophylaxis and end of outbreak, mean days ± SD</td>
<td></td>
<td>4.0 ± 4.8</td>
<td>6.9 ± 10.3</td>
<td>.21</td>
</tr>
</tbody>
</table>
in 19 (76%) of the outbreaks in which chemoprophylaxis was
initiated >5 days after outbreak onset (P = .897). In the
remaining outbreaks, chemoprophylaxis was administered only
to residents on the affected unit (6 [22%] of the outbreaks in
which chemoprophylaxis was initiated ≤5 days after outbreak
onset and 6 [24%] of the outbreaks in which chemoprophylaxis
was initiated >5 days after outbreak onset).

Initiation of chemoprophylaxis >5 days after the onset of
outbreaks was associated with statistically significantly longer
duration of outbreaks, higher incidence rates, and higher case-
fatality rates (table 1). The duration of outbreaks was statisti-
cally significantly longer in facilities that initiated chemopro-
phylaxis >5 days after outbreak onset, compared with the
duration of outbreaks in facilities that initiated chemopro-
phylaxis ≤5 days after outbreak onset (18.3 vs. 6.7 days; P < .001),
adjusting for influenza season year, facility bed capacity, and
proportion of residents vaccinated against influenza (table 2).
Mean incidence rate was statistically significantly higher in fa-
cilities that initiated chemoprophylaxis >5 days after the onset
of outbreaks, compared with the mean incidence rate in facili-
ties that initiated chemoprophylaxis ≤5 days after outbreak
onset (10.5 vs. 6.2 cases per 100 residents; P < .023), adjusting
for the same factors (table 2). Case-fatality rate was statistically
significantly higher in facilities in which chemoprophylaxis
was initiated >5 days after the onset of outbreaks, compared with
case-fatality rates in facilities that initiated chemoprophylaxis
≤5 days after outbreak onset (3.3 vs. 0.5 deaths per 100 resi-
dents with influenza A; P < .005), adjusting for the same factors
(table 2). We tested this hypothesis after examining whether
any outliers were significantly influencing the regression equa-
tion. Four observations met Fox’s criterion (in this case, D
values > .085) for influential cases. After deleting these 4 ob-
servations, the regression analysis was rerun, resulting in no
meaningful changes in the significance of differences, compared
with the findings when the 4 cases were included.

Using linear regression, adjusting for influenza season year,
facility bed capacity, and proportion of residents vaccinated
against influenza (table 3), for each day that the initiation
of chemoprophylaxis was delayed after outbreak onset, outbreaks
lasted 1.3 days longer (P < .001).

**DISCUSSION**

To our knowledge, this is the first large study to examine the
effect of timing of antiviral chemoprophylaxis with amantadine
on the severity and duration of outbreaks of influenza A in
LTCFs over multiple influenza seasons. LTCFs that initiated
amantadine chemoprophylaxis >5 days after the onset of an
outbreak of influenza A had significantly longer duration of
outbreaks, higher incidence rates, and higher case-fatality rates
than did facilities that initiated chemoprophylaxis ≤5 days after
outbreak onset. For each day that initiation of chemoprophyl-
axis was delayed, outbreaks lasted >1 additional day. Further
analyses are necessary to determine whether incidence and case-
fatality rates are decreased with each earlier day of chemopro-
phylaxis initiation. Because we could not recommend non-
treatment to LTCFs, we could not evaluate the effectiveness of
amantadine chemoprophylaxis versus nontreatment.

There are several limitations to this study. In addition to
timing of amantadine chemoprophylaxis, other factors that
were not available for analysis may have affected the outcomes
studied. These additional potential confounders include time-

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**Table 2. Multivariate analysis of covariance in a study of outbreaks of influenza A by timing of chemoprophylaxis.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interval between outbreak and initiation of chemoprophylaxis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤5 days</td>
<td>&gt;5 days</td>
</tr>
<tr>
<td>Duration of outbreak, mean days (95% CI)</td>
<td>6.7 (2.8–10.7)</td>
<td>18.3 (14.2–22.5)</td>
</tr>
<tr>
<td>Incidence rate, mean no. of cases per 100 residents (95% CI)</td>
<td>6.2 (3.7–8.8)</td>
<td>10.5 (7.9–13.2)</td>
</tr>
<tr>
<td>Case-fatality rate, mean no. of deaths per 100 residents (95% CI)</td>
<td>0.5 (–0.86 to 1.8)</td>
<td>3.3 (1.9–4.6)</td>
</tr>
</tbody>
</table>

**NOTE.** The analysis was adjusted for the following covariates: season year, facility bed capacity, and proportion of residents who were vaccinated.

**Table 3. Linear regression analysis of the effect of timing of chemoprophylaxis on the duration of influenza A outbreaks.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstandardized β coefficient ± SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>4.303 ± 20.296</td>
<td>.833</td>
</tr>
<tr>
<td>Time between outbreak and initiation of chemoprophylaxis</td>
<td>1.274 ± 0.176</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Season year 2002–2003*a</td>
<td>−2.968 ± 4.253</td>
<td>.489</td>
</tr>
<tr>
<td>Season year 2003–2004*a</td>
<td>−0.620 ± 2.533</td>
<td>.808</td>
</tr>
<tr>
<td>Facility bed capacity</td>
<td>0.004 ± 0.004</td>
<td>.314</td>
</tr>
<tr>
<td>Percentage of residents vaccinated</td>
<td>−0.0198 ± 0.208</td>
<td>.928</td>
</tr>
</tbody>
</table>

*a Relative to season year 2001–2002.
lness of initiation of infection-control measures, proportion of LTCF staff vaccinated against influenza, secondary vaccination or chemoprophylaxis of unvaccinated residents and staff during outbreaks, the proportion of residents receiving secondary prophylaxis, and demographic characteristics of LTCF residents. In addition, because ascertainment of outbreaks consisted primarily of passive reports and limited laboratory-based active surveillance, it is likely that not all outbreaks of influenza A in New York City LTCFs were identified, potentially resulting in an ascertainment bias. Although the number of outbreaks identified varied by influenza season year, this is less likely to represent underreporting than it is to reflect the severity of the influenza seasons. Interestingly, the number of outbreaks identified in LTCFs in New York City during the study seasons mirrored the overall severity of the influenza seasons nationally in the United States [22–24].

Further, because data on the bed occupancy at each LTCF at the time of an outbreak was not available, we used the maximum occupancy of each LTCF as the denominator in incidence rate calculations. Therefore, it is possible that we underestimated the true incidence rates. However, there is no reason to believe that any potential underestimate differed according to the timing of initiation of antiviral chemoprophylaxis during outbreaks. Finally, it is important to note that the outbreaks analyzed occurred before widespread adamantane resistance was found in circulating influenza strains [25]. Also, data on the adverse effects of amantadine use were not systematically collected. This analysis is limited to the use of amantadine chemoprophylaxis, because neuraminidase inhibitors were infrequently used for treatment and prevention of influenza A in LTCFs in New York City during this period.

If earlier administration of chemoprophylaxis with amantadine decreases the severity of outbreaks of influenza A, strategies are needed to increase the speed of initiation of chemoprophylaxis. For facilities, such strategies could include the following: a high index of suspicion for cases; maintenance of a low threshold for obtaining specimens for influenza infection detection; rapid transportation of specimens to laboratories; use of rapid testing with culture confirmation or onsite testing with subsequent laboratory confirmation; efficient communication of laboratory results to LTCFs; pre-established criteria for defining an outbreak and for initiation of antiviral medication; and prescreening of residents for prescribing of amantadine, along with routine influenza vaccination. Health departments can play an important role in facilitating the implementation of these strategies. For example, they could increase the frequency with which influenza outbreaks are reported by promoting influenza awareness. Beginning in October, health departments could remind infection control practitioners, nursing leadership, and medical directors of LTCFs that residents with cold-like or febrile illness should be tested for influenza. Health departments also could increase ascertainment and minimize time to initiation of antiviral chemoprophylaxis by requiring laboratories to report positive influenza laboratory results from LTCF residents by telephone to personnel at LTCFs and appropriate health departments. In addition, electronic outbreak reporting from LTCFs could enable health departments to provide timely infection control and chemoprophylaxis recommendations to LTCFs at the first indications of an outbreak.

We found that, in LTCFs where chemoprophylaxis was initiated >5 days after the onset of influenza A outbreaks during influenza seasons for the period 2001–2004, there were statistically significantly longer outbreaks, higher incidence rates, and higher case-fatality rates, compared with those in LTCFs where chemoprophylaxis was started sooner. When adamantane resistance is not widespread in circulating influenza strains, these data support prompt initiation of amantadine chemoprophylaxis after identification of influenza A in LTCFs.

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