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Abstract

Background Residents of nursing homes and long-term care facilities are at a higher risk of outbreaks of influenza and of serious complications of influenza than those in the community. In late July 2005, a 90-bed chronic care psycho-geriatric hospital in Sydney, Australia, reported cases of influenza-like illness (ILI) occurring amongst its residents.

Methods An investigation to confirm the outbreak, and its cause, was undertaken. Influenza vaccination levels amongst residents, and the effects of antiviral drugs used for prevention and treatment, were assessed. Oseltamivir was only given to the residents, in the form of both treatment and prophylaxis.

Results A total of 22 out of 89 residents met the clinical case definition of ILI with onset on or after 27 July 2005. This represents an attack rate of 25%. Oseltamivir was commenced on day 9 of the outbreak. Influenza B was identified in six residents as the causative agent of the outbreak. No deaths or acute hospitalization were recorded for this outbreak and there were no further reported cases after the introduction of oseltamivir. Vaccine effectiveness was 75% and the strain of influenza B isolated was well matched to that year's vaccine.

Conclusions There are few data on the use of oseltamivir in influenza B outbreaks. Early antiviral intervention appeared to curtail this outbreak of influenza B in a chronic care facility. We found high vaccine effectiveness in this frail, institutionalized population, highlighting the importance of influenza vaccination for residents of chronic care facilities.

Keywords

Influenza, oseltamivir, antiviral, hospital, vaccination, outbreak

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The use of oseltamivir during an influenza B outbreak in a chronic care hospital

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Background Residents of nursing homes and long-term care facilities are at a higher risk of outbreaks of influenza and of serious complications of influenza than those in the community. In late July 2005, a 90-bed chronic care psycho-geriatric hospital in Sydney, Australia, reported cases of influenza-like illness (ILI) occurring amongst its residents.

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day 9 of the outbreak. Influenza B was identified in six residents as the causative agent of the outbreak. No deaths or acute hospitalization were recorded for this outbreak and there were no further reported cases after the introduction of oseltamivir. Vaccine effectiveness was 75% and the strain of influenza B isolated was well matched to that year's vaccine.

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Introduction

Residents of facilities such as nursing homes and long-stay hospitals are at a higher risk of influenza outbreaks than people living in the wider community. They are especially susceptible because of their frailty, increased age and the presence of multiple co-morbidities. In addition, the closed conditions of the facilities, the close proximity in which the residents live and the frequent contact with staff, volunteers and to a less extent visitors may contribute to the rapid transmission of virus during outbreaks.¹ When influenza outbreaks occur in these facilities, attack rates can range from 10% to 70%;^{2,3} with hospitalization occurring in more than half of ill residents, and death resulting in 30% of cases.^{4–6} Although more severe disease is associated with influenza A outbreaks, influenza B has also been associated

with considerable morbidity and mortality, despite the availability of annual influenza vaccines for several decades.⁷

Neuraminidase inhibitors (NI), such as oseltamivir and zanamivir are useful in the treatment and prophylaxis of influenza virus infections. A double blinded randomized control trial of highly vaccinated long-term care residents verified that oseltamivir pre-exposure prophylaxis led to a 92% reduction in the incidence of laboratory-confirmed influenza ($P < 0.01$).⁸ Although the efficacy of post-exposure prophylaxis with influenza antivirals, especially in these facilities, has not yet been established, observational studies have reported that they are effective in controlling influenza outbreaks.^{9,10} Early administration (within 48 hours of first symptoms) of these products has been shown to reduce symptom duration and severity and the

overall risk of complications by 25–40%.^{11–13} However, many unsolved issues remain regarding outbreak control and the use of antivirals, and as such the use of antivirals during outbreaks in closed environments is still limited in many countries.¹⁴

On 30 July 2005, public health authorities in Sydney, Australia, were informed of an outbreak of respiratory illness in a long-term care psycho-geriatric hospital. The Public Health Unit invited researchers from the National Centre for Immunisation Research and Surveillance to study the role of vaccination and antiviral use during the outbreak. The overall aim of the investigation was to confirm the presence of an outbreak, to determine the causative agent and to control the outbreak.

Methods

Epidemiological investigation

An influenza outbreak was identified on 30 July 2005 in a long-term care psycho-geriatric hospital. This hospital provides long-term care for confused and disturbed elderly residents, for terminally ill patients and those with spinal conditions. Its other specialities are in the geriatric rehabilitation, aged care, respite, transit and psychiatric areas. At the time of the outbreak, the facility had 89 residents including 49 female and 40 male residents, with a median age of 78.3 years (range: 35–98 years) (Table 1). The facility was divided into five units, which were located in three

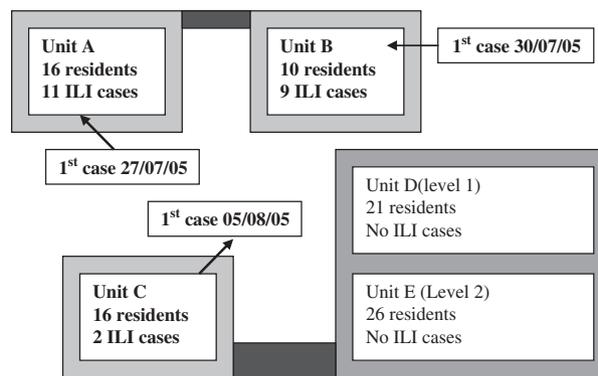


Figure 1. Layout of the hospital and timeline of events.

separate buildings. Residents from units A, B and C had no access to the rest of the facility. Units D and E were located in the same building but on different floors, and both accommodated frail aged residents. Figure 1 shows the layout of the facility and the timeline of outbreak activity. Each unit had a communal living area and dining room.

Case definition for influenza-like-illness (ILI)

Cases of influenza in the hospital were identified using the following case definition: any resident or staff member with fever plus at least two other symptoms (cough, rigours or chills, prostration and weakness, myalgia or widespread aches and pains) and having an onset date on or after 27 July 2005.

Case finding

A standard data collection tool was used to collect information for residents who met the case definition. Data collected on the symptomatic residents included demographic information, symptoms, prophylaxis, vaccination, underlying medical conditions, antibiotic use, hospitalization and death. Similar data were also collected on some of the asymptomatic residents. Receipt of the influenza vaccine in the year of the outbreak was verified against the hospital charts.

At the time of the outbreak, the investigation team collected data on 58 of the 89 residents, which included all residents who reported having an ILL, and 36 residents who were asymptomatic. We also collected information from 23 staff members. As staff vaccination records were not routinely collected by the hospital at the time of the outbreak, we were unable to (i) verify their vaccination history; and (ii) calculate the overall level of staff vaccination in hospital prior to the outbreak.

Public health measures

The Sydney West public health unit was notified of the outbreak 4 days after the onset of symptoms of the first

Table 1. Demographic information relating to residents of the hospital in Sydney, Australia, July 2005

Characteristics	n = 89 (%)
Male	40 (44.9)
Female	49 (55.1)
≤65 years	39 (43.8)
>65 years	50 (56.2)
Living in unit	
Unit A	16 (18.0)
Unit B	10 (11.2)
Unit C	16 (18.0)
Unit D	21 (23.6)
Unit E	26 (29.2)
Co-morbidities	
Huntington's disease	16 (18.0)
Dementia	16 (18.0)
Other psycho-geriatric disorders	10 (11.2)
Symptoms	
Acute respiratory	24 (27.0)
Met ILI case definition	22 (24.7)
Vaccinated	
Prior to outbreak	45 (51.0)

ILI, influenza-like illness.

case. Recommendations made to the nursing home included the use of respiratory infection control precautions, cohorting of sick residents, ensuring staff were restricted to the units where they were working, restricting visitors to the facility and postponing trips from the facility.

Of immediate concern was the low rate of vaccination amongst residents. The treating general practitioner was contacted and requested to expedite the administration of influenza vaccine to those who were not vaccinated. Oseltamivir was offered as either treatment to sick residents at 75 mg twice daily for 5 days, or prophylaxis to asymptomatic residents with 75 mg once daily for 10 days. Oseltamivir was not offered to staff members.

Statistical analysis

Data collected were entered and analysed descriptively using Epi-info, CDC, USA (version 3.3.2). Descriptive statistics was used to describe age, symptoms, vaccination rates and hospitalization. Attack rates in residents were calculated by dividing the number of cases in residents by the total number of residents on the first day of the outbreak (day 0). Vaccine effectiveness in residents was calculated as follows: 1 minus the ratio of attack rate in the vaccinated to the attack rate in the unvaccinated.

Laboratory investigation

Specimens for laboratory testing were taken on two occasions. The public health unit initially collected nose and/or throat swabs from residents who displayed an ILI on 30 July 2005. Twenty-two swabs were collected by the public health unit and tested within 24 hours. Nose and throat swabs were also collected by the study team on 1 August 2005, from all residents residing in four of the five units, which included both symptomatic and asymptomatic residents. The study team received these results on 21 September 2005. Direct immunofluorescence was performed on smears of deposits from nose and throat swabs that were acetone-fixed and stained with fluorescein-conjugated monoclonal antibodies against influenza A and B haemagglutinin and nucleoprotein, respiratory syncytial virus, parainfluenza viruses and adenovirus (Chemicon International, Temecula, CA, USA).¹⁵

Results

Over a 9-day period, 24 of 89 residents (27%) displayed acute respiratory symptoms and 22 met the case definition of ILI, with malaise and cough being the two most frequently reported symptoms. Onset of illness occurred between 27 July and 6 August 2005, with a peak of 17 case-residents in the period between 31 July and 3 August 2005 (Figure 2). The overall attack rate for the hospital was

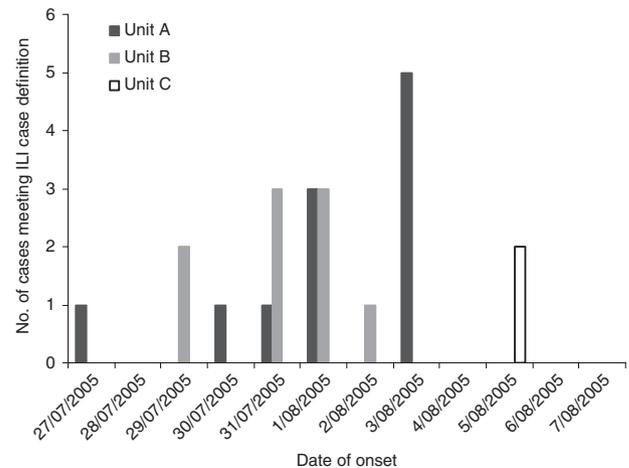


Figure 2. Epidemic curve for influenza-like-illness cases among residents of the hospital, July and August 2005.

25%. For units A, B and C it was 68.8%, 90% and 12.5% respectively. There were no cases in either D or E unit. There were no cases of pneumonia, hospitalization or death among the residents due to influenza.

Oseltamivir was offered as either treatment to sick residents or prophylaxis to asymptomatic residents. This was commenced on 6 August 2005 and was taken by 97% (86/89) of the residents. Of these, 87% (77/89) were given oseltamivir prophylaxis and 10% (9/89) were actively treated. Three of the residents refused to take the drug. Of the residents who reported having ILI, 13 had already been ill for longer than 48 hours, but were offered oseltamivir as a precaution. The average number of days from onset of illness to the initiation of oseltamivir for the units that reported ILI cases was 4–6 days. However, this ranged from 1 day for unit C to 7 days for unit B. The hospital did not report any adverse events occurring in the residents following the administration of the antiviral; however, only low levels of surveillance were undertaken. One resident did discontinue the use of the drug due to feeling nausea. This patient was undergoing cancer treatment at the time of the outbreak, so we could not verify whether it was linked to the drug. Staff members were not offered oseltamivir. As documented in Table 2, there were no further cases after oseltamivir prophylaxis and treatment was commenced.

Residents living in unit B had the highest relative risk of contracting the virus compared with the other units [relative risk: 5.47, 95% confidence intervals (CI): 3.19–9.37, $P < 0.001$]. For all units a strong association also existed between age (65 years and older) and being diagnosed with influenza (relative risk: 2.30, 95% CI: 1.10–4.79, $P = 0.02$) (Table 3).

Of the 58 residents for whom information was collected, only 38% were reported to have been vaccinated before the

Table 2. Summary of the antiviral agent usage on affected units during the outbreak in the hospital

Characteristics	Unit A <i>n</i>	Unit B <i>n</i>	Unit C <i>n</i>
Date of onset of outbreak	27 July 2005	30 July 2005	05 August 2005
No. residents who received oseltamivir for			
Treatment	4	0	5
Prophylaxis	12	10	11
Duration of oseltamivir treatment (days)	5	5	5
Duration of oseltamivir prophylaxis (days)	10	10	10
Time from onset of first case to initiation of oseltamivir (days)	6	7	1
Attack rate (no. cases/total no. residents) (%)	68.8	90.0	12.5
No. case residents with pneumonia/serious complication	0	0	0

Table 3. Univariate analysis for residents who met the influenza-like-illness (ILI) case definition

Variable	Relative risk	95% Confidence intervals		P-value	Chi-square
		Lower	Upper		
Gender	0.98	0.47	2.02	0.95	0.00
Received current influenza vaccine	0.94	0.47	1.86	0.85	0.04
Location					
Unit A	4.56	2.41	8.63	<0.001	20.32
Unit B	5.47	3.19	9.37	<0.001	25.80
Unit C	0.46	0.12	1.76	0.21	1.57
Age above 65 years	2.30	1.10	4.79	0.02	5.62

outbreak. The ILI attack rate was lower in the vaccinated compared to unvaccinated residents (13.9% versus 55.2%) and the vaccine effectiveness for this group of residents was 75% (95% CI: 0.06–1.47). At the time of the outbreak, there was 170 nursing, medical, ancillary and support staff working in the facility. The attack rate of acute respiratory illness among all staff members was 1.2% (2/170), although none fulfilled the criteria of an ILI. No antiviral treatment, prophylaxis or vaccine was given to staff members. However, staff members were restricted to the units where they were working.

Laboratory investigations

Influenza B was detected in six combined nose and throat swabs taken from the residents. No influenza A or other respiratory viruses were detected. One influenza isolate was subtyped as influenza B/Shanghai/361/2002-like, which was well matched to the influenza B strain contained in the 2005 influenza vaccine.¹⁶ Of the residents who had a laboratory-confirmed illness, all of them met the ILI definition and five had received the vaccine that year.

Discussion

We describe an influenza B virus outbreak that affected 25% of residents of a chronic care hospital. The outbreak started on 27 July 2005 with a single ILI case and extended to 21/89 of the residents within a week. The public health unit was notified 4 days after the onset of the first symptoms.

To the best of our knowledge, there is very little published literature available on the effectiveness of oseltamivir in the control of influenza B outbreaks in long-term care facilities (LTCFs). One of the few available comparator studies concluded that prophylaxis was very effective in halting the outbreak.¹⁰ During our outbreak, oseltamivir was offered as either treatment to sick residents or prophylaxis to asymptomatic residents. After the prophylaxis was initiated on 6 August 2005 there were no more cases. We are however unable to conclude whether the cessation of cases was because of the initiation of the drug or due to the outbreak was already started to wane. No major side effects from the use of oseltamivir in this population were reported in this outbreak.

In this outbreak, there was a delay of over a week between the notification and the initiation of prophylaxis. It is recommended by the Centers for Disease Control and Prevention's Advisory Committee on Immunisation Practices that when a confirmed or suspected outbreak of influenza occurs in institutions that house persons at high risk, chemoprophylaxis should be started as early as possible.¹⁷ A recent example of the effects of early initiation of post-exposure chemoprophylaxis was discussed in a paper by Rubin *et al.*¹⁸ The authors found that LTCFs that initiated chemoprophylaxis >5 days after outbreak onset had significantly longer duration of outbreaks (18.3 versus 6.7 days; $P < 0.001$), higher incidence rates (10.5 cases/100 residents versus 6.2 cases/100 residents; $P < 0.023$) and higher case-fatality rates (3.3 deaths/100 residents with influenza A versus 0.45 deaths/100 residents with influenza A; $P < 0.005$) than did LTCFs that initiated chemoprophylaxis ≤5 days after outbreak onset. Their findings make sense: the earlier the diagnosis, the quicker the introduction of barriers to transmission (such as speedier chemoprophylaxis initiation), the lower the number of new vectors, and the lower the impact and extent of an influenza outbreak.¹⁹

The efficacy of treatment with NI is highly dependent on the time of treatment initiation.²⁰ Aoki *et al.*²⁰ analysed the relative improvement in symptoms by the interval between onset of symptoms and treatment. Patients who started receiving treatment 48 hours after the onset of symptoms served as the control group. For the patients who started receiving treatment within 6 hours after the onset of symptoms, the duration of impaired activity was reduced by 6 days, the duration of impaired health was reduced by 3.5 days and the duration of fever was reduced by 2.5 days, compared with the observations for control subjects. The magnitude of the benefit decreased progressively with increases in the delay until initiation of treatment. Therefore, the benefits of treatment are maximized when early treatment is provided. In a retrospective evaluation of oseltamivir use during influenza outbreaks in nursing homes in Ontario, Canada, patients who received oseltamivir within 48 hours after the onset of symptoms were compared with patients who received either no therapy or therapy with amantadine. Patients who received oseltamivir were less likely to be prescribed antibiotics, to be hospitalized or to die ($P < 0.05$, for each outcome).²¹

The use of influenza vaccination for elderly people who have chronic disease and for residents in long-term care institutions is also strongly recommended by the Center for Disease Control and Prevention in the United States.¹⁷ In Australia, the influenza vaccine is recommended by the Australian government and free to anyone over the age of 65 years.²² For residents in long-term care institutions, the vaccine is thought to be around 30–40% effective in preventing upper respiratory illness² and effective in preventing 50–60% of hospitalizations or secondary complications.²³ However, with regard to preventing mortality, there has been recent controversy about the level of effectiveness in elderly people. Previously it was documented that the vaccine was effective in preventing 68% of deaths (17). However, the evidence base for this consisted mainly of observational studies which compared the mortality risks in self-selected groups of vaccinated and unvaccinated elderly people. Simonsen *et al.* suggested that high estimates of influenza vaccine effectiveness for severe outcomes are best explained by an unrecognized selection bias in cohort studies.²⁴

Numerous accounts of influenza outbreaks in aged care facilities (ACFs) and hospital wards have identified staff illness preceding resident illness.^{25,26} In this outbreak, the original source of the illness was not determined; however, it was thought that it might have originated from a staff member who had recently travelled from overseas. In theory, vaccination of anyone who will enter the facilities will result in a reduced rate of introduction of influenza and, thus, in a reduction in the risk of outbreaks. Staff vaccination has been suggested to be as at least as important as

resident vaccination in preventing outbreaks.^{17,27} Salgado *et al.* demonstrated that low levels of healthcare workers (HCW) vaccination significantly correlated to an increased rate of nosocomial influenza infections in hospitalized patients.²⁸ In another study conducted in 12 different long-term care hospitals, HCWs were randomized to either receive the influenza vaccine or not. In hospitals where HCWs were offered vaccination, 61% of 1078 workers were vaccinated. The study reported that vaccination of the HCWs was associated with reductions in total patient mortality from 17% to 10% and a reduction in ILL.²⁹

Identification of an influenza outbreak in a long-term care facility provides an ongoing challenge. Early identification and management of outbreaks may be hampered by the size and conditions of the ACF, the health and age of residents and the difficulties of contacting multiple primary care doctors. There is currently a lack of consensus about how to perform influenza surveillance or whether it is practical and cost-effective to do so systematically.

Active surveillance where there is regular routine contact with the ACF and includes zero-case reporting instead of awaiting passive reporting, complemented by early detection with point-of-care testing has been shown to result in better outbreak control.³⁰ Point-of-care tests are less sensitive (63–81%) than traditional laboratory tests such as direct immunofluorescence and nucleic acid testing, but are highly specific (82–100%).^{31–33} They are useful for identification of influenza outbreaks,³⁴ for example, when performed on specimens from the first few cases in a cluster of respiratory illness.³⁵

Prevention and control systems for influenza virus outbreaks in LTCFs rely on a certain amount of knowledge, interest, resources and compliance by the facilities and their staff. While maintaining high annual vaccination coverage for the elderly and other residents and promoting increased vaccination rate among staff members remains an important method of reducing the impact of influenza, oseltamivir has the potential of being a safe and cost-effective control measure for outbreaks.

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Conflict of Interest

Occasionally, organisations such as CSL, Roche, Sanofi, GSK & Wyeth provide funding for Professor Booy to

attend & present at scientific meetings. Any funding received is directed to a research account at The Children's Hospital at Westmead and is not personally accepted by Professor Booy.

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