琉球大学学術リポジトリ

オセルタミビル予防投与によるインフルエンザ院内感染防止：観察研究と文献学的考察

メタデータ	言語: English 出版者: 琉球大学 公開日: 2016-04-27 キーワード (Ja): キーワード (En): nosocomial infection, influenza virus A, prophylaxis, oseltamivir 作成者: 砂川, 智子, Sunagawa, Satoko メールアドレス: 所属:
URL	http://hdl.handle.net/20.500.12000/33667

Journal of General and Family Medicine 2015, vol. 16, no. 3, p. 143–152.

Special Articles

Prevention of a Nosocomial Infection Caused by Influenza Virus A Using Prophylactic Administration of Oseltamivir: An Observational Study with Review of the Literature

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Influenza virus infection in hospitals is a very important clinical issue. The objective of this study was to describe the effect of oseltamivir in controlling a nosocomial influenza virus infection with an observational study and case report. Intervention was carried out in a ward of the University of the Ryukyus Hospital. Symptomatic staff members were sent home for one week, and the infected inpatients were isolated. In addition, in an episode of influenza infection among the staff members and inpatients, oseltamivir (75 mg once a day for 7 days) was administered to all staff members as well as inpatients who had had close contact with the influenza patients. In the hospital ward, eight staff members (nurses and doctors) and ten hospitalized patients were definitively diagnosed with influenza A viral infection based on results of a rapid diagnostic test. Although a relatively large number of the staff members and inpatients had an influenza virus infection, it was possible that the use of oseltamivir efficiently minimized a nosocomial outbreak. It was very difficult to diagnose influenza A virus infection based on clinical symptoms. It was possible to minimize and end the outbreak immediately by using oseltamivir prophylaxis. With a review of the literature, it is considered that prophylaxis with anti-influenza drugs are highly recommended in hospital settings.

Keywords: nosocomial infection, influenza virus A, prophylaxis, oseltamivir

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Received for publication 19 November 2014 and accepted in revised form 27 March 2015
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Introduction

Influenza can be transmitted between patients and medical staff members (nurses and doctors) in hospital settings and result in increased morbidity and mortality, especially in immunocompromised inpatients.[1,2] In addition, since outbreaks of influenza might result in the functional deterioration of both acute hospital settings and healthcare facilities for care of chronic diseases, it is important to take prompt action to prevent droplet transmission of the influenza virus after the index cases are identified.

Of course, in the hospital setting, all staff members should receive vaccination for influenza. In addition, if the number of patients with influenza increases in the community, staff members should wear surgical masks to prevent droplet infection. However, even though the staff have been vaccinated against influenza virus, it is impossible to prevent all nosocomial influenza virus infections. In addition, hospitalized patients are not necessarily vaccinated, and often have impaired immune systems. Chemoprophylaxis for those who have had close contact with index cases may supplement pre-requisite vaccination to control influenza virus infection.[3]

Although there are many reports concerning the efficacy of chemoprophylaxis to prevent influenza outbreaks, the usefulness of chemoprophylaxis has not been fully established. More specifically, the effectiveness of chemoprophylaxis in the hospital setting[4–16] has not been well established.

This study reports an episode of influenza virus infection among staff members and inpatients at a university hospital during a period of epidemic influenza in the community. In addition, the usefulness of the prophylactic administration of oseltamivir to prevent nosocomial influenza viral infection will be discussed.

Patients and Methods

Epidemiological survey

The average number of influenza patients per hospital per week was evaluated. Then, a plot of influenza patients from January 2009 to March 2011 in Okinawa was made.

During the same period, we counted those (staff members, inpatients, and patients' family members) with an influenza virus infection observed in the University of the Ryukyus Hospital (a specialized university hospital with 600 beds) during 2009–2011.

Identification of cases with influenza virus infection

According to these epidemics observed in community, influenza virus infections were observed in several wards in the University of the Ryukyus Hospital (600 beds). For the purpose of the epidemiological investigation, a case is defined as any person who had an acute respiratory illness with two or more of the following symptoms; cough, sore throat, myalgia, and fever (>37.0°C). A survey was conducted, recording demographic data (name, sex, age, and profession), date of first symptoms, current therapy, and major symptoms (fever, cough, sore throat, myalgia, and headache).

Index cases of influenza were identified by self-reporting. Influenza was diagnosed by clinical examination and an immunochromatographic test for influenza virus A and B antigens (Tauns Laboratories, Inc., Shizuoka, Japan). Patients who had influenza-like symptoms (fever, arthralgia, and upper respiratory symptoms) during influenza outbreaks, and tested positive for influenza antigen, were diagnosed with influenza. Examples of close contact with the index cases included the following: i) physical care, ii) verbal communication without personal protective equipment, and iii) sharing a room. Individuals who were considered to have close contact with the index cases were actively monitored for symptoms for 10 days after identification.

A nasopharyngeal swab was obtained from all patients and immediately examined by rapid diagnostic kits for influenza. The diagnosis of influenza was performed based on clinical symptoms and a definitive diagnosis of influenza was made based on the results of repeated rapid diagnostic kits.

Influenza chemoprophylaxis

Chemoprophylaxis was recommended for hospitalized patients who were considered to have had close contact with index cases in the ward to minimize an outbreak with a hospital burden.

Among several neuraminidase inhibitors (NIs); oseltamivir was used for influenza chemoprophylaxis. Written informed consent was obtained for the administration of these drugs. Adults with full renal function received 75 mg/day of oseltamivir for 7 days. Patients on hemodialysis received a single dose of 75 mg of oseltamivir.

Data concerning staff influenza vaccinations were obtained from the employee health service records.

Control measures

Symptomatic staff members with a definite influenza infection were sent home for one week. Inpatients with influenza infection were isolated under respiratory infection precautions (single room, gloves, mask), and the number of staff members and visitors entering the rooms of patients with influenza was minimized. Staff members and patients with a definite influenza infection were treated by anti-influenza drugs with a standard dosage. In outbreaks, oseltamivir (75 mg orally, once a day, for 7 days) was administered to asymptomatic staff members and inpatients who had contact with infected patients.

Review of the literature

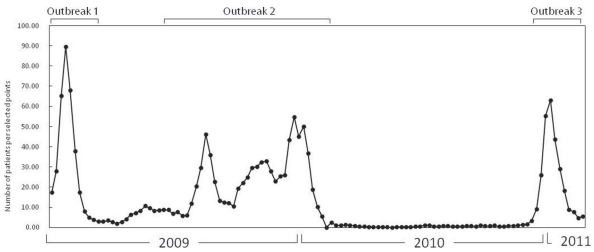
We reviewed articles concerning prophylactic use of oseltamivir through the MEDLINE (keywords were influenza and prophylaxis). Articles not listed in the MEDLINE and those written in languages other than English were excluded.

Results

Epidemiology of influenza in the community

Recently, in Okinawa, Japan, we have experienced three large influenza outbreaks. The first outbreak in the 2008–2009 season was caused by an oseltamivir-resistant H1N1 virus, the second outbreak in the 2009–2010 season was caused by the pandemic H1N1 2009 virus, and the third outbreak was also caused by the pandemic H1N1 2009 virus during the 2010–2011 season (**Figure 1**). Our experience in Okinawa has shown the incidence of influenza was mainly caused by the pandemic H1N1 2009 virus which increased markedly in August 2009, peaked in mid-September, and then declined thereafter. Once again later that year, the incidence of influenza increased, and peaked in December 2009 so, overall, the influenza epidemics lasted 26 weeks.

Figure 1. Plot of influenza patients from January 2009 to March 2011 in Okinawa.
Three outbreaks are indicated by brackets. The horizontal bar demonstrates the number of patients per selected points demonstrated as number of patients referred to one hospital per week.



Number of cases those diagnosed in the University of the Ryukyus Hospital

In the hospital setting, we experienced many cases of influenza virus infection (**Figure 2**). As compared with **Figure 1**, there was similarity between epidemics in Okinawa and numbers of patients (staff members, inpatients, and patients' family members) with influenza virus infection in the University of the Ryukyus Hospital (**Figure 2**).

Episode of nosocomial outbreak of influenza (Figure 3), observational study, case report

In January 2011, we experienced outbreak of influenza virus infection (caused by the pandemic H1N1 2009 virus) in the west 10th ward (the ward of dermatology and the urology department). On January 29th, 2011, one staff member complained of a respiratory illness that met the case definition. On January 30th, another staff member and seven inpatients (A, B, C, D, E, F, and G in **Figure 3**) in the west 10th ward complained of a respiratory illness that met the case definition and were diagnosed as having influenza using the rapid diagnostic kit. On January 31st, one staff member and three inpatients (H, I, and J in **Figure 3**) complained of a respiratory illness that met the case definition and were diagnosed as having influenza using the rapid diagnostic kit.

On February 1st, 2011, to prevent nosocomial influenza

Figure 2. Number of patients with influenza infection from January 2009 to March 2011 in the University of the Ryukyus Hospital.
As shown in **Figure 1**, three influenza epidemics recently occurred in Okinawa, Japan. During these three epidemics, if the number of patients increased in Okinawa prefecture, the number of patients diagnosed in our university hospital (staff members, inpatients, or patients' family members) also increased. Horizontal bar demonstrates number of patients with influenza confirmed by the rapid diagnostic test.

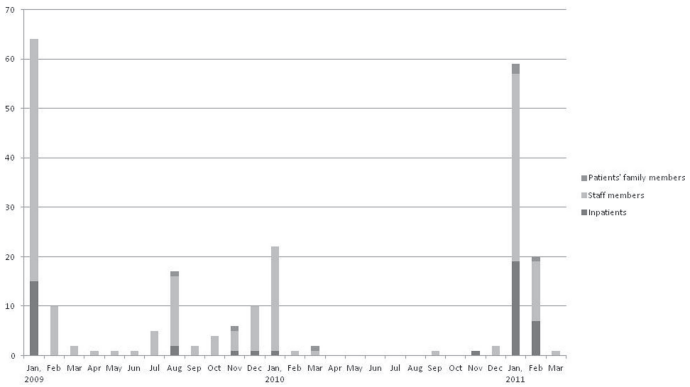
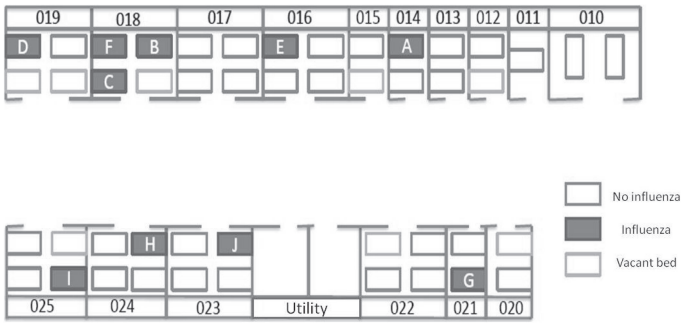


Figure 3. An episode of influenza viral infection at our university hospital (in the west ward of the 10th floor).
Within two days, ten admitted patients were diagnosed to have influenza A by a rapid diagnostic test.



A virus infection inside hospital, we started a prophylactic treatment with oseltamivir. Oseltamivir (75 mg/day, once a day for 7 days) was prophylactically administered to the remaining staff members and inpatients with a written informed consent. After the oseltamivir prophylaxis, there was no occurrence of influenza A virus infection in admitted patients. On February 2nd, 2011, however, one patient's family member, who had not received oseltamivir, complained of a respiratory illness and was diagnosed as having influenza. After February 4th, 2011, no influenza patients were observed. Secondary bacterial pneumonia was observed in one inpatient, fortunately however, since most inpatients were not immunocompromised, no inpatients died. Since all staff or inpatients who met the criteria were examined by the rapid diagnostic test, there was little possibility that we missed an influenza virus infection.

Although the index case was a staff member, all staff members had been vaccinated in November, 2010. Among the 69 staff members and inpatients who took oseltamivir, influenza A viral infection occurred in five staff members within three days after prophylactic administration.

Figure 4. Clinical features (degree of fever) of inpatients with influenza in the west ward of the 10th floor.
Since nosocomial infection was strongly suspected, we evaluated temperatures of inpatients diagnosed to have influenza infection. As shown in this figure, highest temperature was 37.7 ± 0.82°C (mean ± standard error) at one day after the diagnosis of influenza.

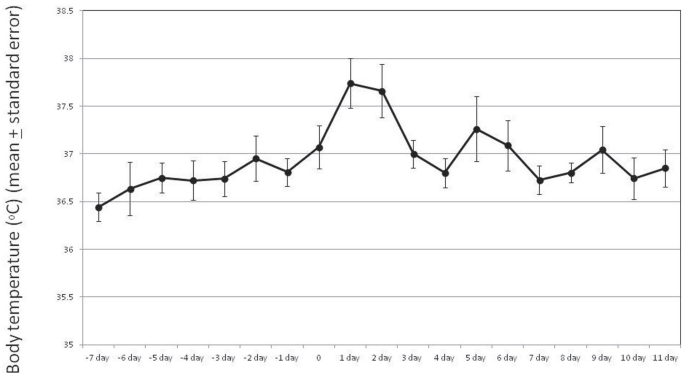
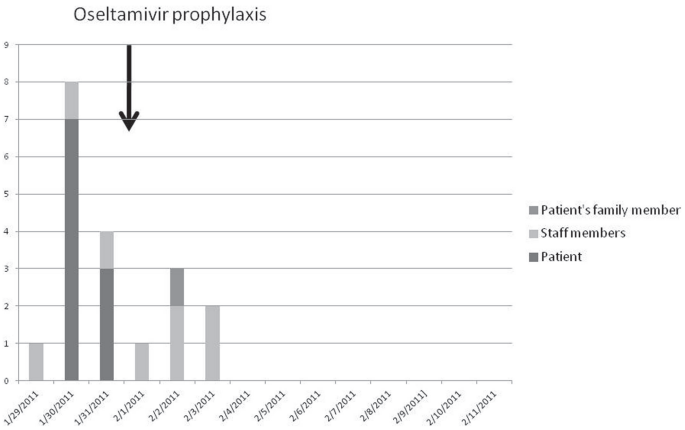


Figure 5. An episode of influenza viral infection at our university hospital (in the west ward of the 10th floor).
Prophylactic treatment of oseltamivir was started from February 1st, 2011. Although 44 staff members and 25 patients took oseltamivir, influenza A viral infection occurred in 5 of the staff within 48 hours after prophylactic administration. One patient's family who did not take oseltamivir had an influenza A infection on February 2nd, 2011. However, influenza A infection was not observed from February 4th, 2011.



Clinical features of patients with influenza (Figure 4)

We evaluated sequential temperatures of inpatients before and after being diagnosing as having influenza infection. However, mean increase of body temperature was slight. As shown in **Figure 4**, mean highest temperature was 37.7 ± 0.82°C (mean ± standard error). Therefore, it was very difficult to diagnose influenza infection based on a higher body temperature without the rapid diagnostic kit. In addition, since clinical symptoms for medical staff members were more trivial than patients, it was very difficult to diagnose as influenza without the rapid diagnostic kit (data not shown).

Review of the literature (Table 1)

There are many reports regarding influenza prophylaxis. Although, there are few reports concerning prophylaxis of nosocomial infection before the outbreak of pandemic A H1N1,[10,16] there are many articles concerning the prophylactic use of NIs in nosocomial settings after the outbreak of pandemic A H1N1 (**Table 1**).[4–9,11–14]

Table 1. Prophylactic use of anti-neuraminidase inhibitors againt influenza virus infection

Author (year)	Drugs	Country	Type of virus	Situation	Duration	Effect
Anekthananon (2013)*	Oseltamivir or Zanamivir	Thailand	A (H1N1), A (H3N2), B and pdm09 A (H1N1)	Health workers	16 weeks	Effective
Reisinger (2013)	Oseltamivir	USA	ND	Children in a community setting	6 weeks	Safe
Booy (2012)*	Oseltamivir	Australia	A (H3N2), B	Aged care facilities	5 days	Effective
Ison (2012)*	Oseltamivir	USA	pdm09 A (H1N1)	Transplant recipients	12 weeks	Effective
Shinjoh (2012)	Oseltamivir or Zanamivir	Japan	A, B	Pediatric wards	7–10 days	Effective
Fallo (2012)	Oseltamivir	Argentina	pdm09 A (H1N1)	Household contact	ND	Effective
Tsagris (2012)	Oseltamivir	Greece	pdm09 A (H1N1)	Neonatal ICU	10 days	Effective
Upjohn (2012)	Oseltamivir	Australia	pdm09 A (H1N1)	Health care workers	10 days	the usefulness of oseltamivir postexposure prophylaxis will be limited
Maltezou (2012)	Oseltamivir	Greece	pdm09 A (H1N1)	Neonatal unit	10 days	Safe and effective
Kute (2011)	Oseltamivir	India	pdm09 A (H1N1)	Renal allograft recipients	10 days	Effective
van Velzen (2011)	Oseltamivir	Sweden	pdm09 A (H1N1)	Nursery and primary school children	10 days	High overall compliance
Coleman (2011)	Oseltamivir	Canada	A, B	Health care workers	5–155 days	Long-term antiviral prophylaxis was generally well tolerated with good compliance
Pannaraj (2011)	Oseltamivir	USA	pdm09 A (H1N1)	Neonatal ICU	10 days	Oseltamivir appears to be well tolerated
Higa (2011)	Oseltamivir or Zanamivir	Japan	A (H3N2, H1N1)	Hospital	Oseltamivir (5–7 days) or Zanamivir (10 days)	Effective
Leung (2011)	Oseltamivir	China	pdm09 A (H1N1)	Household transmission	ND	Effective
Rohn (2011)	Oseltamivir	Austria	A (H1N1)	Donor-recipient	10 days	Effective
te Beest (2010)	Oseltamivir	Netherlands	avian H7N7	Poultry workers	ND	Protective effect
Lee (2010)	Oseltamivir	Singapore	A (H1N1)	Military	10 days	Effective
Komiya (2010)	Oseltamivir or/and Zanamivir	Japan	pdm09 A (H1N1)	Household transmission	7–10 days	Effective
Strong (2010)	Oseltamivir	United Kingdom	pdm09 A (H1N1)	Primary school	10 days	Benefits of mass treatment

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Author (year)	Drugs	Country	Type of virus	Situation	Duration	Effect
Weston (2010)	Oseltamivir	Australia	pdm09 A (H1N1)	Primary school	ND	Successful public health clinic providing antiviral prophylaxis
Kimberlin (2010)	Oseltamivir	USA	pdm09 A (H1N1)	Summer campers	10 days	Effective
Marfo (2009)	Oseltamivir	USA	pdm09 A (H1N1)	Newly transplanted kidney recipient	5 days	Effective
Garrison (2009)	Oseltamivir	USA	pdm09 A (H1N1)	Summer campers	10 days	Resistant strains
Wallenstein (2009)	Oseltamivir	United Kingdom	pdm09 A (H1N1)	School outbreaks	10 days	Compliance with oseltamivir chemoprophylaxis was high
Seale (2009)	Oseltamivir	Australia	B	Chronic care hospital	10 days	Oseltamivir has the potential
Risa (2009)	Oseltamivir	USA	A	Locked behavioral health unit	ND	Pharmacologic prophylaxis can help stem outbreaks
Belmaker (2009)	Oseltamivir	Israel	avianH5N1	Poultry workers	7 days	Adherence
Kitching (2009)	Oseltamivir	United Kingdom	pdm09 A (H1N1)	Primary and two secondary schools	10 days	Restrict widespread use of prophylaxis
Odaira (2009)	Oseltamivir or Zanamivir	Japan	pdm09 A (H1N1)	Household contacts	7–10 days	The effectiveness of prophylaxis for household contacts was not determined
Gaillat (2008)	Oseltamivir	France	A (H3N2)	Home for the elderly	7 days	Recommended
Fujita (2008)	Oseltamivir	Japan	A	Hospital	5 days	Effective
Laforce (2007)*	Zanamivir	World-wide	A (H3N2, H1N1)	Community	28 days	Efficacious
Ambrozaitis (2005)*	Zanamivir	World-wide	A (H3N2, H1N1), B	Unvaccinated residents of long-term care facilities	14 days	Effective
Gravenstein (2005)*	Zanamivir	World-wide	A, B	Highly vaccinated long-term care population	14 days	Effective
Hayden (2004)*	Oseltamivir	World-wide	A (H3N2, H1N1), B	Households	10 days	Efficacious
Harling (2004)	Oseltamivir	United Kingdom	Influenza-like illness	Nursing homes	10 days	Potential usefulness of oseltamivir
Bowles (2002)	Oseltamivir	Canada	A (H3N2)	Nursing home	8–10 days	Effective
Monto (2002)*	Zanamivir	World-wide	A (H3N2, H1N1), B	Households	10 days	Effective
Welliver (2001)*	Oseltamivir	USA	A (H3N2, H1N1), B	Households	7 days	Effective
Peters (2001)*	Oseltamivir	USA	A (H3N2, H1N1), B	Frail older subjects	42 days	Effective
Kaiser (2000)*	Zanamivir	United Kingdom	A (H3N2), B	Close contact with index cases	5 days	Effective
Hayden (2000)*	Zanamivir	USA	A (H3N2, H1N1), B	Households	10 days	Effective
Hayden (1999)*	Oseltamivir	USA	A (H3N2, H1N1)	Healthy, non-immunized adults	42 days	Effective
Monto (1999)*	Zanamivir	USA	A (H3N2, H1N1)	Healthy, non-immunized adults	28 days	Efficacious

*Radomized trials

In hospital settings, all reports concluded that the prophylactic uses of NIs are effective and safe to control influenza virus nosocomial infection.[4–14,16]

Discussion

This report emphasizes the usefulness of anti-influenza drugs (oseltamivir) in preventing a nosocomial outbreak of influenza during a period of epidemic influenza.

In Japan, among four NIs, oseltamivir, zanamivir, and laninamivir are approved to use for both treatment and prophylaxis of influenza. Early administration of NIs reduces the duration and severity of symptoms as well as the overall risk of complications.[17–19]

In hospital settings, several observational studies have reported that post-exposure NIs prophylaxis is effective in controlling outbreaks.[5–16] Although most of them are observational studies, a double-blind randomized control trial found that long-term use of oseltamivir for influenza prophylaxis was effective for transplant patients to reduce the incidence of influenza.[4] On the other hand, in school settings, it has been pointed out that extensive use of chemoprophylaxis may be impractical and costly.[20–22]

Although the NIs are being introduced in clinical practice and will probably be useful in controlling outbreaks more easily,[18,29] amazingly, there were few reports which evaluated the efficacy of prophylactic use of anti-neuraminidase inhibitors in hospitals before the prevalence of pandemic 2009 A (H1N1).[10,16] Higa et al. retrospectively evaluated the use of neuraminidase inhibitor chemoprophylaxis for prevention of nosocomial spread of influenza in a university hospital.[10] They have demonstrated that when both the index cases and the close contacts were hospitalized patients, the incidence of influenza was significantly lower among the close contacts who received chemoprophylaxis than among those who did not. Fujita et al. have reported the usefulness of osertamivir prophylaxis (five days duration) in a nosocomial outbreak in a gynecology/obstetrics department.[16] In addition, Lee et al. evaluated the efficacy of ring chemoprophylaxis (geographically targeted containment by means of prophylaxis) with oseltamivir to control outbreaks of the 2009 H1N1 influenza in semiclosed environments.[12,13]

In hospital and nursing home settings, health care workers (HCW) have been occasionally been identified as index cases in outbreaks.[23,24] Up to 23% of HCW might present clinical or subclinical influenza infections at the time of epidemics.[25] It has been reported that the influenza vaccine is effective in preventing influenza infection in HCW and may reduce the number of days absent.[26] In addition, it has been demonstrated that the attack rate of influenza outbreaks in nursing homes and chronic care facilities depends to some extent on the vaccination status of residents and staff members.[27,28] However, in our university hospital, since all staff members including the first staff member infected had received a vaccination for influenza virus in November 2010, prevention of nosocomial influenza virus infection seems to be impossible by vaccination alone.

In our experience, clinical symptoms of influenza virus infection were trivial especially in staff members as reported previously.[30] In this literature, the median temperature was 36.7°C for those testing positive for H1N1 and 36.3°C for those testing negative.[30] Of those testing positive for H1N1, 58/85 (68%) were afebrile (temperature, $\leq$37°C).[30] Therefore, epidemiological and microbiological diagnosis using a rapid diagnostic test and the quick institution of infection control measures prevented the influenza virus infection's spread to most of the inpatients.

Our experiences have suggested the usefulness of oseltamivir in preventing nosocomial influenza virus infection. With a review of the literature, we consider that prophylaxis with anti-influenza drugs should be highly recommended in hospital settings.

Conflict of interest: None to declare.

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