A Model-based Assessment of Oseltamivir Prophylaxis Strategies to Prevent Influenza in Nursing Homes

Carline van den Dool, Eelko Hak, Marc J.M. Bonten,[1] and Jacco Wallinga[1]

Prophylaxis with neuraminidase inhibitors is important for controlling seasonal influenza outbreaks in long-term care settings. We used a stochastic individual-based model that simulates influenza virus transmission in a long-term care nursing home department to study the protection offered to patients by different strategies of prophylaxis with oseltamivir and determined the effect of emerging resistance. Without resistance, postexposure and continuous prophylaxis reduced the patient infection attack rate from 0.19 to 0.13 (relative risk [RR] 0.67) and 0.05 (RR 0.23), respectively. Postexposure prophylaxis prevented more infections per dose (118 and 323 daily doses needed to prevent 1 infection, respectively) and required fewer doses per season than continuous prophylaxis. If resistance to oseltamivir was increased, both prophylaxis strategies became less efficacious and efficient, but postexposure prophylaxis posed a lower selection pressure for resistant virus strains. Extension of prophylaxis to healthcare workers offered little additional protection to patients.

The prophylactic use of neuraminidase inhibitors is a key component of influenza outbreak control in healthcare institutions (*1*,*2*). Based on its proven efficacy in reducing susceptibility, duration of illness, and infectiousness in household studies (*3*–*6*), oseltamivir is now the antiviral agent recommended for prophylactic use in nursing homes. Although the efficacy of oseltamivir has not been extensively assessed in the elderly, some observational and experimental studies suggest beneficial effects of both continuous and postexposure prophylaxis in containing outbreaks and reducing the number of severe complications among nursing home residents (*2*,*7*–*10*).

During the 2007–08 and 2008–09 influenza seasons, the number of isolated influenza A (H1N1) viruses with resistance to the neuraminidase inhibitor oseltamivir increased considerably (*11*,*12*). Following the emerging resistance against the M2-inhibitors amantadine and rimantadine, the efficacy of this class of neuraminidase inhibitors may also be threatened (*13*). Given the speed at which resistant strains have spread and the large variability of influenza activity, it has been impossible to obtain evidence on how resistance has affected influenza control strategies from randomized controlled trials. This effect can, however, be derived using modeling studies (*14*,*15*). Therefore, we developed a mathematical model of influenza transmission in long-term care facilities to study different scenarios and to perform multiple simulations that minimize the probability of chance outcomes. We primarily determined the effect and efficiency of postexposure and continuous exposure prophylaxis strategies with oseltamivir, as compared with no prophylaxis, on infection attack rates among patients in a long-term care nursing home department. We also determined the influence of increased introduction of resistant virus strains on both strategies and assessed the potential benefits of extending prophylaxis to healthcare workers (HCWs).

Methods

Population and Model

We simulated the occurrence of influenza virus outbreaks during an 80-day period in a typical long-term care

Author affiliations: University Medical Center, Utrecht, the Netherlands (C. van den Dool, E. Hak, M.J.M. Bonten, J. Wallinga); University Medical Center, Groningen, the Netherlands (E. Hak); and National Institute for Public Health and the Environment, Bilthoven, the Netherlands (J. Wallinga)

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[1]These authors contributed equally to this article.

nursing home department (30-bed unit with 15 two-bed rooms and a team of 30 HCWs) in the Netherlands. HCWs worked 8-hour shifts; according to a weekly schedule 5, 3, and 1 HCW(s) worked during the day, evening, and night shifts, respectively, which has been observed in some nursing homes in the Netherlands. The average length of stay for a patient was 14 months (*16*,*17*). Because we simulated a small population where chance events can have major effects, we used a stochastic transmission model. The model is described in the online supporting information (online Technical Appendix, available from www.cdc.gov/EID/content/15/10/1547-Techapp.pdf) and has been described in detail in a previous study (*18*). Here, we describe the essential elements of the model's structure for the baseline scenario (parameters for the baseline scenario are shown in Table 1).

Infection Cycle

According to a standard model for infectious disease transmission, persons could be in 1 of several stages of influenza virus infection: susceptible, infected but not yet infectious (exposed), infectious, or recovered/immune (Figure 1) (*19*). The durations of the exposed and infectious periods were exponentially distributed with means of 1.4 days; the resulting generation time equaled 2.8 days, which agrees with observations of generation times during influenza epidemics (*20*,*21*). At the start of the influenza season, 30% of the adult nursing home population was assumed to be immune to infection because of cross protection from earlier infections (*22*). Since the elderly have weakened immune systems (*23*,*24*), but exact estimates are absent, we made the most conservative assumption that their immune systems had no memory of previous infections.

Influenza Vaccination

According to our model, both patients and HCWs could receive influenza vaccine before the influenza season. The average vaccination rate was 75% for nursing home patients (*25*) and 40% for HCWs (*2*). We assumed that for each person vaccination either led to perfect immunity against infection or had no effect (*18*). In a previous study, we showed that this all-or-nothing assumption for vaccine-induced immunity yielded similar results to those of an alternative assumption of incomplete immunity in which vaccinated persons had a lower probability of acquiring infection upon contact with an infectious person (*18*). The assumption of all-or-nothing immunity due to prophylaxis has also been made in other modeling studies (*26*). We assumed the vaccine efficacy against influenza virus infection in healthy adults, and thus HCWs, was 73% (*27*). For elderly nursing home patients, no statistically significant vaccine efficacy against infection has been observed (*28*). However, because other evidence showed that the vaccine protected against influenza disease and complications, we assumed patient efficacy to be 25% (*28*,*29*).

Table 1. Parameter values baseline scenario*

Parameter	Value	Reference
No. beds	30	
No. HCWs	30	
Time step (= shift), h	8	(*18*)
Minimum duration of simulation, d	80	
Discharge/mortality rate, per d	1/425	(*16,17*)
Rate of becoming infectious after infection, per d	1/1.4	(*20,21*)
Infection recovery rate, d	1/1.4	(*20,21*)
Prior immunity HCWs	30%	(*22*)
Prior immunity patients	0	
Vaccine uptake patients	75%	(*25*)
Vaccine uptake HCWs	40%	(*2*)
Vaccine efficacy (against infection)		
Patients	25%	(*28*)
HCWs	73%	(*27*)
Transmission probability per casual contact	0.13	(*18*)
Close/casual transmission probability ratio	2	
Mean visitor frequency/patient/d	0.7	(*31*)
Minimum duration of postexposure prophylaxis, d	14	(*2*)
Minimum duration of postexposure prophylaxis after last detected case, d	8	(*2*)
Parameters in uncertainty analyses		
Probability of disease developing after infection (range)	0.5 (0.30–0.7)	(*4*)
Probability of disease developing after infection, during prophylaxis (range)	0.2 (0.05–0.4)	(*4*)
Oseltamivir efficacy against infection (range)	0.53 (0.2–0.8)	(*4*)
Oseltamivir reduction in infectiousness (range)	0.2 (0–0.5)	(*4*)

*HCW, healthcare worker.

Prophylaxis with Oseltamivir

We compared 2 strategies of prophylaxis with oseltamivir to a control situation in which no neuraminidase inhibitors were used: continuous (seasonal) prophylaxis was given to all patients during 8 weeks (the longest period of prophylaxis described in effectiveness studies) (*30*) around the peak of the influenza season; or postexposure prophylaxis was started for all patients as soon as 1 patient had a laboratory-confirmed influenza virus infection. Because recognition of a possible influenza infection is required before doing a laboratory test, we assumed that only the fraction of infected patients in whom influenza disease developed (the symptomatic patients) could trigger the start of postexposure prophylaxis. We assumed that, for every first symptomatically infected person, the delay between the start of infectiousness and the start of prophylaxis followed a distribution with a mean of 3.5 days. This interval was determined by the time to onset of symptoms, the time to recognition of symptoms, the time to a positive laboratory test, and the delay to start of prophylaxis (online Technical Appendix). Postexposure prophylaxis was given to all patients in the department for at least 2 weeks and was continued until no new cases occurred during a period of 8 days (*2*). Because we did not have data on the efficacy of oseltamivir in elderly persons, we used estimates from household studies (*4*) as the best available evidence. We assumed oseltamivir induced immunity to infection by wild-type strains in 55% of the susceptible patients as soon as it was administered and for the duration of prophylaxis. Immunity did not develop in the other patients, but when they were infected they were considered to become less infectious than persons who did not take oseltamivir (*26*). Based on estimates of the total reduction in infectiousness in persons treated with oseltamivir (*4*), we assumed the probability that the virus was transmitted during contact with a susceptible person was reduced by 20%. In the online Technical Appendix, we describe some uncertainty analyses that we performed for the parameters describing oseltamivir efficacy.

Influenza Disease

On the basis of household studies, we assumed that influenza disease would develop in 50% of patients infected with influenza virus (*4*). For those receiving oseltamivir prophylaxis, this probability was only 20% (*4*).

Contacts

A person's risk of being infected depended on the number and type of contacts with infectious persons. We distinguished between casual and close contacts; casual contact was considered as conversation and close contact occurred with physical contact. We parameterized the contact model; the expected numbers of contacts, specified by type of persons and kind of contact, matched the number of contacts that we observed in 2 nursing home departments in the Netherlands (*18*). The probability of contact between 2 persons, given their type (HCW or patient), as well as the probability that this contact was close (physical contact), is given in Table 2. During the night shift, patients did not have contact with other patients, except for their roommates, who were assumed to be casual contacts. During the day and evening shifts, patients could also have contact with visitors. All contacts with visitors were considered close. The expected number of visitors was based on a study in the Netherlands on nursing home patients and visitors and was estimated to be 0.7 visitors per patient per day (*31*).

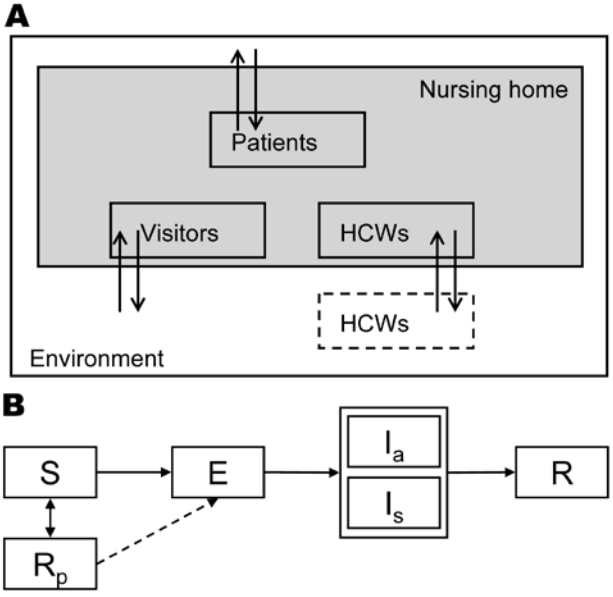

Figure 1. Schematic diagram of our stochastic individual-based model. A) The different types of persons in the nursing home: patients, healthcare workers (HCWs), and visitors. B) The time course of infection: S, susceptible; E, exposed; I_a, infectious and asymptomatic; I_s, infectious and symptomatic; R, recovered/immune; R_p, immune while using prophylaxis. For all patients and HCWs in the model, we kept track of their stage in this infection cycle in time. If the influenza strain that is transmitted is resistant to oseltamivir, persons in the R_p department can still become infected (dashed arrow).

Transmission

For every pair of persons with a casual or close contact, a probability existed that the virus was transmitted if the persons involved in the contact were infectious and susceptible. This probability was determined by sampling from a Bernoulli distribution with mean set equal to the transmission probability. For a casual contact, the transmission probability was 0.13; we chose this probability be-

Table 2. Contact probabilities between persons in a nursing home department*

Person	Contacted person	Probability of contact	Probability of close contact given casual contact
Patient	Patient	0.07	0.06
Patient	HCW	0.52	0.69
HCW	HCW	0.91	0.31

*HCW, healthcare worker.

cause the expected infection attack rate among patients in the absence of HCW vaccination was similar to observed attack rates for influenza-like-illness (*18*,*25*,*32*). For close contacts, the probability of transmission was assumed to be 2× as high as that of casual contacts.

Influenza in the Community

The rate at which influenza virus was introduced into the nursing home by HCWs, visitors, and patients depended on the prevalence of the virus in the community; we used a simulation of an influenza epidemic in a large population (online Technical Appendix). In each simulation, a constant proportion of infections in the community was assumed to be caused by resistant strains.

Oseltamivir Resistance

Resistant viruses were assumed to be completely insensitive to oseltamivir, and therefore prophylaxis had no effect on the susceptibility of a person who was exposed to a resistant strain. We also assumed that use of oseltamivir neither affected the infectiousness nor the development of symptoms in a person infected with a resistant strain. Apart from oseltamivir sensitivity, resistant and nonresistant strains were assumed to be similar. Infection with 1 of the strains conferred cross-protection against infection with other strains during the season.

Outcomes

We defined the infection attack rate and the disease attack rate as the total number of infections or influenza diseases among patients, respectively, divided by the total number of patients in the nursing home department during the study period. We distinguished between infections caused by oseltamivir-sensitive and -resistant strains and compared scenarios with increasing prevalence of oseltamivir resistance. Based on the distribution of infection attack rates in a nursing home in the absence of preventive measures (*18*), we used the proportion of infection attack rates of ≥0.3 as a proxy for the probability of a large outbreak. We calculated the absolute and relative risk reductions for both strategies of prophylaxis (efficacy) and determined the fraction of infections caused by resistant strains. We also computed the number of daily doses of prophylaxis needed to prevent 1 infection or disease (DNP) as the total number of doses administered divided by the number of influenza infections or diseases prevented (the absolute risk difference) (efficiency). Information on the statistical precision of the effect estimates can be found in the online Technical Appendix.

Alternative Scenarios

In addition to the baseline scenario previously described, we considered an alternative scenario in which both patients and HCWs received continuous or postexposure prophylaxis according to the same rules. Postexposure prophylaxis was started after detection of infection in a patient and was given to all patients and all HCWs. We also studied a scenario in which the HCW vaccination rate was only 10%, as was observed in the Netherlands (*33*). Here we considered prophylaxis to patients only and to patients and HCWs.

In the online Technical Appendix, additional scenarios are described for the following circumstances: 1) different delays between the start of infectiousness of the first symptomatic patient and the start of postexposure prophylaxis, 2) different levels of influenza virus activity in the community, 3) higher percentage of HCWs vaccinated, 4) lower patient vaccine uptake, 5) greater percentage of patients with prior immunity, and 6) a 60-bed nursing home department.

Results

Baseline Scenario

In the absence of resistance, the prophylactic use of oseltamivir reduced the number of influenza virus infections among patients during the influenza season. The infection attack rate among patients decreased from 0.19 in the control setting without prophylaxis to 0.13 (relative risk [RR] 0.67) when postexposure prophylaxis was given to all patients (first 2 bars, Figure 2, panel A). The fraction of large outbreaks with an infection attack rate of ≥0.3 decreased from 0.31 to 0.17 (RR 0.55), and outbreaks with attack rates >0.4 rarely occurred (Figure 3). If continuous prophylaxis was given for 8 weeks, the infection attack rate decreased to 0.05 (RR 0.23) (Figure 2, panel B), and the percentage of large outbreaks decreased to 0.03 (RR 0.09). Because of continuous prophylaxis, not only did large outbreaks disappear, but also the percentage of departments without any patient infection increased (Figure 3). Rates of influenza disease decreased from 0.10 to 0.06 (RR 0.60) and 0.01 (RR 0.13), respectively, for the 2 different strategies of prophylaxis (Figure 1, panels C, D). Although the number of infections that could be prevented was higher for continuous prophylaxis, the DNP was ≈3× higher with this strategy than with postexposure strategy (Figure 4). Without resistance, the DNP was 118 for postexposure prophylaxis and 323 for continuous prophylaxis.

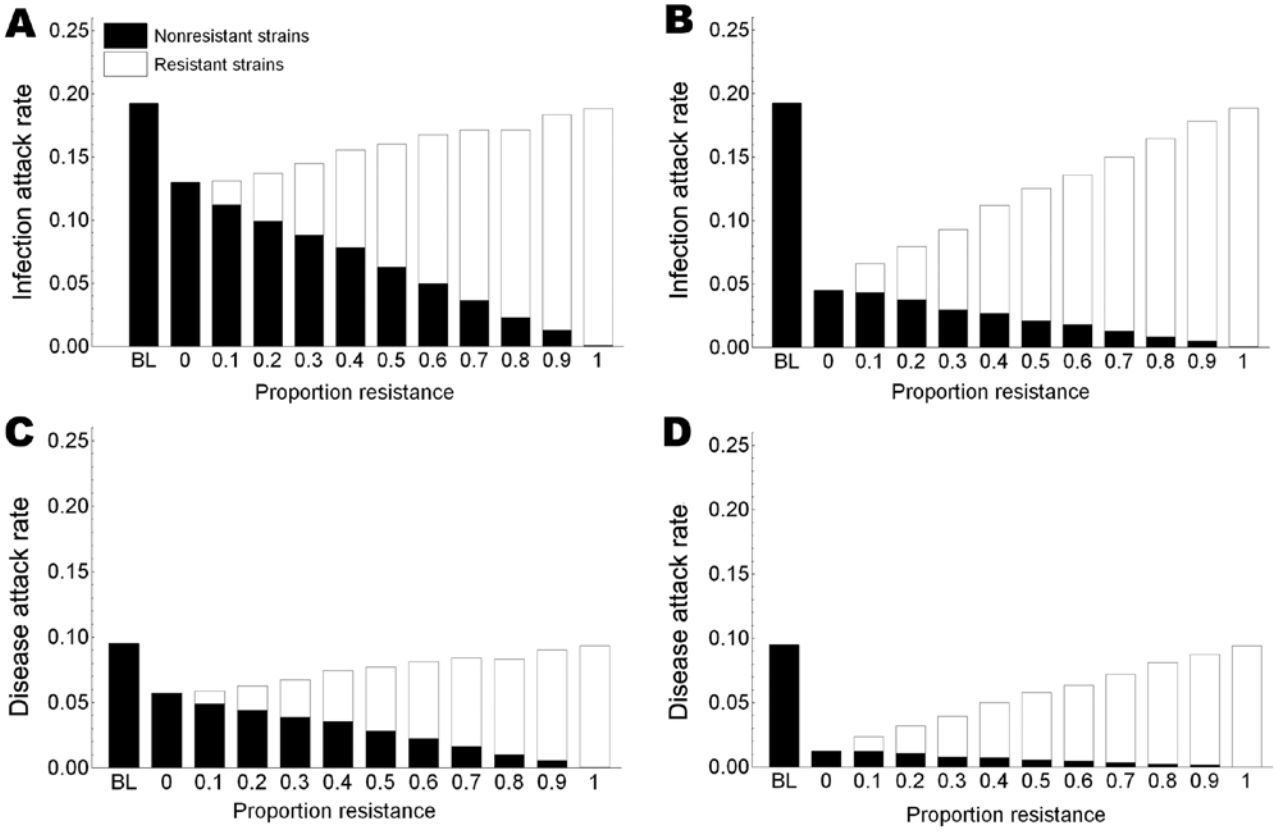

Figure 2. Effects of prophylaxis with oseltamivir on influenza virus infection and disease rates among nursing home patients. The effects of both postexposure and continuous prophylaxis strategies are shown for different proportions of resistant virus strains in the community and compared with a control setting without prophylaxis and resistance. Panels A and C, postexposure prophylaxis given to all patients; panel B and D, continuous prophylaxis for 8 weeks. BL, baseline.

Resistance

An increase in the proportion of oseltamivir-resistant influenza virus strains in the community reduced the efficacy of prophylaxis with oseltamivir against infection and disease (Figure 2). In addition, both prophylaxis strategies became less efficient and the DNP increased rapidly, in particular for the continuous prophylaxis strategy (Figure 4). Prophylaxis caused a selection pressure for resistant strains; the percentage of infections caused by resistant strains in the nursing home was higher than in the community (Figure 5). The selection of resistant strains was most pronounced for continuous prophylaxis strategy.

Alternative Scenario: Prophylaxis Extended to HCWs

Extension of prophylaxis strategies to include both HCWs and patients offered little additional protection to

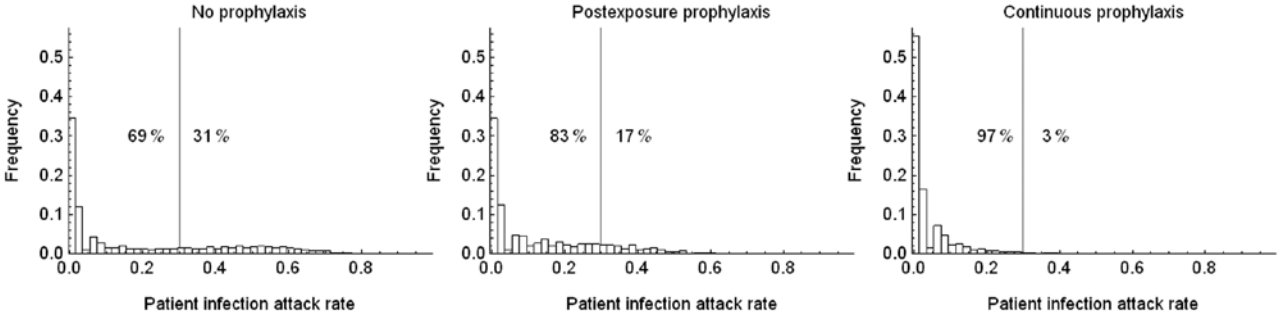

Figure 3. Distribution of influenza virus infection attack rates among patients who received no prophylaxis, postexposure prophylaxis, and continuous prophylaxis, in the absence of resistance.

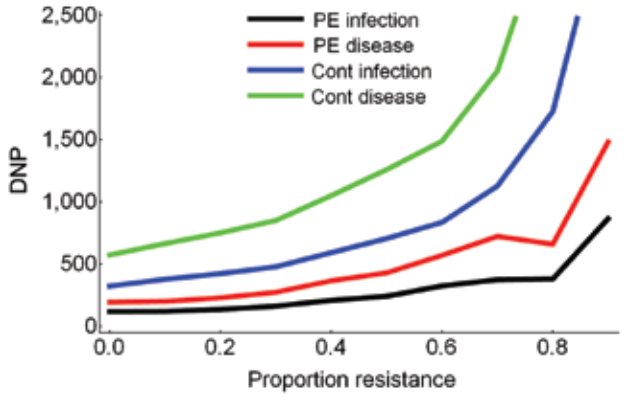

Figure 4. The number of daily doses of oseltamivir needed to prevent 1 influenza virus infection or disease (DNP). Results are shown for both postexposure (PE) prophylaxis and continuous (cont) prophylaxis for increasing proportions of oseltamivir-resistant virus strains in the community.

patients (Figure 6). In the absence of resistance, postexposure and continuous prophylaxis reduced the infection attack rate in HCWs from 0.14 to 0.10 and 0.05, respectively. The attack rate among patients decreased from 0.19 to 0.12 (RR 0.65) and 0.03 (RR 0.15), respectively. Taken together, the DNP for infection (of either patient or HCW) was 140 for postexposure prophylaxis and 366 for continuous prophylaxis; the total number of doses administered was 2 × as high as in the scenario in which only patients received prophylaxis.

When the HCW vaccination rate was 0.1, the infection attack rate among patients without prophylaxis was 0.23. This could be reduced to 0.15 (RR 0.67) when postexposure prophylaxis was given to patients alone and to 0.14 (RR 0.63) when it was given to HCWs as well (Figure 6). Continuous prophylaxis given to patients only or to both patients and HCWs could reduce the infection attack rate to 0.06 (RR 0.26) and 0.04 (RR 0.16), respectively. However, the number of doses required per department was approximately 6 × higher for continuous prophylaxis than for postexposure prophylaxis. Results of other alternative scenarios and the uncertainty analyses are described in the supporting information (online Technical Appendix).

Discussion

Our model predicts that in the absence of resistance, both postexposure prophylaxis and continuous prophylaxis can reduce the number of influenza virus infections in nursing home patients during annual influenza epidemics. Although continuous prophylaxis will prevent more cases, postexposure prophylaxis prevents more cases per dose. If resistance to oseltamivir increases, both prophylaxis strategies become less efficacious and less efficient, with more selection for resistance during continuous prophylaxis. Extension of prophylaxis to HCWs is not expected to have a large effect on the attack rates among patients.

For the results of our modeling study to be correctly interpreted, we must discuss some possible limitations. First, we did not distinguish between different subtypes of influenza circulating in the community. The oseltamivir-resistant strains that dramatically increased in number globally during the last 2 influenza seasons were all influenza A (H1N1) strains and resistance against oseltamivir seemed to be limited to the N1 serotype only. During the 2007–08 season, H1N1 strains were responsible for approximately 60% of influenza virus infections in Europe, which is uncommon when data for the last decade are examined (*34*). The remaining influenza virus infections were caused by A/H3N2 subtype and B type viruses. Thus, even if all influenza A (H1N1) strains acquired resistance against oseltamivir, levels of resistance of ≥60% are not very probable unless resistance develops as well in the other influenza A subtypes and in influenza B. Second, we did not take into account de novo resistance in persons on prophylaxis. We assumed the probability of emergence of resistance was very low (*26*) and, as we studied a small population, the effect on the outcome was assumed to be negligible. Third, we used estimates on the efficacy of oseltamivir prophylaxis from household studies because we did not have data specific for elderly people. More accurate assessment of efficacy and comparison of preventive measures in nursing homes will require new estimates from studies in senior populations. Finally, we studied a 30-bed department instead of an entire nursing home. If an outbreak occurs in 1 department, it might be necessary to start prophylaxis in other nearby departments as well. However, the effects of prophylaxis for individual departments will not be different.

Our model confirmed the beneficial effects of prophylaxis with oseltamivir in reducing the number of infections

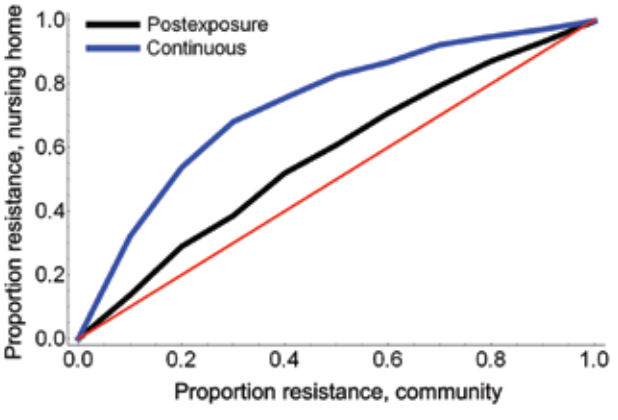

Figure 5. The proportion of infections with oseltamivir-resistant influenza virus strains among nursing home patients for increasing proportions of resistance in the community.

and preventing large outbreaks as has been suggested by some observational and experimental studies (*7–9*). We have not considered the effects of prophylaxis on the number of complications or deaths, but these can be assumed to be somewhat higher than for infection because oseltamivir also prevents complications when taken after infection (*9,35*). Our results suggest a large difference in both efficacy and efficiency between the postexposure and continuous prophylaxis strategies. Although continuous prophylaxis can protect more patients, it also requires large stocks of antiviral drugs and is therefore costly; postexposure prophylaxis might be the preferred strategy. Furthermore, our model suggests that extending prophylaxis to HCWs does not prevent many additional infections among patients when compared with prophylaxis of patients only. Even when the number of infections prevented in HCWs was included, the number of daily doses needed to prevent 1 infection was higher than the number of daily doses needed when prophylaxis was given to patients only. This prediction might be of use for the evaluation of influenza prevention guidelines for nursing homes. Currently, the Dutch guideline for prevention of influenza in nursing homes recommends postexposure prophylaxis for both patients and HCWs (*1*). CDC recommends prophylaxis to nonvaccinated HCWs only, or in case of a mismatch between the vaccine strains and the circulating virus strains, to all HCWs (*2*). Although the latter strategy is expected to be more efficient, the effect on infection attack rates among patients will be less extensive than with prophylaxis of all HCWs. In the postexposure strategy, 1,388 doses of oseltamivir were given to HCWs for every additional prevented infection in a patient. This number was very high compared with the 7 HCW vaccinations needed to prevent 1 infection in patients observed in our previous study (*18*). Therefore, protection of patients by reducing the number of infections in HCWs seems to be more efficiently obtained by increasing vaccine administration among HCWs than by including them in prophylaxis strategies.

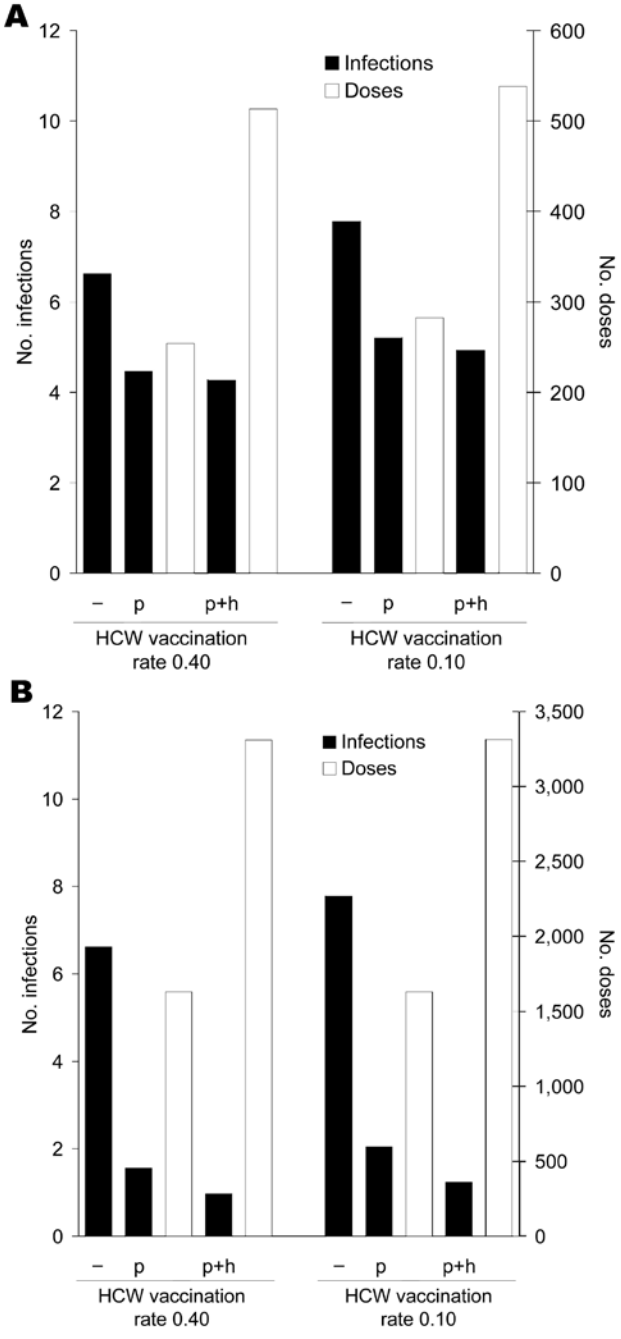

Figure 6. A) Average number of influenza virus infections among patients and B) average number of administered doses of oseltamivir in a 30-bed nursing home department during 1 influenza season. For the postexposure and continuous prophylaxis strategies, results are shown for prophylaxis of patients only (p) and of both patients and healthcare workers (HCWs) (p+h) and compared with a control setting without prophylaxis (–). HCW vaccination rates of 0.4 and 0.1 are considered.

Our study suggests that the selection pressure for resistance is lower for postexposure than for continuous prophylaxis. Moreover, the efficiency of postexposure prophylaxis appears to be less sensitive to the level of resistance than that of continuous prophylaxis. During the 2007–08 influenza season, the prevalence of oseltamivir-resistant influenza A (H1N1) strains in Europe increased from <1% in previous years (*11*) to 25% on average, with a national prevalence ranging from 2.5% in Spain up to 66% in Norway (*36*). During the 2008–09 influenza season almost all influenza A (H1N1) strains were oseltamivir resistant (*12*). Oseltamivir use in Europe was low in both years and, in the absence of an apparent selection pressure for resistance, predicting whether resistance will disappear, persist, or increase next season is difficult. Our findings indicate that increasing resistance should be included in the decision-making process for prevention of influenza in healthcare settings. Use of other antiviral agents that are not as associated with resistance should be considered as an alternative

prevention strategy (*37*). Household studies suggest that prophylaxis with zanamivir, for example, can give similar results as prophylaxis with oseltamivir (*4*). However, zanamir prophylaxis should be studied in more detail in the nursing home population. Future modeling studies should also address other relevant issues such as the use of combination or cycling therapy approaches (*38*) to retain the protection offered by current antiviral drugs.

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Dr van den Dool is a researcher in the Clinical Epidemiology group of the Julius Center for Health Sciences and Primary Care at the University Medical Center Utrecht. Her main research interest is the epidemiology and modeling of infectious diseases, in particular, the prevention of influenza in healthcare institutions.

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Address for correspondence: Carline van den Dool, Julius Center for Health Sciences and Primary Care, Str. 6.131, UMC Utrecht, P.O. Box 85 500, 3508 GA Utrecht, the Netherlands; email: c.vandendool@umcutrecht.nl

A Model-based Assessment of Oseltamivir Prophylaxis Strategies to Prevent Influenza in Nursing Homes

Technical Appendix

Model and Simulation Algorithms

For a detailed description of the model and simulation algorithms we refer to the supporting information in (*1*). We here give the figures referred to in the main text as well as additions and changes to the model structure as described in (*1*).

Influenza in the Community

The rate at which influenza virus was introduced into the nursing home by HCWs, visitors and patients depended on the prevalence of the virus in the community. The spread of influenza in the community of 100,000 individuals outside the nursing home was described by four variables: s, the proportion of susceptible individuals in the community, e, the proportion of exposed individuals in the community, i, the proportion of infectious individuals in the community, r, the proportion of recovered and immune individuals in the community. The daily influenza infection incidence, λ s, and the prevalence, i, in the community (Figure S1) were used in the nursing home model as the hazard rate for HCWs of becoming infected outside the nursing home and the probability that visitors and new patients who entered the nursing home were infectious, respectively. We assumed that during the season a constant fraction φ of all infections was caused by resistant strains (Table S1).

A Stochastic Simulation Model of Influenza Epidemics in a Nursing Home: State Variables

The state of each bed (j=1,2…n) was indicated as x(t,j) and consisted of one variable that took one out of eight possible values: {vacant, susceptible (S), exposed (E), infectious (I), recovered (R), exposed to an oseltamivir resistant virus strain (E_R), infectious with an oseltamivir resistant virus strain (I_R), immune by prophylaxis (R_p)}. The state of each health care worker (HCW) (j=1,2,…m) was indicated as y(t,j) and consisted of two variables. The first variable took one out of two possible values: {at work, not at work}. The second variable took one out of seven possible values: {susceptible (S), exposed (E), infectious (I), recovered (R), exposed to an

oseltamivir resistant virus strain (E_R), infectious with an oseltamivir resistant virus strain (I_R), immune by prophylaxis (R_p)}. At each moment t, the state of the system was completely characterized by the state vectors x and y. For convenience, we also used aggregate variables whose values were completely determined by the state variables:

- the number of patients that were infectious with a non-resistant virus strain at time t, $I_P(t)$;
- the number of HCWs at work that were infectious with a non-resistant virus strain at time t, $I_H(t)$;
- the number of patients that were infectious with an oseltamivir resistant virus strain at time t, I_{RP} (t); the number of HCWs that were infectious with an oseltamivir resistant virus strain at time t, I_{RH} (t).

Update Rules

At each time step Δt the values of the state variables were updated to account for transitions. The probability of each of these transitions to occur was specified according to the rules in Table S2.

Table S1. Parameters in the model

Symbol	Parameter	Default	Units	Ref
n	Number of beds	30		
m	Number of HCWs	30		
Ät	Time step (shift)	8	hours	
T	Minimum duration of simulation	80	days	
ì	Discharge/mortality rate	1/425	day^{-1}	(*2,3*)
ó	Rate of becoming infectious after infection	1/1.4	day^{-1}	(*4,5*)
ã	Infection recovery rate	1/1.4	day^{-1}	(*4,5*)
r_c	Prior immunity HCWs	0.3		(*6,7*)
r	Prior immunity patients	0		
u_1	Vaccination rate patients	0.75		(*8*)
u_2	Vaccination rate HCWs	0.4		(*9*)
	Probability of contact between			
c_{11}	Patient – patient	0.07	$shift^{-1}$	
c_{12}	HCW – patient	0.52	$shift^{-1}$	
c_{22}	HCW – HCW	0.91	$shift^{-1}$	
	Probability of close contact between			
$ð_{11}$	Patient – patient	0.06	$contact^{-1}$	
$ð_{12}$	HCW – patient	0.69	$contact^{-1}$	
$ð_{22}$	HCW – HCW	0.32	$contact^{-1}$	
ñ	Close/casual transmission probability ratio	2		
	Vaccine efficacy (against infection)			
ve_1	Patients	0.25		(*10*)
ve_2	HCWs	0.73		(*11*)
p_c	Transmission probability casual contact	0.13	$contact^{-1}$	(*1*)
g	Average number of visitors	0.7	$patient^{-1}\ day^{-1}$	(*12*)
	Minimum duration of post-exposure prophylaxis	14	days	(*9*)
	Minimum duration of post-exposure prophylaxis after last detected case	8	days	(*9*)
ä	Probability of developing disease after infection	0.5		(*13*)
$ä_P$	Probability of developing disease after infection during prophylaxis	0.2		(*13*)
pe_s	Oseltamivir efficacy against infection	0.53		(*13*)
pe_i	Oseltamivir reduction in infectiousness	0.2	$contact^{-1}$	(*13*)
ö	Fraction of resistant virus strains in the community	0 – 1.0		

Table S2. Transitions and probabilities in the model

	Transition	Probability[#]
Patient flow		
discharge or death	$P(x(t+\Delta t,j) = vacant \mid x(t,j) = \neg vacant)$[¶]	ì Ät
admission	$P(x(t+\Delta t,j) = S \mid x(t,j) = vacant)$	$(1 - u_1 ve_1)$ n ì Ind(P_o (t)=0) Ät + $(1 - u_1 ve_1)$ n ì Ind(P_o(t)=1) $(1-pe_s)$ Ät *[$]
admission	$P(x(t+\Delta t,j) = E \mid x(t,j) = vacant)$	e n ì (1-ö) Ät
admission	$P(x(t+\Delta t,j) = I \mid x(t,j) = vacant)$	i n ì (1-ö) Ät
admission	$P(x(t+\Delta t,j) = R \mid x(t,j) = vacant)$	$u_1 ve_1$ n ì Ät
admission	$P(x(t+\Delta t,j) = E_R \mid x(t,j) = vacant)$	e n ì ö Ät
admission	$P(x(t+\Delta t,j) = I_R \mid x(t,j) = vacant)$	i n ì ö Ät
admission	$P(x(t+\Delta t,j) = R_p \mid x(t,j) = vacant)$	$(1 - u_1 ve_1)$ n ì Ind(P_o(t)=1) pe_s Ät *[$]
HCW flow		
working	$P(y(t+\Delta t,j) = \{at\ work, \cdot\})$[‡]	w(t+Ät,j)
at home	$P(y(t+\Delta t,j) = \{not\ at\ work, \cdot\})$	1-w(t+Ät,j)
Course of infection of patients		
infection by non-resistant strain	$P(x(t+\Delta t,j) = E \mid x(t,j) = S)$	$ë_1$(t) Ät
becoming infectious from non-resistant strain	$P(x(t+\Delta t,j) = I \mid x(t,j) = E)$	ó Ät
recovery from non-resistant strain	$P(x(t+\Delta t,j) = R \mid x(t,j) = I)$	ã Ät
infection by resistant strain	$P(x(t+\Delta t,j) = E_R \mid x(t,j) = S)$	$ç_1$ (t) Ät
becoming infectious from resistant strain	$P(x(t+\Delta t,j) = I_R \mid x(t,j) = E_R)$	ó Ät
recovery from resistant strain	$P(x(t+\Delta t,j) = R \mid x(t,j) = I_R)$	ã Ät
gain immunity by prophylaxis	$P(x(t+\Delta t,j) = R_p \mid x(t,j) = S$ and $t=P_{start})$ [$]	pe_s
loss of immunity by prophylaxis	$P(x(t+\Delta t,j) = S \mid x(t,j) = R_p$ and $t=P_{stop})$ [$]	1
infection during prophylaxis	$P(x(t+\Delta t,j) = E_R \mid x(t,j) = R_p)$	$ç_1$(t) Ät
Course of infection of HCWs		
infection at work by non-resistant strain	$P(y(t+\Delta t,j) = \{\cdot,E\} \mid y(t,j) = \{at\ work, S\})$	$ë_2$(t) Ät
infection at home by non-resistant strain	$P(y(t+\Delta t,j) = \{\cdot,E\} \mid y(t,j) = \{not\ at\ work, S\})$	ë s (1-ö) Ät
becoming infectious from non-resistant strain	$P(y(t+\Delta t,j) = \{\cdot,I\} \mid y(t,j) = \{\cdot,E\})$	ó Ät
recovery from non-resistant strain	$P(y(t+\Delta t,j) = \{\cdot,R\} \mid y(t,j) = \{\cdot,I\})$	ã Ät
infection at work by resistant strain	$P(y(t+\Delta t,j) = \{\cdot,E_R\} \mid y(t,j) = \{at\ work, S\})$	$ç_2$(t) Ät
infection at home by resistant strain	$P(y(t+\Delta t,j) = \{\cdot,E_R\} \mid y(t,j) = \{not\ at\ work, S\})$	ë s ö Ät
becoming infectious from resistant strain	$P(y(t+\Delta t,j) = \{\cdot,I_R\} \mid y(t,j) = \{\cdot,E_R\})$	ó Ät
recovery from resistant strain	$P(y(t+\Delta t,j) = \{\cdot,R\} \mid y(t,j) = \{\cdot,I_R\})$	ã Ät
gain immunity by prophylaxis	$P(y(t+\Delta t,j) = \{\cdot,R_p\} \mid y(t,j) = \{\cdot,S\}$ and $t=P_{start})$ [$]	pe_s
loss of immunity by prophylaxis	$P(y(t+\Delta t,j) = \{\cdot,S\} \mid y(t,j) = \{\cdot,R_p\}$ and $t=P_{stop})$ [$]	1
infection at work during prophylaxis	$P(y(t+\Delta t,j) = \{\cdot,E_R\} \mid y(t,j) = (14))$	$ç_2$(t) Ät
infection at home during prophylaxis	$P(y(t+\Delta t,j) = \{\cdot,E_R\} \mid y(t,j) = \{not\ at\ work, R_p\})$	ë s ö Ät

Table S2 (continued)

Forces of infection of non-resistant strains		
For patients		
Day	$ë_1(t) = ë_{11}+ë_{12}+ë_{vis}$	$ë_{11}= (ð_{11}\ ñ +(1-ð_{11}))\ p_c\ c_{11}\ I_P(t)$
Evening	$ë_1(t) = ë_{11}+ë_{12}+ë_{vis}$	$ë_{12}= (ð_{12}\ ñ +(1-ð_{12}))\ p_c\ c_{12}\ I_H(t)$
Night	$ë_1(t) =Ind(x(t,j+Neighbor(j))=I)\ p_c+ë_{12}$ *	$ë_{vis}= g\ ñ\ p_c\ i\ (1-ö)$
For HCWs		
At work	$ë_2(t)= ë_{21} +ë_{22}$	$ë_{21}= (ð_{21}\ ñ +(1-ð_{21}))\ p_c\ c_{21}\ I_P(t)$
		$ë_{22}= (ð_{22}\ ñ +(1-ð_{22}))\ p_c\ c_{22}\ I_H(t)$
Forces of infection of resistant strains		
For patients		
Day	$ç_1(t) = ç_{11}+ç_{12}+ç_{vis}$	$ç_{11}= (ð_{11}\ ñ +(1-ð_{11}))\ p_c\ c_{11}\ I_{RP}(t)$
Evening	$ç_1(t) = ç_{11}+ç_{12}+ç_{vis}$	$ç_{12}= (ð_{12}\ ñ +(1-ð_{12}))\ p_c\ c_{12}\ I_{RH}(t)$
Night	$ç_1(t) =Ind(x(t,j+Neighbor(j))=I)\ p_c+ç_{12}$ *	$ç_{vis}= g\ ñ\ p_c\ i\ ö$
For HCWs		
At work	$ç_2(t)= ç_{21} +ç_{22}$	$ç_{21}= (ð_{21}\ ñ +(1-ð_{21}))\ p_c\ c_{21}\ I_{RP}(t)$
		$ç_{22}= (ð_{22}\ ñ +(1-ð_{22}))\ p_c\ c_{22}\ I_{RH}(t)$

see table S1 for the meaning on the symbols used
¶ we use ¬vacant to denote any possible state except vacant
‡ we use {at work, ·} to denote any possible state where the first state variable is equal to the state at work
* we use Ind(x(t,j)=J) to mean an indicator function that returns the value 1 if its argument is a correct expression, and 0 if its argument is false; we use Neighbor(j)=j-1+2 Mod[j,2] as a function that returns the index of the roommate of the patient, such that Neighbor(1)=2, Neigbor(2)=1
$ P_{start} and P_{stop} determine the moments of start and end of prophylaxis with oseltamivir; $P_o(t)$= 1 if prophylaxis is being administered.

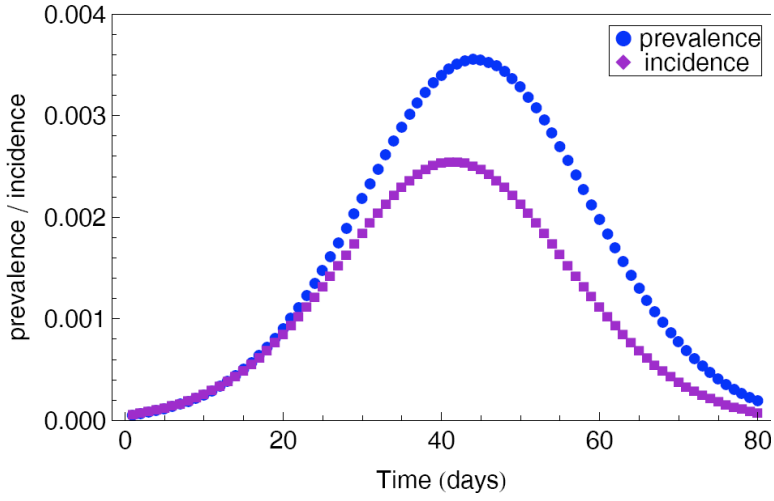

Figure S1. Incidence and prevalence of influenza virus infections in the community.

Prophylaxis with Oseltamivir

Continuous prophylaxis was given during 8 weeks around the peak of the community influenza epidemic, starting from t=15 to t=71. Post–exposure prophylaxis was started for all patients as soon as one patient had a laboratory-confirmed influenza virus infection. Since

recognition of a possible influenza virus infection is required before doing a laboratory test, we assumed only the fraction of infected patients that develop influenza disease (the symptomatic patients) could trigger the start of post-exposure prophylaxis. We assumed that for every first symptomatically infected individual the time between becoming infectious and the start of prophylaxis followed a distribution that was determined by

- the time to onset of symptoms
- the time to recognition of symptoms
- the time to a positive laboratory test
- the time until administration of prophylaxis

For each of these steps the assumed time distributions for the baseline scenario are shown in Figure S2 a to d. The total delay distribution resulting from summation of these steps had a mean delay of 3.5 days (Figure S3a). In Figures S3b and c, distributions of the delay for alternative scenarios are shown, with means of 1.75 and 6 days, respectively. The means and ranges of the duration of the four steps in the different scenarios are shown in Table S3.

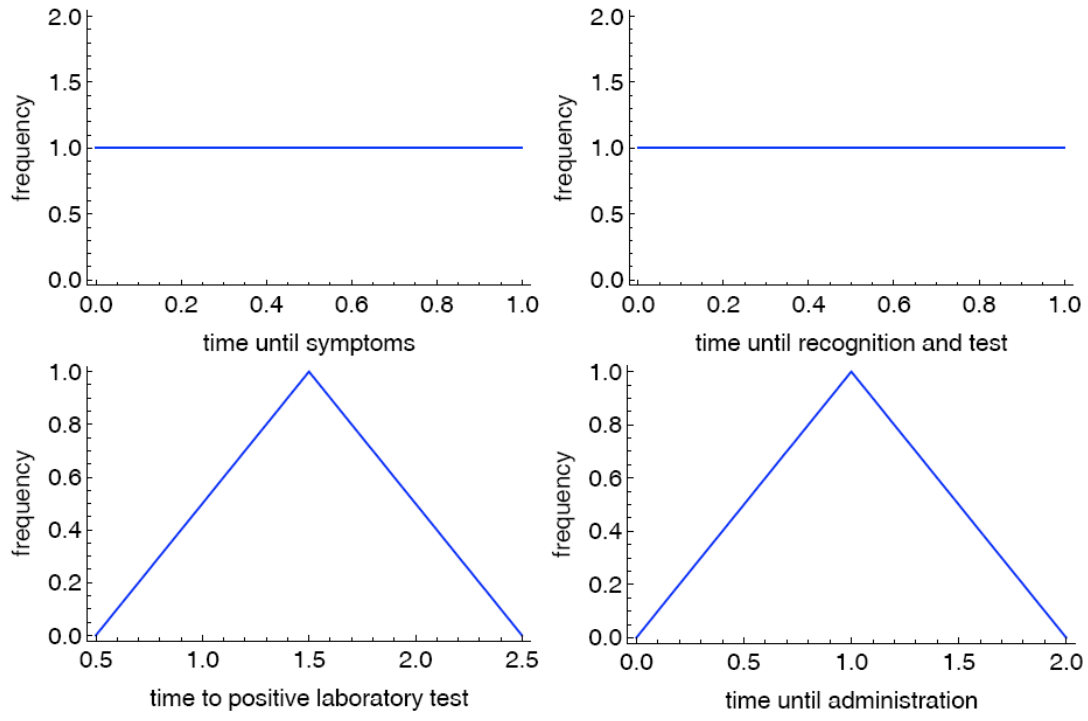

Figure S2. Assumed time distributions for the several steps leading to the delay between the start of infectiousness of the first symptomatically infected individual and the start of post-exposure prophylaxis.

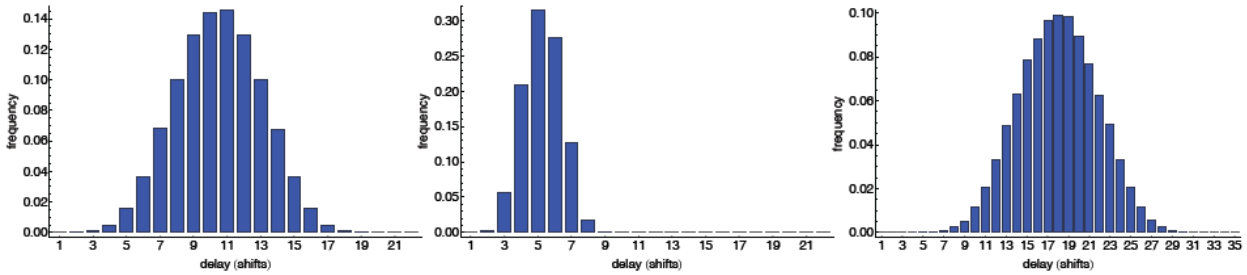

Figure S3. Distributions of the delay between the start of infectiousness of the first symptomatically infected individual and the start of post-exposure prophylaxis with means of 3.5 days, 1.75 days and 6 days, respectively.

Table S3. Mean duration and range of the steps leading to the delay between the start of infectiousness of the first symptomatically infected individual and the start of post-exposure prophylaxis for three scenarios.

Step	Duration (days) Mean (range)	Duration(days) Mean (range)	Duration(days) Mean (range)
Time to onset of symptoms	0.5 (0-1)	0.5 (0-1)	0.5 (0-1)
Time to recognition of symptoms and test	0.5 (0-1)	0.25 (0-0.5)	1 (0-2)
Time to positive laboratory test	1.5 (0.5 -2.5)	0.75 (0.5-1)	2.5 (1.5-3.5)
Time until administration	1.0 (0-2)	0.25 (0-0.5)	2 (0 – 4)
Total	3.5 (0.5-6.5)	1.75 (0-3)	6 (1.5-10.5)

Table S4. Precision of the effect estimates, as mean and 95% bootstrap confidence interval for the baseline scenario based on 4000 simulations, and an alternative scenario (reduced vaccine uptake of patients) based on 2000 simulations.

	RR PE	RR cont	NNT PE	NNT cont
Baseline scenario	0.67 (0.64-0.70)	0.23 (0.22-0.24)	118 (105-135)	323 (309-339)
Patient vaccine uptake 0.4	0.66 (0.62-0.70)	0.24 (0.22-0.26)	97 (82-115)	268 (254-283)

Precision of the Effect Estimates

In the main text we did not give confidence intervals around the effect estimates because these depended on the number of simulations we performed. The 95% bootstrap confidence intervals around the effect estimates (Table S4), show us that the 4000 simulations for the baseline scenario and the 2000 simulations for the alternative scenarios sufficed to obtain reliable effect estimates (Table S4).

Uncertainty analyses

We used Latin hypercube sampling (*15,16*) to do uncertainty analyses for the four parameters describing oseltamivir effectiveness. Therefore we chose a likely range for the parameter values in question and drew actual values from a uniform distribution over this range. For every scenario under study we made 50 different parameter sets such that the whole range of possible values for each of the four parameters was represented equally. We varied the parameter oseltamivir efficacy against infection over a range from 0.2 to 0.8 based upon the reported

confidence intervals (top row), the reduction in infectiousness caused by oseltamivir from 0 to 0.5 (second row), the probability of developing disease (symptom probability) without prophylaxis from 0.3 to 0.7 (third row) and the probability of developing disease during prophylaxis from 0.05 to 0.4 (bottom row), according to the estimated confidence intervals. The results are shown in figure S4 for both post-exposure and continuous prophylaxis. The influenza virus attack rate among patients showed a strong negative correlation with the efficacy of oseltamivir to protect against infection for both strategies of prophylaxis. A less strong correlation was present with the oseltamivir induced reduction in infectiousness. The probability of developing disease was weakly correlated with the patient infection attack rate for the post-exposure, but not for the continuous prophylaxis strategy. The probability of developing disease during prophylaxis did not have a large impact on the attack rate.

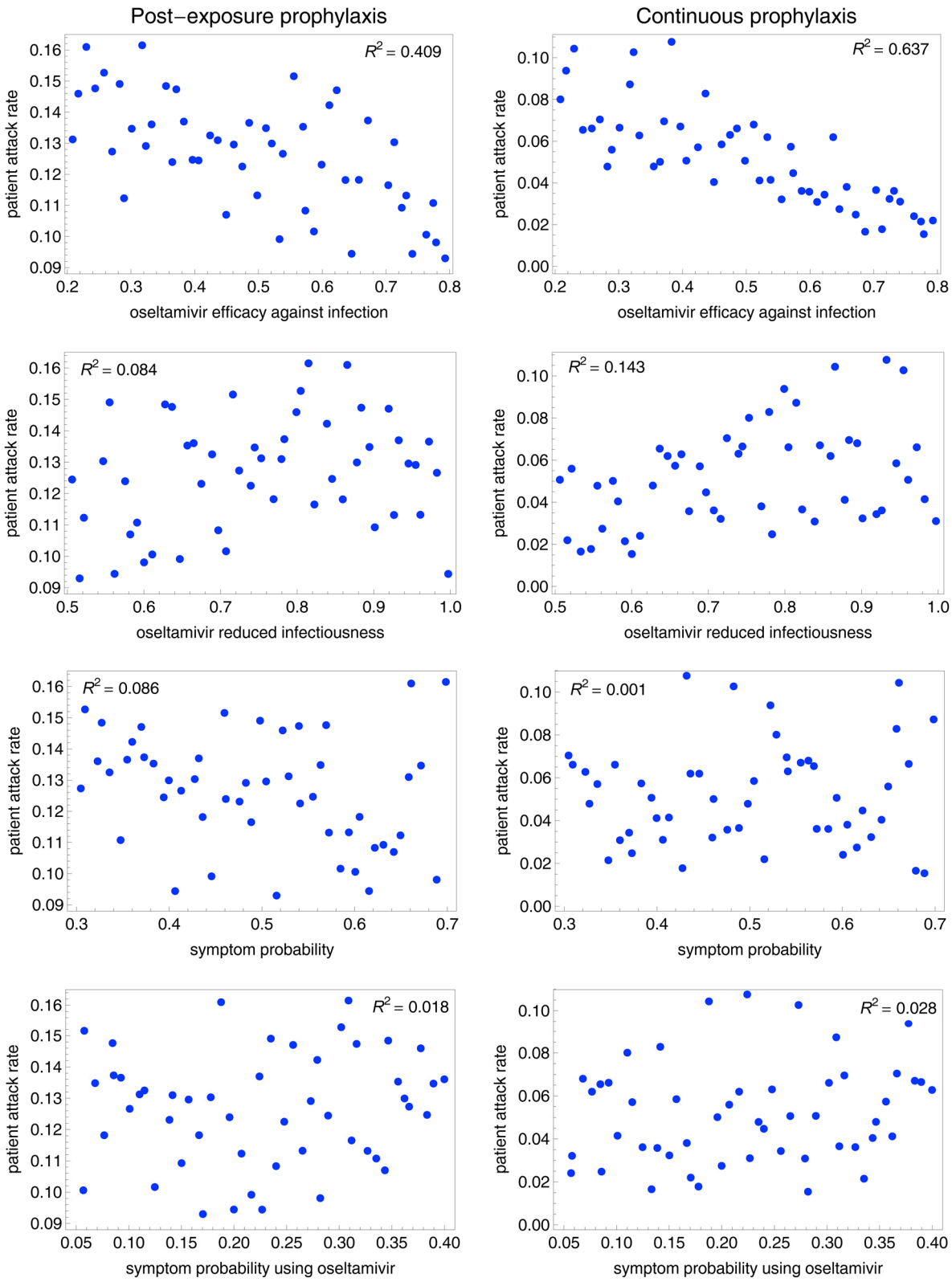

Figure S4. Results of uncertainty analyses. We varied the parameters oseltamivir efficacy against infection, oseltamivir reduction in infectiousness and symptom probability (probability of developing disease) with or without prophylaxis.

Alternative Scenarios

Table S5 shows the results of some additional scenarios:

1) Two scenarios with delays between the start of infectiousness of the first symptomatic patient and the start of post-exposure prophylaxis of 1.75 and 6 days instead of 3.5 days. Changes in the delay did not have a large influence on the results.

2) Two scenarios with higher and lower influenza virus activity in the community (with community attack rates of 15 and 5 percent as compared to 10 percent in the baseline scenario). Apparently the number of doses needed to prevent one infection was not very sensitive to the annual influenza activity when prophylaxis was given post-exposure. With continuous prophylaxis, the number of prevented cases increased with higher influenza prevalence and the strategy became more efficient, although it did not approximate the efficiency of post-exposure prophylaxis.

3) A scenario in which the HCW vaccination rate was 0.75 instead of 0.4. In this scenario the influenza virus attack rate among patients was already decreased in the absence of prophylaxis. Although the relative risk reductions for both strategies of prophylaxis were similar to those in the baseline scenario, the DNP increased due the lower actual number of infections prevented.

4) A scenario in which the patient vaccine uptake was 0.40 instead of 0.75. In this scenario, the infection attack rate was slightly increased in the absence of prophylaxis, which increased the efficiency of prophylaxis.

5) A scenario in which 30% instead of 0% of the patients was immune at the start of the season. In this scenario the effectiveness and efficiency of prophylaxis decreased since more individuals were protected prior to prophylaxis and a lower number of infections was prevented.

6) A scenario for a larger department with 60 beds. In this simulation we assumed the ratio of patients and HCWs and the average number of contacts per person per day to be the same as we had observed in the 30-bed departments. The effect of prophylaxis became slightly higher in this scenario due to the higher attack rate in the absence of prophylaxis.

Table S5. Effects and efficiency of post-exposure prophylaxis (compared with no prophylaxis) in reducing influenza virus infection attack rates among nursing home patients for different scenarios (see text above).

		Mean infection attack rate			*Relative risk*		*Daily doses needed to prevent one infection*	
Scenario		No	Post-exposure	Continuous	Post-exposure	Continuous	Post-exposure	Continuous
0	Baseline	0.19	0.13	0.05	0.67	0.23	118	323
1a	1.75-day delay	0.19	0.11	-	0.59	-	99	-
1b	6-day delay	0.19	0.15	-	0.78	-.	161	-
2a	High virus activity	0.31	0.20	0.08	0.64	0.26	104	206
2b	Low virus activity	0.11	0.08	0.03	0.69	0.26	127	579
3	HCW vaccine uptake 0.75	0.13	0.09	0.03	0.70	0.24	155	471
4	Patient vaccine uptake 0.4	0.23	0.15	0.06	0.66	0.24	97	268
5	Prior immunity patients 0.3	0.10	0.08	0.03	0.74	0.27	218	378
6	60-bed department	0.26	0.13	0.06	0.51	0.21	97	229

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