HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2024 July 22.

Published in final edited form as:

Clin Infect Dis. 2024 May 15; 78(5): 1336–1344. doi:10.1093/cid/ciad764.

Modeling the Impacts of Antiviral Prophylaxis Strategies in Mitigating Seasonal Influenza Outbreaks in Nursing Homes

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Abstract

Background.—Antiviral chemoprophylaxis is recommended for use during influenza outbreaks in nursing homes to prevent transmission and severe disease among non-ill residents. Centers for Disease Control and Prevention (CDC) guidance recommends prophylaxis be initiated for all non-ill residents once an influenza outbreak is detected and be continued for at least 14 days and until 7 days after the last laboratory-confirmed influenza case is identified. However, not all facilities strictly adhere to this guidance and the impact of such partial adherence is not fully understood.

Methods.—We developed a stochastic compartmental framework to model influenza transmission within an average-sized US nursing home. We compared the number of symptomatic illnesses and hospitalizations under varying prophylaxis implementation strategies, in addition to different levels of prophylaxis uptake and adherence by residents and healthcare personnel (HCP).

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding authors.

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Results.—Prophylaxis implemented according to current guidance reduced total symptomatic illnesses and hospitalizations among residents by a median of 12% and 36%, respectively, compared with no prophylaxis. We did not find evidence that alternative implementations of prophylaxis were more effective: compared to full adoption of current guidance, partial adoption resulted in increased symptomatic illnesses and/or hospitalizations, and longer or earlier adoption offered no additional improvements. In addition, increasing uptake and adherence among nursing home residents was effective in reducing resident illnesses and hospitalizations, but increasing HCP uptake had minimal indirect impacts for residents.

Conclusions.—The greatest benefits of influenza prophylaxis during nursing home outbreaks will likely be achieved through increasing uptake and adherence among residents and following current CDC guidance.

Keywords

influenza; nursing home; antiviral; prophylaxis; mathematical model

Seasonal influenza causes substantial morbidity and mortality in the United States, with 140 000–710 000 hospitalizations and 12 000–52 000 deaths attributed to influenza annually [1]. This burden is concentrated among older adults who are more vulnerable to severe outcomes following influenza infection, in part due to aging immune systems and underlying comorbidities [2–4]. Nursing homes, which typically serve this older population, are particularly vulnerable to the rapid spread of influenza and often experience high attack rates during facility outbreaks [5]. Infection can be introduced by healthcare personnel (HCP), visitors, or newly admitted residents. Subsequent virus transmission is exacerbated by congregate living environments with facility units often occupied at high densities, residents sharing rooms and communal spaces, and frequent, high-intensity contact between residents and HCP [6, 7]. Such heightened exposure combined with residents at increased risk of severe disease can lead to high morbidity and mortality rates [8, 9].

Administration of influenza antivirals, like oseltamivir, can reduce the burden and severity of influenza during nursing home outbreaks [10, 11]. Antiviral treatment is recommended as soon as possible for any resident with suspected or confirmed influenza to reduce disease severity and virus shedding [12, 13]. Antivirals can also be administered as chemoprophylaxis to protect non-ill residents at risk of influenza exposure against infection or subsequent disease [14], and reduce onward transmission if infection occurs [15, 16]. According to interim guidance from the US Centers for Disease Control and Prevention (CDC), oral oseltamivir should be administered as prophylaxis to all non-ill residents living on the same unit when at least 2 residents become ill within 72 hours and at least 1 has laboratory-confirmed influenza [12, 13]. Residents taking prophylaxis who subsequently become symptomatic should be switched to an antiviral treatment course. Prophylaxis may also be offered to HCP to reduce short-staffing risks [17], and to residents of unaffected units if contact between units is likely. Although prophylaxis is recommended to continue for a minimum of 2 weeks and for at least 7 days after the last laboratory-confirmed case of influenza, this is at least one aspect of current guidance that is not universally implemented [18]. For healthcare facilities, implementing a standardized protocol for outbreak prevention and control is challenging due to differences in patient characteristics, facility size, and

availability of resources including testing and antiviral supplies [5]. Identifying how different implementations of prophylaxis impact influenza outbreaks in nursing homes is crucial to understanding transmission dynamics and informing future guidance.

We can use mathematical modeling to help elucidate respiratory virus spread and control in nursing homes by simulating transmission dynamics within facilities and exploring the impact of counterfactual intervention scenarios, such as increased testing or vaccination policies [19–22]. Here, we develop a mathematical model of influenza transmission within a US nursing home to assess the potential impact of influenza antiviral prophylaxis on mitigating resident morbidity. We also explore whether this impact could be improved by varying prophylaxis implementation relative to current guidance, and varying levels of prophylaxis uptake among residents and HCP.

METHODS

Model Structure

We developed a discrete-time stochastic compartmental model representing an average-sized US nursing home with 100 residents and 100 HCP based on national data from the Centers for Medicare and Medicaid Services (CMS) (see the Supplementary Information for equations and implementation details). Following CMS Minimum Dataset 3.0 (MDS) data on patient discharge dates, we partitioned the resident population into 78 short-stay residents and 22 long-stay residents, with the former having a higher rate of entering and exiting the facility (Supplementary Table 1) [23]. All individuals were initially susceptible (S) but upon infection became latently infected (or “exposed,” E), then asymptomatically (A) or symptomatically (I) infected and infectious, and finally were either hospitalized (H) or recovered without hospitalization (R). We did not explicitly model influenza-associated deaths, but these are assumed to occur outside the nursing home in a fraction of hospitalized residents. Symptomatic individuals received antiviral treatment (Tr), whereas those in other states were eligible to receive antiviral prophylaxis (Figure 1). We assumed asymptomatic and symptomatic infections were equally transmissible and incorporated additional outbreak mitigation measures through vaccination and isolation of symptomatic cases. Vaccination was completed before the outbreak and was modeled as a reduction in the proportion of individuals developing symptomatic infection. Thus, vaccination reduced the risk of influenza illness without directly impacting transmission. Isolation of symptomatic residents was incorporated through a reduction in their frequency of contacts with other residents and HCP, whereas symptomatic HCP were assumed to isolate at home and did not contribute to further transmission within the facility. Both residents and HCP began isolation the day of symptom onset.

Implementation of Antiviral Prophylaxis and Treatment

Prophylaxis modulated infection dynamics in 4 distinct ways: (i) susceptible individuals were less susceptible to infection, (ii) infectious individuals were less infectious, (iii) infectious individuals recovered faster, and (iv) symptomatic individuals were less likely to be hospitalized. The latter 3 assumptions (ii–iv) also applied to individuals taking antiviral

treatment for symptomatic illness. Baseline values for these assumptions were informed by previous literature but varied in subsequent sensitivity analyses (Supplementary Table 1).

We initially modeled antiviral prophylaxis and treatment with oseltamivir according to interim CDC guidance. We assumed symptomatic infections were laboratory-confirmed and thus could be used to determine times of prophylaxis implementation and cessation. Antiviral treatment was administered to symptomatic individuals on average 1 day following symptom onset, whereas prophylaxis was initiated and available to everyone once 2 or more residents developed symptomatic infection within 72 hours. We assumed a fixed proportion of residents and HCP would uptake prophylaxis immediately upon initiation, and that new residents entering the facility would uptake prophylaxis at that same rate. Prophylaxis was stopped once 7 days had passed with no new symptomatic cases among residents.

Oseltamivir treatment was administered as 2 doses per day for 5 days, whereas prophylaxis was administered as 1 dose per day for the duration of the intervention or until individuals discontinued prophylaxis. Individuals taking prophylaxis who subsequently developed symptomatic infection were switched to treatment dosing. We initially assumed residents continued prophylaxis for the duration of the intervention (due to high risks of developing severe disease), whereas HCP were compliant for an average of 5 days due to adverse side effects and reduced perceptions of risk [24].

Model Calibration and Alternative Prophylaxis Scenarios

Infection was seeded in the nursing home through one asymptomatically infected short-stay resident (seeding through one long-stay resident or HCP gave similar results [Supplementary Figure 1]). Including an additional constant rate of infection importation from the community did not change model dynamics at reasonable values and was omitted from further analyses (Supplementary Figure 2). We performed 500 model simulations and tracked the number of symptomatic illnesses, hospitalizations, and antivirals used. We summarized influenza burden during each simulated outbreak through the total number of symptomatic cases and hospitalizations that occurred; the maximum number that occurred on any given day (as a measure of potential strain on the system); the clinical attack rate (ie, the number of symptomatic cases divided by the nursing home capacity); and the case-hospitalization ratio (ie, the percentage of symptomatic cases that were hospitalized). Each quantity was calculated separately for residents and HCP.

We calibrated the model, with and without prophylaxis in place, by varying the basic reproduction number, R_0, and the risk of a symptomatic resident becoming hospitalized to capture previously reported attack rates and case-hospitalization ratios (Supplementary Table 1, Supplementary Information) [5, 10, 25–27]. Our resulting value for R_0 is higher than typical estimates for seasonal influenza in the community and reflects increased transmission in congregate settings [28, 29]. We assumed higher contact rates between residents and HCP than among residents or among HCP [19, 20] but varied this assumption in sensitivity analyses. All other parameters were taken from previous literature (Supplementary Table 1) [15, 16, 30–40].

The calibrated model was used to compare different scenarios for prophylaxis initiation and duration. Prophylaxis duration scenarios included fixed-time scenarios (eg, 10 or 14 days of administration [18]) and case-based scenarios that were less or more stringent than interim guidance (for example, until 3 days or 10 days with no new cases). We also explored alternative case thresholds for prophylaxis initiation, ranging from 1 to 7 symptomatic cases occurring within 7 days (the look-back period was extended from 72 hours to allow sufficient time for additional cases to occur, and thus ensure a fair comparison across initiation scenarios). Finally, we examined the effect of prophylaxis under different levels of resident and HCP uptake (5%–95% of individuals) and compliance.

We assessed the robustness of our results using one-way sensitivity analyses. Candidate parameters (including R_0, resident and HCP contact rates, and antiviral effectiveness) were systematically varied between reasonable ranges while keeping all other parameters fixed. The model was re-simulated 200 times for each parameter value under a given prophylaxis scenario. The model was implemented in R version 4.0.3 using the odin package [41, 42].

RESULTS

We first compared our baseline scenario (prophylaxis implemented according to current guidance) to a scenario in which there was no prophylaxis and antivirals were solely administered to treat symptomatic individuals. The addition of prophylaxis resulted in a median 12% reduction in symptomatic illnesses and 36% reduction in hospitalizations among residents (Table 1, Figure 2). There was also a reduction in the number of symptomatic residents at the peak of the outbreak (Table 1). Although there was no change in the total number of HCP with symptomatic illness, the peak number was reduced, indicating a decrease in the risk of staffing shortages. The predicted outbreak size in the baseline prophylaxis scenario was most sensitive to R_0 and the effectiveness of antivirals in reducing susceptibility to infection (Supplementary Figure 3). However, our general finding that prophylaxis mitigates influenza burden compared with no prophylaxis is robust to reasonable changes in these parameters (Supplementary Figures 4 and 5).

When comparing alternative prophylaxis duration scenarios (ie, “fixed-time” durations for a set number of days or “case-based” durations until a certain number of days with no new cases), we found that all scenarios resulted in a decrease in the total number of hospitalizations among residents compared to no prophylaxis (Figure 2D). However, fixed-time scenarios had minimal impact on reducing the likely number of symptomatic illnesses among residents, while the impact of case-based scenarios depended on the number of days prophylaxis was continued after the last identified case (Figure 2C). Current guidance (ie, 7 days of continued prophylaxis) had a greater impact on reducing outbreak size than scenarios with fewer days of continued prophylaxis, and a similar impact to a scenario with 10 days of continued prophylaxis.

In addition to different prophylaxis duration scenarios, we investigated different thresholds for prophylaxis initiation. Assuming a lower threshold for initiation than current guidance (after 1 case was identified rather than 2) did not substantially impact total hospitalizations or symptomatic illnesses, or peak symptomatic illnesses among residents (Figure 3).

However, later initiations (eg, once 5 or more cases were identified) resulted in higher and earlier peaks in symptomatic illnesses (Figures 3C and 3D). Thus, although initiation earlier than current guidance offered minimal improvements, reaction following the first 3 cases was still beneficial in delaying and dampening resulting outbreaks.

Finally, we examined how prophylaxis use among residents and HCP influenced outbreak size. We found that direct effects were strong: increasing uptake among residents reduced the likelihood of observing large numbers of symptomatic illnesses and hospitalizations among residents (Figures 4A and 4B). However, increasing uptake among HCP had no such effect, suggesting any indirect effects of HCP prophylaxis reducing transmission to residents were relatively weak (Figures 4C and 4D). The latter finding was not driven by the short average duration of HCP adherence to prophylaxis (5 days) as instead assuming adherence for the duration of the intervention did not substantially change likely burden estimates (Figures 4E and 4F). Similarly, our results were robust to increasing the contribution of HCP to facility transmission through (i) increasing contact rates among HCP, and between HCP and residents (Supplementary Figure 3); and (ii) assuming a 24-hour delay in the isolation of symptomatic HCP (Supplementary Figure 6). These results suggest that maintaining high levels of uptake and adherence among residents is most crucial to improving the impact of prophylaxis during influenza outbreaks.

DISCUSSION

We developed a mathematical model of influenza virus transmission in a nursing home to assess the impact of antiviral prophylaxis in mitigating resident morbidity during an influenza outbreak. Oseltamivir prophylaxis implemented according to current CDC guidance reduced illnesses and hospitalizations among residents by a median of 12% and 36%, respectively, in addition to delaying and dampening outbreak peaks. We did not find evidence that alternative implementations of prophylaxis would be more effective: shorter durations or delays in initiation resulted in increased symptomatic illnesses and/or hospitalizations among residents, whereas longer durations or earlier initiation offered no meaningful improvements compared with current guidance.

Nursing home residents often experience high rates of morbidity and mortality during influenza outbreaks [5, 8, 9]. A 36% reduction in hospitalizations suggests substantial mitigation of severe disease in this vulnerable population and supports the use of current prophylaxis guidance. However, many facilities do not strictly adhere to current guidance [18]. The reasons for nonadherence are not fully understood, but shorter durations of prophylaxis or delays to initiation could occur if insufficient influenza testing supplies and antivirals are available within a facility at outbreak onset [43]. Maintaining an adequate supply of antivirals, or preparing advance arrangements with distributors, could facilitate prompt and successful implementation of prophylaxis guidance and thus reduce influenza burden. Although our model estimated a median of 419 dose-packs would be required for treatment and prophylaxis of residents and HCP in a nursing home with 100 residents and 100 HCP (Table 1), there was substantial variation across simulations. Further data are needed to determine sufficient antiviral supplies for seasonal preparedness in nursing home settings. Additional analyses could also assess the cost-effectiveness of different prophylaxis

strategies and identify other potential barriers to complete implementation of CDC guidance. Finally, given that extending prophylaxis beyond the currently recommended period did not substantially improve outbreak mitigation, prophylaxis should not be continued for longer than needed. This would allow preservation of potentially limited antiviral resources.

When assessing the impact of individual prophylaxis uptake and adherence, we found that increasing these values among HCP did not substantially reduce resident influenza burden. Results were similar whether we assumed symptomatic HCP isolated the day of symptom onset or 24 hours later. Although we did not model universal precautions that could reduce transmission from asymptomatic HCP, such as mask wearing and hand hygiene practices [12], these would likely reduce the estimated impact of HCP prophylaxis further. Our work supports previous findings of weak indirect effects of HCP vaccination in long-term care facilities and suggests prophylaxis mitigation efforts are most effective when focused on sustaining high levels of uptake and adherence amongst residents [44, 45].

There are several caveats to our modeling approach. First, we did not include the potential importation of influenza virus infection from the community as it did not impact model dynamics at reasonable values. Although transmission risk from external sources may be underestimated, our baseline R_0 value should account for generally high levels of transmission in congregate settings with connections to the wider community [29]. Second, we assumed homogeneous mixing within resident and HCP subgroups and did not partition individuals among distinct wards within the facility. Therefore, our model reflects a nursing home with high inter-ward connectivity; for example, through staff sharing and/or resident mixing. The population was also structured such that most residents were short-stay residents. This assumption was driven by available data on patient discharge dates, which may be biased towards those with shorter stays (who are more likely to be discharged). Although our model was not sensitive to varying the number of short-stay residents (Supplementary Figure 3), our results may be most generalizable to facilities with large short-stay units. Third, prophylaxis was initiated within 1 day of outbreak declaration across all individuals taking prophylaxis and did not account for delays that may occur due to operational and/or resource constraints, such as limited testing or antiviral supplies. Although the optimistic speed of prophylaxis implementation may result in fewer infections in the first few days following outbreak declaration, the burden is likely small in relation to infections over the entire outbreak. Fourth, we assumed residents perfectly complied with prophylaxis once initiated due to the potential benefits in protecting against severe disease. However, adverse side effects of oseltamivir may lead to decreased compliance in some residents and attenuate the impact of prophylaxis, similar to the effects of decreased uptake among residents (Figures 4A and 4B). Fifth, we assumed perfect ascertainment of symptomatic infections. The rate of symptomatic infection was informed by age-specific estimates from an influenza household transmission study that defined symptomatic illness as the occurrence of at least one of: fever, cough, sore throat, difficulty breathing, chest pain, nasal congestion, muscle aches, headache, diarrhea, or vomiting [35]. This definition does not fully overlap with that employed by current guidance (signs of acute respiratory illness, temperature change, or behavioral change [12, 13]) and may impact our estimates of the number of detected cases. Nevertheless, our scenarios with prophylaxis initiated following a greater number of symptomatic cases (Figure 3) can provide some indication of the impacts

of delayed initiation due to case under-ascertainment. Future model iterations could also incorporate the use of testing to capture influenza surveillance and detection in nursing homes more closely, including challenges associated with finite testing supplies, imperfect test sensitivity, and potential delays to receiving test results. Finally, we did not consider the emergence of oseltamivir-resistant influenza strains. During the 2022/2023 season, 99.9% of tested viruses were susceptible to oseltamivir and so resistance was extremely rare [46]. Nevertheless, resistance emergence could be modeled in future work to explore how such events might influence the impact of prophylaxis in nursing homes.

In this work we developed a mathematical framework to model influenza transmission and antiviral use in a US nursing home. By comparing the burden of symptomatic illness and hospitalization under varying levels of prophylaxis implementation, we found that current guidance performs well in reducing illnesses and hospitalizations among residents. The greatest improvements to prophylaxis impact are likely achieved through increasing uptake and adherence among nursing home residents, in addition to promptly following current guidance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

The authors have no funding sources or conflicts of interest to declare. R. B. S. reports that the Society for Healthcare Epidemiology of America partially sponsored travel to IDWeek 2022. There are no data associated with this work. Code needed to reproduce the analyses are available at https://github.com/CDCgov/flu-nursing-home-model.

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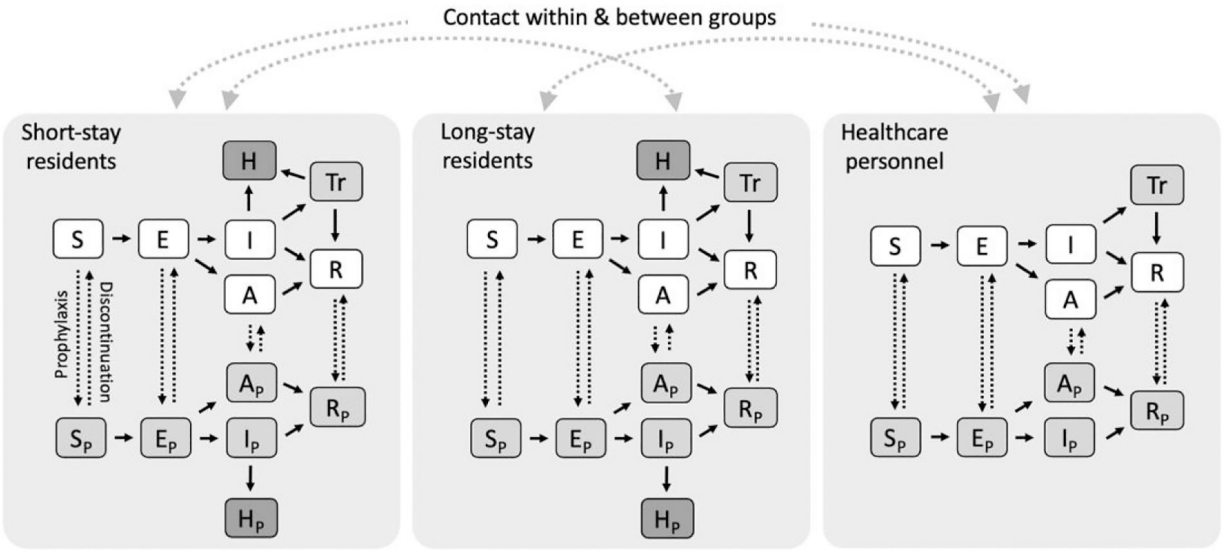

Figure 1.

Model schematic. The population is partitioned into short-stay residents, long-stay residents, and healthcare personnel. Individuals in each of these subpopulations are either susceptible (S), exposed (E), asymptomatic (A), or symptomatically infected (I), recovered without hospitalization (R) or hospitalized (H). Contact can occur between individuals in the same subpopulation, or with individuals in a different subpopulation (at potentially different rates). Antivirals are administered to symptomatically infected individuals as treatment (Tr) or as prophylaxis to individuals in all other states (denoted by the subscript P). Dashed lines represent individuals initiating or discontinuing a course of prophylaxis.

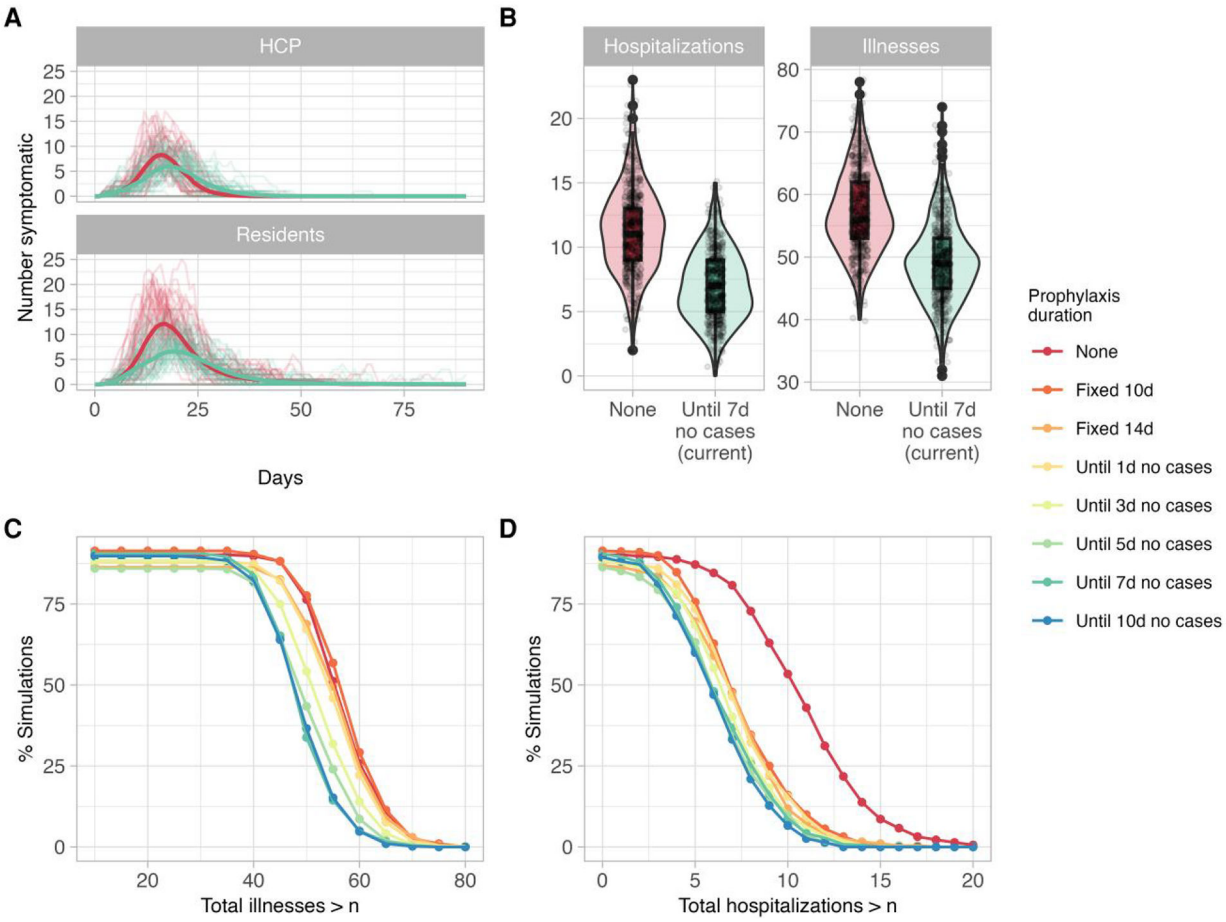

Figure 2.

Prophylaxis reduces the burden of symptomatic illness and hospitalization when administered according to current guidance. *A*, Number of symptomatic illnesses in HCP (*top*) and residents (*bottom*) in days since introduction into the facility under no prophylaxis ("None") or prophylaxis administered according to current guidance (ie, until 7 d with no new cases). Thin lines show 40 randomly sampled simulations and thick lines show the mean of all 500 simulations. *B*, Distribution of the total number of hospitalizations (*left*) and symptomatic illnesses (*right*) among residents across all 500 simulations of each prophylaxis scenario. *C-D,* Percentage of simulations with total number of resident symptomatic illnesses (*C*) or hospitalizations (*D*) above a certain threshold, n, for each prophylaxis scenario. Each point on the *x*-axis represents a different value of n. For example, a value of 20 on the *x*-axis in panel *C* represents simulations with total symptomatic illnesses >20. Abbreviation: HCP, healthcare personnel.

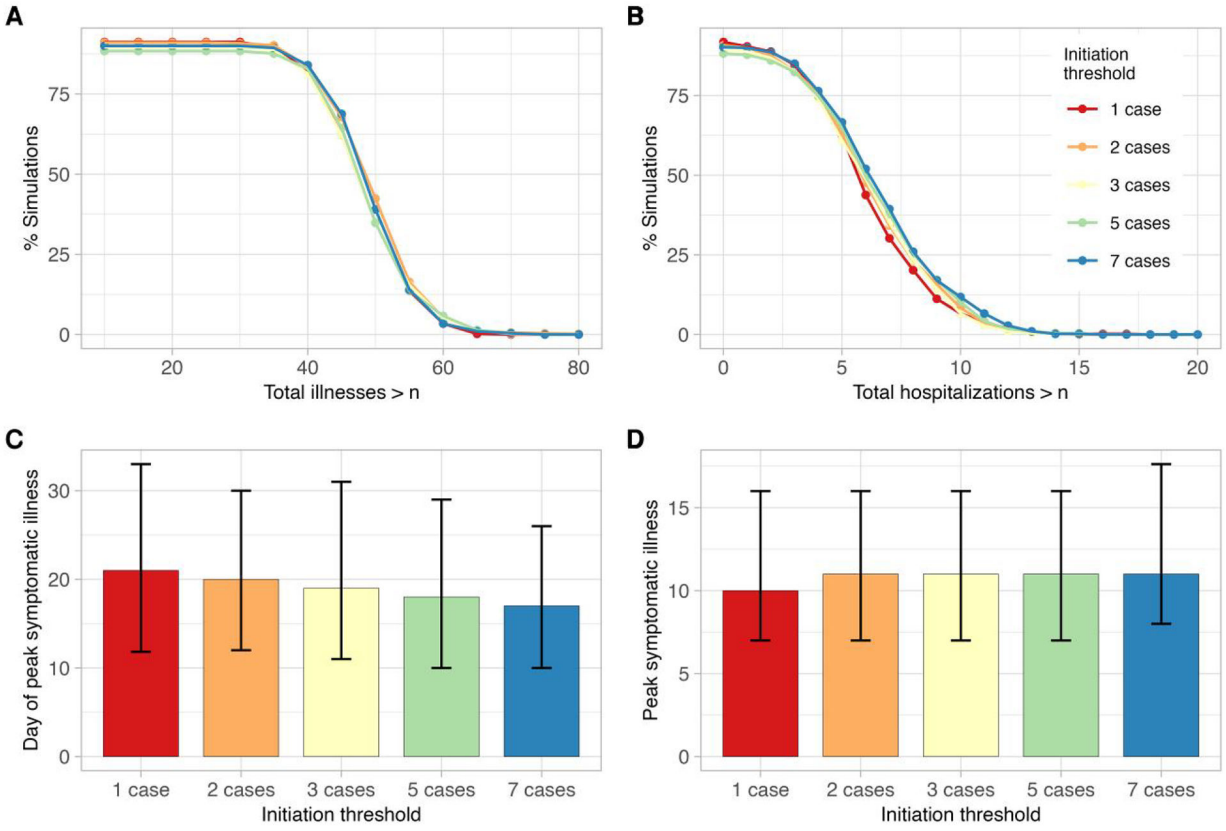

Figure 3.

Early prophylaxis initiation can delay and dampen epidemic peaks. *A-B,* Percentage of simulations with total number of resident symptomatic illnesses (*A*) or hospitalizations (*B*) above a certain threshold for each prophylaxis initiation scenario. Current guidance is represented by the 2 case initiation threshold. Each point on the *x*-axis represents a different value of n. For example, a value of 20 on the *x*-axis in panel *A* represents simulations with total symptomatic illnesses >20. *C*, Day of peak symptomatic illnesses among residents. *D*, Number of symptomatic residents at the peak. In panels *C* and *D*, bars show median values across 500 simulations and error bars are the 95th percentiles.

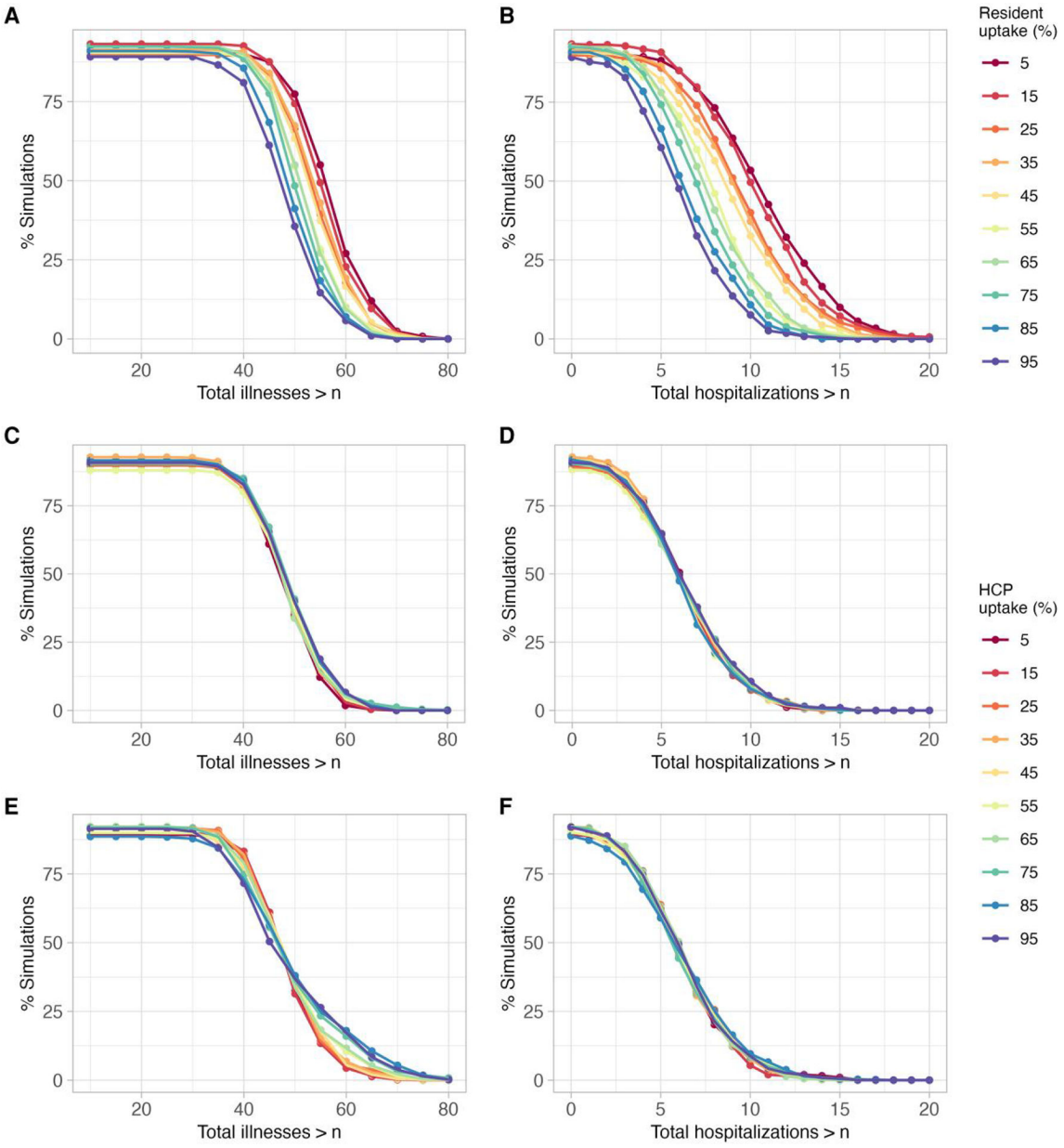

Figure 4.

Direct protection of residents is more impactful than indirect protection through HCP prophylaxis. Percentage of simulations with total number of resident symptomatic illnesses (*A*, *C*, *E*) or hospitalizations (*B*, *D*, *F*) above a certain size. Panels *A* and *B* show outcomes for different levels of prophylaxis uptake among residents; panels *C* and *D* show outcomes for different levels of prophylaxis uptake among HCP assuming adherence for 5 d, on average; panels *E* and *F* show outcomes for different levels of prophylaxis uptake among HCP assuming adherence for the duration of the outbreak. Each point on the *x*-axis represents a different value of n. For example, a value of 20 on the *x*-axis in panel *A*

represents simulations with total symptomatic illnesses >20. Abbreviation: HCP, healthcare personnel.

Table 1.

Outbreak Characteristics When Either No Prophylaxis Is Implemented, or Prophylaxis Is Implemented According to Current Guidance

	No Prophylaxis	Current Prophylaxis Guidance	Median Percentage Reduction In Burden With Prophylaxis
Total hospitalizations, residents	11 (6–17)	7 (3–11)	36%
Total illnesses, residents	57 (43–70)	49 (37–62)	12%
Total illnesses, HCP	32 (23–40)	32 (23–42)	0%
Peak[a] illnesses, residents	17 (12–23)	11 (7–16)	35%
Peak illnesses, HCP	13 (8–19)	10 (6–15)	23%
Treatment dose-packs[b] used, residents	42 (3–53)	46 (33–57)	…
Treatment dose-packs used, HCP	25 (6–34)	26 (19–35)	…
Prophylaxis dose-packs used, residents	…	311 (214–437)	…
Prophylaxis dose-packs used, HCP	…	36 (26–47)	…

Values represent median outcomes (95th percentiles) across all simulations in which an outbreak occurred with more than two symptomatic residents.

Abbreviation: HCP, healthcare personnel.

[a]Maximum number that occurred on any given day.

[b]Dose-packs contain 10 antiviral pills.