

Assessing the use of antiviral treatment to control influenza

S. C. KRAMER¹ AND S. BANSAL^{1,2*}

¹Department of Biology, Georgetown University, Washington, DC, USA

²Fogarty International Center, National Institutes of Health, Bethesda, MD, USA

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SUMMARY

Vaccines are the cornerstone of influenza control policy, but can suffer from several drawbacks. Seasonal influenza vaccines are prone to production problems and low efficacies, while pandemic vaccines are unlikely to be available in time to slow a rapidly spreading global outbreak. Antiviral therapy was found to be beneficial during the influenza A(H1N1)pdm09 pandemic even with limited use; however, antiviral use has decreased further since then. We sought to determine the role antiviral therapy can play in pandemic and seasonal influenza control using conservative estimates of antiviral efficacy, and to assess if conservative but targeted strategies could be employed to optimize the use of antivirals. Using an age-structured contact network model for an urban population, we compared the transmission-blocking ability of a conservative antiviral therapy strategy to the susceptibility-reducing effects of a robust influenza vaccine. Our results show that while antiviral therapy cannot replace a robust influenza vaccine, it can play a role in reducing attack rates and eliminating outbreaks, and could significantly reduce public health burden when vaccine is either unavailable or ineffective. We also found that antiviral therapy, by treating those who are infected, is naturally a highly optimized strategy, and need not be improved upon with expensive targeted campaigns.

Key words: Antiviral drugs, control, infectious disease epidemiology, influenza, influenza vaccines.

INTRODUCTION

Influenza causes yearly epidemics, and has been responsible for four pandemics during the last 100 years [1, 2]. Infection leads to high levels of severe complications and death in both young children and the elderly [2, 3]. Vaccines are widely accepted as the best tool to combat influenza [2]; however, current vaccines exhibit several shortcomings. A new vaccine must be developed each year, and circulating strains

must be predicted months before an epidemic occurs. In the case of a pandemic, an effective vaccine is unlikely to be available until several months after the pandemic begins [4]. Influenza vaccines are generally believed to be 70–90% effective; however, a recent meta-analysis by Osterholm *et al.* revealed that influenza vaccine efficacy found in ten randomized controlled trials was only 59% on average, and furthermore, found little or no evidence of vaccine efficacy in those aged <18 or >64 years [5, 6]. While this finding by no means shatters our vaccine-led influenza control efforts, it reminds us of the need to continue to develop better influenza vaccines and therapeutics, as well as more efficient strategies to distribute these interventions.

* Author for correspondence: Dr S. Bansal, 406 Reiss Science Building, 37th and O Streets NW, Washington, DC 20057-1229, USA.
(Email: sb753@georgetown.edu)

Antiviral drugs, such as the neuraminidase inhibitors oseltamivir and zanamivir, may be attractive alternatives to current vaccines. Unlike influenza vaccines, antiviral drugs are not strain-specific [7], and they take effect almost immediately [8]. Furthermore, while vaccines must be provided before an outbreak occurs to those thought to be at risk of infection, antivirals are used to treat those who have already been infected, ensuring that those individuals most in need of protection are targeted. When used to treat infected individuals within 48 h of symptom onset, antivirals reduce the probability that an infected individual will transmit influenza to his/her contacts [9–12]. In this study, we aimed for a systematic understanding of the population-level impact of antiviral usage, and sought to answer the following questions. (1) For seasonal influenza, can antivirals replace vaccination, especially in the case of poor vaccine match or a shortage in vaccine supply? (2) In the case of a pandemic, when faced with no vaccine for several months, what impact will the use of antivirals have? (3) Are there targeted uses of antivirals that optimize their impact? Without a greater understanding of the potential transmission-reducing effects of antiviral drugs, we cannot confidently declare vaccination to be the most effective influenza control strategy available.

Previous modelling studies assessing the population-level impact of antivirals have helped establish the potential of antiviral treatment as an influenza control strategy, but most of these studies have revealed greatly varying results. Carrat *et al.* and Ferguson *et al.* found that treating 63% or 45% of clinically ill individuals with antivirals leads to only a 7% or 15% reduction in pandemic size, respectively [13, 14], while a study by Pepin *et al.* found that 40% coverage of infected individuals can reduce seasonal epidemic transmission by 30% [15]. A study by Longini *et al.* also considered the impact of prophylactic treatment of close contacts of infected individuals, and found that prophylaxis of 80% of all exposed individuals is nearly as effective as vaccinating 80% of the population [16]. While this study showed antiviral treatment to be an effective control measure, it relied on specific contact prophylaxis based on unrealistically intensive contact tracing. Finally, a recent study by Black *et al.* used mathematical modelling to better understand why antivirals were ineffective at containing the A(H1N1)pdm09 pandemic, and found that early treatment and prophylaxis of individuals in infected households is crucial if influenza transmission

and pandemic doubling time is to be significantly reduced [17]. This study is closest in nature to our own, aiming for a quantitative assessment of the use of antivirals in a simple epidemiological model with social structure. Our study differs from the work of Black *et al.* because we aimed not to explain the lack of population-level impact of antivirals during the A(H1N1)pdm09 pandemic, but rather to consider the scenarios under which antiviral use would be viable in future pandemics as well as seasonal epidemics. Using a network model where individual hosts are ‘nodes’, and interactions (i.e. contacts) that may allow influenza transmission are ‘edges’ (details in Methods below and Fig. 1), we simulated susceptible-infected-recovered (SIR) epidemics to assess the impact of antiviral treatment strategies on influenza control. We also developed a parallel intervention model of trivalent inactivated vaccine (TIV) use, to consider the impact of antivirals as judged against the well-understood and widely accepted case of vaccination.

METHODS

Population model

We used a semi-empirical contact network model which captures the interactions that underlie respiratory disease transmission within an urban population. The model was based on demographic data from Vancouver, British Columbia, Canada [18–20]. Individuals in the network were assigned an age and age-appropriate activities (school, work, hospital, etc.). Interactions between individuals reflect household size, employment, school, and hospital data. The model population includes 10 304 individuals in the following age groups: toddlers (<3 years), pre-school children (3–4 years), school-age children (5–18 years), adults (19–64 years), and elderly individuals (≥ 65 years), who may live in the community or in a nursing home. Overall, the average degree (number of contacts) in our network is 16.11. Additional network characteristics are described in section S1 of the online Supplementary material.

Epidemic and pandemic models

We defined the transmissibility of a disease, T , as the average probability that an infectious individual would transmit the disease to a susceptible contact. This per contact probability of transmission

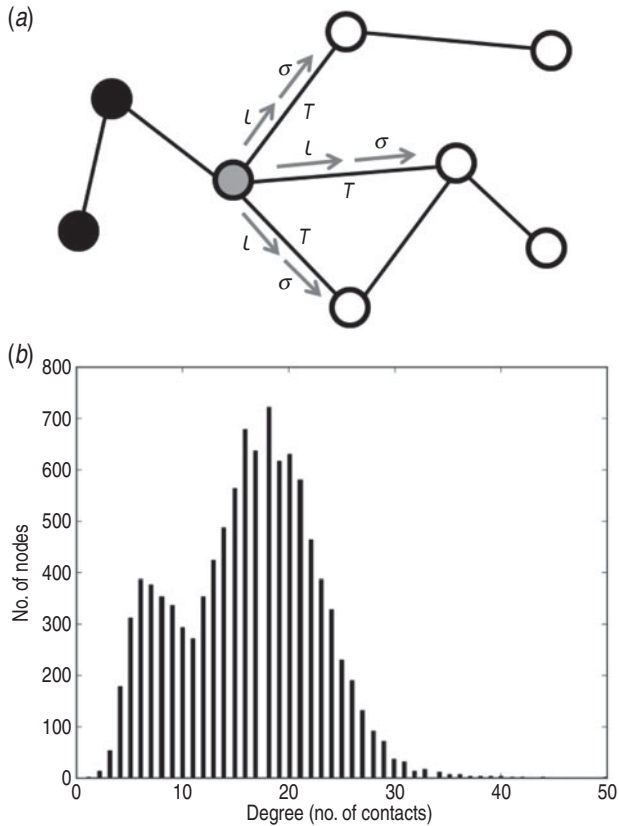


Fig. 1. Urban contact network schematic and connectivity profile. (a) Simple example of a contact network model, where circles (i.e. *nodes*) represent individuals and lines connecting them (i.e. *edges*) represent contacts over which influenza can spread. Black nodes are recovered, gray are infected, white are susceptible. Infected nodes infect susceptible contacts with probability $T = \iota\sigma$, where T is transmissibility, ι is infectivity, σ is susceptibility. (b) The frequency distribution of number of contacts per individual, or degree in the urban contact network model. The network contains 10 304 individuals with an average degree of 16.11.

summarized the susceptibility, σ (e.g. immune response) and the infectivity, ι (e.g. viral shedding) of individuals. The transmissibility of a given interaction was then defined as the product of the infectivity of the infected individual and the susceptibility of the susceptible individuals ($T = \iota\sigma$). When no intervention was implemented, $\iota = T$ and $\sigma = 1$ for all individuals. The transmissibility value was also linearly related to the key epidemiological parameter, R_0 , which denotes the average number of individuals to which each infected individual spreads the infection early in the epidemic. This value takes into account both transmissibility and network structure, as described in section S1 (Supplementary material). Transmissibility values were chosen such that seasonal

Table 1. *Efficacy and coverage values for each influenza control scenario used (values for efficacy and realistic vaccine coverage are weighted averages of values for all age groups)*

Control scenario	Efficacy	Coverage	
		Random	Realistic
Seasonal vaccine	64.5%	20%	24.7%
2009 vaccine	79.5%	30%	29.1%
High coverage vaccine	64.5%	40%	45.4%
Relaxed antiviral treatment	20%	Varies	30%
Rapid antiviral treatment	40%	Varies	30%

influenza infected 20% of the population [1] and pandemic influenza infected 40% [21] when no control strategies were implemented; to enable comparison to actual influenza epidemics and pandemics, the resulting transmissibility values were converted to corresponding R_0 values, based on the population structure of the urban network. The seasonal transmissibility in our model was 0.0643 ($R_0 = 1.14$) while the pandemic transmissibility was 0.0767 ($R_0 = 1.36$). For comparison, basic reproduction numbers have been estimated to be about 1.2–1.4 for seasonal epidemics [1], and to be about 2–3 during the 1918 pandemic [22] and 1.3–1.7 during the A(H1N1)pdm09 pandemic [23].

Epidemics and pandemics were modelled using a SIR simulation model. Beginning with an entirely susceptible population, infection was seeded at one random individual. Each infected individual infected their own susceptible contacts with probability, T ; and infectious periods were assumed to be constant across the population. We simulated 5000 such outbreaks, and an outbreak was classified as a large-scale epidemic if over 5% of the population was infected (Supplementary Fig. S1). Attack rate was defined as the proportion of the total population infected, averaged over all large-scale epidemics; epidemic likelihood was defined as the frequency of large-scale epidemics in all outbreaks.

Vaccination

We modelled the effects of a seasonal vaccine and two pandemic vaccines, one with low coverage and high efficacy, as seen during the A(H1N1)pdm09 pandemic [24, 25], and one with high coverage and low efficacy (see Table 1). Vaccination was implemented as a reduction in susceptibility for each vaccinated

individual according to age-specific efficacies of TIV (see Supplementary Table S2 and details below), as influenza vaccines generally have no impact on influenza symptoms or shedding [26]. Vaccination was employed before an outbreak began, and individuals were assumed to be protected by the time influenza spread began. Once an outbreak had started, no further individuals were vaccinated.

Vaccine efficacy

Most vaccine studies measure vaccine efficacy by comparing attack rates in vaccinated populations to those in unvaccinated populations, and are useful for understanding the population-level effects of vaccine. We reviewed population-level estimates for age-specific seasonal vaccine efficacy across multiple clinical trials, meta-analyses, and reviews (references in Supplementary section S5). We report the summarized results of our review in Supplementary Table S3, and the vaccine efficacies used for this study in Supplementary Table S2.

In our study, we incorporated vaccine efficacy at the individual-level. We defined σ as an age-specific individual-level susceptibility. We then defined S_v , the desired attack rate in individuals who have been vaccinated in the age group in question, as $S_v = S_n(1 - E)$, where S_n is the expected attack rate in the age group when no control strategies are implemented and E is the population-level vaccine efficacy for the age group. We inferred σ^* for each age group by fitting S_v , the true attack rate in individuals who had been vaccinated in the age group by having a reduced level of susceptibility, σ , to S_v using a two-type analytical percolation model [27].

For Figure 3, vaccine efficacy was gradually reduced by a factor, r , as,

$$1 - (1 - r)(1 - \sigma) = \sigma + r(1 - \sigma) = \sigma_{\text{new}}.$$

We note that a reduction in individual-level efficacy corresponded to an increase in σ .

Random vaccination

For the seasonal scenario (Fig. 2a), vaccine was distributed to 20% of the population, based on CDC data from several epidemics occurring prior to 2009 [28]. A coverage level of 30% was employed for the 2009 pandemic vaccination scenario, based on CDC coverage data for the monovalent A(H1N1)pdm09 vaccine [25], and the high coverage pandemic vaccination scenario was implemented at 40% coverage, to model increased

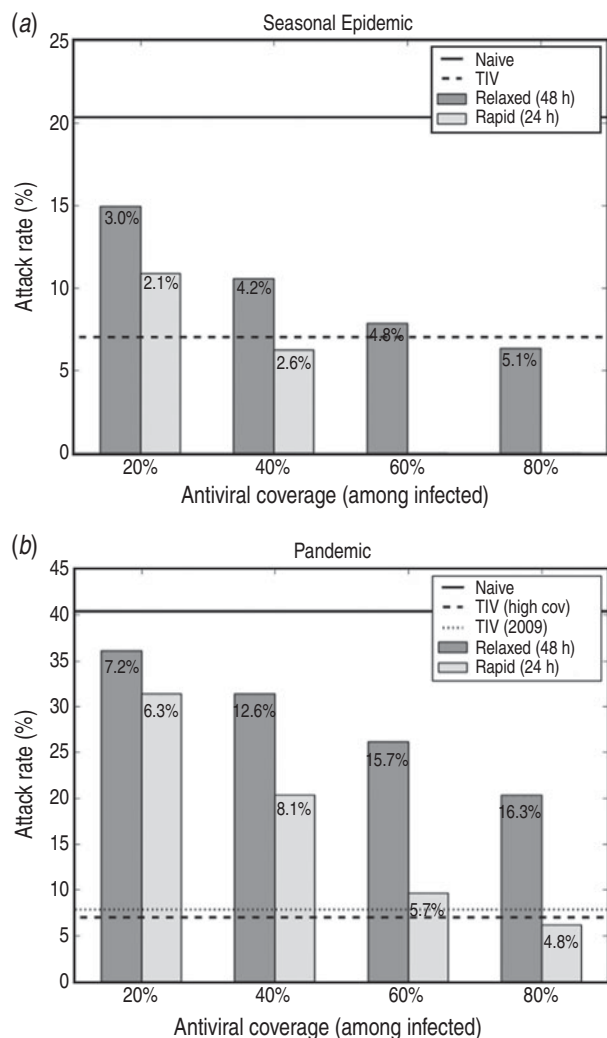


Fig. 2. Attack rates when antivirals were allocated randomly during (a) seasonal epidemics and (b) pandemics. Horizontal lines show attack rates in populations using no control strategies ('naive'; —) and vaccination (- - -; in (b) both model pandemic vaccines are shown). Both relaxed (dark grey) and rapid (light grey) scenarios are displayed. Percent of infected individuals treated is shown along the x axis, and percent of total population treated is shown within the bars. Results are only shown for those simulations in which at least 5% of the population was infected. Error bars are not shown, as standard errors for attack rates were all below 0.008. TIV, Trivalent inactivated vaccine.

awareness and panic which may lead to higher coverage levels in a pandemic more severe than the relatively mild A(H1N1)pdm09 pandemic. Here, all vaccines were distributed randomly, irrespective of age.

Realistic vaccination

Realistic, age-specific vaccination coverage levels for both the seasonal and low coverage pandemic

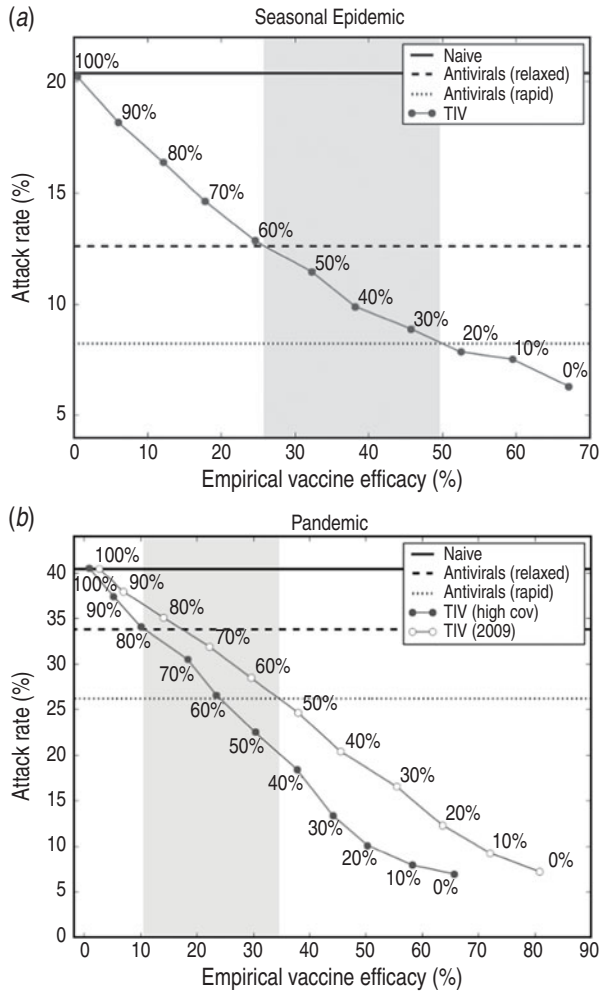


Fig. 3. Attack rates for (a) seasonal epidemic and (b) pandemic influenza when vaccines of varying efficacy were employed at realistic, age-based coverage levels. Horizontal lines show mean attack rates for naive populations (—) and populations using antiviral treatment at realistic 30% coverage (- - -; both scenarios shown). Sloped lines show mean attack rates for populations using vaccine; both pandemic vaccines are shown in (b). Vaccine efficacies are displayed on the x axis, percent reduction in individual-level vaccine efficacy for all age groups is given beside each data point. Results are only shown for simulations in which at least 5% of the population was infected. Standard errors were consistently below 0.003. TIV, Trivalent inactivated vaccine.

vaccines were derived from CDC data (Supplementary Table S1, weighted averages in Table 1, references in Supplementary section S5). For the high coverage pandemic vaccine, we simply doubled the seasonal coverage levels for each age group. Nursing home residents were the exception, as they were already vaccinated at 90% coverage during the realistic seasonal scenario.

Antivirals

We modelled the effects of antiviral treatment by reducing the infectivity of a specified proportion of infected individuals over the course of an outbreak. Because individuals did not receive treatment until after infection, antiviral treatment had no impact on susceptibility. Individuals were selected for treatment as they became infected, and infectivity was reduced prior to the next round of infections, such that the infected individual infected its contacts with reduced probability.

Treatment timing, efficacy and coverage

Antiviral drugs reduce influenza transmissibility if used within 48 h of symptom onset, and become more effective if treatment is started earlier. We modelled two antiviral treatment scenarios: one in which all treated individuals were treated within 48 h (relaxed scenario), and one in which all treated individuals were treated within 24 h (rapid scenario). We anticipate a realistic scenario to be a combination of these scenarios. Timing of treatment was modelled by altering the efficacy of antiviral drugs on individual infectivity, based on the results of household transmission studies [9–12]. Thus, antiviral effectiveness was 20% for the relaxed scenario and 40% for the rapid scenario (Table 1). Antiviral efficacy values are reported directly in [10]. Values were calculated from the remaining studies as $E = 1 - (SAR_T/SAR_U)$, where E is antiviral efficacy, and SAR_T and SAR_U are the reported secondary attack rates among contacts of treated and untreated individuals, respectively. If a study reported secondary attack rates separately for contacts of individuals treated within 24 h and within 48 h of symptom onset, efficacy values for both treatment scenarios were calculated. We report the results of our review in Supplementary Table S4. Finally, averages weighted by the number of treated index cases in each study were calculated and rounded down to obtain conservative estimates. The desired coverage was achieved by treating infected individuals randomly.

Targeted strategies

We modelled three targeted antiviral strategies. We modelled a strategy preferentially treating children (ages 5–18 years) by treating a certain proportion of infected children until the desired coverage level was achieved. If all infected children were treated and coverage among infected individuals remained below

the desired level, antiviral drugs were distributed randomly among the remaining age groups to achieve the designated coverage level. We implemented antiviral prophylaxis by treating a given proportion of infected individuals randomly, and additionally selecting randomly a single susceptible contact of each treated individual and reducing this contact's susceptibility. We continued to randomly choose contacts of each treated individual until a susceptible contact was identified. If a treated individual had no remaining susceptible contacts, no prophylaxis was given. We assumed that antiviral prophylaxis reduced susceptibility by 70% [10, 12]. Finally, we implemented early antiviral treatment at the population level by treating all infected individuals until 1% or 2% of the entire population had received treatment. We compared this strategy to a baseline scenario in which infected individuals were treated at a realistic coverage level of 30% until the desired percentage of the entire population was treated.

RESULTS

Random vaccination and antiviral treatment

To assess the potential of antiviral treatment in reducing epidemic and pandemic attack rates, we first compared the impact of random allocation of either vaccination or antiviral treatment on influenza attack rates in a fully susceptible population (see Supplementary Table S5 and Supplementary Fig. S2 for results when realistic levels of natural immunity are included). Vaccination was implemented at the coverage levels specified (Table 1), and antiviral treatment was implemented at a range of coverage levels (Fig. 2). Antiviral coverage is reported as a proportion of the infected population size (e.g. 20%, 40%, etc.) unless otherwise specified.

When the relaxed antiviral treatment strategy was employed against seasonal influenza, 80% coverage of infected individuals was required to reduce epidemic attack rates by the same amount as random vaccination. When the rapid strategy was used, 40% coverage was required, and no large-scale epidemics emerged when coverage was 60% (Fig. 2a). In the case of a pandemic, the relaxed strategy did not reach the population-level effectiveness of either pandemic vaccine at any coverage level tested, and the rapid strategy was more effective than both vaccines only at 80% coverage (Fig. 2b).

Figure 2 also displays the percent of the total population treated in each scenario. As coverage of infected

individuals increased, these values first increased, then decreased as fewer individuals became infected, suggesting that coverage among infected individuals, and not among the population as a whole, is important for population-level antiviral effectiveness. Furthermore, the rapid strategy consistently outperformed the relaxed strategy, even though fewer members of the overall population were treated, indicating the importance of initiating treatment soon after symptom onset.

The limits of vaccination

We next considered the impact of vaccine efficacy on influenza control to determine the minimum overall vaccine efficacy beyond which antiviral use is more effective at reducing attack rate. Here, we assumed 30% antiviral coverage (similar to coverage observed during the A(H1N1)pdm09 pandemic [12, 15, 29]) and realistic age-based vaccine coverage levels (Supplementary Table S1). We chose realistic vaccine coverage levels to better illustrate the actual population-level impact of vaccines, rather than their impact were they to be distributed ideally. In Figure 3, we found that vaccines began to reduce seasonal epidemic attack rates by more than random, realistic antiviral treatment at vaccine efficacies between about 25% and 50%, depending on the timing of antiviral treatment. During a pandemic, vaccines began to outperform antivirals at efficacies between about 10% and 35%, depending on treatment timing.

Targeted antiviral control

To maximize use of antivirals, we compared several targeted strategies for antiviral use during influenza pandemics (see Supplementary Fig. S3 for seasonal results). Preferentially treating children aged 5–18 years resulted in a slight reduction in attack rate when infected individuals were treated within 48 h of symptom onset (Fig. 4a). When treatment occurred within 24 h of symptom onset, this reduction was larger. Notably, this significant reduction was achieved despite the fact that coverage levels in the entire population were lower than when antivirals were allocated randomly (compare to Fig. 2b). In addition, it is key that the effect of preferentially treating children did not always increase with coverage level, as all infected children were reached by 40% antiviral coverage.

When one susceptible contact of each treated infected individual was provided with prophylactic

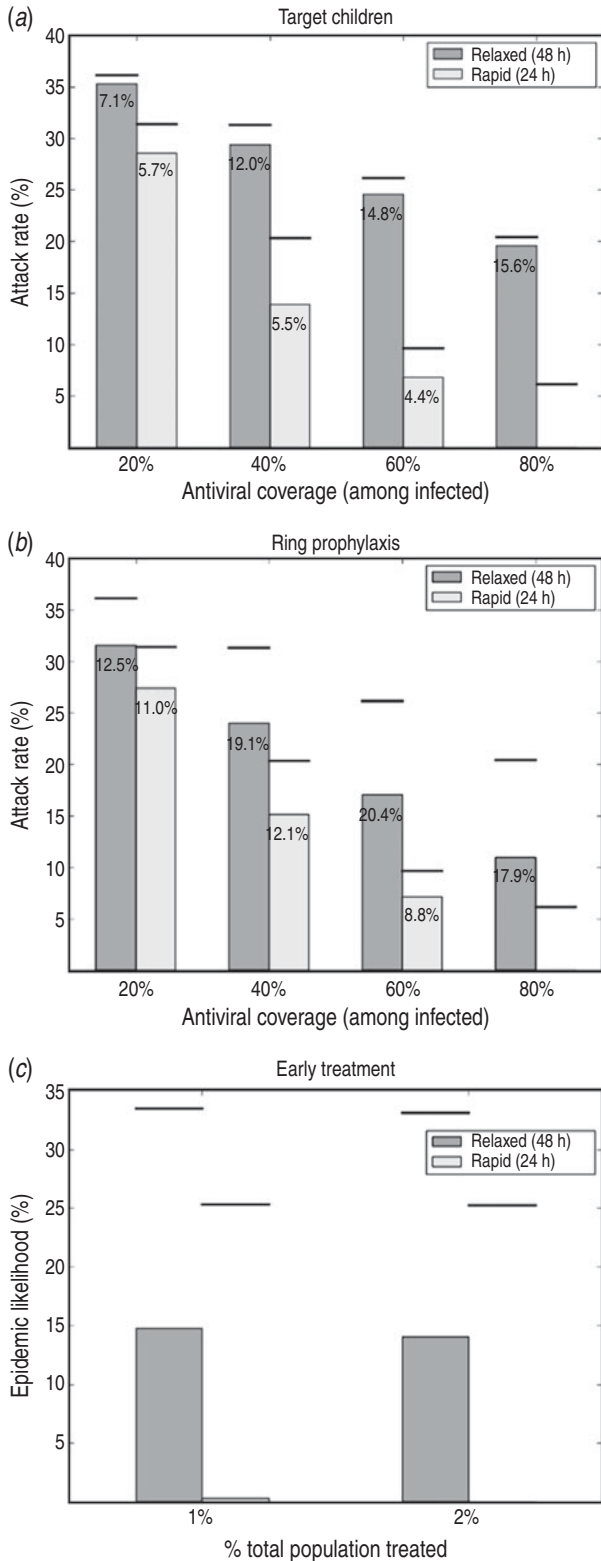


Fig. 4. Impact of targeted antiviral treatment strategies. (a, b) Attack rate (y axis) when (a) school-age children were preferentially treated or (b) ring prophylaxis was used compared to random antiviral treatment (horizontal lines above bars) at various levels of antiviral coverage among infected individuals. Percent of entire population treated is

treatment, attack rate was significantly decreased in both antiviral treatment scenarios. However, while the impact of prophylaxis increased with coverage in the relaxed case, once 40% of infected individuals were treated in the rapid case, the population-level impact of prophylaxis began to decrease. This was due to the greater efficacy of treatment in the rapid case, which prevented onward transmission regardless of prophylactic treatment. It is worth noting that the superior impact of this strategy on attack rates required higher antiviral treatment levels in the population as a whole (compare to Fig. 2b).

Last, we considered the impact of early treatment at 1% and 2% coverage of the total population, with the aim of halting the momentum of the outbreak and preventing it from becoming a large-scale epidemic. Results were compared to epidemic likelihood when the same overall number of individuals was treated over the course of the epidemic. We note that these coverage levels are far lower than those achieved in the previous sections. The likelihood of reaching a large-scale pandemic outbreak was diminished greatly in both the relaxed and rapid cases using early treatment, and epidemics were particularly rare in the rapid case.

DISCUSSION

Influenza antivirals are licensed for use in many countries, but are not widely employed during seasonal epidemics in most countries (with notable exceptions such as Japan, where antiviral coverage rates of up to 60–80% are reached [30]). Antivirals were also not widely prescribed during the A(H1N1)pdm09 pandemic. In this study, our goal was to assess the potential impact of antivirals in the case of seasonal and pandemic influenza using conservative estimates of antiviral efficacy, and to determine if more targeted (yet still conservative) strategies could be employed to optimize the use of antivirals. Specifically, we chose to compare the susceptibility-reducing effects

displayed within bars. (c) Epidemic likelihood (y axis) when all infected individuals were treated until a certain percentage (x axis) of the total population had received treatment, compared to when 30% of infected individuals were treated until the same overall coverage levels were reached (horizontal lines above bars). Results shown only for pandemic influenza. Simulations in which less than 5% of the population was infected are not shown. Standard errors were below 0.002 for panels (a–c).

of vaccines to the transmission-blocking ability of antiviral therapy. We used a semi-empirical contact network model for an urban population to study the population-level effectiveness of antiviral treatment. Network-based models allow us to consider the individual-level and contact-level impact of reductions in susceptibility and infectivity due to interventions, and the age structure of the population model allows for age-specific variation in efficacy, coverage, and control strategies. We note that our results represent a best-case scenario for current influenza vaccine efficacy. For seasonal influenza, vaccine efficacy varies considerably from year to year; indeed, the 2012 meta-analysis by Osterholm *et al.* found that the TIV was only significantly efficacious during eight of the 12 influenza seasons analysed [5]. In addition, vaccine shortages occurred in over half of influenza seasons between 1999 and 2009 [6]. Our results show that antiviral treatment could significantly reduce public health burden when vaccine is either unavailable or ineffective.

As an appropriate vaccine is unlikely to be available during the first wave of future influenza pandemics, intensive treatment of infected individuals with antiviral drugs could be crucial in mitigating the impact of a pandemic while a vaccine is in development. These results also held for higher pandemic transmissibility values, similar to those observed during the 1918 pandemic (Supplementary Fig. S4). Seasonal vaccines may be available, but, as influenza pandemics are generally caused by novel strains, such vaccines may not be efficacious enough (10–35% efficacy) against a pandemic strain to outperform realistic antiviral treatment strategies. Indeed, estimates of 2008 and 2009 seasonal vaccine efficacy against the A(H1N1)pdm09 pandemic strain vary greatly [31–33]. In order to minimize the emergence of resistance in such a scenario, Moghadas *et al.* recommended initially treating a relatively low proportion of infected individuals, then greatly increasing coverage before the pandemic is able to spread too widely [34]. However, it is important to emphasize that antiviral drugs are unlikely to greatly reduce pandemic attack rates in the long term; therefore, it is still essential that an effective vaccine be developed as quickly as possible. We also emphasize that our results are based on conservative estimates (from household studies) of antiviral efficacy to reduce infectivity. Our sensitivity analyses (Supplementary Fig. S5) demonstrated that if reduction in infectivity is higher or if future work leads to improved antivirals, the

impact of antiviral therapy could greatly increase. Furthermore, we found that antiviral treatment outperformed vaccination at lower coverage levels when network contact heterogeneity was low (Supplementary Fig. S6).

When it comes to influenza vaccination, various studies have found that prioritizing certain age groups (e.g. school-age children) [18, 35, 36] or occupation groups (e.g. healthcare workers) [18, 37] is significantly preferred over random distribution. Our study found that this is not true of antiviral distribution. Targeting school-age children and contacts of infected individuals certainly reduced attack rates (when preferentially treating children, this effect was significantly greater with increasing antiviral efficacy, as demonstrated in Supplementary Fig. S7), and, when children were preferentially treated, these lowered attack rates were achieved with fewer courses of antiviral drugs. However, the additional cost of launching a targeted antiviral campaign may outweigh the benefits. Antiviral treatment, in itself, is a highly optimized strategy; by treating those who are already infected, it naturally captures those who are highly connected and most likely to spread infection. Thus, it is likely that random allocation of antivirals will remain the preferred strategy during most influenza outbreaks. The timing of antiviral treatment, on the other hand, both at the individual-level (early during an individual's infection period) and at the population-level (early during an outbreak), does have an impact worth aiming for. Efforts should be made to treat infected individuals as soon as possible, as this increases the efficacy of the drug at the individual level and prevents onward transmission, and to treat infected individuals as soon as an outbreak emerges, as this can greatly reduce the likelihood of the outbreak becoming a large-scale epidemic. These findings are in agreement with the recent results of Black *et al.* [17].

While influenza antiviral therapy is significantly effective in reducing infection burden even with random distribution, it does require active healthcare-seeking behaviour on the part of infected individuals. A recent study by CDC found that of those with influenza-like illness during the autumn wave of the A(H1N1)pdm09 pandemic, 40% of adults and 56% of children reported seeking healthcare for their symptoms [38]. Of the adults who sought care, 26% were diagnosed with influenza, and a further 36% were then treated with antiviral drugs [38]. Other studies have found similar but varied estimates (13–40%) for the proportion of

infected individuals who were prescribed antiviral drugs during the A(H1N1)pdm09 pandemic [12, 29]. The success of antiviral strategies thus hinges on increasing healthcare-seeking rates for influenza by making care accessible at locations other than hospitals and physicians' offices, as is possible with influenza vaccination. Our sensitivity analyses (Supplementary Fig. S5) show that an increase in coverage levels can have a large impact on attack rates, and can compensate for low antiviral efficacy or delayed treatment initiation.

Our study does have some limitations. First, it is important to emphasize that the impact of antiviral drugs on infectivity has not been well-studied, and the parameters used here are estimates obtained from household studies. Our sensitivity analyses (Supplementary Fig. S5) considered a wide range of antiviral efficacy values, and show that variation in antiviral efficacy can lead to marked changes in influenza attack rates. Additionally, we did not explicitly consider the impact of antiviral therapy on severe illness or mortality. Current guidance from CDC and WHO emphasizes the importance of administering antiviral therapy to patients who are hospitalized with severe or progressive illness caused by suspected influenza and in high-risk outpatients. It is essential that antivirals continue to be used as currently recommended to treat these individuals, even when a vaccine is available. In fact, some preliminary analyses (Supplementary Fig. S8) indicated that targeting those individuals at highest risk for complications and death due to influenza (e.g. the elderly and children aged <5 years) could be a prudent strategy as it would result in comparable attack rates for both seasonal and pandemic influenza to those of random antiviral allocation, but would be expected to be more effective at reducing complications and death. Furthermore, we did not consider the risk of antiviral resistance, primarily because our results indicated that widespread use of antiviral drugs is not the best way to reduce influenza attack rates. Although resistance to oseltamivir and zanamivir has been limited historically, even in Japan, where coverage rates are typically high [39], the 2007–2008 season brought us a strain of oseltamivir-resistant seasonal H1N1 virus that circulated globally [2]. We plan, in future work, to consider the impact of various antiviral distribution strategies on the emergence and spread of resistance. Last, our seasonal influenza scenario did not incorporate pre-existing immunity,

which is likely to be present in seasonal outbreaks. However, as our sensitivity analyses show (Supplementary Fig. S2), the inclusion of appropriate levels of pre-existing natural immunity did not qualitatively alter our findings.

Despite the significant potential of antiviral drugs in the absence of an effective influenza vaccine, our results indicated that even vaccines of suboptimal efficacy are expected to outperform realistic antiviral strategies in both seasonal and pandemic scenarios. While exceptions to this conclusion may be made for countries such as Japan, where antivirals are regularly employed and coverage levels are particularly high, it is clear from previous research that achieving such high coverage rates in the United States and other countries unaccustomed to widespread antiviral use will be difficult. Additionally, even if high levels of coverage were to be achieved, such high coverage levels would increase the chance of widespread emergence of antiviral resistance, rendering the drugs ineffective in reducing disease transmission or severity. Indeed, Chao *et al.* demonstrated that an antiviral coverage level of only 30% would allow a resistant strain of influenza to spread worldwide, assuming this strain was equally transmissible to the wild-type strain [40]. Thus, we conclude that antivirals are not an appropriate substitute for influenza vaccines.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0950268814002520>.

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DECLARATION OF INTEREST

None.

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