

# Pre-dispensing of antivirals to high-risk individuals in an influenza pandemic

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We consider the net benefits of pre-dispensing antivirals to high-risk individuals during an influenza pandemic, where the measure of the benefit is the number of severe outcomes (such as deaths or hospitalizations) prevented by antivirals in the whole population. One potential benefit of pre-dispensing is that individuals to whom antivirals have been pre-dispensed may be able to initiate treatment earlier than if they had to wait to obtain and fill a prescription, reducing their risk of progression to severe disease. If this benefit exceeds the side effects of misuse for the category of individuals to whom antivirals were pre-dispensed, and if antiviral supply exceeds overall population demand (which appears relevant for several countries including US in the 2009 H1N1 pandemic), pre-dispensing a quantity of antivirals not exceeding the difference between supply and demand is always beneficial. In this study, we consider the net benefits of pre-dispensing antivirals under various scenarios, including demand exceeding supply, and derive mathematical conditions under

which antiviral pre-dispensing is advantageous on balance. For individuals whose relative risk of severe outcome is high enough, such as immunosuppressed individuals (particularly children) and possibly individuals with neurological disorders, pre-dispensing is always beneficial at a given level of antiviral stockpile with modest assumptions on the relative benefit of early treatment by a pre-dispensed course, regardless of the overall population demand for antivirals during the course of an epidemic. Making additional assumptions on either the overall population demand for antivirals (which appear relevant for the 2009 H1N1 pandemic) or on the relative benefit of pre-dispensing would make pre-dispensing net beneficial with inclusion of a larger number of persons such as pregnant women and morbidly obese adults.

**Keywords:** Antivirals, high-risk individuals, influenza, pre-dispensing

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## Introduction

A key objective for the response to the autumn wave of pandemic influenza A/H1N1 (H1N1pdm) in the Northern Hemisphere is to reduce severe morbidity and mortality that would result from an unmitigated pandemic. Broadly, such responses may be divided into two groups: (i) efforts to reduce population-wide transmission of the virus and thereby protect individuals from becoming infected, either permanently (vaccination) or for a period of time until vaccines become widely available (non-pharmaceutical interventions), and (ii) efforts to protect individuals at particularly high risk of complications from becoming infected or, if infected, from developing severe disease. Here, we concentrate on aspect (ii) of the response via the usage of antiviral drugs.

The ability of antiviral drugs to alleviate symptoms and shorten their duration is well documented for seasonal

influenza, particularly if antivirals are taken during the earlier stages of influenza infection.<sup>1–3</sup> A 2003 study suggests a 60% reduction in influenza hospitalization rates for patients who received early antiviral treatment for seasonal influenza.<sup>4</sup> For H1N1pdm, recent data<sup>5</sup> show that among hospitalized patients, severe outcomes (ICU admission and/or death) were less likely in patients who received antiviral treatment within 2 days of symptom onset; the same conclusion is true for lethal outcomes in hospitalized patients in ref. [6].

Several recent studies suggest that most severe outcomes for H1N1pdm infection occur in individuals with pre-existing medical conditions,<sup>5–12</sup> although the exact percentages vary between the studies. This has been recognized in several countries, where prompt antiviral prescription to symptomatic high-risk individuals is recommended.<sup>13–17</sup> However in several countries, including US, such a prescription requires a doctor visit. Such a visit may be prob-

lematic to symptomatic individuals with underlying health conditions and may not occur promptly enough for various reasons, including a possible wait for symptoms to go away. Pre-dispensing antiviral drugs so that individuals in high-risk groups have access to medications immediately upon becoming symptomatic without the need to seek a prescription or fill it in a time of possible scarcity may be a valuable strategy to reduce their risk of severe disease or mortality. Pre-dispensing here is defined as a policy (most likely implemented by an individual physician) of prescribing and urging a patient to fill the prescription for a course of neuraminidase inhibitor in advance of any known infection with H1N1pdm. The patient would be instructed to begin self-treatment (possibly following communication with the physician) upon meeting a definition of a suspected H1N1pdm infection.

The benefit of using a pre-dispensed course of antivirals versus one obtained by prescription is hard to assess. However, if one believes that such a benefit does exist and exceeds the side effects for the category of individuals to whom antivirals were pre-dispensed, pre-dispensing of antivirals is always advisable in a situation when the population demand for antivirals is smaller than the available supply. This is because pre-dispensing a quantity of antivirals not surpassing the difference between supply and demand would not deprive anybody of an antiviral course, and a pre-dispensed course is more likely to prevent a severe outcome than a course obtained by prescription during the epidemic. The scenario of supply exceeding demand appears relevant to several developed countries with a large supply of antivirals, and evidently to the US due to strict current prescription guidelines for low risk individuals.<sup>13</sup> This simple rationale is perhaps the main practical motivation behind antiviral pre-dispensing in a current H1N1 epidemic.

In a scenario when demand exceeds supply, there is additional benefit to pre-dispensing having to do with the fact that a pre-dispensed course of antivirals would end up in the hands of a high-risk rather than a low-risk person, and thus is more likely to prevent a severe outcome. There is also harm to pre-dispensing in this case resulting from the fact that some antivirals will be in the hands of individuals who will not need them, and hence will be wasted, depriving others who do need them of access.

In this study, we examine the net benefits of pre-dispensing antivirals under various levels of population demand. We define conditions under which pre-dispensing a defined quantity of antivirals, one course each to a subpopulation at high risk of death or hospitalization from H1N1pdm infection would provide a net benefit in terms of reducing severe outcomes compared to a policy of leaving them in state and national stockpiles for distribution only to infected patients. At a given level of antiviral supply and relative benefit of early treatment there may be some

groups of individuals with sufficiently high relative risk of dying such that pre-dispensing is always beneficial regardless of the overall population demand for antivirals during the course of an epidemic. Under certain assumptions about the overall demand for antivirals – namely, that it is not too close to the total supply – one can show that there is a net benefit to pre-dispensing to a larger class of high-risk persons (those with risk above the population average, but not in the highest-risk category). We will attempt to quantify these situations in the context of limited available data on severe outcomes in high-risk individuals.

## Benefits and harms of pre-dispensing

To fix notation, we assume here that we seek to optimize the number of lives saved (i.e. minimize the number of lives lost due to H1N1pdm); however, with suitable modifications to the definitions of all terms, we could equally attempt to prevent hospitalizations or intensive care admissions. There are at least two possible benefits, and three harms, to pre-dispensing. The first benefit of pre-dispensing is that a patient possessing a pre-dispensed course of antivirals will likely begin therapy earlier in the course of H1N1pdm infection than one must acquire a prescription (possibly including a visit to a physician) and fill it, thereby most likely delaying treatment. This benefit accrues whether or not there is a shortage of antivirals, because it simply reflects the time required to acquire and fill the prescription. A second possible benefit occurs if the demand for antivirals exceeds supply, so that not all patients who attempt to acquire antivirals can do so. In this situation, pre-dispensing a course assures that it is in the hands of someone who, if untreated, would be likely to develop severe disease, rather than (potentially) going to someone who will not likely develop severe disease, and whose benefit from taking the antiviral would therefore be less.

The first harm of pre-dispensing occurs only if total demand for antivirals exceeds supply, namely, a pre-dispensed course is unavailable to anyone who may need it other than the person who has received it and who may not get infected. If demand exceeds supply, this means one more person, possibly someone who would benefit greatly from having the antiviral is unable to obtain it. A second harm of pre-dispensing is the possibility that a pre-dispensed course will be used by a high-risk individual who would not otherwise be able to obtain an antiviral drug, and this usage will lead to a severe side effect. We have no way of assessing the likelihood of such an outcome; in particular, the major severe side effects reported to date are neuropsychiatric events in oseltamivir recipients, and the manufacturer's data review concludes that there is no evidence of a causal link between oseltamivir and these adverse events.<sup>18</sup> We will not model this second harm in

our analysis. Yet another possible harm to pre-dispensing is preliminary evidence that people treated with antivirals have lower levels of antibodies compared to people who were not (B. Cowling, private communication). We are not aware of data quantifying additional risk for re-infection, if any, after antiviral treatment compared with no antiviral treatment. Therefore, we will not model this potential harm either.

To assess the net benefit or harm from pre-dispensing, we define some notation, summarized in Table 1 (see Appendix B for a formal description). We divide the whole (total) population into two groups: a *high-risk group* for which we are considering pre-dispensing, and *the general population*, which includes all individuals not in the high-risk group. These constitute respectively a proportion  $q$  (high-risk) and  $1 - q$  (general population) of the total population. Within the general population, risks may vary, so some individuals may be at higher risk than others. All quantities in our notation are defined as proportion of the total population, hence lie between 0 and 1. Let  $T$  be the total supply of antivirals (as a proportion of the population); thus, if enough antivirals are available for treatment of 20% of the population, then  $T = 0.2$ . Let  $D$  be the demand for antivirals in the general population, that is the

number of individuals who would receive antiviral treatment in the general population if supply were not limiting; in practice, some of this demand may be unmet as the supply is constrained. Let  $p_d$  be the death rate (per capita) from the infection over the whole course of the epidemic in the whole population (if no antivirals are used); the death rate in a high-risk group is  $R \cdot p_d$ . Note that these death rates are not conditional on infection (i.e. are not case-fatality proportions) but are unconditional, reflecting the risk of infection times the risk of dying from infection. Here, the number  $R$  is the relative risk of dying in a high-risk group compared with the whole population.  $R$  can be estimated from the existing epidemic data while  $p_d$  may be hard to estimate *a priori*; however, we shall see that  $p_d$  is factored out of our equations and need not be known. Let  $p_s$  be the probability that a course of antivirals obtained during the epidemic saves the life of a person who would die otherwise. We assume that this probability is the same between high-risk individuals and members of the general population. This key assumption may be incorrect, and is discussed later. Let  $B \cdot p_s$  be the probability that a *pre-dispensed* course of antivirals would save a life of a high-risk person who would die otherwise.  $B$  can be thought of as the 'relative benefit' in preventing mortality of receiving a pre-dispensed course of antivirals compared with receiving a non-pre-dispensed course by a high-risk individual who would die otherwise.  $B$  captures the benefit of early versus delayed treatment; however,  $B$  also may be reduced to the extent that a pre-dispensed course is taken for non-influenza illness, in which case it cannot subsequently save a life. Thus  $B$  exceeds one to the extent that early treatment is better than delayed treatment, but it is decremented in proportion to the probability that the course is wasted before it is needed. If a pandemic is imminent or ongoing, the risk of wastage is small, especially outside of the season (winter in temperate climates) when other respiratory infections are most common.

Finally, let  $L$  be the total number of people in the general population who would die during the epidemic and whose lives would be saved if they received antivirals upon demand. As the total fraction of the whole population (general + high-risk) who would die during the epidemic and whose lives would be saved if they received antivirals during the course of the epidemic is  $p_d \cdot p_s$ , clearly  $L \leq p_d \cdot p_s$ . We make additional assumptions about how the probability of receiving antivirals behaves if demand exceeds supply; these are made explicit in Appendix A.

With this notation in place, we can define the conditions under which it is advantageous to pre-dispense 1 course each to a proportion  $q$  of the population. Our main result is the following:

**Main result:** Pre-dispensing saves more lives than not pre-dispensing when any of the following conditions hold:

**Table 1.** Parameters of the model, as a proportion of the total population (including high-risk and general populations)

Parameter	Definition
$T$	Supply of antivirals, before pre-dispensing, as a fraction of total population size
$D, D'$	Number of antiviral courses used by the general population ( $D$ ) or total population ( $D'$ ) if no supply constraint, as fraction of the total population size
$L$	Total number of lives in the general population that would be saved under no pre-dispensing, if no supply constraint
$q$	Proportion of persons in the high-risk group to whom pre-dispensing of one course is considered, hence also the number of courses considered for pre-dispensing, as a fraction of the total population
$p_s$	Probability that a course of antivirals obtained during the epidemic would save a life of a person who would die otherwise, absent any pre-dispensing
$B$	Relative benefit (in terms of probability of saving life) for a high-risk person to be treated early (with a pre-dispensed course) compared to being treated with a non-pre-dispensed course. Thus $p_s \cdot B$ is the probability that a pre-dispensed course of antivirals would save a life of a high-risk person who would die otherwise
$p_d$	Death rate from the epidemic in the whole population, if no antivirals were used
$R$	Ratio between the death rate in the high-risk group and the whole population

1. Supply of antivirals exceeds demand even after pre-dispensing ( $D \leq T - q$ ), and  $B > 1$ .

2. Demand  $D$  in the general population exceeds supply  $T$  even without pre-dispensing, and the following conditions are met:

$$B > \frac{T}{D} \text{ and } R > \frac{1}{D(B - T/D)}$$

3. Supply  $T$  exceeds demand  $D$  in the general population without pre-dispensing, but after pre-dispensing, demand exceeds supply ( $T - q \leq D \leq T$ ), and the following conditions are met:

$$B > 1 \text{ and } R > \frac{D + q - T}{Dq(B - 1)}$$

4. Sufficient condition: The above results show that no matter what the demand for antivirals, pre-dispensing is advantageous when

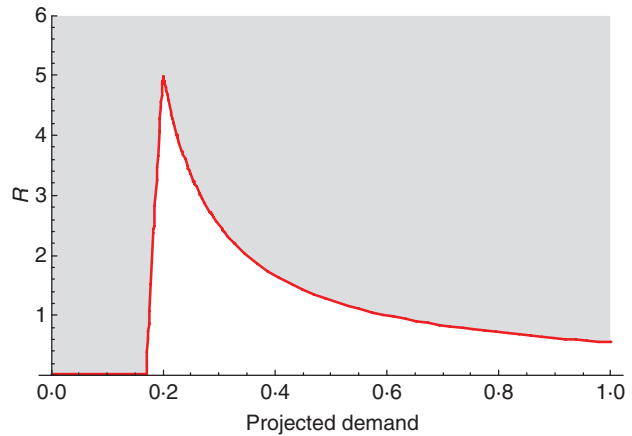
$$B > 1 \text{ and } R > \frac{1}{T(B - 1)}$$

The justification of this result and the assumptions underlying it are presented in Appendix A. The sufficient condition at the end tells us when a group is at high enough risk that it is worth pre-dispensing to them even if we have no idea of the expected antiviral demand.

This result can be seen graphically in Figures 1–3, which consider a hypothetical case in which there is a supply adequate for  $T = 0.2$  of the population, and pre-dispensing to  $q = 3\%$  of the total population is under consideration. The parameter that varies between the figures is the relative benefit  $B$  of saving a life by a pre-dispensed course versus a course obtained by prescription. We are not aware of data allowing an assessment of this parameter; we consider three scenarios:  $B = 2$  (Figure 1),  $B = 1.3$  (Figure 2) and  $B = 1$  (Figure 3). We consider it likely that  $B = 1$  is an extreme case and that in reality  $B > 1$ .

The far left side of each of the figures shows low levels of demand, in which there is no harm to pre-dispensing, so pre-dispensing to any group for which  $B > 1$  may be beneficial. At the far right, competition for antivirals is strong, so all antivirals are used, mostly by the general population, and it is beneficial to pre-dispense even to a group that gets modest benefit from antivirals to capture the benefit of early treatment. In the middle, when demand is similar to supply, it is beneficial to pre-dispense only to groups that benefit disproportionately from antivirals ( $R > 5$  for  $B = 2$ ,  $R > 16.7$  for  $B = 1.3$  and never for  $B = 1$ ).

Finally, we note that it is not always true that the benefit increases with the quantity of antivirals pre-dispensed. Under certain conditions, it would be better to pre-dispense to a subset of the high-risk population, defined as

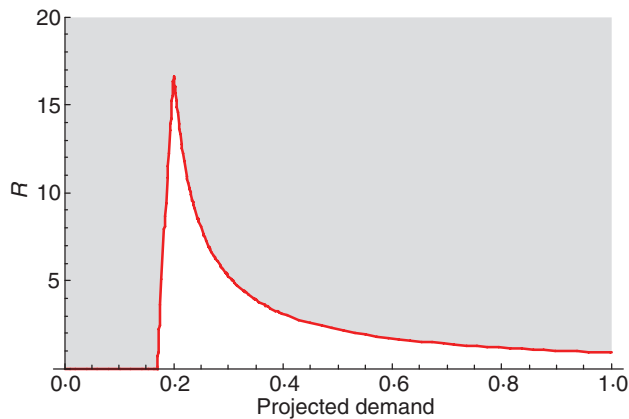


**Figure 1.** Pre-dispensing is beneficial (shaded area) when  $R$  exceeds a certain threshold that depends on the projected demand. Here, a supply adequate for  $T = 20\%$  of the population is assumed, and pre-dispensing to  $q = 3\%$  of the total population is under consideration. Also, we assume that treatment of a high-risk person with a pre-dispensed course is twice as likely to be life-saving as if treatment is with a non-pre-dispensed course, because pre-dispensing allows earlier initiation of treatment ( $B = 2$ ). For low-projected demand (below  $D < T - q = 0.17$ ), there is no harm to pre-dispensing, and pre-dispensing even to groups that will gain below-average benefit from antivirals is better than no pre-dispensing. For very high-projected demand ( $D$  near 1) pre-dispensing is beneficial even for very modest values of  $R$ , because competition for antivirals is strong, and pre-dispensing has a relative benefit compared with acquisition by ill persons. For projected demand comparable to the supply ( $D \sim T = 0.2$ ), pre-dispensing is valuable only for groups for whom antivirals are considerably more valuable than the general population, because each course pre-dispensed comes at the expense of someone else who could use it, yet it does not strongly increase the chance that a high-risk individual gets treated (as that individual would likely receive a course anyway without pre-dispensing).

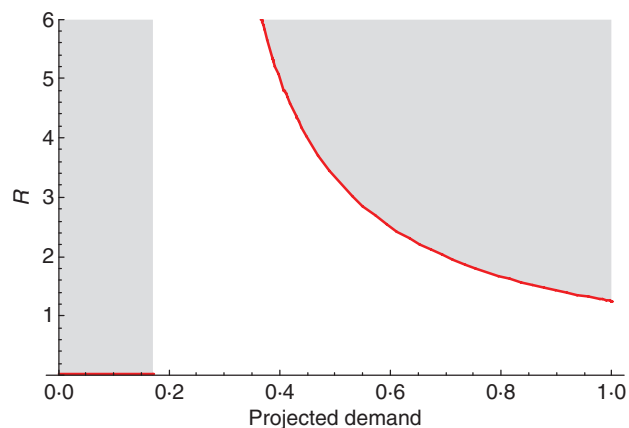
those with a risk above a certain threshold. This is discussed further in Appendix C, where a simple criterion is given ensuring that each successive pre-dispensed dose increases the net benefit, provided that the quantity of antivirals pre-dispensed is not too large.

## Interpretation of these conditions

Pre-dispensing is most advantageous for groups that have the highest mortality rate (high  $R$ ) and that benefit most from pre-dispensed antivirals compared to non-pre-dispensed ones (high  $B$ ). These factors capture the demand-independent aspect that it is useful to position antivirals with individuals who can be most helped by having them close at hand, rather than getting them after they become ill. A second benefit of pre-dispensing is to ensure access of antivirals to those who will benefit the most from them. This benefit is greatest when demand is very high, because in such circumstances the high-risk individuals are very likely to need antivirals, but not to get them. Thus the ben-



**Figure 2.** If pre-dispensed courses are 1.3 times more likely to be lifesaving than non-pre-dispensed courses taken by the same person, the conditions for benefits of pre-dispensing are somewhat more restrictive. Parameters are as in Figure 1, except that treatment of a high-risk person with a pre-dispensed course is 1.3 times more likely to be life-saving than treatment with a non-pre-dispensed course ( $B = 1.3$ ). In the worst-case scenario for pre-dispensing, if demand=supply, then pre-dispensing is beneficial only for a group with relative risk 17 of severe outcomes.



**Figure 3.** If pre-dispensed courses are no more likely to be lifesaving than non-pre-dispensed courses taken by the same person, the conditions for benefits of pre-dispensing are even more restrictive. Parameters are as in Figure 1, except that treatment of a high-risk person with a pre-dispensed course is equally likely to be life-saving as treatment is with a non-pre-dispensed course ( $B = 1$ ). In particular, in this situation if demand = supply, it is never beneficial to pre-dispense a course, because it may go to someone who does not need it, and it confers no benefit purely from being pre-dispensed.

efits of pre-dispensing are greatest for larger values of  $R$ ,  $B$  and  $D/T$ . The costs of pre-dispensing – lost opportunities for individuals who do not receive pre-dispensed courses – are zero when demand is low enough (as all who need the antivirals can receive them) then increase, but not as fast as the benefits. Qualitatively, then, pre-dispensing is most advantageous when demand is very high or very low, and

least likely to be advantageous when demand just exceeds supply. Even there, however, if the benefit of a pre-dispensed course is significantly larger than that of a non-pre-dispensed course, pre-dispensing is valuable for individuals who can benefit more from treatment than the general population.

## Risks of pre-dispensing

The major risk of pre-dispensing is that courses that would otherwise be life-saving (when used from the stockpile) will be pre-dispensed, then not used by someone for whom they would be more likely to be life-saving. We can consider what has been written so far from another perspective: this risk is most acute when demand is near supply  $T/D \sim 1$ , when individuals not in the group to be pre-dispensed would benefit from treatment by pre-dispensed antivirals but cannot obtain them because they have been pre-dispensed. This risk is also most important when pre-dispensing and consequent early use are not very beneficial (low  $B$ ).

The idea of pre-dispensing was previously considered in the context of pre-pandemic sale of antiviral ‘Medkits,’ special packaging of oseltamivir or zanamivir for home storage to be saved until a pandemic occurred. A number of concerns were raised regarding such Medkits, resulting eventually in a lack of approval by the Food and Drug Administration (<http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4385m1-final.pdf>). One of these concerns was the issue of equity – if Medkits were to be purchased by individuals, individual decision-making and ability to pay would influence access. Another concern was the risk of inappropriate use or wastage. A key difference between pre-pandemic distribution of antivirals and pre-dispensing just prior to or in the middle of a wave of pandemic influenza is that the time frame for wastage is much shorter in the present case. Thus, we expect that  $B$  will primarily reflect the advantage of early versus delayed treatment, for which there is some evidence.<sup>1–5</sup>

It is also worth mentioning that unlike the situation with antibacterial medications – which can promote drug resistance even when used to treat non-bacterial infections, because of their effect on bystander flora,<sup>19</sup> anti-influenza drugs do not promote resistance when used to treat non-influenza infections. In the 2009 H1N1 pandemic, resistance levels appear to be very low – for instance in the UK, where extensive antiviral usage takes place, resistance levels were estimated to be 0.17%.<sup>20</sup> Moreover, prior mathematical modeling studies<sup>21,22</sup> have shown that if the epidemic is already large at the time that large-scale antiviral treatment begins, then resistant strains will be unlikely to ascend to high frequency in the population before the epidemic is over, even in the



absence of vaccination. Thus, we think that additional antiviral usage which may result from pre-dispensing will have a very minor impact on antiviral resistance levels in the current H1N1 pandemic.

## Benefits of early antiviral treatment for preventing severe outcomes

A key source of uncertainty in our estimates is the relative benefit  $B$  for preventing a severe outcome by a pre-dispensed course of antivirals versus one obtained by prescription by an individual who would die otherwise. In this section, we describe data from ref. [5,6] showing a reduction in probability of a severe outcome resulting from early antiviral treatment. We also explain why it is difficult to estimate  $B$  from data.

Data in ref. [6] show that among hospitalized H1N1pdm patients, 18/357 (5%) of those who received antiviral treatment within 48 hours died; the same numbers for all patients who received any antiviral treatment are 70/701 (10%). If we think of those hospitalized patients who received antivirals within 48 hours as a proxy for the pre-dispensed individuals who would progress into a severe condition, and all individuals in the study who received antivirals as a proxy for individuals who would progress into a severe condition and receive antivirals during the epidemic, then ratio of probabilities  $1.98 = (70/701)/(18/357)$  can be thought of as a ratio of probabilities of dying given that you receive antivirals upon infection during the course of the epidemic versus having a pre-dispensed course.

Data in ref. [5] show that among hospitalized H1N1pdm patients, 13/75 (17.3%) of those who received antiviral treatment within 48 hours were either transferred to ICU or died; the same numbers for all patients who received any antiviral treatment are 56/200 (28%). Using the same proxies as above, the ratio of probabilities  $1.62 = (56/200)/(13/75)$  can be thought of as a ratio of probabilities of being transferred to ICU or dying given that you receive antivirals upon infection during the course of the epidemic versus having a pre-dispensed course.

Those proxies may be inaccurate. Having antivirals pre-dispensed may work better than merely receiving them within 48 hours after symptom onset. Additionally, both datasets are based on a time period before the CDC guidelines on 8 September 2009<sup>13</sup> recommending prompt treatment of symptomatic high-risk individuals without a lab test confirmation; at the same time, those datasets address hospital patients, many of whom received antivirals promptly, presumably upon a first doctor visit.

Regardless of whether the proxies are accurate, they do not yield enough information to get an estimate of  $B$ , the relative benefit of preventing a severe outcome (death or ICU admission) by a pre-dispensed course versus a course

obtained upon infection by a person who would progress into this outcome otherwise. To see that, coming back to the study in ref. [5], let  $p$  be the proportion of hospitalized patients who would die or need to be transferred to ICU unless they receive antivirals. The relative benefit of preventing a severe outcome is then

$$B = \frac{p - 0.173}{p - 0.28}$$

Here, the numerator represents individuals who were spared a bad outcome because of early antiviral treatment, and the denominator represents individuals who were spared a bad outcome because of any antiviral treatment. Thus, if  $P = 0.35$ ,  $B = 2.52$ ; if  $P = 0.5$ ,  $B = 1.48$ , etc. Data in ref. [5] show that among hospital admissions who never took antivirals, 9/68 (13.25%) either died or were transferred to ICU. It appears that people who did not take antivirals fared best; for the data in ref. [6], they fared slightly worse than people who took antivirals after 48 hours since symptom onset. This is because of a bias that we already encountered in E. Goldstein *et al.*, (unpublished data) – bad, deteriorating cases were given late antivirals; as a consequence, the group without antivirals has a disproportionate share of good cases. In other words, given high levels of treatment, the reverse causal relation between treatment and outcome makes an estimate of the treatment effect difficult.

While we cannot render an estimate of  $p$  from data, we note that 59/268 (22%) of patients in ref. [5] neither received antivirals nor died or were admitted to ICU. Thus, we estimate that  $P \leq 1 - 0.22 = 0.78$  and hence  $B \geq 1.21$ . An equality would be a very conservative estimate, which assumes that all the 144 individuals who were treated with antivirals and did not die and were not transferred to ICU had a good outcome because of antiviral treatment. There are additional reasons why this is an underestimate of  $B$ . Data from ref. [24] suggest that 17% of H1N1 deaths were never hospitalized, and some of them could have benefited from pre-dispensing. Additionally our estimates on the chances of avoiding ICU admission or death are based on hospitalized patients, while some people could avoid hospitalization by using a pre-dispensed course of antivirals. We believe that in reality  $B$  should be bigger than 1.21.

## Relative risks for certain high-risk groups

In this section, we attempt to assess relative risks for a severe outcome from H1N1 infection for certain high-risk groups for which data is available. Our data sources are refs [5,6,8,25] (MIDAS High Risk Segmentation Group, D. Wagener, private communication, 2009). The estimates below are crude and based on limited available data.

Pregnant women constitute 1% of the US population.<sup>8</sup> An estimate in ref. [8] suggests that they are about four times more likely to be hospitalized as a result of H1N1 infection compared with general public. The percentages of pregnant women among hospitalized patients in refs [5] and [6] are 6.6% and 9.6% correspondingly. The percentage of pregnant women among deaths in ref. [6] is 5.1%; the percentage of pregnant women among deaths or ICU admissions in ref. [5] is 9%. We therefore estimate the relative risk for hospitalization for pregnant women to be between 4 and 9.6, and the relative risk for death or ICU admission to be between 5.1 and 9.

Morbidly obese adults (BMI  $\geq$  40) constitute 4.8% of the adult US population,<sup>25</sup> and correspondingly 3.63% of the whole US population. Data in ref. [6] suggest that morbidly obese adults constitute 18.6% of hospitalized cases, and 31.5% of fatal cases. Data in ref. [5] (which has a lower percentage of adults compared with ref. [6]) suggest that 14.3% of hospitalized patients were morbidly obese adults; among patients who died or were transferred to ICU, 20.6% were morbidly obese adults.

Thus, we estimate that the relative risk for hospitalization for morbidly obese adults ranges from 3.95 to 5.11, whereas the relative risk for ICU admission or death ranges from 5.68 to 8.68.

We draw our data on the percentages of immunosuppressed individuals in different age groups in the US from MIDAS High Risk Segmentation Group (D. Wagener, private communication, 2009). The National Health Interview Survey (NHIS), conducted annually by the Centers for Disease Control and Prevention (CDC), was used as a principal source for prevalence data from MIDAS High Risk Segmentation Group (D. Wagener, private communication, 2009). Specific sources are: Cancer in past 3 years 2006 data (National Health Interview Survey, 2006); HIV/AIDS 2006 data CDC Surveillance, 2007 Report <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2007report/default.htm>; ESRD (US Renal Data System, Table D.11); Transplants data (Organ procurement and Transplantation Network, 2009).

Immunosuppression is very rare in children, accounting for less than 0.18% of the population of children, thus less than 0.044% in the overall population (MIDAS High Risk Segmentation Group, D. Wagener, private communication, 2009). At the same time, immunocompromised children represent 6.4% of all H1N1-related hospitalizations in ref. [5] and 5.3% of all H1N1-related hospitalizations in ref. [6]. They also represent 3/118 (2.5%) of all deaths in ref. [6]. Thus, we estimate the relative risk for hospitalization to be between 120 and 145, and the relative risk for death to be 57. Another way to look at those numbers is to note that there are around 130 000 immunocompromised children in the US. There were 17 838 laboratory-confirmed influenza

associated hospitalizations in the US between 30 August and 31 October.<sup>26</sup> Assuming a total of 30 000 H1N1pdm-associated influenza hospitalizations in the US and the percentages of immunocompromised children among the hospitalized from refs [5] and [6], we get that approximately one in 75 immunocompromised children is hospitalized with H1N1 in the US. Using the CDC estimate of over 200,000 H1N1 related hospitalizations ([http://www.cdc.gov/h1n1flu/estimates\\_2009\\_h1n1.htm](http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm)), one concludes that approximately one in 11 immunocompromised children is hospitalized with H1N1 in the US.

Immunocompromised adults represent 1.9% of the US population (MIDAS High Risk Segmentation Group, D. Wagener, private communication, 2009). They represent 10.2% of all hospitalizations and 30.5% of all fatalities in ref. [6]. Immunocompromised adults represent 10.7% of hospitalizations in ref. [5]. Immunocompromised individuals represent 17.9% of all deaths or ICU admissions in ref. [5]; presumably most of them are adults. Thus, we estimate the relative risk for hospitalization for immunocompromised adults to be between 5.4 and 5.6, and their relative risk for death between 9.4 and 16.1.

We have no data on prevalence of individuals with neurological (neurocognitive and neuromuscular) disorders. At the same time, children with neurological disorders represent 9.9% of all hospitalizations in ref. [5]. Children with neuromuscular disorders represent 4.5% of all hospitalizations, and 3.4% of all deaths in ref. [6]. Moreover, children with neurological disorders have an increased relative risk for respiratory failure given hospitalization.<sup>27</sup> Adults with neuromuscular disorders represent 11.9% of all deaths in ref. [6]. People with neurocognitive or neuromuscular disorders each represent 13.4% of deaths or ICU admissions in ref. [5].

## Implications for decision-making

On current evidence, we believe that there are groups in the population for whom the relative risk  $R$  of death or of other severe outcomes, such as hospitalization, substantially exceeds 1. These groups include pregnant women,<sup>5,6,8,28</sup> children and adults with neurological conditions,<sup>5,6,29</sup> persons with immunosuppression and certain chronic diseases,<sup>5,6,13</sup> morbidly obese individuals (BMI  $\geq$  40),<sup>5,6</sup> and some of the other high-risk groups.<sup>5,6,13</sup> We believe it is also plausible to expect that pre-dispensed antivirals are more likely to be life-saving (or to prevent hospitalizations or other severe outcomes) than those that are not pre-dispensed ( $B > 1$ ), because wastage is relatively unlikely given the short time frame between when pre-dispensing and usage could occur, and because early treatment is likely to have benefits in preventing progression to more severe condition.<sup>4-6</sup>

At the same time, given the generally mild nature of H1N1 infections, a number of developed countries with

large antiviral stockpiles will likely have antiviral supply greatly exceeding population demand. The same conclusions appear to be valid for the US, which has a relatively small stockpile compared with some countries, but also a restrictive antiviral usage policy for low-risk individuals.<sup>13</sup> Under these conditions, pre-dispensing a quantity of antivirals not exceeding the difference between supply and demand is always beneficial.

Even if one is uncertain about the population demand for antivirals during the course of the epidemic, one can include certain categories of individuals for pre-dispensing given a measure of belief about the relative benefit  $B$ . We concentrate on the situation in the US; in particular, we assume that the available antiviral stockpile can cover 20% of the population.

If one thinks that  $B$  is as low as 1:3 (Figure 2), one can still, regardless of the demand levels, include certain groups like immunocompromised children. One should probably also include immunocompromised adults due to a high relative risk for fatality (16:1) observed in a large study.<sup>6</sup> People with neurological disorders should probably also be included due to high rates of hospitalizations, fatalities and ICU admissions in ref. [5,6]. If one thinks that  $B$  is at least 2 (Figure 1), one should include additional groups in the pre-dispensing category, such as pregnant women, morbidly obese adults, and possibly some additional groups for which we have no prevalence data.

We again want to emphasize that the above considerations apply given uncertainty whether supply surpasses demand. If one believes that supply does exceed demand (which appears to be relevant for several countries, including US), pre-dispensing a quantity of antivirals not exceeding the difference between supply and demand is beneficial.

## Discussion

In the setting of an autumn wave of pandemic influenza in developed countries of the Northern Hemisphere that already possess significant antiviral stockpiles, pre-dispensing of a portion of these stockpiles to individuals at high risk of severe outcome of infection may be a means to prevent death and other severe outcomes by improving the efficiency of use of a limited stockpile. In this study, we consider the net benefits of a pre-dispensing policy, where the measure of the benefit is the number of severe outcomes (such as deaths or hospitalizations) prevented by antivirals in the whole population.

Determination of whether such a policy is beneficial depends on the assumptions one makes. One general set of assumptions which appears relevant to a number of developed countries is as follows: antiviral supply exceeds demand, and pre-dispensing antivirals is beneficial to the category of individuals to whom antivirals were pre-dis-

pensed. Under those assumptions, pre-dispensing a quantity of antivirals not exceeding the difference between supply and demand is always beneficial.

If one is uncertain about the overall population demand for antivirals, pre-dispensing to certain high-risk groups may still be justified under the assumptions of our Main result and Appendix A; our conclusions based on available H1N1pdm data are summarized in the Implications for decision-making section. One additional assumption that should be highlighted in this context is that, as used in the absence of pre-dispensing, antivirals are equally likely to save the life of a treated member of the high-risk group as a treated member of the general population given that both of them would die without treatment. If treatment is less effective among members of high-risk groups who would die without treatment, then the benefits of pre-dispensing are reduced; if it is more effective, they may be increased.

A key source of uncertainty in our estimates is the relative benefit  $B$  for preventing a severe outcome by a pre-dispensed course of antivirals versus one obtained by prescription by an individual who would otherwise have a severe outcome. This benefit should be assessed against a strategy of identifying high risk persons, educating them to contact their provider for symptoms, and encouraging providers to provide rapid empiric therapy including via telephone. While there is no data to assess  $B$  directly, we have estimated the reduction in probability of a severe outcome by early antiviral treatment based on data in refs [5,6]. Ref. [4] gives additional evidence that early antiviral administration is beneficial in preventing severe outcomes. Similarly, there is evidence that a policy allowing for broader versus more limited use of antivirals in symptomatic individuals is beneficial for reducing mortality;<sup>30</sup> this benefit was observed both on a population level (Chile versus Argentina), and in a category of pregnant women.

We have avoided cost-effectiveness considerations in our analysis as there are several unknowns involved, including the cost of pre-dispensed antivirals (government versus private rates). We note however that for some groups with the highest risk for severe outcomes, such as immunocompromised children, pre-dispensing may be, among other things, cost-effective.

We recommend that under a pre-dispensing policy, patients should be advised to consult their physician promptly even after initiating treatment with antivirals. Such a consultation is important both for preventing a misdiagnosis for another disease and for proper monitoring of an ailment in a high risk individual.

Finally, we would recommend that the total proportion of the stockpile pre-dispensed be limited (perhaps to 20% of the stockpile or less). There are several reasons for that. One of them is that the conditions defined in this study



guarantee that pre-dispensing is beneficial in terms of decreasing the mortality provided certain assumptions about temporal patterns of antiviral distribution hold. The most flexible assumption we require is assumption (b) in Appendix A. This assumption may be violated under the following scenario: antiviral supply nears depletion and only the most severe cases get antivirals. To deal with such a scenario, we recommend to set aside a certain quantity of antivirals for safekeeping.

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## Appendix

### Appendix A. Justification of the main result

In this appendix, we derive the main result by calculating or finding a bound on the number of lives saved by antiviral treatment in the high-risk group (a proportion  $q$ ) and in what we term the ‘general population,’ which is the total population without the high-risk individuals, a proportion  $1 - q$ .

Let us first list the assumptions we are making about the temporal patterns of antiviral demand used in our main result:

- (a) For condition (ii) to imply the benefit of pre-dispensing, we need that among the people who receive antivirals, the proportion of them who would die otherwise does not change in time.
- (b) For conditions (iii) and (iv) to imply the benefit of pre-dispensing, we need that among the people who receive antivirals, the proportion of them who would die otherwise does not increase in time.
- (c) For condition (i), no additional assumptions are needed. Condition (b) is more flexible than (a) and can be interpreted as follows: consider persons infected during the epidemic. As time progresses, the proportion of them who will require antivirals may increase due to panic, etc. – suppose the increase is by a factor of  $X$ . The people who would die without antivirals are the severe cases and the proportion of them who receives antivirals (given availability) is probably large – thus even if it increases it time, we assume that the increase is by a factor of at most  $X$ .

There are four conditions to consider:

Condition (i): Supply exceeds demand and  $B > 1$

In this case, all persons in the general population who demand antivirals would get them under the no pre-dispensing scenario – thus pre-dispensing would result in no loss of lives in that category compared to no pre-dispensing. As  $B > 1$ , persons to whom antivirals were pre-dispensed are more likely to survive under pre-dispensing than through acquiring antivirals during the epidemic. Moreover, not all among them who need antivirals would necessarily acquire them during the epidemic – thus pre-dispensing is clearly beneficial.

Condition (ii): In the absence of pre-dispensing, demand exceeds supply,  $D > T$

To fix notation, let  $D' \geq D$  be the demand for antivirals in the total population.

Among the  $q$  individuals in the high-risk group,  $qRp_d$  of them would die without antivirals. Of those,  $qRp_d p_s B$  will be saved by pre-dispensed antivirals. Under no pre-dispensing, not all of those  $qRp_d$  people may demand antivirals; among the latter, a fraction  $\frac{T}{D'} \leq \frac{T}{D}$  of them would get antivirals, so at most  $qRp_d p_s \frac{T}{D'}$  lives would be saved (Table 2).

Turning now to the general population, if all the demand was met, the total number of lives saved without pre-dispensing would be  $L$ . However, given scarcity, only  $\frac{T}{D'} L$  lives are saved (Table 2), because the remaining individuals do not receive antivirals. If antivirals are pre-dispensed, the remaining demand is  $D$  and the supply is  $T - q$ . Thus, a fraction  $\frac{T-q}{D}$  of the demand in the general population is met, and the number of lives saved is thus  $\frac{T-q}{D} L$  (Table 2).

Using these figures (summarized in Table 2), there is a net gain in lives saved if the total number saved under pre-dispensing exceeds that saved without pre-dispensing, that is, if

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## Competing interests

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**Table 2.** Numbers of lives saved in the general population and high-risk group under no pre-dispensing versus pre-dispensing, case 2 (demand exceeds supply)

	No pre-dispensing	Pre-dispensing
General population	$\frac{T}{D'}L$	$\frac{T-q}{D}L$
High-risk group	at most $\frac{T}{D'}qRp_d p_s$	$qRBp_d p_s$

$$L \frac{T-q}{D} + qRp_d p_s B \geq L \frac{T}{D'} + qRp_d p_s \frac{T}{D'}. \quad (A1)$$

Rearranging terms, using the facts that  $L \leq p_s p_D$  and  $D' \geq D$ , and dividing by  $q$ , a sufficient condition is then

$$\frac{1}{D} \leq R(B - T/D) \quad (A2)$$

which is condition (ii).

Condition (iii)  $T - q \leq D \leq T$

The argument is similar to the previous case.

Among the high-risk group, without pre-dispensing nearly all or all demand will be satisfied (there may be some competition if  $D \leq T \leq D'$ ), so at most  $qRp_d p_s$  lives will be saved. With pre-dispensing, the situation will be as above.

Among the general population, without pre-dispensing, at most  $L$  lives will be saved. With pre-dispensing, a fraction  $\frac{T-q}{D}$  of the demand is met, and this fraction corresponds to the earlier demand, when antivirals are still available. Condition (b) implies that at least  $\frac{T-q}{D}L$  lives are saved in the general population under pre-dispensing. All this is summarized in Table 3. Repeating the comparison of equation (A1) for the entries in Table 3, we obtain condition (iii).

Condition (iv) no assumptions on demand.

If  $D \leq T$ , the result follows from Conditions (i) and (iii), because they use the same assumption (b) as condition (iv). If  $D > T$ ,  $T - q$  courses were obtained by the general population under the pre-dispensing scenario, and at most  $T$  courses under the no pre-dispensing scenario. The rest of the proof is similar to the one in condition (iii), replacing  $L$  by the number persons who could be saved by antivirals given to the first  $T$  individuals in the general population upon demand.

Remark: In the arguments above, we assumed that under the pre-dispensing scenario, the pre-dispensed cohort will not require additional antivirals. This assumption can be relaxed; we need only assume that the additional demand for the pre-dispensed cohort under the pre-dispensing scenario will not exceed its demand under the no pre-dispensing scenario. In this case, very similar results can be established; in particular, condition (iv) remains true.

## Appendix B. Formal description of the parameters $p_s$ , $R$ and $B$ .

Suppose that for every individual who is either a member of the high-risk group  $G = h$  or the whole (total) population  $G = w$ , we can define an outcome  $O(t)$  that depends on the (possibly counterfactual) treatment  $t$  received, where either  $O = d$  (died) or  $O = s$  (survived) and either  $t = U$  (untreated), or  $t = S$  (treated from the stockpile), or  $t = P$  (treated from a pre-dispensed course, and that course has not been previously wasted). Then

$$p_D = \Pr[O(U) = d | G = w]$$

$$p_s = \Pr[O(S) = s | O(U) = d] = \Pr[O(S) = s | O(U) = d, G = w] = \Pr[O(S) = s | O(U) = d, G = h]$$

$$R = \frac{\Pr[O(U) = d | G = h]}{\Pr[O(U) = d | G = w]}$$

$$B = \frac{\Pr[O(P) = s | O(U) = d, G = h]}{\Pr[O(S) = s | O(U) = d, G = h]}$$

We are interested in the probability that treatment (non-pre-dispensed) will save a life in the total population, which is

**Table 3.** Numbers of lives saved in the general population and high-risk group under no pre-dispensing versus pre-dispensing, case 3 (supply exceeds demand before pre-dispensing, but not after)

	No pre-dispensing	Pre-dispensing
General population	at most $L$	at least $\frac{T-q}{D}L$
High-risk group	at most $qRp_d p_s$	$qRBp_d p_s$

$$p_d p_s = \Pr[O(U) = d, O(S) = s | G = w];$$

in the probability that treatment without pre-dispensing will save a life in the high-risk group, which is

$$\begin{aligned} p_D p_s R &= \Pr[O(U) = d | G = h] \frac{\Pr[O(U) = d | G = h]}{\Pr[O(U) = d | G = w]} \Pr[O(S) \\ &= s | O(U) = d, G = h] \\ &= \Pr[O(S) = s, O(U) = d | G = h] \end{aligned}$$

and in the probability that a high-risk person who received a pre-dispensed course would thereby have his life saved, which is

$$p_D p_s R B = \Pr[O(P) = s, O(U) = d | G = h]$$

### Appendix C. When does the benefit increase with the number of courses pre-dispensed?

While pre-dispensing to high-risk groups is beneficial compared with no pre-dispensing, if condition (iv) holds, it is not true in general that the benefit of pre-dispensing increases with the quantity of antivirals pre-dispensed. Consider for example one high-risk group whose size equals (or surpasses) the antiviral supply. As we keep on pre-dispensing, coverage level for the rest of the population goes to 0 while the relative risk of dying in the high-risk group stays uniformly bounded. Thus, at some point equation (iv) will be violated (with the new coverage level and the relative risk), and in fact it is not advisable to pre-dispense the whole supply to the group under no a-priori assumptions on the demand  $D$ . However, we have the following simple criterion:

**BENEFIT INCREASES WITH THE AMOUNT PRE-DISPENSED:**

Suppose the relative risk of dying  $R \geq 1$ , and assumption (b) in Appendix A holds. The benefit of pre-dispensing is guaranteed to increase with quantity of antivirals pre-dispensed as long as the total quantity  $q$  of antivirals pre-dispensed obeys

$$\frac{T-q}{1-q} \geq \frac{1}{R(B-1)} \quad (C1)$$

To show this, let the quantity  $q$  of antivirals pre-dispensed obey the inequality (C1). To show that the benefit of pre-dispensing was increasing, take any intermediate quantity  $q_I \leq q$ . We need to show that equation (iv) was still true after pre-dispensing  $q_I$  courses of antivirals. Note that after this pre-dispensing, the coverage level and the relative risks have changed. The coverage level became

$$T_I = \frac{T-q_I}{1-q_I} \geq \frac{T-q}{1-q} \geq \frac{1}{R(B-1)} \quad (C2)$$

Also, as a result of pre-dispensing, we have removed some individuals with the risk of dying higher than the one for the general population. Thus, the probability of dying for an average individual left after pre-dispensing is lower than the one before pre-dispensing; hence the relative risks of the high-risk groups have only increased. As equation (C2) for the new coverage level holds with original relative risks, condition (iv) in our Main result holds with the new coverage levels and relative risks (after pre-dispensing  $q_I$  courses of antivirals). This implies that pre-dispensing  $q - q_I$  courses after pre-dispensing the initial  $q_I$  courses would be beneficial.

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