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Estimating the United States Demand for Influenza Antivirals and the Effect on Severe Influenza Disease During a Potential Pandemic

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Following the detection of a novel influenza strain A(H7N9), we modeled the use of antiviral treatment in the United States to mitigate severe disease across a range of hypothetical pandemic scenarios. Our outcomes were total demand for antiviral (neuraminidase inhibitor) treatment and the number of hospitalizations and deaths averted. The model included estimates of attack rate, healthcare-seeking behavior, prescription rates, adherence, disease severity, and the potential effect of antivirals on the risks of hospitalization and death. Based on these inputs, the total antiviral regimens estimated to be available in the United States (as of April 2013) were sufficient to meet treatment needs for the scenarios considered. However, distribution logistics were not examined and should be addressed in future work. Treatment was estimated to avert many severe outcomes (5200–248 000 deaths; 4800–504 000 hospitalizations); however, large numbers remained (25 000–425 000 deaths; 580 000–3 700 000 hospitalizations), suggesting that the impact of combinations of interventions should be examined.

Keywords. influenza; antivirals; neuraminidase inhibitors; hospitalization; death.

An outbreak of human infections with a new avian influenza A(H7N9) virus [H7N9], was first reported in eastern China by the World Health Organization on 1 April 2013 [1]. This novel influenza virus was fatal in approximately one-third of the 135 confirmed cases detected in the 4 months following its initial identification [2], and limited human-to-human H7N9 virus transmission could not be excluded in some case clusters in China [3, 4]. As part of ongoing pandemic preparedness activities, the Centers for Disease Control and Prevention rapidly conducted a comprehensive review of the potential impact of influenza countermeasures after the initial cases were reported, including the use of antiviral drugs to treat and control a future influenza pandemic.

Antiviral treatment has received considerable attention in pandemic planning and will likely be an important part of any response to a widespread influenza outbreak [5–8]. Currently neuraminidase inhibitors (NAIs) are the only licensed agents with activity against the majority of circulating influenza viruses [9]. Pandemic planning has largely focused on these agents, particularly oseltamivir, which is licensed for most ages and is easily administered [9]. While large-scale epidemiologic studies of NAI effectiveness against as yet unknown influenza virus strains are not feasible, the early use of NAIs has been shown in randomized controlled trials to decrease duration of illness in otherwise healthy persons with acute uncomplicated influenza caused by circulating seasonal influenza viruses [10–18]. In addition, observational studies among hospitalized patients with influenza suggest that early oseltamivir treatment reduces both the severity of disease and

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mortality [19, 20]. Given the anticipated demand for NAIs during a potential influenza pandemic, it is important to regularly assess estimates of the drug supply, including stockpiles, and re-evaluate the projected effect of antiviral treatment on pandemic morbidity and mortality.

In this article, we present estimates of the potential US demand for NAIs modeled across several hypothetical influenza pandemic scenarios, and include estimated ranges for their possible effect on averting hospitalizations and deaths. Notably, although this work was conducted in response to the discovery of the H7N9 virus, the pathogen characteristics used in our model were chosen to reflect a range of severe and transmissible influenza strains and were not directly based on H7N9 because it is not possible to predict the transmissibility and severity of illness if this virus adapts and causes widespread human illness [21]. Also, to inform decisions during a public health response, we used a simplified model that could be rapidly developed and analyzed.

METHODS

Pandemic Scenarios

Two clinical attack rates (20% and 30%) and 2 case severity levels (high and low risks of hospitalization [1.05%, 4%] and mortality [0.084%, 0.5%] per clinical case) were used to define the pandemic scenarios analyzed and are described in-depth in Meltzer et al [22] and in Table 1. These parameters were chosen to represent hypothetical pandemics of moderate to high transmissibility and case-severity and are based on a recently

Table 1. Input Values Used to Estimate the Demand for Neuraminidase Inhibitors and Effect of Treatment on Hospitalization and Death for Hypothetical Influenza Pandemic Scenarios

Parameter	Value	Reference
Number of influenza infections in each age-group (0–9, 10–19, 20–59, ≥60 y)	20% AR (millions)[a]: 17.8, 25.4, 70.4, 13.8 30% AR (millions)[a]: 26.1, 33.8, 105.4, 22.7	[22]
% of influenza infections that are symptomatic	50%	[23, 24]
% symptomatic who seek care in each age-group (0–9, 10–19, 20–59, ≥60 y)	Low severity: 60%, 60%, 50%, 60% High severity: 70%, 60%, 50%, 70%	Assumed in line with [25, 26]
% outpatients diagnosed as having influenza & prescribed NAIs[b]	15%, 70%	Assumed in line with [25, 26]
% inpatients diagnosed as having influenza & prescribed NAIs[b]	50%, 100%	Assumed
Prescription of NAIs for noninfluenza ILI as a % of those receiving NAIs for influenza	40%	Assumed
Number receiving chemoprophylaxis[c]	10% of the total number of antiviral regimens dispensed	Assumed in line with [27]
Proportion nonadherent to course (or saving for personal stockpile)	20%	Assumed in line with [27]
Hospitalization risk	Low severity: 1.05% High severity: 4%	[22]
Mortality risk among hospitalized cases[d]	Low severity: 6.24% High severity: 9.76%	Based on [22]
Mortality risk among outpatients[d]	Low severity: 0.02%	Based on [22]
	High severity: 0.11%	
Antiviral effectiveness (AVE) on hospitalization[e]	Low effect: 11% High effect: 42%	[28]
Antiviral effectiveness (AVE) on death	Low effect: 23% High effect: 66%	[29]
Average number regimens used per outpatient receiving treatment	1	Assumed
Average number regimens used per inpatient receiving treatment	2	Assumed
Incubation period	1.4 d	[30]

Abbreviations: AR, attack rate; ILI, influenza-like illness; NAI, neuraminidase inhibitors.

[a] The numbers of infections were obtained from the output of a transmission-dynamic model described in Meltzer et al [22]. The numbers are for total infections and must be multiplied by the proportion symptomatic to get the number clinically ill in each age-group.

[b] The "low diagnosis and treatment scenario" uses the lower estimates while the "high diagnosis and treatment scenario" uses the upper estimates.

[c] The total number of antiviral courses dispensed for patients with influenza and noninfluenza illness was multiplied by 10/9 so that 10% of the final number of regimens distributed would be disseminated for chemoprophylaxis in line with previous work [27]. A multiplier of 10/9 ensures that 90% (ie, 9/10) of the final number of regimens distributed corresponds to the number of regimens used for influenza and noninfluenza illness, resulting in 10% used for chemoprophylaxis.

[d] The case fatality rate was dichotomized into risks of death for outpatients and hospitalized cases so that the effects of treatment among these 2 groups could be better assessed. See the Supplementary Material for details of calculations.

[e] The antiviral effectiveness against hospitalization was assumed to be the same as the effect against lower respiratory tract complications requiring antibiotic treatment [28] since pneumonia and other lower respiratory tract infections cause substantial hospitalizations and are a leading cause of death [31–33].

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developed scale of the public health impact of influenza pandemics [21]. We describe the model in detail below.

We used 2 treatment scenarios, one with a low treatment level (proportion of influenza cases who are diagnosed and prescribed NAIs) among both outpatient and inpatient cases, and another with a high treatment level in these groups. These scenarios can provide lower and upper estimates of the potential range of demand for NAIs and should not be interpreted as being the most likely scenarios. We also used 2 estimates of the effect of NAIs against hospitalization and death. The treatment levels and effectiveness estimates are described further in the "Model Details" section and in Table 1. These epidemic and treatment characteristics produced the 16 scenarios analyzed (2 attack rates × 2 severity levels × 2 treatment rates × 2 antiviral effectiveness levels). An analysis using a scenario of no antiviral use was included to show the absolute effect of antiviral treatment.

Model Overview

We developed a spreadsheet model to estimate the demand for NAIs and the resulting number of hospitalizations and deaths that could be averted with the use of NAI treatment. We did not distinguish between types of NAIs used in the model (eg, oseltamivir or zanamivir) and assumed that pediatric populations could be treated directly with pediatric drug formulations or that pediatric suspension could be made from adult capsules [34]. We assumed that the impact of seasonal influenza on demand for antiviral treatment and severe disease would be negligible during the severe pandemic scenarios considered.

We calculated the potential demand for NAIs across age groups (0–9, 10–19, 20–59, ≥60 years) for a range of pandemic scenarios using methods based on previous work [27]. To do so, we used assumptions regarding the clinical attack rate [22], the proportion of the population that would likely require treatment, seek medical care and be prescribed NAIs [25, 26], the number of regimens that may be dispensed for chemoprophylaxis or saved for a personal stockpile, and the proportion of those with noninfluenza illness who may also receive NAI treatment [27]. We modeled the provision of antiviral treatment using the 16 scenarios described above.

To calculate the potential impact of NAI treatment on severe influenza-associated complications, we combined estimates of the number of regimens correctly dispensed to influenza cases with estimates of adherence and the possible effect of NAIs on the risks of hospitalization and death. Individuals could experience both hospitalization and death, or either outcome, or neither.

All analyses were conducted using Microsoft Excel, version 2010. Antiviral demand, hospitalizations, and deaths were calculated for each age group and each day of the pandemic and then summed over ages and days for presentation purposes. All parameter values used are listed in Table 1. Further details, along with full formulas used for calculations, are provided in the Supplementary Material.

Antiviral Supply

Antiviral "supply" was defined by the quantity of NAIs estimated to be available in the United States as of April 2013. The sources of drug supply included NAIs available in the federal (ie, Centers for Disease Control and Prevention Strategic National Stockpile [CDC SNS]) and state stockpiles; and quantity of product estimated to be in commercial inventories or which could be manufactured for the United States within 12 weeks (shortest time from beginning of epidemic to peak across scenarios). As of April 2013, the total number of NAI regimens used in this model, and estimated to be available in the United States in the event of a pandemic, was 104 million.

Model Details

Antiviral Demand

A treatment regimen of NAI consisted of enough medication for 5 days of twice-daily dosing [9]. We assumed that outpatients receiving treatment in the community would receive 1 regimen, whereas hospitalized cases would receive an average of 2 regimens (10 days of treatment). Following previously published assumptions regarding NAI regimens for outpatients, we assumed that some regimens would be dispensed to individuals with influenza-like illness (ILI) due to other pathogens (40% of the number of regimens dispensed to influenza outpatients), 20% of patients would not adhere (and which includes those who save a course for a personal stockpile), and 10% of all regimens dispensed would be provided to patients for use as chemoprophylaxis, [see reference [27] and Table 1]. All inpatients were assumed to adhere to treatment. Similar to the assumption for outpatients, we assumed that regimens would also be dispensed to inpatients with respiratory symptoms with a noninfluenza etiology (40% of the number of regimens dispensed to influenza inpatients). We assumed that a greater proportion of influenza inpatients were treated than influenza outpatients, which assumes that clinicians factor illness severity into treatment decisions and do not rely entirely on the results of rapid testing which may have low sensitivity [35].

The estimated demand for antiviral regimens was calculated by the following equations:

$$\begin{aligned}\text{Antiviral demand} = {} & \text{number regimens used by outpatients} \\ & + \text{number regimens used by inpatients} \\ & + \text{number of regimens used for chemoprophylaxis}\end{aligned}$$

$$\begin{aligned}\text{Number regimens used by outpatients} = {} & \text{number clinically ill} \times \text{proportion seeking outpatient care} \times \text{proportion outpatients diagnosed \& prescribed NAIs} \times \text{Avg. number regimens per outpatient} \times (1 + \text{multiplier for non-influenza ILI patients})\end{aligned}$$

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Number regimens used by inpatients = number hospitalized influenza cases × proportion hospitalized cases diagnosed & prescribed NAIs × Avg. regimens per inpatient × (1 + multiplier for non-influenza ILI patients)

Number of regimens used for chemoprophylaxis = total of regimens given for outpatients × chemoprophylaxis multiplier

Parameter values are listed in Table 1. The amounts of NAIs potentially needed for each scenario were then compared to the estimated United States antiviral supply (as of April 2013). We plotted the cumulative antiviral demand over time for each scenario assuming that the incubation period would be approximately 1.4 days based on data for seasonal influenza [30]. Because of limited data regarding antiviral effectiveness related to day of therapy initiation, we assumed that all patients would receive treatment on the second day of clinical symptoms. This assumes that patients would start treatment slightly quicker than seen with seasonal influenza infection due to concern over the severity of infection, which maximizes the benefits of treatment [36–38]. To explore variations in treatment start further, we conducted a sensitivity analysis (see later in "Methods" section).

Antiviral Impact on Hospitalizations

The estimated impact of NAI treatment on hospitalizations was calculated by the following equation:

$$\begin{aligned}\text{Hospitalizations averted} = {} & \text{number clinically ill} \\ & \times \text{proportion seeking outpatient care} \\ & \times \text{proportion outpatients diagnosed \& prescribed NAIs} \\ & \times \text{adherence} \\ & \times \text{risk of hospitalization} \\ & \times \text{NAI effect against hospitalization}\end{aligned}$$

Definitions of the equation parameters are as follows: 'Adherence' = proportion who sufficiently adhere to the treatment regimen for it to be effective; 'Risk of hospitalization' = per-capita risk of hospitalization among symptomatic influenza cases; and 'NAI effect against death' = reduction in the risk of death due to influenza as a result of NAI treatment.

For the purposes of this analysis, the antiviral effect against hospitalization was assumed to be the same as the NAI treatment effect against lower respiratory tract complications from influenza requiring antibiotic treatment [28]. Pneumonia and other lower respiratory tract infections cause substantial hospitalizations and are a leading cause of death [31–33]. A range of treatment effects was obtained by using the upper and lower 95% confidence interval (CI) estimates for this outcome (Table 1).

Antiviral Impact on Deaths

In this analysis, NAI treatment was assumed to reduce the risk of death by 3 possible mechanisms: (1) deaths directly averted among treated hospitalized patients, (2) deaths among non-hospitalized cases directly averted by treatment of outpatients, and (3) deaths avoided by outpatient treatment averting severe disease which would have required hospitalization and could have progressed to death. The latter 2 mechanisms were considered separately because we used different case-fatality rates for outpatients and inpatients.

Estimates of the direct effect of NAI treatment against death were based on an observational study of oseltamivir treatment among patients with influenza A(H5N1) [29]. This data source was used because it estimated the effect of oseltamivir against death for a novel, severe avian influenza, which is in line with the goals of our analysis, and because it is the largest study of this type to our knowledge to have been conducted. We obtained a range of treatment effects by using the upper and lower 95% CI estimates from Adisasmito et al [29]. We assumed the same effect of NAI treatment on all treated persons and across age groups. We also assumed the same antiviral effect for treated inpatients and outpatients.

The estimated impact of NAI treatment on reducing deaths was calculated by the following equation:

$$\begin{aligned}\text{Deaths averted} = {} & \text{number deaths averted due to inpatient Rx} \\ & + \text{number deaths averted due to outpatient Rx}\end{aligned}$$

Number deaths averted due to inpatient Rx = number hospitalized cases × proportion hospitalized cases diagnosed & prescribed NAIs × inpatient mortality risk × NAI effect against death

Number deaths averted due to outpatient Rx = number clinically ill × proportion seeking outpatient care × proportion outpatients diagnosed & prescribed NAIs × adherence × (outpatient mortality risk × NAI effect against death + risk of hospitalization × NAI effect against hospitalization × inpatient mortality risk)

Definitions of the equation parameters are as follows (duplicate parameters are defined above): Rx = NAI treatment; 'NAI effect against death' = reduction in the risk of death due to influenza as a result of NAI treatment (assumed to be the same for inpatients and outpatients).

Sensitivity Analyses

To determine which variables had the greatest influence on the main outcomes (ie, antiviral usage, hospitalizations averted, deaths averted), we varied each of the 4 main variables (treatment rate, attack rate, severity, average antiviral effectiveness) one at a time over their full uncertainty range and recorded their impact. Notably, the time between symptom onset and treatment initiation is likely one of the most important variables influencing antiviral effectiveness and, during a severe

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pandemic, it could be longer or shorter than previously seen depending on prescribing capacity and logistical challenges in meeting demand for treatment. We explored this issue by varying the average antiviral effectiveness over a wide range [28, 29] with low effectiveness reflecting delayed treatment initiation and high effectiveness reflecting rapid treatment. Further data on the effect of antiviral treatment with time since initiation would be useful for informing future work on pandemic preparedness.

RESULTS

Antiviral Demand

There were an estimated 64 million symptomatic cases in the 20% clinical attack rate scenario, whereas there were approximately 94 million symptomatic cases in the 30% clinical attack rate scenario. The expected number of NAI regimens needed to meet treatment demands ranged from a low of 9.0 million for the 20% attack rate-low severity-low treatment level scenario, up to 68.5 million for the 30% attack rate-high severity-high treatment level scenario (Table 2). We conducted a sensitivity analysis to determine which variables had the largest impact on the number of antiviral courses required for treatment (Figure 1), and which are listed here in order of importance: diagnosis and treatment rates, attack rate, severity, and antiviral effectiveness. Note that an increase in antiviral effectiveness resulted in slightly fewer regimens required since an increase in effectiveness meant fewer hospitalizations occurred and consequently fewer regimens were required to treat inpatients.

In our model, the total antiviral drug supply was not fully depleted in any scenario (Figures 2 and 3). However, the demand for antiviral treatment slightly exceeded the number of NAI regimens in the federal CDC SNS for the 30% attack rate-high severity-high treatment-low antiviral effectiveness scenario (estimated antiviral demand = 68.5 million regimens, approximate SNS size = 68 million regimens, Figure 2).

Burden of Disease and Impact of Antiviral Treatment

Although the outputs from the model demonstrated that a large number of hospitalizations and deaths could be averted with timely antiviral use, additional hospitalizations and deaths remained despite treatment, and varied greatly by pandemic and treatment scenarios (0.58–3.7 million hospitalizations and 25 000–425 000 deaths, Table 2). These additional hospitalizations and deaths were more influenced by the magnitudes of the risks of hospitalization and death rather than by the attack rate since the former were varied over a wider range. The results of a sensitivity analysis (Figure 1) show that the numbers of hospitalizations averted were most influenced by the following factors (in order of importance): diagnosis and treatment rates, antiviral effectiveness, severity, and attack rate. However, the number of deaths averted was most influenced by (in order of importance): severity, antiviral effectiveness, diagnosis and treatment rates, and attack rate. The ordering and impact of the variables is different for the number of deaths averted compared to the number of hospitalizations averted due to differences in the change in hospitalization risk and risk of death across scenarios, different ranges for treatment effectiveness against each endpoint, and because the change in treatment levels was greater for outpatients (where hospitalizations were averted) than for inpatients (where the majority of deaths occurred).

The absolute numbers of hospitalizations and deaths averted differed greatly depending on the scenario (5200–248 000 deaths averted and 4800–504 000 hospitalizations averted), but the proportions of outcomes averted for both were more consistent (Table 2). For example, when there was a low proportion of influenza cases diagnosed and treated and a low antiviral effect, less than 1% of hospitalizations and approximately 10% of deaths were averted regardless of the attack rate and risks of hospitalizations and death. These were the lowest proportions of severe outcomes averted across all scenarios. Alternatively, the highest proportions of severe outcomes averted occurred when there was a high proportion of influenza cases diagnosed and treated and a high antiviral effect (13% of hospitalizations averted and 53% of deaths averted).

DISCUSSION

We developed a simple model that could estimate the potential demand and impact of NAI treatment across a range of hypothetical influenza pandemics, and that could be rapidly implemented to inform decisions during a public health response. For the scenarios considered, the total NAI regimens met treatment needs, even when a large proportion of influenza cases were diagnosed and treated. NAI treatment averted many hospitalizations and deaths in all scenarios (5200–248 000 deaths averted; 4800–504 000 hospitalizations averted). However, large numbers of severe outcomes still occurred (25 000–425 000 deaths and 580 000–3.7 million hospitalizations), emphasizing the need for use of multiple strategies, including vaccination, new treatment approaches, and social distancing during a severe pandemic. The most influential variable that impacted total NAI demand and the number of hospitalizations averted was the diagnosis and treatment rate, while the severity of a pandemic had the greatest impact on the number of deaths averted.

Other research has suggested that the demand for antiviral treatment may be greater than estimated here [39]. A model of potential antiviral needs for Canada indicated that more than 40% of the population could seek treatment in a severe pandemic whereas our estimates indicated that 3%–20% of

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Table 2. Neuraminidase Inhibitor[a] Demand and Impact of Treatment for Hypothetical Influenza Pandemic Scenarios

Scenario Description		No. Regimens Used	Total Hospitalizations[b]	Hospitalizations Averted (%)[b]	Total Deaths[b]	Deaths Averted (%)[b]
Estimated NAI supply:						
Federal CDC Strategic National Stockpile: 68 million regimens[c]						
State stockpiles: 29.6 million regimens[c]						
Commercial sources: 6.8 million regimens[c]						
AR: 20%: Low severity[d,e]						
Low diagnosis & treatment[f]	No NAI use[g]	N/A	668 412	N/A	53 483	N/A
	Low AVE	9 021 832	663 606	4806 (0.7)	48 278	5205 (9.7)
	High AVE	9 002 867	650 059	18 353 (2.7)	38 819	14 664 (27.4)
High diagnosis & treatment[f]	No NAI use[g]	N/A	668 412	N/A	53 483	N/A
	Low AVE	41 289 820	644 962	23 450 (3.5)	42 235	11 248 (21.0)
	High AVE	41 104 757	578 868	89 544 (13.4)	25 262	28 221 (52.8)
AR: 20%: High severity[d,e]						
Low diagnosis & treatment[f]	No NAI use[g]	N/A	2 544 002	N/A	318 350	N/A
	Low AVE	11 628 770	2 525 705	18 297 (0.7)	287 366	30 984 (9.7)
	High AVE	11 556 533	2 474 106	69 896 (2.7)	231 065	87 285 (27.4)
High diagnosis & treatment[f]	No NAI use[g]	N/A	2 544 002	N/A	318 350	N/A
	Low AVE	46 357 172	2 454 731	89 271 (3.5)	251 396	66 954 (21.0)
	High AVE	45 652 292	2 202 988	341 014 (13.4)	150 373	167 977 (52.8)
AR: 30%: Low severity[d,e]						
Low diagnosis & treatment[f]	No NAI use[g]	N/A	986 559	N/A	78 939	N/A
	Low AVE	13 298 364	979 475	7 084 (0.7)	71 257	7682 (9.7)
	High AVE	13 270 413	959 510	27 049 (2.7)	57 298	21 641 (27.4)
High diagnosis & treatment[f]	No NAI use[g]	N/A	986 559	N/A	78 939	N/A
	Low AVE	60 981 710	951 924	34 635 (3.5)	62 336	16 603 (21.0)
	High AVE	60 708 379	854 306	132 253 (13.4)	37 285	41 655 (52.8)
AR: 30%: High severity[d,e]						
Low diagnosis & treatment[f]	No NAI use[g]	N/A	3 754 880	N/A	469 877	N/A
	Low AVE	17 146 177	3 727 913	26 966 (0.7)	424 150	45 727 (9.7)
	High AVE	17 039 714	3 651 868	103 012 (2.7)	341 059	128 818 (27.4)
High diagnosis & treatment[f]	No NAI use[g]	N/A	3 754 880	N/A	469 877	N/A
	Low AVE	68 460 807	3 623 030	131 850 (3.5)	371 044	98 833 (21.0)
	High AVE	67 419 725	3 251 215	503 665 (13.4)	221 942	247 935 (52.8)

Abbreviations: AR, attack rate; AVE, average antiviral effect; CDC, Centers for Disease Control and Prevention; N/A, not applicable; NAI, neuraminidase inhibitors.

[a] We assessed only the demand for NAI (oseltamivir and zanamivir) and their treatment impact since they are the only licensed agent with activity against all currently circulating influenza viruses [9] and compose the majority of the state and federal influenza antiviral stockpiles.

[b] Hospitalizations and deaths refer only to those caused by influenza and do not consider those from background causes (eg, underlying medical conditions such as cancer). The percentages of hospitalizations and deaths averted relative to the scenario of no antiviral use are given in parentheses.

[c] As of April, 2013, there were approximately 68 million NAI regimens in the CDC Strategic National Stockpile and an estimated 29.6 million regimens in State level stockpiles. Also, as of April, 2013, there were approximately 6.8 million regimens either in existing commercial inventories or which could be manufactured for the US within 12 weeks for a total number of regimens available in the US in the event of a pandemic of 104 million. These numbers are subject to change based on depletion of inventory (eg, product expiration, use), and changes in manufacturing capacity.

[d] AR refers to the clinical AR (ie, percent of the total US population that becomes symptomatically ill with influenza).

[e] 'Low severity' and 'high severity' refer to different scenarios regarding case fatality and hospitalization rates. Low severity: case hospitalization rate = 1.05%, fatality rate among hospitalized cases = 6.24%, fatality rate among outpatients = 0.02%.

High severity: case hospitalization rate = 4%, fatality rate among hospitalized cases = 9.76%, fatality rate among outpatients = 0.11% [21].

[f] See Table 1 for the values used for the 'low diagnosis and treatment scenario' and 'high diagnosis and treatment scenario'.

[g] The scenario of no antiviral use was included to represent a baseline scenario. It can also be used to represent what could happen if antiviral resistance to both stockpiled NAIs emerged early in a pandemic.

the entire US population may seek treatment. Estimates by Greer and Schanzer indicated that an average of 0.65–1.4 antiviral regimens per person could be required to meet treatment demands if 70% of all acute respiratory infections occurring during a pandemic presented for care and all seeking care were prescribed antiviral treatment since such symptoms are

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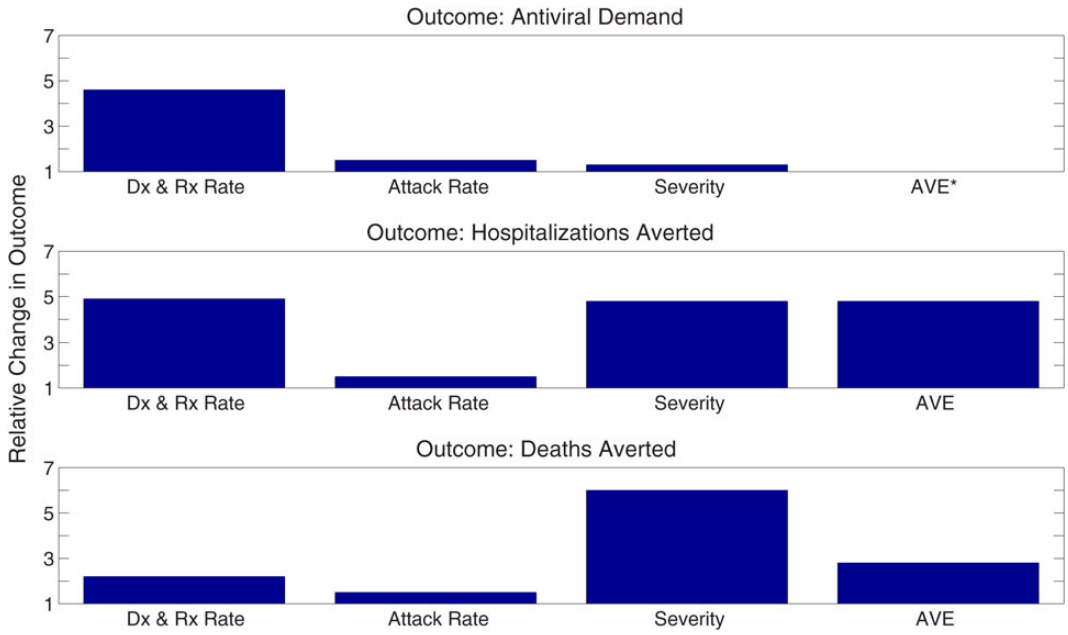

Figure 1. Impact of variables on number of antiviral courses used, hospitalizations averted, and deaths averted compared to baseline scenario (20% attack rate-low severity-low treatment level-low antiviral effectiveness scenario) Dx & Rx Rate = combined diagnosis and treatment rate for medically attended, symptomatic outpatients (low: 15%; high: 70%) and inpatients (low: 50%; high: 100%). Attack rate = clinical attack rate (low: 20% of US population; high: 30% of US population). Severity = risk of hospitalization per clinical case (low: 1.05%; high: 4%) and risk of death per clinical case (outpatients - low: 0.02%; high: 0.11%; inpatients - low: 6.2%; high: 9.7%). AVE = average antiviral effectiveness against hospitalization (low: 11%; high: 42%) and death (low: 23%; high: 66%). *The effect of antiviral effectiveness on the number of antiviral regimens dispensed is too small to be presented on the graph. To determine which factors had the greatest influence on the main outcomes (ie, antiviral usage, hospitalizations averted, deaths averted), we varied each of the 4 main variables (diagnosis and treatment rates, attack rate, severity, antiviral effectiveness) one at a time over their full uncertainty range and recorded their impact. As an example, a value of 5 for the effect of 'Antiviral Effectiveness (AVE)' on hospitalizations averted can be interpreted as an expected 5-fold increase in the number of hospitalizations averted when the antiviral effectiveness was varied from its lowest values (11% against hospitalization, 23% against death) to its highest values (42% against hospitalization, 66% against death) and the other variables (Dx & Rx Rate, Attack Rate, Severity) were left at their lower bound values. See Table 1 and "Methods" section for further description of scenarios and parameter values.

nonspecific and can be caused by a range of infections other than influenza [39]. The higher estimates of antiviral demand by Greer and Schanzer are a result of the authors using higher estimates of care-seeking and prescription rates to influenza cases, more widespread distribution of antivirals to noninfluenza cases due to treatment of those with noninfluenza respiratory illness, and larger attack rates than our model [39]. Carrasco et al analyzed the antiviral needs of a range of countries including the United States and showed that an antiviral stockpile sufficient for 25% of a country's population should be maintained in order to minimize fatalities and economic costs [40]. Kelso et al modeled an influenza epidemic in a small Australian town (population 30 000) and found that a stockpile that covered approximately 10% of the population would be sufficient to meet treatment needs for an epidemic with an unmitigated attack rate of 25%, if half of all symptomatic cases were treated within 24 hours after symptom onset, and there were no other interventions [41]. However, distribution of antivirals for non-influenza ILI was not considered [41]. Stockpiles sufficient for 30% of the population were estimated to be required when 90%–100% of clinical cases were treated for pandemic scenarios where the baseline clinical attack rate was 30%–34%, though again antiviral distribution for noninfluenza ILI was not considered [42, 43].

Prior work has assessed the impact of NAI treatment against hospitalization and death during an influenza pandemic. Atkins et al estimated that 8.2 million NAI regimens were used in the United States during the mild-moderate 2009 H1N1 pandemic and that this level of treatment averted 8000–13 000 hospitalizations and 400–650 deaths [27]. The ranges for hospitalizations averted by these authors are consistent with the ranges we obtained for the low severity-low attack rate-low diagnosis and treatment scenarios (5000–18 000 hospitalizations averted). However, the estimated range of deaths averted for the same set of scenarios in our model was 5000–14 000, far higher than the estimates of Atkins et al (400–650 deaths averted) [27]. The discrepancy between the estimates appears to be largely due to the inclusion of inpatient treatment in our model, since Atkins et al only modeled deaths occurring among inpatients, treatment

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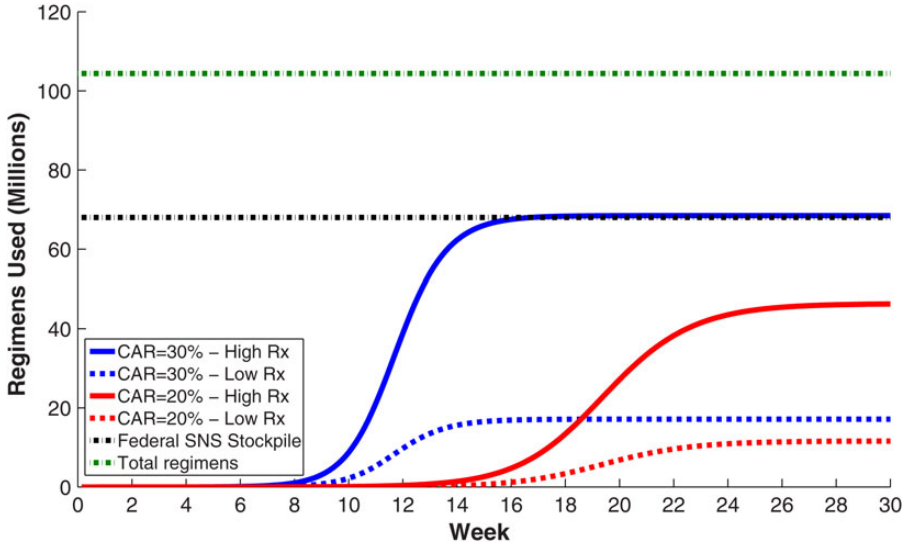

Figure 2. Cumulative antiviral demand in US for hypothetical, high-severity pandemic influenza scenarios. CAR = clinical attack rate (% of US population with clinical influenza illness over entire pandemic). High Rx = high level of diagnosis and treatment for inpatients (100% treated) and medically attended, symptomatic outpatients (70% treated). Low Rx = low level of diagnosis and treatment for inpatients (50% treated) and medically attended, symptomatic outpatients (15% treated). Federal SNS Stockpile = number of courses in federal strategic national stockpile (68 million). Total regimens = total number of courses in federal strategic national stockpile, state stockpiles, and commercial sources (104 million). Solid blue line: 30% clinical attack rate, high level of antiviral diagnosis and treatment; dashed blue line: 30% clinical attack rate, low level of antiviral diagnosis and treatment; solid red line: 20% clinical attack rate, high level of antiviral diagnosis and treatment; dashed red line: 20% clinical attack rate, low level of antiviral diagnosis and treatment; dashed black line: number of antiviral courses in Federal strategic national stockpile; dashed green line: combined number of courses in federal strategic national stockpile, state stockpiles, and commercial sources. The lower bound of treatment effectiveness was used in obtaining results since these values resulted in slightly more antiviral courses being required and so are conservative when assessing the adequacy of stockpiles (see Figure 1 and "Results" section). See Table 1 and "Methods" section for further description of scenarios and parameter values.

only occurring among outpatients, and used a similar risk of death among inpatients compared to the low severity estimate considered here. Additionally, we estimated that 175–770 deaths would be averted in the low severity-low attack rate-low diagnosis and treatment scenarios when we included only this mechanism by which deaths can be averted, and which closely matches the estimates of Atkins et al [27].

Although our model used a methodology that accounts for a variety of pandemic scenarios, a number of limitations warrant highlighting. Because the characteristics of a future influenza pandemic are unknown, uncertainty exists as to the "best" model inputs (eg, healthcare-seeking behavior, possibility of antiviral resistance based on historical data). Consequently, we used a variety of estimates of the numbers of people seeking care and receiving antivirals in order to produce a range of estimates for planning purposes and wide ranges on other parameters including antiviral effectiveness.

Our model included several assumptions and may have produced results that overestimate the number of antiviral courses distributed to patients in a timely manner, particularly during a severe pandemic. Specifically, we assumed that anyone requiring antiviral drugs was able to access the medication, and that payment for product or dispensing fees were not barriers. Our model also assumed perfect distribution and dispensing of antivirals and does not factor in logistical realties/challenges of the pharmaceutical and public health supply chains. Additionally, although we used ranges for the proportion of cases that would likely be treated, we did not include provider and public sentiment about the effectiveness and desirability of antivirals that may positively or negatively influence uptake during a pandemic. Our model also assumes that anyone who needed an antiviral drug regimen would receive it, with no supply or distribution challenges. If accounted for, these challenges could cause the number of antiviral regimens actually needed in a future pandemic to be higher than the estimates here. Furthermore, the supply data used in our model is based on the amount of product available at a specific point in time. It is important to note that as supply dynamics change (eg, changes in commercial manufacturing/product availability, expiration of public health stockpiles, changes in decisions on how much to stockpile) the amount of antiviral drugs that are available would change impacting these results.

Also, we may have underestimated the amount of antivirals needed for a severe pandemic scenario. Our model included a

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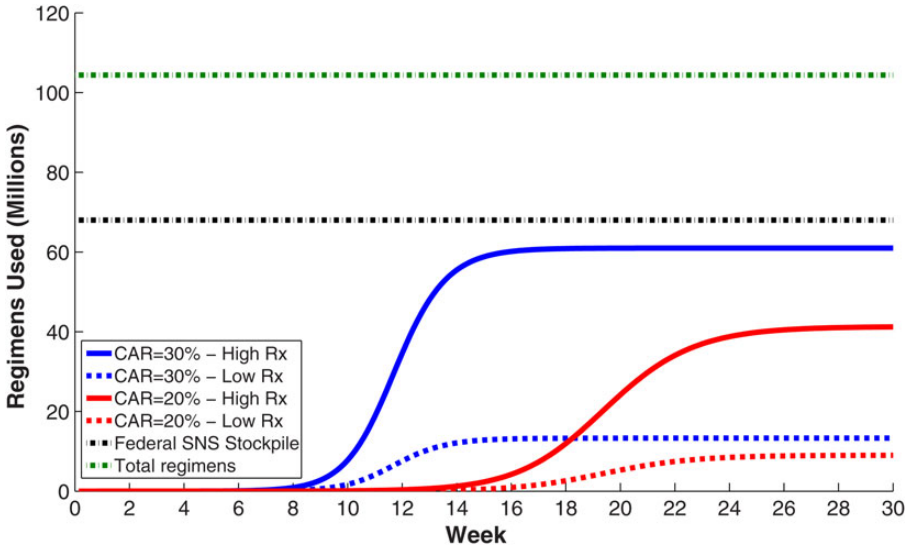

Figure 3. Cumulative antiviral demand in United States for hypothetical, low-severity pandemic influenza scenarios. CAR = clinical attack rate (% of US population with clinical influenza illness over entire pandemic). High Rx = high level of diagnosis and treatment for inpatients (100% treated) and medically attended, symptomatic outpatients (70% treated). Low Rx = low level of diagnosis and treatment for inpatients (50% treated) and medically attended, symptomatic outpatients (15% treated). Federal SNS Stockpile = number of courses in federal strategic national stockpile (68 million). Total regimens = total number of courses in federal strategic national stockpile, state stockpiles, and commercial sources (104 million). Solid blue line: 30% clinical attack rate, high level of antiviral diagnosis and treatment; dashed blue line: 30% clinical attack rate, low level of antiviral diagnosis and treatment; solid red line: 20% clinical attack rate, high level of antiviral diagnosis and treatment; dashed red line: 20% clinical attack rate, low level of antiviral diagnosis and treatment; dashed black line: number of antiviral courses in Federal strategic national stockpile; dashed green line: combined number of courses in federal strategic national stockpile, state stockpiles, and commercial sources. The lower bound of treatment effectiveness was used in obtaining results since these values result in slightly more antiviral courses being required and so are conservative when assessing the adequacy of stockpiles (see Figure 1 and "Results" section). See Table 1 and "Methods" section for further description of scenarios and parameter values.

modest estimate of antiviral use for prophylaxis that accounted for 10% of the total number of antiviral regimens dispensed. As pandemic severity increases, it is likely that demand for prophylaxis would increase, thus impacting the amount of antivirals available for treatment [41, 44]. More detailed modeling of antiviral use and distribution strategies, including the prioritization of treatment over prophylaxis, could help identify ways to better match antiviral demand with supply and improve access to these medications [45].

Our use of a static model implicitly assumed that there is negligible effect of antiviral treatment on cases' infectiousness and gives conservative estimates of the numbers of hospitalizations/deaths averted if there are large indirect effects. Surprisingly, it has been shown that oseltamivir treatment could reduce the risk of disease among a case's contacts while not reducing the risk of infection (where infection was determined using viral culture and serological tests) [46]. Consequently, the authors of the treatment analysis have recommended using only very low values of the effect of antiviral treatment on reducing infectiousness and further data are needed to clarify these findings [46].

Lastly, we may have under or overestimated the impact of NAIs because we assumed the same effect of NAI treatment across age groups and also used an average effect of NAIs with respect to time since symptom onset. In particular, the time between symptom onset and initiation of treatment may be different during a pandemic than in the studies from which antiviral effectiveness estimates were obtained, which could increase or decrease the effectiveness of antiviral treatment and consequently the number of hospitalizations and deaths averted. Data on the effectiveness of influenza antivirals against severe endpoints are limited [19, 20], as are data on how the effectiveness of treatment could vary with time since symptom onset [47]. Therefore, we conducted a sensitivity analysis to explore this issue by varying the average antiviral effectiveness over a wide range, with low effectiveness reflecting delayed treatment initiation and/or low susceptibility of the pandemic strain to treatment and high effectiveness reflecting rapid treatment and high susceptibility of the pandemic strain to treatment. A recent article on the effectiveness of antiviral treatment in averting mortality among patients hospitalized with influenza during the 2009 H1N1 pandemic found that the odds of death were reduced by 50% (95% CI, 23%, 63%) when treatment was initiated within 48 hours of symptom onset [47]. These results are consistent with our assumed range of antiviral effectiveness against

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death based on H5N1 data (range: 23%–66%) [29] and the assumption that treatment would be initiated an average of 2 days after symptom onset. We found that the number of hospitalizations averted are strongly influenced by treatment effectiveness (380% increase in hospitalizations averted comparing the highest effectiveness scenario to the lowest effectiveness scenario, Figure 1), while the number of deaths averted were less affected by the level of antiviral effectiveness (180% increase in deaths averted comparing the highest effectiveness scenario to the lowest effectiveness scenario). This is due in part to the fact that antiviral effectiveness against hospitalization was varied over a 4-fold range while effectiveness against death was varied over approximately a 3-fold range. Notably, antiviral effectiveness had a negligible impact on the number of antiviral courses required to meet treatment needs.

Our model also has several strengths. We included several pandemic scenarios which allowed us to create a range of antiviral needs and potential treatment effects. Also, we based our parameter estimates on sources from the literature where possible and included an assessment of the most important sources of uncertainty regarding antiviral demand and the impact of treatment. Furthermore, we constructed the model to be simple enough to be used by researchers and public health practitioners with little training in such methods.

New distribution methods could help ensure the timely availability of antiviral treatment. For example, the implementation of nurse triage telephone lines to facilitate antiviral prescribing could help reduce treatment delays [48, 49] and pre-dispensing of antivirals to individuals at high risk of complications from influenza has also been suggested as a means of ensuring timely treatment of those most at risk of severe outcomes [50]. Temporary vaccination clinics were used to increase coverage during the 2009 H1N1 pandemic vaccination campaign and such dispensing points could also be considered for antiviral distribution [51]. However, we did not include these alternative distribution methods in our models.

Risk of death could also be affected by the demand for limited hospital beds and medical equipment, especially at the epidemic's peak, which was not considered here. Our model does not include the possible effects of treatment on reducing onward transmission which could be included in future work using a dynamic model [42, 52, 53]. Additionally, the reader should note that our model assumes that the influenza virus causing the pandemic in these modeling scenarios is susceptible to antiviral treatment. Finally, antiviral resistance has been detected in both seasonal and pandemic influenza viruses and in avian influenza viruses and there is no way to predict if resistance would emerge in a future pandemic [54–56].

As of April 2013, the United States' antiviral supplies including stockpiles appear sufficient to meet treatment needs in the epidemic scenarios considered, contingent on there being limited NAI resistance, limited chemoprophylaxis, and modest prescribing rates for non-influenza illness. Although our analyses indicated that many hospitalizations and deaths would occur even with a large amount of NAI treatment during a pandemic, they suggest that any effect that NAI treatment may have is highly dependent upon achieving high coverage levels. Our findings of the limited impact of a single intervention reinforces the need to consider combining interventions to mitigate the severity of an influenza pandemic as described in prior work [53, 57–63]. In summary, these results highlight the need to develop strategies to educate patients and clinicians regarding early treatment benefits, maintain stockpiles of antiviral drugs to support preparedness efforts, improve and refine means of rapidly distributing and dispensing government stockpiled supplies, deploy other mitigation strategies concomitantly with antivirals, and develop new strategies to control influenza in the early stages of a pandemic.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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