

# RESEARCH

## Pandemic Influenza: Antiviral Preparedness and Health Care Workers

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### ABSTRACT

**Objectives:** The primary objective of this study was to determine the preparedness for pandemic influenza of hospitals, in terms of amount of antiviral drugs on hand and employee vaccination rates, in the Finger Lakes region (FLR) of western New York.

**Methods:** A survey of the 17 FLR hospitals was conducted via e-mail during the period of June 2007 to August 2007.

**Results:** A total of 13 of 17 hospitals responded for a response rate of 76.5%. Only 23.1% of responding hospitals stockpile antiviral drugs. Vaccination rates for personnel with patient contact ranged from 36.8% to 76.1%.

**Conclusions:** Hospitals in the FLR have insufficient quantities of antiviral agents stockpiled to provide for the protection of health care workers, and influenza vaccination rates for health care workers are low. To ensure that a high level of care is maintained during a pandemic, health care workers need to be provided with appropriate protection. This can be accomplished if hospitals stockpile antiviral agents designated for the treatment and prophylaxis of health care workers with patient contact and their families.

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**Key Words:** pandemic influenza, antiviral drug, vaccination rates, stockpiling, hospital preparedness

The threat of an influenza pandemic is constant and the occurrence of one virtually inevitable. A novel influenza virus could spread worldwide and produce devastating effects. The H1N1 "Spanish" influenza resulted in at least 50 million deaths worldwide during the pandemic period of 1918–1920.<sup>1</sup> The clinical attack rate was 29.4%,<sup>2</sup> the case fatality rate was at least 2.5%,<sup>3</sup> and there were more than 675 000 excess deaths in the United States alone. Current fear of an influenza pandemic revolves around the highly pathogenic avian influenza A/H5N1 strain, which has spread quickly geographically. As of March 23, 2009, the mortality rate for human infection with H5N1, since 2003, is 62.1% in 412 cases worldwide.<sup>4</sup> Although there is no clear evidence of human-to-human transmission, H5N1 or another strain could undergo reassortment with a circulating human influenza A strain resulting in the emergence of a highly pathogenic virus with efficient and sustainable human-to-human transmission. The threat of a pandemic was most recently demonstrated by the H1N1 outbreak earlier this year. An often referenced mathematical model based on data derived largely from the less severe 1957 and 1968 pandemics estimates that the next influenza pandemic will result in 89 000 to 207 000 deaths, 314 000 to 734 000 hospitalizations, 18 to 42 million outpatient visits, and 20 to 47 million additional illnesses in the United States.<sup>5</sup>

The impact of pandemics, however, can be mitigated through preparedness. One significant component of an

obviously multifaceted plan is the use of antiviral agents, which the World Health Organization recommends stockpiling. Widespread use of antiviral drugs could reduce morbidity, influenza-related complications, hospitalizations, mortality, and stress on the health care system. It is critical that the essential services of hospitals be maintained. Providing for the protection of health care workers with patient contact (HCW/PC) would reduce worker absenteeism and allow hospitals to maintain a high standard of care. To accomplish this, antiviral drugs need to be stockpiled in advance of an influenza pandemic.

### ANTIVIRALS

There are 4 antiviral agents approved for the treatment and prophylaxis of influenza infections: the adamantanes, amantadine and rimantadine, and the neuraminidase inhibitors, oseltamivir and zanamivir. Both classes of drugs need to be administered within 48 hours of symptom onset to be effective. Although data from previous pandemics show that the adamantanes are effective,<sup>6</sup> a single-point mutation can confer high-level cross-resistance to amantadine and rimantadine, and such mutations are fairly stable with little reversion to wild-type susceptible virus after therapy cessation.<sup>7</sup> Because there is a high rate of adamantane resistance<sup>8</sup> and adamantane-resistant strains demonstrate no decrease in pathogenicity or transmissibility relative to wild-type strains,<sup>9</sup> the adamantanes should not be used in the event of pan-

demically and should not be stockpiled. It is clear that oseltamivir is the best choice for stockpiling given its efficacy,<sup>10-12</sup> safety profile, association with reduction in secondary complications (including a 26.7% reduction in antibiotic use, a 55% reduction in the incidence of lower-respiratory tract complications requiring antibiotics, and a 59% reduction in hospitalizations<sup>13</sup>), and the decreased fitness of oseltamivir-resistant viruses in terms of infectivity, replicative ability, and pathogenicity.<sup>14,15</sup> Although the prevalence of oseltamivir resistance was previously low, during the 2007–2008 influenza season a substantial increase in prevalence was noted in the United States, with 10.9% of influenza A (H1N1) viruses tested found to be oseltamivir resistant.<sup>16</sup> Of the limited number of H1N1 viruses tested thus far in the 2008–2009 season, 98% have been found to be oseltamivir resistant, but all retain susceptibility to the other 3 antivirals.<sup>16</sup> In accordance with this data, a recent Centers for Disease Control and Prevention (CDC) Health Advisory on the treatment of and prophylaxis for influenza recommended that oseltamivir should be used alone only if the predominant virus in the community is H3N2 or influenza B, and zanamivir should be used in the case of suspected H1N1 infection.<sup>16</sup> This recent change in prevalence of oseltamivir resistance highlights the importance of surveillance data, especially because we cannot predict the resistance patterns of the next pandemic virus. Although zanamivir has shown similar benefits and most oseltamivir-resistant variants retain complete susceptibility to zanamivir,<sup>16,17</sup> it is available only as a dry powder delivered through an inhaler, which can be difficult for children and elderly adults to use.

### IMMUNIZATIONS

Although vaccination is the primary means of preventing influenza-related morbidity and mortality and should be an important part of a hospital's pandemic influenza plan, the rate of HCW vaccination is below 40%.<sup>18</sup> In addition, although a human H5N1 prepandemic vaccine was approved in April 2007 and the federal government has already procured 12.2 million courses,<sup>19,20</sup> questions remain regarding its immunogenicity. Given that the production of a new influenza vaccine requires about 6 months,<sup>21</sup> it should be assumed that an appropriate vaccine will not be available during the beginning of a pandemic. Because vaccine supply will increase incrementally with production, an effective and flexible allocation strategy is crucial. In accordance with this, a federal interagency working group recently drafted guidance on pandemic influenza vaccine allocation and developed a system such that multiple groups, some occupationally defined, will be vaccinated simultaneously.<sup>22</sup> The working group defined 4 broad categories (homeland and national security, health care and community support services, critical infrastructure, and general population), each broken up into multiple target groups such that everyone falls into at least 1 group.<sup>22</sup> Each target group is assigned a vaccination tier and all of the groups within a tier have equal priority for vaccination.<sup>22</sup> Tier 1 includes an estimated 3.2 million inpatient health

care providers, 2.5 million outpatient and home health providers, and 1.6 million health care providers in long-term care facilities, among other groups.<sup>22</sup> It is clear that protecting HCW is a priority, although it is also clear that an effective vaccine likely will not be available at the onset of a pandemic. Antiviral drugs will be in particularly high demand during the beginning of a pandemic before an effective vaccine is available. Because the manufacturing time of neuraminidase inhibitors is lengthy and there is limited surge capacity, antiviral agents will need to be stockpiled in sufficient numbers before the onset of a pandemic to be an effective strategy. Stockpiles should consist mainly of oseltamivir, but because resistance to oseltamivir has been detected, they should also include smaller amounts of zanamivir.

### STOCKPILES

The United States is stockpiling antiviral drugs at the federal, state, and local levels. The US Department of Health and Human Services (HHS) maintains the Strategic National Stockpile (SNS), which is meant to supplement state and local supplies in the event of a disaster. The SNS includes oseltamivir, zanamivir, and small amounts of rimantadine. Per World Health Organization recommendations, the national goal is to have enough courses to treat 25% of the population.<sup>20</sup> As of December 2007, the government completed its goal of procuring 50 million courses for the SNS, of which the composition is roughly 80% oseltamivir and 20% zanamivir.<sup>20,23</sup> A total of 44 million courses are intended for pro rata distribution to states, with New York State allocated 2 863 082 courses, and the remaining 6 million courses are intended for outbreak containment.<sup>24</sup> HHS offers states a 25% federal subsidy to purchase 31 million additional courses, and as of September 30, 2008, the states have purchased almost 23 million courses, falling more than 8 million courses short of the stated goal.<sup>24</sup>

Based on the clinical attack rates of previous pandemics, having enough antiviral drugs for the treatment of 25% of the population seems to be a reasonable initial national goal, but it is uncertain whether current dosage recommendations can be applied to the next pandemic virus because the characteristics of such a virus are unpredictable. If the recommended dosage and duration of therapy for antiviral drugs is modified upward it will in effect diminish supplies because greater amounts will be needed for the treatment of each case. According to the National Strategy for Pandemic Influenza Implementation Plan: One Year Summary, "at this time all state and federal stockpiles of antiviral medications should be reserved for treatment of symptomatic patients"<sup>20</sup> and that recommendation has not changed since the time of the publication. Given the geographically widespread and sustained need expected during a pandemic, federal aid would likely be limited. Although CDC will attempt to anticipate antiviral needs, the Implementation Plan for National Strategy for Pandemic Influenza states that medical resources may be insufficient and supply routes may be compromised, and "state, local, and tribal entities should thus anticipate that all sources of external aid may be compromised during a

pandemic.”<sup>25</sup> It is unreasonable to assume that we can rely on the SNS to provide antiviral drugs in sufficient numbers to meet full needs because the SNS is designed only to augment state and local supplies and delivery is subject to real and potential delays. The New York State Department of Health maintains the Medical Emergency Response Cache, whose assets included 1 050 000 courses of oseltamivir and 227 889 courses of zanamivir (pending) as of 2007,<sup>26</sup> with the goal of purchasing enough antiviral drugs for the treatment of all New Yorkers who develop influenza illness<sup>27</sup>; however, Medical Emergency Response Cache supplies, just like SNS supplies, are available only for treatment.

## GUIDELINES

Because there is only a limited supply of antiviral drugs during a pandemic, guidelines regarding its use are necessary. Government stockpiles are still designated primarily for treatment, but the recent increase in antiviral production capacity has allowed HHS to reconsider its initial strategy for antiviral use and to consider expansion of its recommendations.<sup>19</sup> New recommendations, outlined in the publication *Guidance on Antiviral Drug Use During an Influenza Pandemic*, suggest that antiviral drugs be used for multiple purposes, including initial containment, prevention of spread at US borders, treatment of people with pandemic influenza, prophylaxis of HCW and emergency services workers, and postexposure prophylaxis (PEP) of additional health care and emergency services personnel not at a high risk for exposure, immunocompromised individuals, and people living in group settings.<sup>23</sup> The working group emphasizes that pandemic preparedness requires collaboration between government and private sectors at multiple levels. HHS recognizes that the number of courses required to implement working group recommendations is far greater than the number maintained in public sector stockpiles and that full implementation will require stockpiling by employers.<sup>23</sup> As such, public sector stockpiles will be used for containment, treatment, and delaying spread to the United States, whereas private sector stockpiles will be used for outbreak prophylaxis and PEP of health care and emergency services workers (an estimated 103 million courses) and PEP of immunocompromised people.<sup>23</sup> In contrast, a position paper from the American College of Physicians recommends that the federal government provide sufficient money to purchase antivirals for the treatment of 25% of the population and also for the prophylaxis of HCW/PC and for public safety officers.<sup>28</sup> This federal inter-agency group based its recommendations on assumptions that outbreaks will last 12 weeks, an effective vaccine will be initially unavailable, community mitigation strategies will reduce the attack rate from 30% to 15%, and that antiviral efficacy and regimens will remain the same as for seasonal influenza.<sup>23</sup> The latter 2 assumptions are unreasonably optimistic and the uncertainty associated with reliance on antiviral stockpiling should be acknowledged.<sup>29</sup>

In the end, the government is expecting the private sector to stockpile more courses than the public sector. Such heavy reliance on the private sector, when there are so many barriers

to employer stockpiling and the stakes are so high, is both unrealistic and dangerous.<sup>29</sup> The HHS working group does recognize barriers to employer stockpiling, including cost, limited shelf life, potential for government seizure, and potential liability.<sup>23</sup> In response, on October 10, 2008, HHS Secretary Michael Leavitt issued a declaration regarding influenza antivirals, in which he stated that governmental planners are only afforded liability immunity if antivirals are procured through voluntary means.<sup>30</sup> This declaration, which falls under the Public Readiness and Emergency Preparedness Act (PL 109-148), was meant to address concerns regarding the potential for government seizure of stockpiles. This declaration also specifies that entities involved in the distribution of antivirals are protected from tort liability.<sup>30</sup> In its guidance for employer stockpiling, HHS continuously advises cooperation and coordination between government and private entities to allow for optimal community pandemic preparedness.<sup>30</sup> With regard to shelf-life issues, new programs make it possible for employers to pay an annual fee for the antiviral drug manufacturer to hold a specified quantity of antiviral guaranteed to be delivered within 48 hours of request and payment, at the time a pandemic is declared.<sup>30</sup>

Many of the issues an employer would expect to face when considering stockpiling are not an issue for hospitals because they have in-house pharmacies. In terms of amount to stockpile, HHS explicitly recommends outbreak prophylaxis for HCW with high exposure risk and because community outbreaks are anticipated to last 12 weeks, this could mean up to 8 antiviral drug courses per person.<sup>30</sup> Although it is clear that HHS has newly prioritized HCW and recognizes both their increased risk for exposure and the danger of high rates of absenteeism, it is also clear that the government has no intention of stockpiling additional courses for the prophylaxis of HCW.

During a pandemic, when hospitalization rates are exceedingly high and transmission of influenza in a hospital setting presents a significant issue, the health care system must be maintained. It is likely that many hospitals will be overwhelmed following both a large surge in patients and high rates of health care worker absenteeism. The recent severe acute respiratory syndrome (SARS) outbreak demonstrated how HCW can be disproportionately affected during the outbreak of an infectious disease.<sup>31</sup> The federal government recommends that institutions anticipate an absenteeism rate of 40% during the peak of a pandemic for a period of 2 weeks.<sup>25</sup> A survey of New Yorkers found that the reasons reported most often for not being willing to come to work during a catastrophe were concern for family (47.1%) and self (31.1%).<sup>32</sup> Instead of forcing this issue, it can be minimized by providing for the safety of HCW and their families. This can be partially addressed through education and nonpharmaceutical measures, but the role of antivirals should be considered. A study that examined absenteeism during a bioterrorism event found that onsite treatment of HCW and families decreases absenteeism relative to treatment of HCW alone.<sup>33</sup> Another study found that health care worker prophylaxis

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allows for a high standard of care to be delivered during an influenza pandemic and thus reduces overall morbidity and mortality.<sup>34</sup> Although the government recognizes that outbreak prophylaxis for household members of critical health care and emergency service workers is a potential strategy for reducing worker absenteeism, it also estimates that this would require about 116 million antiviral courses.<sup>23</sup> This number of courses does not appear to be feasible at this time.

The primary objective of this study was to determine the preparedness of hospitals, in terms of amount of antiviral drugs on hand and employee vaccination rates, in the Finger Lakes Region (FLR). The FLR consists of 9 counties in western-central New York, including 17 hospitals and representing a primarily rural region with some mid-sized cities.

## METHODS

To determine the level of regional preparedness, a survey of the 17 FLR hospitals was conducted via e-mail during the period June 2007–August 2007. The emergency preparedness coordinator of each hospital was contacted and multiple follow-up requests were made if there was no response initially. Clarifications were made via e-mail as well. Hospitals were asked the following questions:

1. What are your hospital's par levels for amantadine, rimantadine, oseltamivir (Tamiflu), and zanamivir (Relenza)? [A par level is a predetermined inventory amount, below which hospitals must reorder supplies.]
2. How many courses of the above are stockpiled? [A course refers to a treatment course, which for oseltamivir is 75 mg twice daily for 5 days, for zanamivir is 2 inhalations (10 mg total) twice daily for 5 days, for amantadine is 100 mg twice daily continued for 24–48 hours after symptom disappearance, and for rimantadine is 100 mg twice daily for 7 days.]

3. What is the total number of personnel (medical and non-medical staff) with patient contact?

4. How many of the above personnel received influenza vaccination through the hospital?

## RESULTS

The results of the survey appear in Tables 1 and 2 and Figure. The 17 FLR hospitals can be divided into 3 groups: those with fewer than 100 beds (6 hospitals), those with 100 to 200 beds (5 hospitals), and those with more than 200 beds (6 hospitals). Thirteen of the 17 FLR hospitals responded (76.5%). Response rates were fairly consistent across size groupings with 5 of 6 hospitals having fewer than 100 beds, 4 of 5 hospitals having 100 to 200 beds, and 4 to 6 hospitals with more than 200 beds. Numerous attempts were made to follow up with the hospitals that did not respond, but information could not be obtained. Of the 13 hospitals that responded, only 3 (23.1%) indicated that they currently stockpile an antiviral drug for influenza. None of the 3 hospitals have sufficient amounts stockpiled (ie, enough to provide for the protection of HCW/PC), and 2 have amantadine, a drug unlikely to be effective, stockpiled. Hospital B, which has more than 200 beds, has 10,000 capsules (1000 treatment courses) of oseltamivir stockpiled. Hospital G, which has more than 100 beds, has 60 capsules of amantadine and 10 capsules (1 treatment course) of oseltamivir stockpiled. Hospital H, which has more than 200 beds, has 50 courses of amantadine and 50 courses of rimantadine stockpiled, and reported that they would soon have 100 courses of oseltamivir stockpiled. Relative to the number of HCW/PC, all of the above hospitals fall significantly short of having enough courses on hand to treat all HCW/PC. All 13 hospitals have working stocks of amantadine, despite the fact that the CDC advised against its use for the 2007–2008 flu season due to the high level of resistance, and 12 have working stocks of oseltamivir. Only 5

### TABLE 1

FLR Influenza Antiviral Drug Supplies\*

Hospital	Amantadine		Rimantadine		Oseltamivir		Zanamivir	
	Par Level	Stockpiled	Par Level	Stockpiled	Par Level	Stockpiled	Par Level	Stockpiled
A	7	0	7	0	2	0	0	0
B	29	0	8	0	16	1000	0	0
C	14	0	0	0	2	0	0	0
D	7	0	0	0	3	0	0	0
E	1	0	0	0	0	0	0	0
F	10	0	0	0	2	0	0	0
G	14	4	0	0	10	1	0	0
H	21	50	21	50	15	100	0	0
I	9	0	0	0	6	0	0	0
J	10	0	0	0	16	0	0	0
K	14	0	14	0	80	0	0	0
L	5	0	7	0	8	0	0	0
M	7	0	0	0	2	0	0	0

\*The numbers listed refer to treatment courses and were rounded down to the nearest whole number to reflect complete courses. Although rimantadine, oseltamivir, and zanamivir have well-defined treatment durations, the prescribing directions for amantadine indicate that it should be continued for 24 to 48 hours after symptom disappearance. For the purposes of a common unit for better comparison, duration of treatment was chosen for amantadine. We chose 7 days, to reflect both the average duration of symptoms and average length of treatment with other antivirals.

hospitals have working stocks of rimantadine, and none of the hospitals keep any supplies of zanamivir.

The vaccination rate for HCW/PC ranged from 36.8% to 76.1% for hospitals A, B, C, G, and I, and hospital H claimed an average overall compliance rate of around 55%. The total number of employees vaccinated at hospitals J, K, L, and M was lower than the number of HCW/PC.

**DISCUSSION**

It is striking that despite recommendations in favor of hospital stockpiling, only 3 of 13 hospitals stockpiled antivirals and none of them stockpiled sufficient amounts to provide for prophylaxis of HCW/PC. Because large hospitals with more than 200

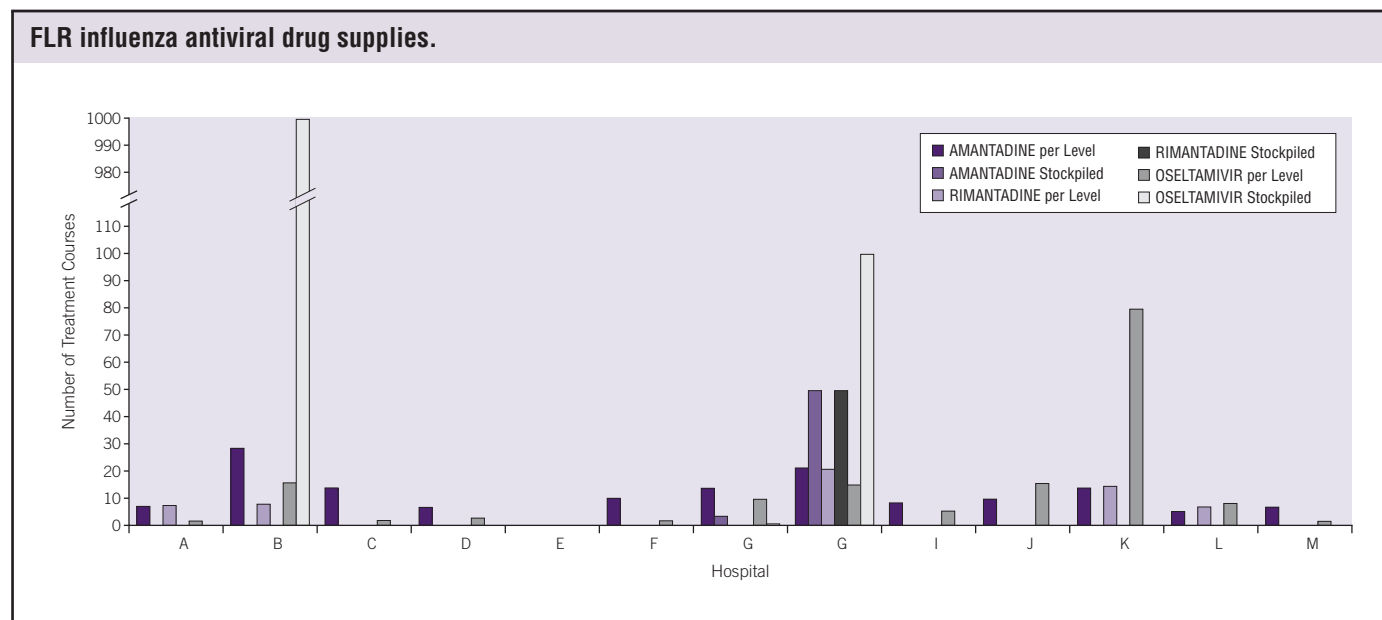
beds seem to be more prepared with regard to stockpiling, and 2 of 4 nonresponders were hospitals with more than 200 beds, it seems likely that had they responded they would have bolstered the percentage of stockpiling FLR hospitals. Contrary to data suggesting that amantadine is not a suitable antiviral to stockpile, most of the hospitals in the FLR have larger working stocks of amantadine than oseltamivir, and 2 of the 3 stockpiling hospitals stockpile amantadine (in addition to oseltamivir). Because it was hard to ascertain specific data on the number of HCW/PC who were vaccinated at the hospital (and clearly they could have been vaccinated elsewhere), it is difficult to draw any strong conclusions regarding FLR vaccination rates; however, the results shown in Table 2 are suggestive of low vaccination rates consistent with reports by others regarding HCW

**TABLE 2**

FLR Vaccination Rates*			
Hospital	Personnel With Patient Contact	Personnel With Patient Contact Who Were Vaccinated at Hospital	Total Personnel Vaccinated at Hospital
A	3000	1200 (40.0%)	Unknown
B	8000	2940 (36.8%)	Unknown
C	320	180 (56.3%)	Unknown
D	858	Unknown	1175
E	268	Unknown	1175
F	Unknown	Unknown	Unknown
G	759	350 (46.1%)	Unknown
H	394 (inpatient contact)	Unknown	Overall compliance 55%
I	560	426 (76.1%)	Unknown
J	454	Unknown	443
K	892	Unknown	585
L	2659	Unknown	1308
M	460	Unknown	357 (employees + volunteers)

\*Many of the responding hospitals did not specifically track the number of personnel with patient contact who were vaccinated at the hospital, but instead gave the total number of personnel who were vaccinated at the hospital.

**FIGURE**



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vaccination rates. Therefore, even if the pre-pandemic vaccine is efficacious, we should not expect to rely on vaccination as the primary means of protection during a pandemic.

To ensure the highest standard of care, sufficient antivirals need to be available for the prophylaxis of HCW/PC and for the treatment of HCW/PC and their families. Because the government does not have enough antivirals for use as prophylaxis, hospitals should maintain their own stockpiles; however, as seen in Table 1, less than 25% of the hospitals in the FLR stockpile an influenza antiviral agent and none of the hospitals maintain sufficient stockpiles based on the number of HCW/PC. Many hospitals have the resources and means to stockpile and quickly and efficiently distribute antivirals to HCW.<sup>35</sup> Although there are certainly barriers to stockpiling, the effects of not adequately protecting HCW/PC would be profound. Hospital stockpiles, composed primarily of oseltamivir but also small amounts of zanamivir, should be sufficient to provide for the prophylaxis of HCW/PC and for the treatment of immediate family members. The group to receive prophylaxis could be broken down further by amount of patient contact (eg, duration, type, frequency) if stockpiling proved prohibitively expensive.

One of the weaknesses of this study is that it is a one-time “snapshot” of the status of the hospitals in the FLR; however, a snapshot is still helpful because it identifies our starting point, thus enabling further planning. Another weakness is that we did not fully address the status of city, county, or state medication caches that may be used in the event of a pandemic. This study should help planners in those entities (hospital, regional hospital associations, city, county, and state) by identifying hospital needs.

## CONCLUSIONS

Hospitals in the FLR have only limited quantities of antiviral agents stockpiled for use on their HCW. In addition, influenza vaccination rates for HCW in the FLR are unacceptably low. HCW need to be given higher priority because they will be at greater risk than the general population and are crucial for maintaining a high standard of care. Antiviral drugs should be designated for the treatment and prophylaxis of HCW/PC and for the treatment of their immediate families. At this time, however, federal and state stockpiles are designated for treatment only. Hospitals should stockpile antiviral drugs (primarily oseltamivir but also zanamivir) to provide for prophylaxis of HCW/PC and for treatment of their immediate family. The FLR is grossly unprepared for a pandemic with regard to antiviral stocks, and hospitals need to act quickly.

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