ABSTRACT

The outbreak of H5N1 avian influenza in Asia raises serious concerns about an influenza pandemic of the kind seen in 1918. In addition, the recent federal response to Hurricane Katrina highlights the need for advanced local preparation for biological disasters. It is clear that there will not be enough vaccine early in an influenza pandemic. Without vaccine, the role of antivirals, especially oseltamivir (Tamiflu™), in treatment and prophylaxis becomes of paramount importance. It is unlikely that the Centers for Disease Control and Prevention (CDC) will be able to stockpile enough oseltamivir to protect every first responder in the United States. Thus, it is important that local governments and hospitals consider stockpiling oseltamivir for the treatment and/or prophylaxis of local first responders.

Key words: pandemic, influenza, oseltamivir, Tamiflu™, antivirals, first responders

INTRODUCTION

It is estimated that the 1918 influenza pandemic claimed 40 to 50 million lives, 500,000 of those in the United States.¹ The ongoing outbreak of avian influenza (H5N1) in Southeast Asia claimed 60 lives between January 28, 2004, and September 29, 2005,² and has posed the possibility of a pandemic that could claim up to 150 million lives worldwide if human-to-human transmission were to become efficient.³ A recent model suggests that such a pandemic could cost the United States between $71 and $167 billion.⁴

First responders, including healthcare personnel, police, and emergency management personnel, will be at the highest risk of exposure during their care of infected patients. This group will require rapid access to medications, vaccines, and personal protective equipment (PPE). The response to Hurricane Katrina demonstrates that, even with advance notice, the federal government is not capable of intervening quickly enough to provide adequate protection for first responders.⁵ It is therefore incumbent upon local governments and hospitals to provide such protection in the event of a pandemic influenza outbreak. Because vaccine will not be available early in a pandemic, and PPE and infection control practices will not be adequate to contain influenza, local governments and hospitals should consider stockpiling the antiviral oseltamivir (Tamiflu™). The rationale for this recommendation is outlined below.

CONCERNS

Vaccine will not be available early in a pandemic

According to the World Health Organization (WHO), influenza vaccine will be in limited supply during the first part of a pandemic and may not be available at all.⁶ The mass production of vaccine using current techniques cannot be accomplished in fewer than six to eight months, even under the most optimal conditions.⁷ A pandemic influenza strain could spread around the world in half that time.⁸ More rapid vaccine production methods (e.g., reverse genetics) are unlikely to be widely available before the next pandemic occurs. At present, there is no commercially available vaccine for H5N1 avian influenza.

Pandemic influenza will be deadlier over a wider range of the population

The groups at increased risk of complications...
from influenza during typical yearly outbreaks are very predictable and are the basis for yearly vaccination recommendations by the Centers for Disease Control and Prevention (CDC). These groups, which make up approximately 30 percent of the population, include the elderly, young children, and the immunocompromised population. Although many first responders are targeted for yearly vaccination, this group (usually aged 24 to 50) is generally at low risk for serious complications from influenza. Yearly influenza epidemics may lead to a few sick days, but death and debility are rare and unexpected among first responders.

A pandemic influenza outbreak, however, will result in much higher rates of morbidity and mortality across a wider range of the population. In fact, during the 1918 influenza pandemic, the highest mortality rates occurred among young adults between the ages of 15 and 35. Thus, a large part of the first responder workforce will be at high risk for influenza complications. Without vaccine, first responders will be left to rely on antiviral medications and effective infection control practices.

**Standard infection control practices may not provide adequate protection during a pandemic**

Influenza is generally transmitted through respiratory droplets, and droplet precautions are recommended to control spread of the virus in a healthcare setting. Even with such precautions in place, healthcare worker attack rates during influenza outbreaks are as high as 59 percent. Furthermore, first responders will be at high risk of acquiring influenza in the community, where infection rates as high as 15 to 25 percent can be expected in an unimmunized population. Viral shedding of influenza occurs one to two days before symptoms and can continue for seven days after symptoms begin. Infants and immunocompromised individuals may shed for weeks. Thus, containment of pandemic influenza will be almost impossible. In contrast, the Severe Acute Respiratory Syndrome (SARS) coronavirus shedding peaks seven to 10 days after symptoms begin, making this disease more easily contained with current infection control practices.

**The benefits of stockpiling oseltamivir locally**

If the mortality rate for the next pandemic approaches that seen in the current avian influenza (H5N1) outbreak in Southeast Asia (52 percent), it may be difficult to persuade frightened first responders to care for sick patients. In this setting, the role of antivirals becomes very important, especially if vaccine is unavailable. The WHO and, more recently, the CDC have suggested that, in the absence of vaccine, stockpiling of antiviral drugs may be an alternative strategy for managing the next influenza pandemic.

Unfortunately, the H5N1 avian strain is resistant to the relatively cheap adamantanes rimantadine and amantadine, and future pandemic influenza strains are likely to be resistant as well. This leaves the neuraminidase inhibitors oseltamivir and zanamavir as the antiviral drugs of choice for stockpiling. Zanamavir is difficult to administer (inhaled powder) and is not widely available. Therefore, the CDC, the WHO, and several countries have chosen to stockpile oseltamivir. Unfortunately, these centrally located stockpiles may be useless if pandemic influenza simultaneously descends upon many US cities, in which case antivirals will not arrive promptly enough to protect first responders. On the other hand, local stockpiles created by hospitals and city governments could be quickly and efficiently disseminated based on the needs of local responders.

There are four potential strategies for using antivirals during an influenza outbreak: 1) chemoprophylaxis for the entire influenza outbreak/season (or until vaccine is available), 2) post-exposure chemoprophylaxis, 3) treatment of infected patients, and 4) a combination of chemoprophylaxis and treatment. Chemoprophylaxis is the best strategy to prevent the spread of influenza. Several nursing home studies of influenza prevention support the use of prophylactic antivirals. In a model of the 1957 to 1958 influenza pandemic (H2N2), targeted antiviral prophylaxis of close contacts of influenza cases for eight weeks reduced the attack rate from 33 percent to 2 percent. However, this strategy is prohibitively expensive for most hospitals and local governments. For instance, the cost of administering prophylactic oseltamivir (75 mg/day) for six to eight weeks (the
average length of a pandemic outbreak in a community) to up to 10,000 hospital workers in a 600-bed hospital would range between $1 to $2 million (pharmacy data). This stockpiling cost would be incurred every five years as the expiration date approached. 

The most reasonable strategy is one that focuses primarily on treatment of ill first responders with additional targeted chemoprophylaxis of heavily exposed workers (e.g., respiratory therapists, those intubating influenza patients). This is financially feasible and offers adequate protection to first responders caring for influenza-infected patients during a pandemic outbreak. Recent studies have demonstrated that neuraminidase inhibitors administered as treatment (75 mg twice a day for five days) within 48 hours of symptoms not only decrease the duration of illness but also decrease the incidences of hospitalization, antibiotic use, and mortality. First responders could easily be monitored for symptoms (e.g., fevers, myalgias) of influenza. It is likely that such monitoring would identify the majority of ill workers and thus allow timely administration of antiviral therapy.

Even with optimal infection control practices, approximately 25 to 30 percent of first responders will become ill during an influenza pandemic. Using a 600-bed hospital with 10,000 employees as an example, between 2,500 and 3,000 people would require treatment with a five-day course of oseltamivir (10 pills). The total cost to stockpile enough oseltamivir using this strategy would be $100,000 to $120,000 (pharmacy data). Additional stockpiling for limited chemoprophylaxis and treatment of patients and high-risk contacts could be expected to add another $20,000 to $40,000. Given the five-year expiration date on capsules oseltamivir, the cost per year for a 600-bed hospital would be $24,000 to $32,000. Costs to smaller hospitals would be considerably less. Local governments could stockpile for nonhospital first responders with economic support from the state and federal governments. The federal government currently has plans to stockpile enough oseltamivir for 81 million people. Much of this stockpile could be stored locally, where it would be immediately accessible to first responders.

**CONCLUSION**

In summary, hospitals and local governments should take on some of the burden of stockpiling oseltamivir. When the next influenza pandemic
occurs, there will almost certainly not be enough vaccine available to protect the citizenry and, if mortality rates are high, it may be difficult to convince first responders to continue to care for patients with influenza. The availability of antivirals, especially oseltamivir, will be of paramount importance, as they offer the possibility of both chemoprophylaxis and treatment. Even if the CDC maintains a large stockpile of antivirals, it is unlikely that this cache will be efficiently distributed in the early stages of a rapidly spreading influenza pandemic. The demand for this drug will be too great, too diffuse, and too immediate. Hospitals should consider stockpiling enough oseltamivir to offer a combination of treatment and chemoprophylaxis to employees and patients. Furthermore, the CDC should help local governments establish their own stockpiles for nonhospital first responders. The cost is both reasonable and justifiable when one considers the inevitability of future influenza pandemics.

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