

## 2009 H1N1 Influenza Issue Brief

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### The Use of Antivirals for 2009 H1N1 Influenza Virus Infection

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Use of antiviral medication is a key element of U.S. plans for responding to an influenza pandemic. Consequently, portions of federal and some state stockpiles of antivirals were distributed in response to the current 2009 H1N1 influenza epidemic. How best to utilize these medications during a pandemic is a complex question that warrants careful consideration.

In the Strategic National Stockpile (SNS), which is managed by the Centers for Disease Control and Prevention (CDC), the federal government has stockpiled antivirals, mostly oseltamivir (Tamiflu®), for use during a pandemic. Influenza antiviral medications are approved for both the treatment and prevention (prophylaxis) of influenza A; however, for a variety of reasons, they are not prescribed for the majority of patients with seasonal influenza.

The CDC and the Food and Drug Administration (FDA) have issued guidance to assist healthcare providers and public health officials in determining who should receive antivirals during the current H1N1 influenza epidemic (see below).<sup>1</sup> Given what is known about the 2009 H1N1 flu epidemic at this time, we believe that the federal government's guidance is scientifically sound and provides sufficient latitude for clinicians and public health officials to make decisions based on the unique circumstances in their communities. It is possible that this guidance could change as the epidemic unfolds, so it is important to regularly check CDC antiviral guidance updates.

### What Antivirals Can Be Used for 2009 H1N1 Influenza?

To date, the 2009 H1N1 influenza virus has been sensitive (susceptible) to the neuraminidase inhibitors oseltamivir (Tamiflu®) and zanamivir (Relenza®). CDC has issued detailed guidance for the use of these antivirals for treatment and prophylaxis of 2009 H1N1 influenza among various population groups (eg, adults, children, and pregnant women).<sup>1</sup> Currently, the virus is resistant to the M2 inhibitor class of antivirals, which includes amantadine and rimantadine.<sup>1</sup>

### Is the Development of Antiviral Resistance a Major Concern?

In the past, influenza viruses have demonstrated the capability of becoming resistant to antivirals. As the neuraminidase inhibitors are used more widely, there is a risk that the 2009 H1N1 influenza virus may become resistant to that class of antivirals as well. Resistance could develop as a result of mutation or genetic reassortment with an already resistant influenza virus. During the past year, nearly all isolates of the predominant seasonal influenza virus in the U.S. have been resistant to Tamiflu®.<sup>2</sup>

## Should We Limit Our Use of Antivirals at This Time?

Given our understanding of the H1N1 influenza epidemic at this time, some recommendations for the use of antivirals are straightforward, while others are complicated. There are important risks associated with using antivirals too broadly for treatment and prophylaxis, and the benefits of their use must be weighed against these risks. The principal risks are depletion of finite supplies of antivirals and promotion of antiviral resistance.

In past influenza pandemics, such as those in 1918 and in 1957, an initial wave of mild illness occurred that was followed by a second, more severe wave of illness 6 months later.<sup>3</sup> Given this history, we must be mindful of the need to preserve as many treatment options as possible for a potential second wave of H1N1 influenza in the Fall of 2009.

Even if a vaccine for 2009 H1N1 influenza is ready by the Fall, it is not likely to be 100% effective or available to everyone. Therefore, we will still need antivirals to treat those who do get sick and/or to treat or prevent illness in those who are unable to get vaccinated (eg, due to allergies or contraindications). Also, while pharmaceutical companies are ramping up their production of antivirals, their capacity to do so does have some limitations.<sup>4</sup>

## Does the U.S. Have Enough Antivirals for an H1N1 Influenza Pandemic?

The amount of antiviral courses needed during an epidemic or a pandemic would depend on the number of people infected and the severity of the disease. If antivirals are used prudently and given only to those who truly have a medical need for them, there is probably a sufficient supply of Tamiflu® and Relenza® for the current epidemic, as well as for a more severe pandemic.

It is less clear whether there would be sufficient supplies for a more severe pandemic if the currently stockpiled antivirals were used much more broadly than for treatment, such as for widespread prophylaxis (ie, prevention of infection).

Roche and GlaxoSmithKline, the respective makers of Tamiflu® and Relenza®, have also reported that they are ramping up global production of their antivirals in response to H1N1.<sup>4</sup>

## How Many Antiviral Courses Are Stockpiled in the U.S.?

Federal and state governments have made significant investments in stockpiling antiviral medications in recent years.

- **Federal.** Several years ago, the U.S. Department of Health and Human Services (HHS) set a national goal of stockpiling 81 million treatment courses of the antivirals Tamiflu® and Relenza® to prepare for a severe pandemic in which 25% of the population could need to take antivirals. The SNS now has approximately 50 million treatment courses of these antivirals (primarily Tamiflu®). The SNS does not include additional regimens that the Department of Defense and the Veterans Administration stockpile for treatment and prophylaxis.<sup>5</sup>
- **State and Local Jurisdictions.** Within the past few years, HHS offered states a 25% subsidy to purchase antivirals to stockpile for a pandemic. To date, states have stockpiled 23 million courses of

antivirals, but they still need to purchase 8 million additional courses to meet the national goal of 81 million courses. In addition, pharmacies stock antivirals to treat seasonal influenza.

- **Employers.** Some employers have stockpiled antivirals for their employees and, in some cases, for their customers. A portion of this stockpiling is occurring through employer stockpiling programs developed by Roche and GlaxoSmithKline.<sup>6,7</sup>

### Why Didn't States Purchase All of the Antivirals They Needed to Help Meet the National Goal?

HHS gave states the option to purchase these medicines but did not require them to do so. HHS also provided states with a federal subsidy of \$170 million, which carried with it the requirement that states pay for 75% of the cost of the medicine. However, many jurisdictions that were facing budgetary or other challenges (eg, political opposition and medication storage, rotation, and shelf-life issues) did not purchase their full allocation of antivirals under the subsidy.<sup>8,9</sup> Also, CDC will provide states with a certain percentage of antivirals from the SNS when needed.

To date, states have purchased 23 million of 31 million antiviral courses to meet the national stockpiling goal of 81 million courses. It is estimated that purchasing the additional 8 million courses will cost \$122 million.<sup>10</sup> Additional funding would be needed to purchase antivirals that would be given prophylactically to healthcare and critical infrastructure workers to prevent them from becoming ill.<sup>10</sup>

### Have Stockpiled Antivirals Been Used in the 2009 H1N1 Influenza Response?

Yes. For the 2009 H1N1 influenza outbreak, the federal government released a total of 11 million antiviral treatment courses from the SNS to all 50 states.<sup>11</sup> In April 2009, HHS Secretary Sebelius announced that the agency will spend \$251 million to replace these 11 million treatment courses to replenish the SNS and will purchase an additional 2 million courses to replace the 400,000 treatment courses provided to Mexico for H1N1 and to have on hand for other outbreak needs.<sup>11</sup>

### Why Doesn't the U.S. Government Stockpile Enough Antivirals for Every American?

During a pandemic, not everyone will become infected and even fewer will need to take antivirals for treatment. For example, during the severe 1918 influenza pandemic, 30% of the U.S. population contracted the disease.<sup>12</sup> So, even though the U.S. has a population of more than 300 million, we do not necessarily need to stockpile enough antivirals for every person in order to be prepared for a pandemic. The HHS goal was for the U.S. to have enough antivirals stockpiled to be able to treat about 25% of the total population during a severe pandemic.

### Have Antiviral Shortages Occurred in the U.S. during the 2009 H1N1 Influenza Outbreak?

Shortages can occur if there is a run on pharmacies by people who want to have antivirals on hand "just in case" or if antivirals are prescribed to people who are at low risk of infection. There is evidence that prescriptions for and sales of antivirals surged during this outbreak.<sup>13</sup> It is possible that spot shortages occurred at some

pharmacies in the U.S.; however, large quantities of antivirals are stockpiled in the SNS and also by many state and local governments.

In May, CDC and FDA noted the potential for spot shortages of medications and asked consumers to “avoid purchasing excessive quantities of medical products that treat or fight influenza so that these products continue to be available to those most in need.”<sup>14</sup> FDA also asked people to inform the agency of fraudulent products or criminal activities related to H1N1 and began posting a list of websites hosting fraudulent products related to 2009 H1N1 influenza (ie, products not authorized by FDA and for which FDA had issued a warning).<sup>15,16</sup>

### Do Other Countries Stockpile Antivirals?

Many nations have stockpiled antivirals to prepare for a possible influenza pandemic. For example, it has been reported that France and England have enough antiviral courses for half of their populations, Australia has enough for about one-third of its population, and Hong Kong has enough for about 3 times its population.<sup>17</sup>

### Is the FDA Doing Anything to Expand the Use of Antivirals for H1N1 Influenza?

In response to the 2009 H1N1 influenza outbreak, the FDA issued several Emergency Use Authorizations (EUAs) at the end of April 2009.<sup>18-20</sup> An EUA allows FDA to authorize the use of an unapproved medical product or an unapproved use of an approved medical product during certain types of emergencies.<sup>18</sup> For the current response, the H1N1 flu EUAs, among other things:

- Allow for use of Tamiflu® to treat and prevent influenza in children under 1 year of age (Tamiflu® is currently approved by the FDA for the treatment and prevention of influenza in patients 1 year and older, so the EUA expands the population that could receive the medicine).
- Allow for distribution of both Tamiflu® and Relenza® to large segments of the population without complying with federal label requirements otherwise applicable to dispensed drugs and to be accompanied by written information about the emergency use of the medicines.

In addition, FDA established an antiviral team for the purpose of identifying and evaluating antivirals that could be used for prevention and treatment of the 2009 H1N1 influenza virus and facilitating access to the medicines.<sup>21</sup> The antiviral team is also in communication with manufacturers “to explore potential investigational options” for treating the virus.<sup>21</sup>

### We Concur with CDC Guidance on the Use of Antivirals for the 2009 H1N1 Influenza Virus.

CDC has issued detailed interim guidance on the use of the antivirals Tamiflu® and Relenza® for 2009 H1N1 influenza treatment and prophylaxis.<sup>1</sup> This guidance includes recommendations for using each medicine for treatment and prophylaxis of adults and children.<sup>1</sup> CDC has also issued additional interim guidance and considerations for treatment and prophylaxis of the following high-risk groups: infants and young children,<sup>22</sup> HIV-infected adults and adolescents,<sup>23</sup> pregnant women,<sup>24</sup> and patients with cardiovascular disease.<sup>25</sup>

CDC’s antiviral recommendations for H1N1 might change as additional data become available, so it is important to regularly check CDC H1N1 updates.

## References

1. U.S. Centers for Disease Control and Prevention. *Interim Guidance on Antiviral Recommendations for Patients with Novel Influenza A (H1N1) Virus Infection and Their Close Contacts*. May 6, 2009. <http://www.cdc.gov/h1n1flu/recommendations.htm>. Accessed May 7, 2009.
2. U.S. Centers for Disease Control and Prevention. Antiviral drug-resistant strains of seasonal influenza virus. December 18, 2008. <http://www.cdc.gov/flu/professionals/antivirals/resistance.htm>. Accessed April 29, 2009.
3. Barry JM. Where will the swine flu go next? [OpEd] *New York Times* April 27, 2009. <http://www.nytimes.com/2009/04/28/opinion/28barry.html?scp=1&sq=barry%20op%20ed&st=cse>. Accessed April 29, 2009.
4. Global drug industry responds to H1N1 flu outbreak. *Drug Industry Daily* May 4, 2009.
5. U.S. Department of Health and Human Services. *Guidance on Antiviral Drug Use during an Influenza Pandemic*. December 2008. [http://www.pandemicflu.gov/vaccine/antiviral\\_use.pdf](http://www.pandemicflu.gov/vaccine/antiviral_use.pdf). Accessed April 30, 2009.
6. Hoffmann-LaRoche, Inc. Antiviral stockpiling solution: the Roche Antiviral Protection Program. <http://www.pandemictoolkit.com/tamiflu-supplyordering/stockpiling-dilemma.aspx>. Accessed April 30, 2009.
7. GlaxoSmithKline. Pandemic planning. <http://www.pandemicplan.gsk.com>. Accessed April 30, 2009.
8. Trust for America's Health (TFAH). *Ready or Not? 2008*. December 2008. <http://healthyamericans.org/reports/bioterror08>. Accessed April 30, 2009.
9. Association of State and Territorial Health Officials. *ASTHO Antiviral Survey Summary*. December 2007. <http://www.astho.org/pubs/ASTHOAntiviralSurvey-SummaryFactSheet011008.pdf>. Accessed May 13, 2009.
10. Association of State and Territorial Health Officials. *Emergency Supplemental Appropriations Request to Support State and Local Swine Flu Response*. April 2009. <http://www.astho.org/pubs/SwineFluEmergencySuppRequest4-29-09.pdf?PHPSESSID=9082ea2c6c57ae84e7102ef7ce7f4746>. Accessed May 13, 2009.
11. Secretary Sebelius takes two key actions on Strategic National Stockpile [news release]. Washington, DC: U.S. Department of Health and Human Services; April 30, 2009. <http://www.hhs.gov/news/press/2009pres/04/20090430a.html>. Accessed May 5, 2009.
12. U.S. Department of Health and Human Services. *HHS Pandemic Influenza Implementation Plan. Part I of II*. November 2006. <http://www.hhs.gov/pandemicflu/implementationplan/pdf/introduction.pdf>. Accessed April 29, 2009.

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13. Johnson LA. Amid swine flu, sales of antiviral drugs surging. *Lake County Record-Bee* May 4, 2009. [http://hosted.ap.org/dynamic/stories/U/US\\_SWINE\\_FLU\\_DRUGS?SITE=CALAK&SECTION=HOME&TEMPLATE=DEFAULT](http://hosted.ap.org/dynamic/stories/U/US_SWINE_FLU_DRUGS?SITE=CALAK&SECTION=HOME&TEMPLATE=DEFAULT). Accessed May 5, 2009.
14. U.S. Food and Drug Administration. FDA and CDC information on potential “spot shortages” of supplies for treating and preventing novel influenza A (H1N1). <http://www.fda.gov/oc/opacom/hottopics/H1N1flu/shortages.html>. Accessed May 5, 2009.
15. U.S. Food and Drug Administration. Report suspected fraudulent products or criminal activity associated with H1N1 flu virus (swine flu). <http://www.fda.gov/oci/flucontact.html>. Accessed May 5, 2009.
16. U.S. Food and Drug Administration. Fraudulent 2009 H1N1 influenza products list. <http://www.accessdata.fda.gov/scripts/h1n1flu/>. Accessed May 5, 2009.
17. See, eg, Bradsher K. Quick action by Hong Kong reflects experience of SARS. *New York Times* May 2, 2009.
18. U.S. Food and Drug Administration. Emergency Use Authorizations questions and answers. April 28, 2009. [http://www.fda.gov/h1n1flu/eua\\_faq.html](http://www.fda.gov/h1n1flu/eua_faq.html). Accessed April 30, 2009.
19. U.S. Food and Drug Administration. Dear Health Care Professionals 2009 H1N1 Flu Virus [letter]. May 7, 2009. <http://www.fda.gov/oc/opacom/hottopics/H1N1flu/healthprofessional.html>. Accessed May 13, 2009.
20. U.S. Centers for Disease Control and Prevention. Emergency Use Authorization (EUA) of medical products and devices. <http://www.cdc.gov/h1n1flu/eua/>. Accessed May 6, 2009.
21. Statement of Joshua M. Sharfstein, MD, Principal Deputy Commissioner and Acting FDA Commissioner, before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives. April 30, 2009. <http://www.fda.gov/ola/2009/flu043009.html>. Accessed April 30, 2009.
22. U.S. Centers for Disease Control and Prevention. *Interim Guidance for Clinicians on the Prevention and Treatment of Novel Influenza A (H1N1) Influenza Virus Infection in Infants and Young Children*. May 11, 2009. <http://cdc.gov/h1n1flu/childrentreatment.htm>. Accessed May 12, 2009.
23. U.S. Centers for Disease Control and Prevention. *Interim Guidance—HIV-Infected Adults and Adolescents: Considerations for Clinicians Regarding Swine-Origin Influenza A (H1N1) Virus*. May 3, 2009. [http://cdc.gov/h1n1flu/guidance\\_HIV.htm](http://cdc.gov/h1n1flu/guidance_HIV.htm). Accessed May 5, 2009.
24. U.S. Centers for Disease Control and Prevention. Pregnant women and novel influenza A considerations for clinicians. May 7, 2009. [http://cdc.gov/h1n1flu/clinician\\_pregnant.htm](http://cdc.gov/h1n1flu/clinician_pregnant.htm). Accessed May 7, 2009.

## Center for Biosecurity of UPMC

25. U.S. Centers for Disease Control and Prevention. *H1N1 Flu and Patients with Cardiovascular Disease (Heart Disease and Stroke): Interim Guidance and Considerations for Health Care Providers and for State and Local Public Health Agencies*. May 2, 2009. <http://cdc.gov/h1n1flu/guidance/cardiovascular.htm>. Accessed May 5, 2009.

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