

Guidance on Antiviral Drug Use during an Influenza Pandemic



U.S. Department of Health and Human Services

Guidance on Antiviral Drug Use during an Influenza Pandemic

Summary

The use of prescription antiviral drugs to treat and prevent infection will be an important component of a pandemic influenza response. While current antiviral drug use strategies and publicly maintained stockpiles are targeted primarily for treatment of persons with pandemic illness, expanded antiviral drug production has allowed additional strategies to be considered. An interagency working group, with input from representatives of State, local and tribal public health agencies, considered scientific issues, ethics and values, and perspectives of stakeholders in developing draft guidance on antiviral use strategies and stockpiling. The antiviral drug use guidance in this document replaces the recommendations developed in 2005 which are published as part of the Department of Health and Human Service's (HHS's) pandemic influenza plan. As guidance, this document does not create a requirement; rather, it defines a prudent strategy for antiviral drug stockpiling and use that can contribute to a more effective pandemic response.

The guidance on antiviral use is based on the national pandemic response goals of slowing the spread of pandemic disease, reducing impacts on health, and minimizing societal and economic disruption. The working group recommends the following strategies and settings for antiviral use to meet these goals:

- Containing or suppressing initial pandemic outbreaks overseas and in the United States with treatment and post-exposure prophylaxis (PEP) among individuals identified as exposed to pandemic influenza and/or geographically targeted prophylaxis in areas where exposure may occur;
- Reducing introduction of infection into the United States early in an influenza pandemic as part of a risk-based policy at U.S. borders¹;
- Treatment of persons with pandemic illness who present for care early during their illness and would benefit from such treatment;
- Prophylaxis of high-risk healthcare workers and emergency services personnel for the duration of community pandemic outbreaks;
- Post-exposure prophylaxis of workers in the healthcare and emergency services sectors who are not at high exposure risk, persons with compromised immune systems who are less likely to be protected by pandemic vaccination, and persons living in group settings such as nursing homes and prisons if a pandemic outbreak occurs at that facility.

Antiviral drugs are being stockpiled by HHS as part of the Strategic National Stockpile, (SNS) and by States.² The current public sector stockpile target is 81 million drug regimens: 6 million regimens for containment and for slowing the entry of pandemic

¹ Policies to reduce the introduction of pandemic infection into the United States and the specific strategies for antiviral drug use in support of this objective are still being developed.

² Antiviral drug stockpiles also have been established by the Veterans Administration (VA) and Department of Defense (DoD) for treatment and prophylaxis of targeted groups. VA and DoD stockpiles and strategies are not included in this guidance

disease into the United States, and 75 million regimens for treatment. Implementation of recommendations for prophylaxis of healthcare and emergency services workers who have high-risk exposures and for PEP in recommended settings will depend largely on private sector organizations and businesses purchasing and stockpiling antiviral drugs for their employees. The working group encourages governments, healthcare organizations and other employers, and families and individuals as appropriate, to purchase and stockpile sufficient antiviral drug supply to support recommended antiviral drug use strategies and to plan for effective implementation at the time of a pandemic as part of comprehensive pandemic planning and preparedness.

In addition to the national recommendations on treatment and prophylaxis, businesses that provide goods or services essential to community health, safety, or well-being (“critical infrastructure” sectors) should strongly consider antiviral prophylaxis for critical workers as part of comprehensive pandemic preparedness planning, especially those workers who are individually critical and whose absence would jeopardize provision of essential services. Other employers may consider antiviral prophylaxis for workers to maintain business continuity or protect employees.³ PEP for household contacts of persons with pandemic illness will reduce their risk of infection and may decrease overall rates of pandemic disease in communities. Despite these potential benefits, however, further work is needed to assess the feasibility of this strategy and identify approaches for purchasing and stockpiling the antiviral drugs to support its implementation. Therefore, the working group makes no recommendation for household antiviral PEP at this time.

Antiviral medications from the SNS, other than those targeted for containment and use at U.S. borders, will be allocated *pro rata* and delivered to Public Health Emergency Preparedness Project Areas (includes 50 States, 4 major metropolitan areas, and 8 U.S. territories) when a pandemic occurs. The working group recommends that public sector antiviral drug supply be prioritized for treatment of all persons who may benefit from therapy based on assessment of medical need. Treatment is preferred to prophylaxis in settings of limited antiviral drug supply; targeting some antiviral drug supply for prophylaxis and prioritizing treatment for certain groups would raise significant ethical and logistical challenges. Effective implementation of community mitigation strategies to reduce rates of illness and greater accuracy in diagnosing pandemic influenza illness would reduce antiviral drug needs, potentially leading to an ability to provide some prophylaxis while maintaining a treatment policy. Among prophylactic antiviral drug uses, protecting front-line healthcare and emergency services personnel is the top priority.

Ongoing discussions with stakeholders and the public are important as part of a transparent process and to move forward in addressing implementation issues. Rapid implementation of these strategies during a pandemic will pose substantial challenges. Periodic reassessment of national antiviral drug guidance will be important based on scientific and technological advances. Strategies also should be reassessed when a

³ See Guidance for Employers of Antiviral Drug Prophylaxis at http://pandemicflu.gov/vaccine/antiviral_employers.pdf

pandemic occurs to take into account the characteristics of the virus, epidemiology of disease, and impacts on society.

Background

The use of influenza antiviral medications (specifically, prescription medications that have activity against the influenza virus, also referred to as antiviral drugs or antivirals) will be an important component of a multi-faceted response to an influenza pandemic. Other key response measures include non-pharmaceutical approaches such as social distancing (with multiple strategies described in the guidance on community mitigation⁴), improved hygiene, and use of respiratory protection measures such as facemasks and respirators in appropriate situations. Vaccination against the pandemic influenza virus is likely to provide the most durable protection against pandemic illness but pandemic influenza vaccine only can be developed once the pandemic virus is identified; no vaccine or only limited quantities of stockpiled pre-pandemic vaccine⁵ may be available when the first U.S. pandemic wave starts. Once pandemic vaccine becomes available, it will be administered according to a prioritization strategy that targets high risk and critical occupational groups and vulnerable populations first.⁶

By contrast with pandemic influenza vaccine where availability and supply at the onset of U.S. pandemic outbreaks cannot be predicted, antiviral medications can be stockpiled and availability assured at the onset of the pandemic. Plans for stockpiling antiviral drugs should be based on strategies for their use so that sufficient quantities are on hand to support recommended interventions. The current national target for Federal and State antiviral drug stockpiles is 81 million regimens. This includes 6 million regimens to contain or suppress initial pandemic outbreaks overseas and in the United States, and 75 million regimens targeted for treatment of ill persons. Of the 81 million regimens to be stockpiled, 50 million have been purchased by the Federal Government and 31 million are allocated for State purchase proportional to population, with a 25% Federal cost share. Antiviral agents recommended for inclusion in the stockpile based on a treatment strategy include the neuraminidase inhibitors, oseltamivir (Tamiflu[®]) and zanamivir (Relenza[®]), with about 80% and 20% of the Federal stockpile component made up of the respective agents.⁷ In addition, several million regimens of rimantadine, purchased in a season of influenza vaccine shortage, are still held in the Strategic National Stockpile (SNS). Additional stockpiling of M2-inhibitor antiviral drugs (amantadine and rimantadine) has not been recommended because resistance to these agents among circulating influenza A viruses is frequent and, among susceptible viruses, develops rapidly when they are used to treat influenza A virus infections.

⁴ See <http://www.pandemicflu.gov/plan/community/commitigation.html>

⁵ Pre-pandemic vaccine is vaccine made and stockpiled against novel influenza A virus subtypes. Pre-pandemic vaccine, if available against the influenza A virus subtype that causes the pandemic, is likely to only be partially protective against a pandemic virus because the antigenic match between the vaccine and pandemic viruses likely will be imperfect. Therefore, receipt of pre-pandemic vaccine does not reduce the importance of non-pharmaceutical strategies or of antiviral drug prophylaxis in recommended settings.

⁶ See <http://www.pandemicflu.gov/vaccine/prioritization.html>

⁷ See Working Group's summary of National Strategy for *Pandemic Influenza I Implementation Plan* action item 6.1.6.1., available here: www.pandemicflu.gov/plan/federal/summaryprogress2008.html

The 2005 HHS Pandemic Influenza Plan defines treatment as the primary strategy for antiviral drug use.⁸ Treatment was recommended for several reasons:

- 1) Studies show that for seasonal influenza, treatment with neuraminidase inhibitors within 48 hours of illness onset is efficacious compared to placebo in shortening the duration of influenza illness, and suggest effectiveness in reducing complications, hospitalizations (occurrence and length of stay), and mortality associated with influenza;^{9,10,11,12,13,14}
- 2) Treatment meets the expectations of healthcare providers and patients who present for medical care; and
- 3) In a setting of limited antiviral drug supply, treatment is the most efficient strategy to use available resources, when the direct effects of different drug use strategies are compared.

At the time the 2005 recommendation was made, global production of the neuraminidase inhibitors was limited. In the context of requirements for seasonal influenza use and pandemic stockpiling by the United States and other countries, sufficient drug was not available to support more expanded recommendations and stockpiling. Recent expansion of antiviral drug production capacity – including a U.S. based supply chain for oseltamivir – has made increased stockpiling possible. This, in combination with several recent analyses suggesting substantial potential benefits of prophylactic antiviral drug use in a pandemic, prompted a re-assessment of pandemic antiviral drug use strategies and potential stockpiling targets.

Purpose

This document replaces the 2005 recommendations and provides guidance to Federal, State, local, and tribal planners on antiviral drug use strategies and the number of antiviral regimens that would be needed to support implementation.¹⁵ This guidance supports national pandemic response goals to: 1) stop, slow, or otherwise limit the spread of a pandemic to the United States; 2) limit the domestic spread of a pandemic, and

⁸ U.S. Department of Health and Human Services Pandemic Influenza Plan, Appendix D, www.hhs.gov/pandemicflu/plan/appendixd.html

⁹ Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *Journal of Antimicrobial Chemotherapy* 2003;51:123-9.

¹⁰ Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Archives of Internal Medicine* 2003;163:1667-72.

¹¹ Nordstrom BL, Sung I, Suter P, Szneke P. Risk of pneumonia and other complications of influenza-like illness in patients treated with oseltamivir. *Current Medical Research & Opinion* 2005;2:761-8.

¹² Bowles SK, Lee W, Simor AE, et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999-2000. *J Am Geriatrics Soc.* 2002;50:608-16

¹³ McGeer A, Green KA, Plevneshi A, Shigayeva A, Siddiqi N, Raboud J, Low DE, Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis* 2007;45:1568-75.

¹⁴ Lee N, Chan PK, Choi KW, et al. Factors associated with early hospital discharge of adult influenza patients. *Antivir Ther* 2007;12:501-08.

¹⁵ Note that statements about antiviral drugs in this document and guidance for their use may not represent FDA-approved uses or FDA policy.

mitigate disease, suffering, and death; and 3) sustain infrastructure and mitigate impact to the economy and the functioning of society. As guidance, this document does not create a requirement; rather, it defines a prudent strategy for antiviral drug stockpiling and use that can contribute to a more effective pandemic response. The guidance should be considered “interim”; recommendations should be reassessed as new scientific and technological advances are made, and at the time of the pandemic when the characteristics of the pandemic virus and epidemiology of disease are known.

Process of Developing the Guidance

HHS convened a Federal interagency group that included representatives from Federal agencies¹⁶ and obtained input from State and local public health experts. Tribal health was represented by participants from the Indian Health Service. All working group members were free from conflicts of interest with antiviral drug manufacturers and manufacturers did not present to the working group or influence its deliberations.

In its deliberations, the working group considered the national goals of a pandemic response; results of scientific studies on the effectiveness of antiviral treatment and prophylaxis for seasonal influenza infections; treatment for H5N1 avian influenza infections; surveillance data and studies of antiviral resistance; results of mathematical modeling of antiviral drug and non-pharmaceutical interventions; perspectives of State, local, and tribal health officials; and public values and ethical principles. The potential impacts of antiviral treatment and PEP in households of persons with pandemic influenza disease were estimated using a mathematical model.

Key assumptions underlying estimates of antiviral impacts and the number of regimens needed to support the antiviral drug use strategies include the following:

- The pandemic will be severe with illness rates, hospitalization, and mortality extrapolated from the United States experience in the 1918 pandemic.¹⁷
- Community mitigation strategies¹⁸ *absent antiviral PEP* are assumed to reduce the attack rate of influenza illness in a pandemic by one-half, from 30% to 15% with commensurate reductions in hospitalization and pandemic mortality.
- Antiviral effectiveness and regimens for treatment and prophylaxis during the pandemic are assumed to be the same as for seasonal influenza.¹⁹

¹⁶ Participating Federal agencies included the Department of Health and Human Services (with representation from the Centers for Disease and Prevention, National Institutes of Health, Food and Drug Administration, Indian Health Service, and the National Vaccine Program Office), Department of Homeland Security, Department of Veterans Affairs, Department of Defense, Department of State, and Department of the Treasury

¹⁷ Although pandemic severity could be greater or less than experienced in 1918, extrapolation from this pandemic provides a historical basis for preparedness for a severe pandemic. As pandemic severity will be unknown at the time preparedness and stockpiling occur, planning for a severe pandemic assures sufficient resources if a less severe pandemic ensues.

¹⁸ See <http://www.pandemicflu.gov/plan/community/commitigation.html>.

¹⁹ Although an animal model study showed that a longer duration of treatment increased survival among mice infected with avian H5N1 virus, an expert panel convened by the World Health Organization (WHO) has not recommended changes in dose or duration when treating people with H5N1 infection.

- Diagnosis will be based on clinical findings given the absence of an accurate and rapid point-of-care diagnostic test. Over an entire community pandemic outbreak, the positive predictive value of a clinical influenza diagnosis is assumed to be 35%, i.e., only about one in three persons with clinical signs of influenza-like illness will actually have influenza disease.²⁰
- 60% of cases will be treated (and in scenarios estimating the potential impact and antiviral drug requirements of household post-exposure prophylaxis, all contacts in 60% case households will receive prophylaxis).
- Community outbreaks will last 12 weeks. This longer duration compared with past pandemic outbreaks assumes that community mitigation is effective at slowing transmission of infection in communities consistent with mathematical modeling results.
- There will be no protective effect of vaccine during the first pandemic wave. This conservative assumption is based on the uncertain timing of initial pandemic detection, global spread and vaccine development, uncertain vaccine manufacturing capacity, and the probable need for two vaccine doses to induce a protective immune response.

Quantitative estimates of the number of antiviral drug regimens²¹ needed to completely implement recommended strategies are based on these assumptions and therefore are subject to substantial uncertainty. Estimates should be reconsidered as additional scientific data become available and as new technologies (for example, sensitive and specific point-of-care diagnostic tests) are developed. Estimated stockpiling needs do not include antiviral drugs for a second pandemic wave; it is likely that substantial pandemic vaccination will have occurred by that time and ongoing production of antiviral drugs will provide additional capacity to address needs during subsequent disease waves.

Prophylaxis strategies considered by the Working Group include PEP and outbreak prophylaxis. PEP is given within 48 hours following close contact with a person who has pandemic influenza illness, for example those living in the same household, and requires one regimen per person to implement. Outbreak (“pre-exposure”) prophylaxis is given before exposure occurs at the onset of a community pandemic outbreak and is continued for the entire period of the local outbreak, potentially requiring up to eight antiviral drug regimens per person.²²

²⁰ Current rapid diagnostic tests for seasonal influenza are estimated as 70% sensitive and >90% specific but their accuracy for pandemic influenza is not known. The assumed positive predictive value (PPV) of 35% for a clinical influenza diagnosis is extrapolated from seasonal influenza outbreaks. Higher PPVs have been obtained in clinical investigation settings and among adults in some studies. Although PPV may be higher during a pandemic, especially if the attack rate of influenza is higher, increased care seeking for non-influenza respiratory disease and by the “worried well” also could decrease the value.

²¹ A regimen is defined as 10 drug doses: treatment, provided twice daily for 5 days, and post-exposure prophylaxis, provided once daily for 10 days both require a single regimen. By contrast, prophylaxis for the duration of a community outbreak may require up to 8 regimens for a 12-week outbreak.

²² The package inserts for each antiviral drug should be consulted for the duration of prophylaxis for which efficacy and safety data are available. Any additional safety issues that might arise with increased duration of exposure cannot be predicted with confidence in the absence of longer-term data. If changes in drug regimens are considered that might warrant use of an Investigational New Drug application or an

The working group considered prophylactic antiviral drug use strategies in various populations and settings. Among occupational groups, a key consideration was the risk of occupational exposure as defined by the Occupational Safety and Health Administration (OSHA) risk pyramid.²³ Workers with exposures to persons known or suspected to be infected with pandemic influenza are defined as being at very high and high risk; those who have unavoidable and frequent close contact with persons not known to be infected are defined as being at medium risk; and those without frequent close contacts are defined as being at low risk. A second consideration was the worker's role in maintaining essential community services or continuity of business operations that may be threatened in a severe pandemic. For non-occupational settings, people's health status (e.g., the presence of immunocompromising illness or therapy) and living situation (e.g., residence in a group setting such as a nursing home or prison) were considered. A description of specific groups considered for antiviral drug prophylaxis is provided in the Appendix.

Antiviral Drug Supplies

Guidance on the use of antiviral drugs in a severe influenza pandemic should be linked with the available supply. U.S. antiviral drug strategies and stockpile targets were included in the 2005 HHS pandemic influenza plan and were established when production capacity and supply were limited. Production capacity for both oseltamivir and zanamivir has been increased and now is sufficient to support expanded recommendations. However, these recommendations do not obligate the Federal Government or public sector to purchase or stockpile antiviral drugs for all recommended uses and implementation will depend on the actions of other sectors of society. Pandemic preparedness is a shared responsibility of all levels of government, businesses, families, and individuals. Responsibility for purchasing and stockpiling antiviral drugs for prophylaxis of occupationally defined groups will largely be in the private sector. Federal efforts to reduce barriers to purchasing and stockpiling antiviral drugs are ongoing. Federal guidance for employers is available at http://pandemicflu.gov/vaccine/antiviral_employers.pdf

Recognizing that expanding antiviral drug stockpiles will take time and that some States are unlikely to purchase their full allocation to support treatment of those with pandemic illness, prioritization may be needed until supply is sufficient to support all recommended uses. Public sector stockpiles should be prioritized for treatment because it represents the most efficient use of a limited drug supply, because prophylaxis for some while others are denied treatment would not be perceived as equitable, and because other measures can be implemented to protect workers and reduce the risk of exposure and infection.

In addition to the antiviral drugs that are stockpiled before the pandemic, there is a possibility that oseltamivir production in the United States may provide an opportunity to acquire limited additional supply when a pandemic is imminent and before (or during)

Emergency Use Authorization during an emergency declared by the Secretary justifying such use, FDA should be contacted as far in advance as possible to discuss regulatory needs and recommendations.

²³ See http://www.osha.gov/publications/influenza_pandemic.html

U.S. disease outbreaks. Any additional antiviral drugs that may be produced would provide additional flexibility. Because this supply likely will be limited and can not be predicted in advance, planners should not decrease stockpile targets based on an assumption that ongoing production will fill supply gaps. As all 20th century pandemics have occurred in both fall and winter disease waves (and during the 1918 pandemic, a first spring wave also occurred), this capacity may contribute to preparedness for later waves. Guidance for use of antiviral drugs may be different during a second pandemic wave when many people already would be immune because of prior disease or vaccination and when impacts on critical infrastructures may differ.

Ethical Perspectives

Allocation of antiviral drugs that are in limited supply raises several ethical issues. The following principles were considered by the working group in developing antiviral drug use recommendations:

- A principle of fairness suggests that all persons who are in a similar situation will have similar access to the medication that is available from public sector stockpiles. Availability of treatment will not be based on gender, race, ethnicity, citizenship, or ability to pay.
- A principle of autonomy allows organizations, businesses, and individuals to take steps toward pandemic influenza preparedness, including purchase and stockpiling of antiviral drugs. Promoting autonomy contributes to overall national preparedness, resiliency, and can increase the amount of antiviral drugs available potentially leading to community benefits. While autonomy may result in unequal access to antiviral prophylaxis, public sector stockpiles are targeted to provide a safety-net for all Americans to receive treatment in a fair and equal manner.
- Minimizing the harms of an influenza pandemic may require targeting resources to specific groups that protect health and safety and provide essential community services. The Ethics Subcommittee of the CDC Advisory Committee to the Director advises that targeting limited resources to protect societal interests is ethically appropriate.²⁴
- A principle of reciprocity posits that workers who assume increased risks due to their occupation and who provide benefits broadly to society – such as healthcare workers, firefighters, emergency medical services personnel, etc. – should be protected, if possible.
- Flexibility, defined as the ability to modify recommendations before the pandemic as more information becomes available and at the time of a pandemic when the characteristics of disease are known, also is important.

²⁴ See <http://www.cdc.gov/od/science/phec/guidelinesPanFlu.htm>

These principles are consistent with the values expressed in several public engagement and stakeholder meetings that were held to consider pandemic influenza vaccination prioritization. When asked to rate the importance of potential program goals, participants rated most highly the goals of protecting those who contribute to a pandemic response, who provide care for people with pandemic illness, who maintain essential community services, and who are at increased risk of infection because of their job.

Stakeholder Engagement

Consistent with ethical principles of transparency and inclusiveness and recognizing the value of public input in developing policy, representatives from the working group met with stakeholders in State and local government, public health, healthcare and emergency services, businesses, organized labor, and the public. Objectives of these meetings were to obtain input on the proposed recommendations; identify potential barriers to implementation; and define interventions that would facilitate implementation. Overall, 13 meetings were held with representatives from about 400 organizations who participated either in-person or by telephone. From this process, there was general agreement with expanding the antiviral drug guidance to include prophylactic uses, including consensus support for a recommendation of outbreak prophylaxis for healthcare and emergency services personnel who have frequent exposure to persons with pandemic influenza infection. Additional findings from the stakeholder engagement activities are included in the section on Implementation later in this document.

Recommendations and Rationales

General recommendations

1. The working group endorses the current policy to use a portion of the 6 million antiviral drug treatment regimens in the Strategic National Stockpile allocated for initial containment to support a multifaceted international containment response, if feasible, to slow the introduction of pandemic influenza into the United States, and to respond to the first cases that are introduced, if warranted based on the epidemiological situation. Other countries with stockpiles also are likely to contribute antiviral drugs to support international containment efforts coordinated by the World Health Organization.
2. Recommended antiviral drug use strategies should be reconsidered at the time of a pandemic based on the epidemiology and impacts of the pandemic. Data collected during the pandemic may be critical for policy decisions. Preparation of protocols before a pandemic to facilitate rapid data collection would be useful. Data needs include:
 - a. Attack rate of pandemic illness, case fatality rates, and identification of groups at high risk for severe morbidity and mortality;
 - b. Susceptibility of the pandemic virus to antiviral drugs and monitoring data on the rate of antiviral resistance;
 - c. Estimates of the effectiveness of treatment in preventing severe morbidity and death

- d. Evaluation of increased treatment dose and/or duration, if appropriate based on estimates of effectiveness of the standard regimen; and
 - e. Adverse event surveillance to identify unanticipated adverse events following antiviral treatment and prophylaxis – especially if prophylaxis is continued for longer than FDA approved indications. Current adverse event surveillance systems such as MedWatch should be supplemented with more active approaches.
3. If experience early during an influenza pandemic indicates that a treatment-focused strategy is not optimal because of biological (e.g., lower than anticipated antiviral treatment effectiveness), implementation (e.g., inability to deliver treatment early after illness onset), or behavioral (e.g., worker absenteeism due to fear of infection in the workplace) reasons, a mechanism needs to be in place to consider alternative strategies and provide national guidance. Advice from public health organizations, medical societies, and government advisory committees should be influential for decision making.
4. The public and private sectors should coordinate use of antiviral stockpiles so that available drug supplies most effectively contribute to achieving national pandemic response goals.
5. Information and educational materials should be developed by Federal agencies and advisory groups and disseminated to States and other stakeholders to support appropriate use of antiviral treatment and prophylaxis during an influenza pandemic, emphasize adherence with recommended regimens, and promote effective implementation.
6. Plans should be reassessed intermittently before a pandemic as antiviral drug options and production capabilities change, as planning evolves, as better point-of-care rapid diagnostic tests become available, and as new scientific data are generated on antiviral drug effects and resistance.

Recommended target groups and strategies for antiviral drug use

The working group recommends that antiviral drugs should be used in the following settings (see Table).²⁵

1. Containment or suppression of initial pandemic outbreaks overseas and in the United States – Mathematical model results suggest that a multifaceted response including public health measures and antiviral treatment, post-exposure prophylaxis, and geographically targeted prophylaxis may be effective in containing an initial pandemic outbreak and preventing a global pandemic. Containment, even if not

²⁵ Recommendations do not include antiviral drug use strategies or requirements to protect homeland and national security. The Department of Defense (DOD) currently maintains an antiviral drug stockpile and has developed strategies for antiviral drug use among essential personnel. Other Federal agencies also are considering their specific needs. The DOD general beneficiary population (e.g., dependents of active duty personnel) is included under the civilian guidance.

successful in preventing a pandemic, can slow the spread of disease to the United States allowing more time for preparedness. An international containment response is likely to be coordinated by the World Health Organization and include many international partners.

2. Use of antiviral medications among selected persons presenting for entry at U.S. borders early in the course of a pandemic as part of a risk-based strategy – A risk-based screening strategy will be implemented early in a pandemic in an attempt to slow the spread of the pandemic to the United States. Antiviral prophylaxis for persons with possible exposure to pandemic illness can potentially reduce the risk of infection, transmission, development of illness, severity, mortality and lessen the need for quarantine facilities at ports-of-entry.
3. Treatment of persons with pandemic illness who present for care early during their illness and would benefit from such treatment – Antiviral treatment may reduce the duration of illness, complications, hospitalizations, death, and transmission of infection to others. The effectiveness of treatment is likely to be greatest when started shortly after the onset of symptoms. Pandemic planning should focus on the ability to provide treatment as soon after onset of illness as possible and at least within 48 hours, although a recent study of persons treated at hospital admission suggested that later treatment still may be effective in reducing mortality. Persons who are immunocompromised or immunosuppressed also may benefit from later treatment. In a pandemic, the duration of pandemic viral replication and shedding may be longer than for seasonal influenza and later treatment may provide benefit; studies should be done at the time of the pandemic to provide further guidance.
4. Prophylaxis for the duration of community outbreaks for healthcare workers who have direct high-risk exposures to pandemic influenza patients and for front-line emergency services (e.g., law enforcement, fire, and emergency medical services personnel) – Workers in these occupational settings will be exposed to persons with pandemic illness and be at increased risk of acquiring infection. Moreover, burdens on healthcare and emergency services will be increased in a pandemic and prophylaxis will reduce absenteeism due to illness as well as from fear of becoming infected while at work. Because exposures would be frequent and prophylaxis before exposure is likely to be most effective in reducing illness and absenteeism, outbreak (pre-exposure) prophylaxis is recommended rather than post-exposure prophylaxis.
5. PEP of exposed persons in the healthcare and emergency services sectors who do not have regular contact with ill persons and are not receiving outbreak prophylaxis – Many workers in healthcare and emergency services are important to the delivery of those essential services but are not at high risk for exposure in the occupational setting. Examples might include kitchen and medical records staff at hospitals and 9-1-1 dispatchers for emergency response. PEP is recommended for these workers as this strategy requires fewer antiviral drug regimens compared with outbreak prophylaxis and is likely to provide sufficient protection for less exposed groups.

6. PEP of persons with compromised immune systems who are less likely to be protected by vaccination with pandemic influenza vaccine – Immunocompromised or immunosuppressed individuals are more likely to experience severe, complicated, and fatal pandemic illness if infected, and will shed pandemic virus for longer periods of time increasing the risk of transmitting infection to close contacts. Vaccination, when available, is less likely to protect this group than those with normal immunity. PEP will reduce the risks of infection and its consequences in this group.
7. PEP of persons living in residential settings such as nursing homes, prisons, and homeless shelters when an outbreak occurs in that setting – Antiviral drug PEP is effective in stopping seasonal influenza outbreaks in these settings and is recommended as routine public health practice. In a pandemic, PEP will protect these vulnerable populations in a setting where the risk of disease transmission and severe illness are high.

The total number of antiviral drug regimens needed to fully implement the working group recommendations substantially exceeds current public sector stockpiling targets. As a shared responsibility, implementation will require governments, employers, and families and individuals, as appropriate, to purchase and stockpile sufficient antiviral drugs and to plan for their use at the time of a pandemic. Current public sector stockpiles have been targeted for containment, delaying U.S. pandemic outbreaks, and treatment. Federal agencies have indicated intent to stockpile additional antiviral drugs to support prophylaxis for federally employed high-risk healthcare and emergency services workers. Fully implementing prophylactic antiviral drug strategies will require the establishment of stockpiles by employers in both public and private sectors. This approach is consistent with the role employers play in protecting their workers and operations against other types of risk. Expanding public sector stockpiles to meet updated estimates of treatment needs and to support outbreak control in closed settings merits consideration in future budget processes.

In addition to these recommended uses of antiviral drugs, the working group recognizes that antiviral prophylaxis also may be beneficial in other settings. Businesses that provide services essential to the health, safety, and well-being of communities have a special responsibility to plan to maintain those services in an influenza pandemic.²⁶ Antiviral prophylaxis is one intervention that can protect the health of workers, decrease absenteeism, and help preserve the ability to deliver essential goods and services. Because non-pharmaceutical measures also can provide substantial protection and not all companies have the capability to manage an antiviral drug program that includes stockpiling and dispensing a prescription medication, the working group does not recommend antiviral prophylaxis for essential workers in critical infrastructure businesses other than in the healthcare and emergency services sectors. However, these businesses should strongly consider whether antiviral prophylaxis (post-exposure or outbreak) should be included as part of a comprehensive pandemic preparedness and response plan. Outbreak prophylaxis may be particularly important for workers who are

²⁶ See <http://www.pandemicflu.gov/plan/pdf/cikrpandemicinfluenzaguide.pdf>.

individually critical to the provision of essential services, where their absence during a pandemic would jeopardize the delivery of those services. In addition, employers in all sectors may consider antiviral prophylaxis as a part of business continuity planning for a pandemic.

Post-exposure prophylaxis for household contacts of persons with pandemic influenza illness has been proposed to reduce secondary transmission to close contacts where risk is high and to reduce overall spread of the pandemic in communities. Clinical studies in seasonal influenza show PEP to be very effective in preventing illness among household contacts and mathematical modeling results suggest that this intervention, if widely applied, may reduce pandemic disease in communities. Despite these potential benefits, however, further work is needed to assess the feasibility of this strategy and identify approaches for purchasing and stockpiling the antiviral drugs to support its implementation. Therefore, the working group makes no recommendation for household antiviral PEP at this time.

1 **Table. Settings and strategies for antiviral drug use during an influenza pandemic and rationales.**

2

Setting and target population	Antiviral strategy	Rationale	Pandemic response goals addressed by antiviral strategy	Estimated number of regimens (million)
<i>Recommendations for antiviral drugs from public sector stockpiles</i>				
Initial pandemic outbreaks overseas and in the U.S.	Treatment; PEP, targeted prophylaxis	-- Effective containment of the initial outbreak of a novel influenza virus strain may prevent the pandemic -- Quenching efforts overseas and in the U.S will slow pandemic spread and provide more time for preparedness	Slow pandemic spread	6
Exposed travelers entering the U.S. early in a pandemic	PEP	-- Contributes to a risk-based policy to reduce the entry of infected persons and delay U.S. outbreaks	Slow pandemic spread	
Persons with pandemic influenza illness	Treatment	-- Reduces influenza complications, hospitalization, and death -- Reduces duration of illness and transmission of infection -- Meets patient and provider expectations for medical care	Reduce health impacts	79*
Outbreak control in closed settings (e.g., nursing homes, prisons)	PEP	-- High risk of illness and death when outbreaks occur in closed settings -- Documented success of PEP for seasonal outbreaks -- Consistent with accepted public health practice -- Protects those in whom vaccination may be less effective	Reduce health impacts	5
<i>Recommendations for antiviral drugs primarily from private sector stockpiles</i>				
Healthcare and emergency service workers	Outbreak (pre-exposure) prophylaxis for workers with high-risk exposure	-- Reduces infection and absenteeism in a critical workforce -- Protects those at highest occupational risk -- Reduces chance of transmitting infection to high-risk patients with illnesses other than influenza	Reduce health impacts Minimize societal disruption	103
	PEP given exposure of other workers			
Persons who are severely immuno-compromised	PEP	-- High risk for severe complications and mortality from pandemic influenza, if infected -- Antiviral drugs are the only option for disease prevention	Reduce health impacts	2
TOTAL NUMBER OF ANTIVIRAL DRUG REGIMENS FOR FULL IMPLEMENTATION				195

3 *A prior estimate of 75 million regimens has served as the basis for public sector stockpiling. The 79 million regimen estimate was calculated
4 using updated planning assumptions

Prioritizing antiviral drug use when supplies are limited

Antiviral medications from the Strategic National Stockpile will be allocated to States *pro rata* when a pandemic occurs. Whereas the Federal share combined with State-purchased antiviral drugs was estimated to be sufficient to treat all persons who present for care and may benefit from therapy in a pandemic, not all States have purchased their full allocation. Despite potential shortfalls when antiviral stockpiles are limited, treating all persons based on assessment of medical need is considered preferable to targeting certain priority groups for treatment. This approach better meets the ethical principle of fairness and recognizes the significant uncertainty in estimating stockpiling requirements. Effective implementation of community mitigation strategies to reduce rates of illness and greater care in diagnosing influenza-like illness may help reduce antiviral needs. Monitoring supply and antiviral use rates during a pandemic is important so that adjustments could be made in policy, if needed.

Treatment is preferred to prophylaxis in settings of limited antiviral drug supply as the need is clear and benefits likely to accrue for those who are treated. By contrast with the single regimen needed for treatment, if community mitigation measures are effective at reducing the illness rate in a pandemic to 15% and outbreak prophylaxis is given as eight antiviral drug regimens (to protect the recipient for a 12 week period), it would take about 53 antiviral drug regimens to prevent one infection. Diligent application of non-pharmaceutical measures can offer substantial protection for high-risk and critical workers, and information and education on the effectiveness of these measures can help reduce absenteeism due to fear of infection in the workplace. If needed to maintain critical functions, PEP after unprotected exposures (e.g., in a healthcare setting where respiratory protection with a respirator was not used) may have similar effectiveness and would be more efficient than outbreak prophylaxis when antiviral drug stockpiles are limited.

Reserving some antiviral drugs at the State level to use for outbreak control in closed and high-risk settings is recommended as an effective and efficient use of antiviral drug supply. PEP is recommended as a component of outbreak control *only* in settings defined by a high risk of transmission that may result in an explosive outbreak with high attack rates; a high risk of severe complications and death among those infected; and a lack of other effective control measures. Examples of such settings include long-term care facilities for persons who are elderly or have underlying illnesses, hospital bone marrow transplant units, and jails and prisons. School dormitories may also be a high risk setting if students are unable to return home before the pandemic and if the epidemiology of the pandemic is such that children are at increased risk. Use of antiviral drugs in these settings should be guided by results of an epidemiological investigation and recommendations by public health personnel.

Establishment of antiviral stockpiles by healthcare organizations, long-term care facilities (e.g., nursing homes), businesses, and families that include a person who is immunocompromised will expand antiviral drug availability and allow implementation of the antiviral prophylaxis recommendations without limiting the ability to provide treatment to persons who may benefit. Because separate caches of antiviral drugs will be

procured and stockpiled for these purposes, no prioritization strategy can be proposed as organizations or employers will stockpile to address their specific needs.

Implementation of antiviral drug use recommendations

Although this document does not focus on implementation, the working group considered feasibility as an important factor in making its recommendations. Implementation of these recommendations includes two components: implementing stockpiling and preparedness, and program implementation at the time of a pandemic. Barriers to establishing stockpiles for prophylaxis of healthcare and emergency services workers identified during stakeholder engagement meetings included cost, shelf-life of the drugs, the potential for seizure of private sector stockpiles by State health departments, and liability concerns. Issues of cost and shelf-life may be mitigated through a new program announced by the antiviral drug manufacturers where organizations pay a small annual per regimen fee for the manufacturer to reserve a contracted quantity of antiviral drug and assure current dating; at the time of a pandemic, this drug would be delivered within 48 hours of request with payment of the drug cost.²⁷ Although State and local governments may have the authority to seize stockpiled antiviral drugs, health officials participating on a working group of public health and business representatives convened by the Association of State and Territorial Health Officials (ASTHO) recognized the benefits of enhanced preparedness and coordination between public and private sectors and emphasized that this authority would be very unlikely to be used. Moreover, on October 10, 2008, the Secretary issued a declaration under the Public Readiness and Emergency Preparedness (PREP) Act covering oseltamivir and zanamivir. Under the PREP Act, the Secretary may specify that liability immunity is afforded to the extent countermeasures such as influenza antivirals are obtained through a particular means of distribution. In the influenza antivirals (oseltamivir and zanamivir) declaration, the Secretary specified that liability immunity is provided to governmental program planners, e.g. state and local governments, including tribes, to the extent they obtain oseltamivir and zanamivir through voluntary means of distribution. The Secretary made this specification based upon his finding that the possibility of governmental program planners obtaining antivirals other than through voluntary means would “undermine national preparedness efforts and should be discouraged.”

The PREP Act provides immunity from tort liability (except for willful misconduct) for entities and individuals involved in the development, manufacture, testing, distribution, administration, and use of antivirals. The immunity covers claims of loss caused, arising out of, relating to, or resulting from administration or use of antivirals in accordance with the Secretary's declaration. The declaration defined "administration of [oseltamivir and zanamivir]" to include "public and private delivery, distribution, and dispensing activities relating to physical administration of the countermeasures to recipients, management and operation of delivery systems, and management and operation of distribution and dispensing locations."

²⁷ For oseltamivir see Roche's website, <http://www.pandemictoolkit.com/tamiflu-supplyordering/stockpiling-dilemma.aspx>. For zanamivir, see GSK's website http://us.gsk.com/html/media-news/pressreleases/2008/2008_us_pressrelease_10131.htm

When a pandemic is imminent, distribution of antiviral drugs maintained in the national stockpile will be initiated, with each State receiving a *pro rata* share. Treatment using drugs from public sector stockpiles will be provided at no cost to the patient. During the pandemic, rapid diagnosis and dispensing are critical for optimally effective treatment and PEP. While studies with seasonal influenza show effectiveness if drugs are started within 48 hours of illness onset, more rapid administration of antiviral drugs has been shown to result in greater treatment impact. Pandemic planners are encouraged to develop strategies that will support rapid implementation of treatment and prophylaxis. This requires education so that ill persons seek medical consultation or care soon after symptom onset, timely diagnosis, and rapid dispensing of antiviral drugs. In healthcare and emergency service sectors, workers who provide direct patient care and have high-risk exposure must be identified, and plans must be made for dispensing to support outbreak prophylaxis when local circulation of the pandemic virus is first identified. Monitoring systems must be established to track public sector antiviral drug supply and utilization to assess whether supplies are likely to be adequate for recommended uses, to assess rates and impacts of antiviral drug resistance, and to identify adverse events associated with antiviral drug use.

Uncertainties and Risks

Antiviral treatment and prophylaxis can be important components of an effective pandemic response, reducing pandemic illness and its consequences and contributing to maintenance of essential services and infrastructures. The working group recognizes a number of uncertainties and risks associated with antiviral stockpiling and program implementation. However, the risk of a pandemic, its potential consequences, and the benefits of an effective response justify the substantial expenditures that already have been made in establishing public sector antiviral drug stockpiles and the recommendation to expand antiviral drug use strategies and stockpiling.

There are several uncertainties related to the potential effectiveness and impact of antiviral drugs. Antiviral resistance may limit or eliminate the effectiveness of treatment and prophylaxis for those infected with a resistant virus. Resistant influenza viruses have been identified in some children and adults who have received antiviral treatment for seasonal and avian H5N1 influenza illness but transmission of the resistant virus has been rare. Surveillance during the first part of the 2008 – 2009 influenza season in the United States has identified oseltamivir resistance among most influenza A (H1N1) virus isolates.²⁸ Other seasonal influenza virus isolates and H5N1 isolates remain susceptible. Resistance among seasonal influenza strains does not predict resistance among pandemic influenza viruses. It is unknown whether resistance to zanamivir or oseltamivir may become a problem with widespread use of the drugs during a pandemic. Results of mathematical modeling to assess the impact of antiviral resistance are sensitive to the assumptions on which the model is based but suggest that antiviral treatment and prophylaxis would remain beneficial overall unless some of the pandemic viruses

²⁸ Information on antiviral resistance will be updated in weekly CDC surveillance reports (available at <http://www.cdc.gov/flu/weekly/fluactivity.htm>).

originally introduced into the U.S. at the beginning of a pandemic are both resistant and fully transmissible.

Treatment effectiveness also may be less if the usual dose and duration of therapy are not optimal for a pandemic virus. If recommendations were modified to increase the treatment regimen to increase effectiveness, stockpiled supplies would be used up more rapidly. Because prophylaxis is given to those who are not infected, prophylactic dose and regimen likely would remain unchanged.

There are also sources of uncertainty regarding the quantity of drug to stockpile for treatment and prophylaxis. If the pandemic was more severe, the effectiveness of non-pharmaceutical responses (“community mitigation” measures) was less than anticipated or a greater proportion of people with pandemic illness presented for care, more antiviral drug would be needed for treatment. By contrast, shorter community outbreaks, more accurate diagnosis of influenza, or the availability of improved diagnostic tests would reduce the amount of antiviral drug needed for treatment and prophylaxis. The timeliness and quantity of pandemic vaccine that is available could also have a substantial impact.

It is possible that a pandemic may not occur before the approved expiration date of stockpiled antiviral drugs. Whereas a shelf-life extension program exists for drugs held in the Strategic National Stockpile, based on documentation of potency, this program has not yet been extended to State stockpiles and is unlikely to be extended further to the private sector. Risk that investment in stockpiling antiviral drugs would be lost if drugs becoming outdated may be mitigated through the new program announced by the antiviral drug manufacturers, as described above.

Additional side effects may be identified with much more widespread use of antiviral drugs during a pandemic. Recently, neurobehavioral disorders were observed among a small number of people treated with oseltamivir. While the role of the treatment in the occurrence of this complication is unclear, FDA has added information on these events to the package insert.

Despite the risks and uncertainties associated with antiviral drug stockpiling, the working group considers the recommendations appropriate, the assumptions balanced, and the pandemic threat of sufficient magnitude to justify the investment within the context of other planning and preparedness actions. The Federal government will continue to work with public and private sector partners to reduce uncertainty, mitigate risk, and facilitate effective implementation of national guidance on antiviral drug use.

Next Steps

This interim guidance on antiviral drug treatment and prophylaxis is based on consideration of scientific, behavioral and logistical issues, as well as societal values. Ongoing discussions with stakeholders and the public will be useful as part of a transparent process and to move forward in addressing implementation issues. Antiviral prophylaxis guidance should be reassessed periodically as additional information

becomes available and new infrastructures, capabilities, and materials are developed. Logistical issues surrounding stockpiling (e.g., warehouse requirements for an expanded stockpile) and implementation also should be considered.

The working group recommends the following actions to improve the scientific basis for guidance and the ability to effectively implement an antiviral strategy during an influenza pandemic:

1. Human and animal studies assessing effectiveness of antiviral drug treatment against H5N1 and influenza A viruses of other subtypes with pandemic potential considering timing of drug initiation relative to symptom onset, dose, treatment duration, treatment outcome, and emergence of resistant clones during therapy.
2. Evaluation of approved and investigational antiviral drugs and other modalities (e.g., treatment with hyperimmune globulin or convalescent plasma) for treatment effectiveness in persons who are admitted to hospital or have severe influenza illness or complications at treatment onset.
3. Evaluation of combination therapy with different classes of antiviral agents and impact on treatment effectiveness and emergence of resistance.
4. Development of systems to track drug availability and rate of use in real-time at community levels.
5. Coordination between Federal, State, local, and tribal planners and the private sector on the maintenance and use of antiviral drug stockpiles held in the public and private sectors.
6. Development and pre-positioning of protocols for ongoing data collection during an influenza pandemic that will generate information on antiviral drug effectiveness and optimal dose/duration of treatment, allowing reassessment of recommendations as a pandemic evolves.
7. Ongoing and expanded surveillance for antiviral drug resistance among circulating influenza virus strains and at the time of a pandemic. The development of diagnostics to detect antiviral resistance that can be applied at State health department and hospital would facilitate more robust surveillance.
8. Development of plans for enhanced adverse event surveillance that can be implemented at the time of a pandemic.

Appendix. Potential settings and strategies for antiviral drug use in an influenza pandemic

The working group considered antiviral drug use in a variety of settings. Following is a summary of working group deliberations leading to its recommendations. Note that not all of the antiviral drug use settings and strategies discussed by the working group were recommended in the national guidance.

1. Treatment

Treatment with neuraminidase inhibitors has been shown to shorten the duration of seasonal influenza illness by about 1 – 1.5 days when begun within the first 48 hours after symptom onset.²⁹ A Canadian observational study conducted after regulatory approval suggested that the magnitude of benefit increases with a shorter interval from symptom onset to treatment: among persons presenting for treatment within the first 12 hours of illness, the duration of symptoms was shorter by 3 to 4 days.³⁰ Significant benefit has not been documented when treatment is begun more than 48 hours after symptom onset.

Post-hoc combined analyses of data from randomized controlled trials suggest that early neuraminidase inhibitor treatment of patients with uncomplicated influenza significantly reduces rates of lower respiratory tract complications requiring antibiotic treatment (bronchitis and pneumonia) and hospitalization. For oseltamivir, reductions of 55% and 59% occurred for the respective outcomes. However, the number of persons experiencing these outcomes was limited, confidence limits around these estimates were wide, relatively few persons at high risk of influenza complications were included in the study groups, and the analysis combined subjects from different trials and was not specified in the original protocols.³¹ Epidemiological studies comparing outcomes of patients who did or did not receive oseltamivir treatment also found significant reductions in pneumonia and hospital admission.³² Clinical trials were not powered to assess a potential impact of treatment on influenza mortality because of their limited sample size. Such an impact would be predicted based on the reduction in illness severity, defined by lower respiratory infection or a need for hospitalization.

An epidemiological study in Toronto, Canada, assessed the impacts of oseltamivir treatment at hospital admission for persons with confirmed influenza infection compared with an untreated control group. Most of the treated patients were elderly (mean age 79 years old) and many had underlying health conditions. Mortality in the treated and untreated groups was 3.9% and 10%, respectively. Treatment was associated with a

²⁹ See package labels, Oseltamivir: http://www.fda.gov/cder/foi/label/2002/21087S10lbl_update.pdf ; Zanamivir: <http://www.fda.gov/cder/foi/label/2001/21036s4lbl.pdf>

³⁰ Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *Journal of Antimicrobial Chemotherapy* 2003;51:123-9.

³¹ Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Archives of Internal Medicine* 2003;163:1667-72.

³² Nordstrom BL, Sung I, Suter P, Szneke P. Risk of pneumonia and other complications of influenza-like illness in patients treated with oseltamivir. *Current Medical Research & Opinion* 2005;2:761-8.

significant reduction in mortality (Odds Ratio 0.21, $p = 0.03$).³³ In addition, a study of Canadian nursing home outbreaks showed significantly fewer deaths in nursing homes where oseltamivir was used for treatment compared with nursing homes where no treatment or amantadine treatment was given.³⁴

Treatment effects for pandemic influenza could differ from those for seasonal influenza illness. Oseltamivir and zanamivir were not available at the time of previous pandemics; amantadine which was used during the 1968 pandemic was effective as treatment. Although not a pandemic virus, a case series of patients with avian H5N1 infection reported by WHO found similarly severe outcomes among oseltamivir-treated and untreated persons. Treatment was begun, however, between days 4 and 22 of the illness and many patients had complications including pneumonia at the time therapy was begun.³⁵ More recently, a WHO review suggested that early oseltamivir treatment may reduce H5N1 associated mortality and, because of prolonged replication of this virus, that treatment is warranted even with late presentation.³⁶ *In vitro* and animal model data show that oseltamivir can be effective as treatment of H5N1 avian influenza, though one study suggested that optimal effectiveness may require a longer duration of therapy.³⁷ An expert panel convened by WHO made a strong recommendation for oseltamivir treatment of persons with avian H5N1 influenza infection.³⁸

In addition to its direct effects on duration and severity of illness, treatment may also have indirect benefits. Results of mathematical models suggest that treatment early in the course of illness can reduce transmission to close contacts. The magnitude of this effect is limited because the period of peak infectiousness occurs shortly after symptom onset, generally before treatment begins. Results of mathematical models should be interpreted with caution as they depend on assumptions and parameters which often are based on limited data. Another indirect effect of treatment, associated with shorter illness duration and decreased worker absenteeism, would be a better ability to maintain effective healthcare, emergency services, and other essential community functions. The potential magnitude of this impact cannot be quantified.

In estimating the direct health benefits of treatment and the number of antiviral drug regimens needed to support a treatment strategy, key parameters include the attack rate of

³³ McGeer A, Green KA, Plevneshi A, Shigayeva A, Siddiqi N, Raboud J, Low DE, Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis* 2007;45:1568-75.

³⁴ Bowles SK, Lee W, Simor AE, et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999-2000. *J Am Geriatrics Soc.* 2002;50:608-16

³⁵ Beigel JH, Ferrar J, Han HM, et al. Avian influenza A (H5N1) infection in humans. *N Engl J Med* 2005;353:374-85.

³⁶ Writing committee of the second WHO consultation on clinical aspects of human infection with avian influenza A (H5N1) virus. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med* 2008;358:261-73.

³⁷ Yen HL, Monto AS, Webster RG, Govorkova EA. Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic A/Vietnam/1203/04 influenza virus in mice. *J Infect Dis* 2005;192:665-72.

³⁸ Schunemann HJ, Hill SR, Kakad M, et al. WHO rapid advice guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus. *Lancet* 2007;7:21-31.

pandemic disease, the proportion of persons with pandemic illness who are treated, the responsiveness of the pandemic virus to treatment and the potential need to adjust the dose or duration of treatment, and the ability to target treatment to persons with pandemic illness in the absence of a sensitive and specific point-of-care diagnostic test. We assume an attack rate of 15% for pandemic illness in the context of effective community mitigation and a positive predictive value of a clinical diagnosis of influenza-like illness (ILI) of 35%, as described above. We assume that 60% of persons with pandemic illness will be treated within 48 hours of illness onset; this estimate is slightly more than the approximately 50% of persons with seasonal influenza who seek care at any point during their infection. Health benefits are calculated assuming a 59% reduction in hospitalizations consistent with clinical trials for seasonal influenza, and an assumed 25% reduction in pandemic mortality.

Given these assumptions, for the first wave of a 1918-like pandemic, antiviral treatment could prevent about 144,000 deaths and about 1.85 million hospitalizations. A total of about 79 million antiviral regimens would be needed to support a treatment strategy. This suggests that one death would be prevented for about 550 antiviral regimens and one hospitalization would be prevented for about 40 antiviral regimens. At current Federal contract costs, this translates into a cost of about \$11,200 per death prevented and \$1,000 per hospitalization prevented – a highly cost effective intervention.

2. Post-exposure prophylaxis (PEP) for household contacts of persons with pandemic illness

For seasonal influenza, PEP among household contacts of persons with influenza infection has been shown to be very effective in preventing illness. The effectiveness of PEP using a neuraminidase inhibitor to prevent seasonal influenza illness has been 70% to 90% in household settings when started within 48 hours of the case's illness onset.^{39,40,41} There have been no studies of neuraminidase inhibitor PEP for pandemic influenza or for H5N1 avian influenza where secondary infections in close contacts have been extremely rare; studies in animal models show pre-exposure prophylaxis to be effective in preventing H5N1 infection.

PEP of household contacts will have the direct benefit of preventing infection, illness, and its consequences within the household – a setting where about one-third of all influenza transmission is estimated to occur. In addition, because persons in the house of a case-patient are less likely to become infected when PEP is given, they will not transmit infection to others in the community, reducing the overall spread and burden of influenza disease. Antiviral treatment is likely to have little impact on the overall rate of illness in communities. By contrast, household PEP may be more effective because it is given before people become ill and are infectious to others. The magnitude of this “indirect”

³⁹ Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA* 2001;285:748-74.

⁴⁰ Monto AS, Pichichero ME, Blanckenberg SJ, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis* 2002;186:1582-8.

⁴¹ Hayden FG, Belshe R, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *J Infect Dis* 2004;189:440-49.

benefit depends on the proportion of households that receive prophylaxis, how soon they receive the antiviral medication, and the effectiveness of prophylaxis. Mathematical models have assessed the potential impact of household PEP when applied in combination with non-pharmaceutical interventions including isolation of cases, voluntary quarantine of household members, dismissing children from schools and preventing them from re-congregating elsewhere, and reducing close contacts in communities and workplaces (“social distancing”). Under one scenario where antiviral PEP was implemented in 60% of case households at 24 hours after illness onset in the case-patient, one model predicts an 8% relative reduction in illness attack rate compared with a scenario where antiviral PEP was not included.⁴² Other models, using the same pandemic scenario, suggested smaller incremental benefits of adding antiviral PEP.^{43,44}

Household antiviral PEP also may contribute to the success of community mitigation strategies by improving compliance with recommendations for voluntary household quarantine. Well family members may be more willing to stay home with an ill person if they are protected with antiviral PEP. Some planners have framed this as an ethical issue: if persons are asked to assume greater risk by remaining at home with an ill family member, one should provide protection through household PEP.

In estimating the potential impacts and number of antiviral drug regimens needed to support a household PEP strategy, we assumed that 60% of case households would be included, prophylaxis would be started at 24 hours after illness onset in the case-patient, and that all household contacts would receive the medication. As described above, we assumed the positive predictive value of a clinical diagnosis of influenza is 35%. The impact of PEP on reducing illness attack rates was extrapolated from Ferguson’s mathematical model.

Assuming a 15% attack rate with community mitigation and antiviral treatment, the model predicts a reduction in attack rate to 12.5% with the addition of antiviral PEP. This corresponds to about 155,000 fewer deaths and about 838,000 fewer hospitalizations. Overall, the combination of treatment and household PEP is estimated to reduce pandemic deaths by about 288,000 and hospitalizations by about 2.4 million. To achieve these outcomes, based on the assumptions used in the model, would require a total of about 167 million antiviral regimens. The incremental antiviral requirement for PEP compared with a treatment strategy alone is 88 million regimens. Overall, this strategy could lead to the prevention of one death for about 580 antiviral regimens and prevention of one hospitalization for about 70 antiviral regimens. This represents a cost of about \$11,800 per death prevented and about \$1,400 per hospitalization prevented when treatment and household PEP are combined. Cost per death and hospitalization prevented by the PEP component alone would be about \$14,000 and \$2,600. Again, these estimates represents cost efficient outcomes based on commonly accepted standards and when compared with routinely recommended medical interventions.

⁴² Neil Ferguson, Imperial College, London, UK, unpublished data.

⁴³ Ira Longini, University of Washington, Seattle, WA, unpublished data.

⁴⁴ Steven Eubank, Virginia Tech, Blacksburg, VA, unpublished data

Prevention and cost-effectiveness estimates for antiviral treatment and household post-exposure prophylaxis strategies alone and in combination are shown in the Table.

Table. Health impacts, antiviral drug requirements, and cost-effectiveness of antiviral treatment and household post exposure prophylaxis strategies.

Parameter	Treatment alone	Household PEP alone	Treatment and Household PEP
Number of deaths prevented	144,000	155,000	288,000
Number of hospitalizations prevented	1.845 million	838,000	2.427 million
Number of antiviral regimens	79.4 million	106.4 million	167.1 million
Cost per death prevented*	\$11,200	\$14,000	\$11,800
Cost per hospitalization prevented*	\$900	\$2,600	\$1,400

*Average cost per regimen based on Federal contract price for oseltamivir and zanamivir, the relative proportions of each agent targeted for acquisition for the national stockpile, rounded to the nearest \$100

3. Prophylaxis of critical healthcare workers and emergency service providers

Maintaining effective healthcare and emergency response services (includes Emergency Medical Services, fire, and law enforcement personnel) will be essential in preventing adverse health outcomes and protecting public safety in a pandemic. The healthcare sector will face a massively increased burden while coping with a workforce diminished by illness and possibly other causes of absenteeism – for example, caring for an ill family member or due to fear of becoming infected in the workplace. In a survey of public health personnel in three Maryland county health departments,⁴⁵ only 54% of respondents indicated that they would likely report to work during a pandemic. In a multivariable analysis, one factor significantly associated with the likelihood of reporting was confidence in one’s personal safety. Respondents were not directly asked about antiviral drug treatment or prophylaxis and responses to a hypothetical scenario must be interpreted with caution. Limited information from the 1918 pandemic and experience in Toronto, Canada, during the recent SARS outbreak suggest much lower rates of absenteeism among healthcare workers. Nevertheless, the Maryland findings raise the possibility that absenteeism could be substantial and that antiviral prophylaxis may reduce absenteeism both by preventing illness and by improving perceptions of safety in the workplace.

Several potential strategies for prophylaxis in healthcare and emergency service settings could be considered. Because exposure to ill persons during a pandemic outbreak will be frequent for healthcare workers and emergency service personnel with direct patient

⁴⁵ Balicer RD, Omer SB, Varnett DJ, Everly GS Jr. Local public health workers’ perceptions toward responding to an influenza pandemic. *BMC Public Health* 2006;6:99. www.biomedcentral.com/1471-2458/6/99

contact, post-exposure prophylaxis would be essentially equivalent to outbreak prophylaxis – as soon as one 10-day course of PEP ended, another would likely begin. A modification of the PEP strategy may be to dispense PEP only when “unprotected” exposure occurred. Potential concerns with this approach for those with frequent high-risk exposures include whether it would be sufficient to reduce absenteeism that may occur due to fear of occupational infection, whether unprotected exposures could be accurately identified and how frequently they would occur in a heavily exposed population. In addition, there is a lack of data on the effectiveness of personal protective equipment measures in preventing influenza transmission. A hybrid strategy that includes outbreak prophylaxis for workers with frequent high-risk exposures and post-exposure prophylaxis when unprotected exposure occurs for those who have less frequent or intensive patient contact tailors the intervention to the level of risk and is the preference of the working group. Although data on the effectiveness of outbreak prophylaxis are limited, two studies of zanamivir report protective efficacies in adolescents, healthy and high risk adults in the same range as seen for post-exposure prophylaxis.^{46,47}

Estimating the number of antiviral drug regimens needed to support prophylaxis for healthcare and emergency service workers using this strategy requires defining populations of workers with more frequent higher risk exposures and those at lower risk. Of the approximate 13 million workers in the healthcare sector as defined by the Bureau of Labor Statistics, we estimate that two-thirds of healthcare workers, or about 8.7 million including those in hospital-based, outpatient, home health and long term care positions may have frequent high-risk exposures along with 2 million persons in emergency services sectors, encompassing Emergency Medical Services, fire service and law enforcement personnel. The remaining 4.3 million healthcare sector workers would receive post-exposure prophylaxis when unprotected exposure occurs, estimated as 4 times during a 12 week community outbreak. Based on these estimates, a total of 102.8 million antiviral regimens would be needed. Additional work to define specific groups at higher and lower risk and their respective numbers is needed.

The health benefits of this prophylactic strategy cannot be easily quantified. Several studies suggest that healthcare workers who have patient exposure have increased rates of seasonal influenza infections.^{48,49} In addition to the direct effect of reducing pandemic influenza illness and its consequences, prophylaxis also would reduce the risk of transmission to family members, co-workers, and to patients. Influenza prevention by vaccination of healthcare workers has been shown to reduce nosocomial infection in

⁴⁶ LaForce C, Man CY, Henderson FW, et al. Efficacy and safety of inhaled zanamivir in the prevention of influenza in community-dwelling high-risk adult and adolescent subjects: a 28-day, multicenter, randomized, double-blind, placebo-controlled trial. *Clin Therapeutics* 2007;29:1579-90.

⁴⁷ Monto AS, Robinson DP, Herlocher ML, Hinson JM Jr, Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA* 1999;281:31-35.

⁴⁸ Elder AG, O'Donnell B, McCrudden EAB, et al. Incidence and recall of influenza in a cohort of Glasgow healthcare workers during the 1993-4 epidemic: results of serum testing and questionnaire. *BMJ* 1996;313:1241-2.

⁴⁹ Kawana A, Teruya K, Kirikae T, et al. Syndromic surveillance within a hospital for the early detection of a nosocomial outbreak of acute respiratory illness. *Jpn J Infect Dis* 2006;59:377-9

acute care hospitals⁵⁰ and mortality in long-term care facilities for the elderly.⁵¹ An additional impact would be to reduce absenteeism among workers in these critical sectors, improving the quality of healthcare and public safety. Many studies have shown improved health outcomes with a greater staff-to-patient ratio. During an influenza pandemic when healthcare burden is markedly increased, this effect may be even greater.

4. Prophylaxis of workers in other critical infrastructure sectors

Maintaining community services during an influenza pandemic is essential to achieving national pandemic response goals of mitigating adverse health consequences and reducing societal and economic disruption. In addition to healthcare and emergency services, critical infrastructure sectors defined by the Department of Homeland Security include utilities (electricity, natural gas, water), communications and information technology, transportation, food and agriculture, banking and finance, pharmaceutical, chemical, oil, and postal and shipping. Overall, about 70 million persons are employed in these sectors excluding healthcare and emergency services. A study done by the National Infrastructure Advisory Council (NIAC) developed a preliminary estimate of between 4 million and 8 million persons in these sectors as critical to maintenance of essential functions during a pandemic. By contrast with healthcare and emergency services, these critical workers, in general, will not have high-risk occupational exposure to pandemic infection, as defined by the Occupational Safety and Health Administration's risk pyramid.⁵²

Various measures are available to protect workers and maintain essential functions. Workplace exposures can be reduced by changing practices to decrease close contact between workers including having conference calls instead of meetings, and promoting teleworking and flexible scheduling. Educating workers not to report to work if ill with influenza-like symptoms and allowing leave when a household member is sick also will reduce workplace exposures. Providing education and materials to promote hygiene and the use of facemasks and other personal protective equipment, where appropriate under OSHA recommendations, may reduce the risk exposure to influenza if workplace contacts occur. Guidance for pandemic planning by businesses has been provided.⁵³

Antiviral post-exposure prophylaxis may provide an incremental benefit in preventing disease and could reduce absenteeism. The magnitude of this increment depends largely on what other antiviral and non-pharmaceutical strategies are implemented. Assuming that workers who are ill or exposed to an ill person in their household would receive treatment or PEP under the strategies described above, fewer workers are likely to be exposed in the workplace. In a setting of effective planning and implementation of non-pharmaceutical workplace interventions to reduce close contacts and the risk of infection

⁵⁰Salgado CD, Giannetta ET, Hayden FG, Farr BM. Preventing nosocomial influenza by improving the vaccine acceptance rate of clinicians. *Inf Cont Hosp Epidemiol* 2004;25:923-8.

⁵¹ Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of healthcare workers on mortality of elderly people in long-term care: a randomized controlled trial. *Lancet* 2000;355:93-7.

⁵² See <http://www.osha.gov/Publications/OSHA3327pandemic.pdf>

⁵³ See <http://www.pandemicflu.gov/plan/pdf/cikrpandemicinfluenzaguide.pdf>

if contacts occur, workers and essential functions can be protected, and the additional benefit of antiviral prophylaxis following a workplace exposure likely would be small.

The number of antiviral drug regimens needed to support prophylaxis for critical infrastructure workers outside of the healthcare and emergency services sectors would depend on the prophylaxis strategy and the target population. Two potential target populations may be considered:

- 1) Workers considered critical based on the NIAC analysis (4 – 8 million persons in non-healthcare or emergency service sectors); and
- 2) All workers in critical infrastructure sectors (about 70 million excluding healthcare and emergency services).

If outbreak prophylaxis was provided to all workers considered by NIAC to be critical, 32 – 64 million antiviral drug regimens would be needed. While fewer regimens would be required for a PEP strategy, it may not be feasible or acceptable to the employer or workforce to target only the subset of workers NIAC designates as “critical”: in the setting of a workplace exposure, providing prophylaxis to some exposed workers but not others may not be possible. Therefore, a broad PEP strategy for critical infrastructure, assuming an average of 1 exposure per worker during the course of a community outbreak, would require 70 million regimens based on targeting all workers in these sectors.

5. Post-exposure prophylaxis for outbreak control in closed populations

During seasonal influenza outbreaks, clusters of influenza infections often occur among elderly persons living in long-term care facilities (LTCFs). Factors promoting transmission of infection in LTCFs include frequent close contact between staff and residents and among residents, high patient density, and reduced immune response to vaccination among LTCF residents. Antiviral post-exposure prophylaxis has been shown to be effective in controlling influenza outbreaks in LTCFs and represents a standard public health practice.

Another setting where explosive influenza outbreaks may occur is aboard ships. Cruise ship outbreaks frequently are reported; risk factors include crowding and low vaccination rates among passengers and crews. Many elderly persons are passengers on these ships which increases the number of influenza complications that may be seen. Outbreaks also have occurred on Navy vessels although vaccination of crew members has substantially decreased this risk with seasonal influenza. Jails and prisons represent another high-risk setting due to crowding and a limited ability to apply other measures to reduce transmission of infection.

If one exposure per person is assumed for outbreaks in closed and high-risk settings, about 5 million antiviral drug regimens would be needed for PEP of persons in LTCFs and jails/prisons (estimated populations of 3 million and 2 million persons,

respectively⁵⁴). The number of regimens that may be needed to respond to ship-board outbreaks is uncertain. Recommendations against non-essential travel are likely to be issued during a pandemic and a substantial reduction in the number of persons who choose to take a cruise during a pandemic is likely.

6. Prophylaxis of persons at increased risk of severe influenza for whom vaccination is less likely to be effective

Persons whose immunity is suppressed by disease (e.g., resulting from HIV, leukemia, congenital immunodeficiencies) or due to medical therapies (e.g., receipt of a hematopoietic stem cell transplant [HSCT] or cancer chemotherapy) are at high-risk for influenza complications and mortality and are less likely to be protected by influenza vaccination. Antiviral drug prophylaxis has been shown to be effective in reducing risk of infection and its consequences in immunocompromised groups. Although PEP following household exposure for this high-risk group would be provided under a broad household PEP strategy, PEP also may be given for community exposures. Alternately, protection may be provided through prophylaxis for the duration of a community pandemic influenza outbreak.

Among immunocompromised persons, the largest population is those who have invasive cancer and are receiving chemotherapy. Assuming that the number of immunosuppressed cancer patients is equal to the annual incidence, 1.4 million persons would be included.⁵⁵ Estimating a total of 1.7 million persons who are severely immunocompromised and an average of one non-household exposure per person, 1.7 million antiviral regimens would be required to support PEP. If outbreak prophylaxis were provided for 12 weeks, the total number regimens needed would be 13.6 million.

7. Prophylaxis to reduce the risk of infected persons entering the United States early in an influenza pandemic as part of a risk-based border policy

Policies at U.S. borders to reduce entry of persons with pandemic influenza infection may delay the occurrence of the pandemic wave. Risk-based policies are based on assessing whether incoming travelers may be infected based on their exposure history and whether they have symptoms of influenza illness. Implementing quarantine has been considered for persons exposed during travel to someone who is potentially infected, for example passengers on the same airplane as a possible case. Because facilities for quarantine are limited and this strategy could impose a substantial burden on border enforcement and public health personnel, an alternative may be to provide antiviral prophylaxis and to instruct recipients to report to their local public health authorities if symptoms develop. Because rates of travel may be reduced substantially during a pandemic and border policies to reduce entry of pandemic infection would be implemented only for a short period before the U.S. pandemic wave began, the number of antiviral regimens needed to support this strategy would be limited.

⁵⁴LTCF totals include nursing facilities (about 1.8 million beds) and other residential facilities for elderly persons. Prison and jail estimate from the U.S. Department of Justice (<http://www.ojp.usdoj.gov/bjs/prisons.htm>)

⁵⁵See http://www.cdc.gov/cancer/npcr/npcrpdfs/US_Cancer_Statistics_2003_Incidence_and_Mortality.pdf

8. Other potential settings of post-exposure or outbreak prophylaxis

Post-exposure prophylaxis could be provided broadly in workplaces in addition to healthcare, emergency service, and critical infrastructure sectors. The approach of providing PEP in households, workplaces, and schools has sometimes been referred to as “targeted antiviral prophylaxis” (TAP). A mathematical model of community mitigation strategies with TAP suggests that the combination of interventions may reduce the rate of illness to less than 1% of the U.S. population.⁵⁶ If this outcome occurred, the number of antiviral regimens needed and the logistical challenges with implementation would be limited as PEP rarely would be needed. Despite the optimistic modeling results, however, there is concern about the assumptions on which these projections are based and the ability to achieve the assumed levels of compliance. If effectiveness was less, implementation challenges for TAP and the number of antiviral drug regimens required could be much greater.

Outbreak prophylaxis for household members of critical workers has been proposed as a strategy to decrease absenteeism and improve maintenance of healthcare and other essential services. Protecting workers’ family members would reduce work loss occasioned by caring for an ill family member and, by decreasing concern among workers that they may infect family members based on their occupational exposures. The psychological and behavioral effects of protecting family members on the willingness of critical workers to remain on the job cannot be estimated. Based on an average household size of 2.6 persons, outbreak prophylaxis of critical healthcare and emergency service worker households for 12 weeks would require about 116 million antiviral drug regimens.

⁵⁶ Germann TC, et al. Mitigation strategies for pandemic influenza in the United States. Proceedings of the National Academy of Sciences 2006.



U.S. Department of Health and Human Services