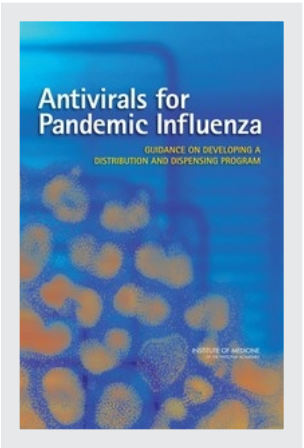

Antivirals for Pandemic Influenza: Guidance on Developing a Distribution and Dispensing Program

DETAILS

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Antivirals for Pandemic Influenza

GUIDANCE ON DEVELOPING A DISTRIBUTION AND DISPENSING PROGRAM

Committee on Implementation of Antiviral Medication Strategies for an Influenza Pandemic

Board on Population Health and Public Health Practice

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **David R. Challoner**, Vice President for Health Affairs, Emeritus, University of Florida and **Kristine M. Gebbie**, School of Nursing, Columbia University. Appointed by the National Research Council and Institute of Medicine they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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APPENDIXES

Summary

In the event of an influenza pandemic, antiviral medication will be one of several strategies deployed to contain the outbreak and to mitigate hospitalization and mortality rates. Although a vaccine well-matched to the pandemic viral strain would be the most effective tool in responding to a pandemic, such a vaccine will not become available for several months after the pandemic begins due to time needed to develop and produce the vaccine. Antivirals are a hoped-for bridge to availability of vaccine.

The federal government, public health agencies at all levels, and their partners are planning to implement a program of antiviral distribution and dispensing during the first wave of the pandemic for treatment and perhaps prevention. The main antiviral drugs stockpiled by the federal and state governments are the neuraminidase inhibitors oseltamivir and zanamivir. These antivirals have been approved by the Food and Drug Administration (FDA) for use in both treating and preventing seasonal influenza.

The Institute of Medicine Committee on Implementation of Antiviral Medication Strategies for an Influenza Pandemic was charged with considering best practices and policies for implementing a program of treatment and prophylaxis. The complete statement of task is provided in Box S-1.

Planning for an influenza pandemic recognizes two basic facts: uncertainty and scarcity. As a starting point, the committee acknowledged that the process of planning is complicated by many unknowns, and that

BOX S-1
Statement of Task

An Institute of Medicine committee would plan and convene a workshop of state and local pandemic influenza planners, as well as national and relevant international influenza experts, to consider best practices and policies for implementing a pandemic influenza antiviral drug program. Components of the program to be addressed include treatment of cases, post-exposure prophylaxis for their household contacts, and prophylaxis of "front-line" health care workers and emergency services personnel. With respect to treatment of cases and post-exposure prophylaxis of their household contacts, key planning issues include, but are not limited to, determining where drugs are dispensed; allocation and distribution of drugs to those sites; diagnostic approach for cases; strategy to enumerate household contacts and assess appropriateness of dispensing drugs for them; potential regulatory barriers to dispensing; and monitoring antiviral drug use and safety. With respect to prophylaxis for targeted health care and emergency services personnel, key issues include, but are not limited to, determining where drugs are dispensed; potential regulatory barriers to dispensing; labor issues that may arise from targeting some workers, but not others; and monitoring antiviral drug use and safety. The committee will review current state plans and lessons learned from drills and exercises, and will explore the challenges and barriers to rapid and efficient distribution of the drugs for treatment and prophylaxis in the general population and in targeted occupationally defined groups. The committee will issue a brief report with conclusions and recommendations regarding components of an effective antiviral program for patients and their household contacts and for prophylaxis of health care and emergency services personnel.

the context of planning may evolve considerably over the coming years, requiring frequent revisiting of planning assumptions, and adapting of policies and plans. For example, it is not known whether the antivirals that are effective against seasonal influenza will be similarly effective against a pandemic strain, and different doses and regimens may be needed for effective treatment and prophylaxis (Hayden and Pavia, 2006; WHO, 2008). The geographic origin (that may or may not be outside the United States) and epidemiologic profile of the disease will only be known once the pandemic has begun and patterns of attack and transmission have become clear. The extent and speed of emerging antiviral resistance also may limit drugs' effectiveness. For discussion and planning purposes, the committee found it helpful to think about the implications of a severe, 1918-type pandemic, occurring in waves, characterized by a mortality rate considerably higher than that of seasonal influenza and a different than usual epidemiologic profile.

This committee's work was informed by relevant documents developed by federal agencies[1] and by the state and local public health community, and by some of the information gathered at the committee's public meetings. Peer-reviewed scientific evidence is largely limited to data on the effectiveness and safety of antivirals, and even that body of data is far short of definitive and continues to evolve as do the influenza viruses of concern. Little to no empirical evidence is available on the logistical aspects of antiviral dispensing and other dimensions of an antivirals program. For these reasons, the basis for the recommendations provided in this report largely represents the expert judgment of a diverse committee based on the limited or incomplete evidence described above.

Moreover, the committee recognizes that parts of this report may only be valid for a few years if major changes (e.g., vaccine technology and availability, antiviral stockpile size, resistance) occur, but the committee believes that some of the parameters it outlines to help guide antiviral dispensing will continue to have relevance. To help facilitate its thinking about the circumstances that would shape a program of distribution and dispensing, the committee describes three simple stockpile scenarios that have different implications for planning depending on the severity of the pandemic: (A) where the supply of antivirals is sufficient either for treating most cases **or** providing a considerable level of prophylaxis **or** a combination of both uses but targeting considerably smaller groups, (B) where sufficient antivirals are available for treatment and narrowly targeted prophylaxis of certain groups with occupational exposure, and (C) where enough antivirals are available to support treatment and a broad program of occupational and perhaps household prophylaxis.

Responding to the charge was difficult. Ultimately, the committee found that antiviral dispensing strategies, including selection of sites and priority groups, are inextricably linked with the amount of antivirals currently available and national goals for antiviral use. For reasons that include the limited antiviral drug stockpile and the not yet clear goals for antiviral use, as discussed in greater detail in Chapter 2, the committee was unable to provide specific guidance in regard to best methods and sites for dispensing. The committee also concluded that identifying priority groups to receive antiviral treatment and prophylaxis (depending on national goals) requires a process of national public and stakeholder engagement similar to that undertaken for pandemic influenza vaccine

[1]These include some documents that are available in draft form (the Department of Health and Human Services' November 6 and 20, 2007, draft guidance documents) or that have been developed as a basis for further discussion (the prioritization scheme for antiviral use developed by the National Vaccine Advisory Committee and included in the 2005 National Pandemic Influenza Plan).

prioritization. Moreover, the committee believes that final determinations regarding priority groups for antiviral use can only be made when data about epidemiologic features of the disease become available (e.g., what age groups have the highest attack rates and mortality rates). In Chapter 3, the committee recommends a process and an entity for real-time decision making, including about prioritization and adjustments based on information emerging during the pandemic. In Chapter 4, the report recommends a first level of prioritization for prophylaxis, discusses characteristics of groups with occupational or household exposure that require consideration, describes advantages and disadvantages of a range of dispensing sites, and examines some legal issues relevant to planning and implementing antiviral dispensing strategies.

The committee noted the planning assumptions made by federal government planners to address uncertainty. The following assumptions concerning the pandemic and antiviral drugs establish the context for the committee's discussion of what is needed to effectively implement an antiviral drug program.

1. A severe pandemic (more so than one that is milder) will require a pre-existing ethical framework to guide decision making about prioritization, so that individual and societal interests and goals are effectively, efficiently, and fairly pursued.
2. Antivirals will be used in conjunction with non-pharmaceutical interventions for which the evidence of effectiveness currently is limited or unclear.
3. Resistance to neuraminidase inhibitors may weaken pandemic influenza response.
4. An increase in dosage and/or length of treatment and prophylaxis (WHO, 2008) may be needed to ensure effectiveness (in the face of resistance and new epidemiologic information), and this will affect the supply of antivirals.
5. Public–private collaboration on a large scale (e.g., private employer antiviral stockpiling for dispensing to large enough groups to enhance flexibility in use of public-sector stockpiles) is unlikely, due to administrative constraints, fiscal limits, and other private-sector concerns about stockpiling.
6. Interjurisdictional coordination in regard to antiviral dispensing (and other aspects of pandemic response) is likely to be challenged by known and unforeseen differences in local circumstances and expectations.
7. Budget challenges, opportunity costs, and other cost–benefit considerations at the state level may affect some jurisdictions' purchasing capability and willingness to stockpile antivirals at levels recommended by federal authorities (ASTHO, 2008).

RECOMMENDATIONS[2]

Based on federal government documents, it is not yet clear whether the goal of antiviral use is treatment, or a combination of treatment and prophylaxis. The Homeland Security Council National Strategy for Pandemic Influenza states that "current plans propose using antiviral medication stockpiles only for treatment once a pandemic is underway. Prophylactic use of antiviral medications will be reserved for initial containment efforts and other highly select circumstances" (Homeland Security Council, 2006:106). The Department of Health and Human Services (DHHS) *Pandemic Influenza Plan* provides "recommendations . . . on the distribution and use of antivirals for treatment and prophylaxis throughout the pandemic phases" (DHHS, 2005:11). The DHHS draft proposed guidance on antiviral use similarly describes use of antivirals for treatment and for a potential range of prophylaxis activities. DHHS references to the stockpile, however, describe it as "antiviral treatment courses for 25 percent of the U.S. population or 81 million treatment courses" (Vanderwagen, 2007), and the DHHS Secretary's *Pandemic Influenza Update IV* (DHHS, 2007c) refers to the stockpile as "81 million treatment courses," which "include 6 million treatment courses set aside for the early stages of an emerging pandemic."

Recommendation 2-1: The committee recommends that the federal government clarify the national goals for antiviral use in an influenza pandemic. If these goals include treatment of all anticipated cases and a level of prophylaxis, fiscal appropriations will be needed to expand the national stockpile to meet these goals.

Unlike federal stockpiles, state and private-sector stockpiles are not covered under the Shelf-Life Extension Program that tests batches of drugs several months before expiration to determine their viability. This means that properly stored antiviral drugs purchased by non-federal entities may expire and need to be discarded before they are used. Given the considerable purchase and opportunity costs and the limited availability of antivirals, it is important to address this issue.

Recommendation 2-2: The committee recommends that the federal government's Shelf-Life Extension Program be expanded to include other public- and private-sector entities that are stockpiling antivirals for use in an influenza pandemic.

[2]Recommendations are numbered by the chapter where they occur and their order in the chapter. There are no recommendations in Chapter 1, so the first recommendation, provided in Chapter 2, is Recommendation 2-1.

A pandemic may occur at a time when non-federal public- or private-sector organizations have on hand expired, but potentially viable, antiviral stocks.[3]

Recommendation 2-3: The committee further recommends that the Department of Health and Human Services develop a process to use the knowledge acquired by the Food and Drug Administration in the operation of the Shelf-Life Extension Program[4] to facilitate the use of properly stored, recently expired medications that exist in supplies outside the Shelf-Life Extension Program in the event these medications are needed because of a shortage.

Some private-sector employers are planning to stockpile antivirals for use by some or all of their employees and others are taking steps to pre-position antivirals with employees in advance of an influenza pandemic. Coordinating with state and local public health agencies could be mutually beneficial (increased flexibility for public stockpiles, sharing of private-sector know-how on distribution, etc.). Also, the use of similar standards for prioritizing scarce resources in the public and private sectors could help avoid public outcry and confusion.

Recommendation 2-4: To promote mutual trust, collaboration, and coordination, memorandums of understanding or similar agreements should be developed between public health agencies and private-sector entities in their jurisdictions. During the pre-pandemic period and in the early stages of a pandemic, such collaborations could facilitate information sharing and awareness of state and local recommendations regarding anticipated best practices in public health and standards of care in response to an influenza pandemic. (These may include prioritization schemes, guidelines for initial treatment of suspected cases, initial post-exposure prophylaxis, reporting of adverse events concerning antivirals, and coordination with state, tribal, and local officials as to who has been given medication.)

An influenza pandemic will require making difficult value-laden deci-

[3]This could perhaps include antivirals in the federal stockpile, depending on the threshold for viability established by the Shelf-Life Extension Program and evidence-based decisions about the usefulness of these drugs.

[4]As part of this program, a collaborative effort between FDA and the Department of Defense, FDA Office of Regulatory Affairs "laboratories test product samples, and in cooperation with FDA's Center for Drug Evaluation and Research, determine if the expiration date for the lot of the product can be extended and for how long" (FDA, 2007a).

sions in the context of scarce resources, evolving scientific and other information, and great societal stress and concern. Beginning a dialogue about ethics in advance, and beginning to outline an ethical framework may prove helpful during response to a pandemic, when time for thoughtful deliberation will be limited.

Recommendation 3-1: The committee recommends that the federal government in collaboration with state, tribal, and local governments support the development of a national ethical framework to guide the allocation of antivirals (and other scarce health resources) during a severe influenza pandemic. Developing the framework should incorporate processes to obtain input from the public and a wide array of stakeholders.

There is no advisory body analogous to the Advisory Committee on Immunization Practices to provide timely scientific advice to the federal government and its partners during the implementation of an antiviral program and other dimensions of pandemic response, including recommendations for rapid mid-course adjustments in antiviral use strategies due to changes in the epidemiology and virology of the disease and its agent.

Recommendation 3-2: The committee recommends that as soon as possible a federal advisory body be formed to advise the federal government and its partners on the planning and implementation of public health and medical responses to an influenza pandemic, including antiviral use. Options for establishing an advisory body include creating a subcommittee under the National Biodefense Science Board or creating a new federal advisory committee to the Department of Health and Human Services.

Communication is a critical dimension of preparing for antiviral distribution and dispensing, with particular attention to the needs of culturally and linguistically diverse communities.

Recommendation 3-3: The committee recommends that state, tribal, and local public health officials preparing for an influenza pandemic develop partnerships with (1) the media, including ethnic media; (2) leaders of local faith communities; (3) community-based clinics; and (4) other trusted organizations and community leaders to convey vital public health information clearly, simply, and in a manner that respects and reflects cultural and linguistic differences.

Although DHHS has facilitated a national dialogue and public

engagement process on prioritization of pandemic influenza vaccine, an analogous process has not been undertaken to consider priorities in the use of antiviral drugs.

Recommendation 4-1: The committee recommends that in the pre-pandemic period, the Department of Health and Human Services undertake an effort similar to that for influenza vaccine priorities—national in scope, inclusive of diverse populations and viewpoints, and in keeping with a shared ethical framework[5]—to discuss and develop a prioritization scheme for antiviral treatment and prophylaxis that is capable of adjustments in real-time in response to the influenza pandemic.

Prophylaxis of select health care workers and others with occupational exposures will be a necessary component of an antiviral program if supplies are adequate to allow this.

Decisions about types and extent of prophylaxis for groups with occupational exposure must take into consideration the potential for facilitating the development of resistance, currently inadequate supply, drug risk and benefit, and unknown epidemiology and virology of the disease and its agent. In order to use scarce antivirals sparingly and strategically, based on available epidemiologic data and local circumstances, the committee recommends the following:

Recommendation 4-2: The committee recommends that pandemic influenza planners at all levels make outbreak prophylaxis for health care and emergency personnel who are in short supply and will have repeated and difficult-to-control exposure a first priority for prophylactic antiviral use. Post-exposure prophylaxis for other health care personnel and emergency responders should be a second priority. Post-exposure prophylaxis of household contacts of infected individuals should be a third priority if stockpiled antivirals are insufficient to meet all prophylaxis objectives.

Recommendation 4-3: The committee recommends that efforts be made to minimize the need for outbreak prophylaxis among health care and emergency responders, and efficiently allocate scarce health resources. Necessary measures include proper and consistent use of personal protective equipment (PPE) and grouping of workers in subsets to stagger their exposure to infected patients, thus reducing

[5]See Chapter 3.

the numbers who need prophylaxis at any given time and shortening the duration of needed prophylaxis.

A pandemic would place unprecedented demands on most existing public health information systems that are being considered for use to track antiviral dispensing. Despite the many barriers, systems for tracking who gets antivirals will be needed, especially in the context of a severe pandemic and with limited supplies. Furthermore, use and expansion of existing systems may constitute the best use of resources. Finally, it is essential to do this work before the pandemic begins.

Recommendation 4-4: The committee recommends that the Department of Health and Human Services support and fund public health agencies to develop or expand information systems for tracking dispensed antivirals. The development or expansion of these systems should make use of existing information resources or systems, consider information technology needs for other dimensions of pandemic influenza response, comply with Centers for Disease Control and Prevention standards, and be interoperable and robust.

For reporting adverse events related to antiviral use, the proposed DHHS draft guidance states that the FDA Adverse Event Reporting System (AERS)/Medwatch should be used. This system is passive and not ideally suited to rapidly capture, interpret, and convey information needed to evaluate a course of action. AERS may not address the need of state and local jurisdictions to monitor and respond to adverse events. Thus, public health agencies and their partners may need some additional measures to prepare for and respond to safety signals, whether real or perceived. It may not be necessary or realistic to attempt to gather comprehensive information about each antiviral drug-related adverse event, but rather, to gather statistically accurate information.

Recommendation 4-5: The committee recommends that the Department of Health and Human Services consider options in addition to the Food and Drug Administration Adverse Event Reporting System to capture adverse events resulting from use of antiviral drugs to ensure active and timely reporting. One option is a network of sentinel sites that can collect data that are representative of antiviral use nationally.

Preparing for pandemic influenza and other emergency events requires not only planning but practicing the use of those plans. The Centers for Disease Control and Prevention (CDC) public health pre-

paredness and Strategic National Stockpile (SNS) guidance documents to grantees (states, territories, and three cities) require them to practice their plans in table-top exercises and subsequent full-scale exercises. However, pandemic preparedness plans or parts of these plans, such as antiviral dispensing plans, also are used by some grantees to respond to disease outbreaks and other public health emergencies, and may help them test and improve the implementation of a wide range of distribution and dispensing sites and mechanisms, in addition to the well-known and exercised SNS point-of-dispensing. The committee understands that aspects of such activities may be used to meet the performance measures requirement in CDC guidance, but not the exercise requirement.

Recommendation 4-6: The committee recommends that federal pandemic influenza grant guidance explicitly state that jurisdictions receiving federal funding may fulfill the exercise requirement through the implementation of response to actual biologic emergency situations or similar events, if the appropriate benchmarks are used, performance is evaluated, and necessary corrective action is taken.

CLOSING OBSERVATIONS

Implementation of an antivirals program for pandemic influenza, whether it occurs in the near or distant future will need to take into account multiple factors, many of which are evolving or will only become apparent in a pandemic (supply of antivirals, shelf-life, resistance, vaccine technology, roles of stakeholders). The epidemiologic characteristics of the pandemic strain—for example, age of greatest impact and/or mortality, mode of spread, rapidity of development of resistance—constitute large unknowns that will affect when, how, and which individuals are provided antiviral medication. Regardless of the final shape of the pandemic, it is clear to the committee that many of these issues need to be prepared for in advance and provide a basis for all decisions. Several overarching goals need to be kept in the forefront: developing in advance an ethical framework, communication and education of the public with clear and consistent messages, the need to reconcile actual supply and antiviral program goals, and flexibility to on the one hand react to the changes in the course of the pandemic and on the other hand, address the diverse needs of localities.

1

Introduction

In the last two decades, the public health community in the United States and internationally began to plan for the possibility of a severe influenza pandemic like that of 1918. The history of influenza viruses shows their potential to mutate or exchange genes with other influenza viruses (for example, a human or mammalian influenza virus and an avian influenza virus that are co-infecting a human or mammalian host). Such genetic reassortment could result in a novel viral strain of great virulence that is capable of efficient human-to-human transmission.

The use of antiviral medications is one of several strategies for mitigating an influenza pandemic that may extend for many months and through multiple waves. Although a well-matched vaccine would be the ideal way to prevent the spread of a pandemic strain, vaccine will likely not be available for several months after the beginning of the pandemic. To attempt to contain the pandemic and decrease mortality until a vaccine is available, the federal government, most states, and some localities plan to use antiviral medications for treatment, and if supplies permit, prophylaxis. The federal government strategy calls for the use of antiviral medications in conjunction with non-pharmaceutical interventions such as social distancing and curtailing or modifying school activities (depending on pandemic level of severity, as described in the Community Mitigation Strategy) (CDC, 2007a).

Two classes of antivirals are available to treat influenza: adamantanes,

also known as M2 inhibitors, and neuraminidase inhibitors.[1] The use of adamantanes is limited due both to their toxicity and the rapid development of viral resistance to this class of drugs. The neuraminidase inhibitors include oseltamivir and zanamivir. These were first approved by the Food and Drug Administration in 1999 for treatment of influenza in adults and oseltamivir also was approved for prevention in individuals 12 years of age and older. In 2005, oseltamivir was approved for prevention of influenza in children under age 12 but no younger than 1 year. In 2006, zanamivir was approved for prophylaxis in adults and children age 7 and older. Antiviral medications consisting largely of neuraminidase inhibitors are currently stockpiled by government at the federal, state, and local levels, and to a limited extent by the private sector, including some employers, health care organizations, and individuals.

Public health agencies began thinking about and planning for mass dispensing of medications and administration of vaccine for a variety of public health emergencies in the 1990s, and with added intensity in late 2001. The public health community has considerable experience with plans and exercises focusing on the distribution and dispensing of antibiotics such as ciprofloxacin and doxycycline in response to deliberate dispersal of a pathogen such as the anthrax bacillus, cause of a non-transmissible disease. Until recently, somewhat less attention has been paid to antiviral dispensing for pandemic influenza, a public health emergency that would pose some different challenges. Single-point chemoprophylaxis after the deliberate dispersal of a pathogen would be fairly straightforward. The spread of pandemic influenza would require ongoing dispensing for different purposes (i.e., treatment, post-exposure prophylaxis, or prophylaxis for the duration of the outbreak), but supplies are unlikely to be adequate for all potential uses. Finally, unlike some types of pathogens (anthrax, brucellosis, tularemia), influenza is transmissible from person to person, and this has implications for the setting and mechanism used to dispense drugs.

AREAS OF UNCERTAINTY AND EXISTING ASSUMPTIONS

There are many unknowns about an influenza pandemic, including when and where a new pandemic strain will emerge, the pattern of its spread, the attack rate and the case-fatality rate, the segments of the population most affected by it, and so on. Furthermore, although neuraminidase inhibitors have been proven to be effective in treating and preventing

[1]Although no other drugs are approved to treat or prevent influenza at the present time, ongoing research is supported by the Department of Health and Human Services on other antivirals (e.g., peramivir).

the spread of seasonal influenza, their effectiveness against a pandemic strain is unknown. It is also not known what potential the virus will have to develop resistance to the antivirals over the course of a pandemic.

In the absence of clear answers to these and other questions, public health agencies at all levels have been making a number of assumptions in their pandemic planning. Some assumptions are based on a complete lack of information, while others are based on incomplete or inconclusive evidence; all will need to be revisited as more information and data become available.

The Department of Health and Human Services (DHHS) *Pandemic Influenza Plan* (2005) assumes that: the pandemic will be moderate, treatment with neuraminidase inhibitors will decrease hospitalization by about half and will decrease mortality, resistance to M2 inhibitors may limit their use, the primary source of antivirals will be federal and state stockpiles, treatment will be most effective in the first 48 hours after disease onset, 35 percent of persons in priority groups (see Box 2-1) will have influenza-like illness and 75 percent of them will present in the first 48 hours, and 80 percent of those admitted to the hospital will be treated (relaxing the 48-hour limit in more ill patients).

The DHHS draft *Proposed Guidance on Antiviral Drug Use Strategies for an Influenza Pandemic*,[2] and the summary of that guidance[3] (which slightly modifies the earlier document) describe some different and additional assumptions including the following:

- The pandemic will be severe (level similar to the 1918 pandemic), with a 30 percent attack rate and 2 percent or greater mortality.
- Community mitigation strategies (when used alone) will halve the attack rate and result in reduced hospitalization and mortality.
- Antiviral effectiveness will be similar to that for seasonal influenza viruses.
- Regimens of antiviral drug treatment and prophylaxis will be the same as those used for seasonal influenza.
- An accurate point-of-care diagnostic test will not be available.
- The positive predictive value of clinical diagnosis (in the absence of accurate point-of-care tests) will be approximately 35 percent.[4]
- Outbreak duration will be 12 weeks.

[2]Dated November 20, 2007.

[3]Dated November 6, 2007.

[4]This means that 35 percent of cases clinically diagnosed as having influenza actually have the pandemic strain as opposed to seasonal influenza or a condition caused by one of several respiratory viruses.

- There will be no vaccine effect (due to uncertain timing and amount of vaccine).
- Sixty percent of cases of influenza will be treated (within the first 48 hours after onset), and their household contacts will be provided prophylaxis.

The following assumptions concerning the pandemic and antiviral drugs set the context for the committee's discussion of what is needed to effectively implement an antiviral drug program.

1. A severe pandemic (more so than one that is milder) will require a pre-existing ethical framework to guide decision making about prioritization, so that individual and societal interests and goals are effectively, efficiently, and fairly pursued.
2. Antivirals will be used in conjunction with non-pharmaceutical interventions for which the evidence of effectiveness currently is limited or unclear.
3. Resistance to neuraminidase inhibitors may weaken pandemic influenza response.
4. An increase in dosage and/or length of treatment and prophylaxis (WHO, 2008) may be needed to ensure effectiveness (in the face of resistance and new epidemiologic information), and this will affect the supply of antivirals.
5. Public–private collaboration on a large scale (e.g., private employer antiviral stockpiling for dispensing to large enough groups to enhance flexibility in use of public-sector stockpiles) is unlikely, due to administrative constraints, fiscal limits, and other private-sector concerns about stockpiling.
6. Interjurisdictional coordination in regard to antiviral dispensing (and other aspects of pandemic response) is likely to be challenged by known and unforeseen differences in local circumstances and expectations.
7. Budget challenges, opportunity costs, and other cost–benefit considerations at the state level may affect some jurisdictions' purchasing capability and willingness to stockpile antivirals at levels recommended by federal authorities (ASTHO, 2008).

CHARGE TO THE COMMITTEE

The Department of Health and Human Services has embarked on a process of stockpiling antivirals for distribution and dispensing as part of a larger and multi-dimensional process of planning for pandemic influenza. The committee was asked to advise DHHS on best practices and

BOX 1-1
Statement of Task

An Institute of Medicine committee would plan and convene a workshop of state and local pandemic influenza planners, as well as national and relevant international influenza experts, to consider best practices and policies for implementing a pandemic influenza antiviral drug program. Components of the program to be addressed include treatment of cases, post-exposure prophylaxis for their household contacts, and prophylaxis of "front-line" health care workers and emergency services personnel. With respect to treatment of cases and post-exposure prophylaxis of their household contacts, key planning issues include, but are not limited to, determining where drugs are dispensed; allocation and distribution of drugs to those sites; diagnostic approach for cases; strategy to enumerate household contacts and assess appropriateness of dispensing drugs for them; potential regulatory barriers to dispensing; and monitoring antiviral drug use and safety. With respect to prophylaxis for targeted health care and emergency services personnel, key issues include, but are not limited to, determining where drugs are dispensed; potential regulatory barriers to dispensing; labor issues that may arise from targeting some workers, but not others; and monitoring antiviral drug use and safety. The committee will review current state plans and lessons learned from drills and exercises, and will explore the challenges and barriers to rapid and efficient distribution of the drugs for treatment and prophylaxis in the general population and in targeted occupationally defined groups. The committee will issue a brief report with conclusions and recommendations regarding components of an effective antiviral program for patients and their household contacts and for prophylaxis of health care and emergency services personnel.

policies for implementing an antiviral drug program, focusing on three key components (see Box 1-1):

- Treatment of cases
- Post-exposure prophylaxis for their household contacts
- Prophylaxis of "front-line" health care workers and emergency services personnel

Accordingly, this report does not discuss issues related to the administration of vaccines or other components of pandemic planning. The report also does not comment in detail on the organization or movement of antiviral supplies at the proximal end of the distribution chain, namely, the Strategic National Stockpile and state stockpiles. Rather the report focuses on the distal end of the distribution chain, i.e., where antivirals are

placed in the hands of individuals for treatment or for prophylaxis.[5] In this report, the word *antivirals* refers to (unless otherwise stated) oseltamivir and zanamivir, the main antiviral medications in the federal government stockpile. The report does not comment on the reasoning for stockpiling a certain ratio of one drug to the other, or examine the research on development of new neuraminidase inhibitors or other classes of antivirals, or on the use of antivirals and/or other drugs in combination to treat or prevent influenza. Further, the committee has not been asked to and does not address what the potential need for prophylaxis for key decision makers and critical infrastructure workers such as those responsible for supporting or maintaining various components of public utilities (see DHHS, 2005); additional antiviral supplies would be needed for those groups if there are prophylaxis goals that include them. Finally, although the committee acknowledges the global effect of an influenza pandemic and the need for antiviral medications outside the United States, these important and challenging issues are beyond the committee's charge and require separate and in-depth treatment elsewhere.

In the second chapter of this report, the committee reviews information related to the effectiveness and safety of antivirals, and some issues pertaining to the available and projected supply of antivirals. In the third chapter, the committee discusses and makes recommendations about three interrelated topics including (1) the ethical principles and goals to be considered for prioritizing scarce resources, (2) a mechanism for decision making that includes real-time input of data and information needed to assess and change the course of pandemic response, including antiviral dispensing strategies, and (3) several areas of communication related to antivirals that will require attention before and during the pandemic.

Study Process

During the course of this 4-month study, the committee gathered information to address its charge through a variety of means (committee biographies can be found in Appendix E). It held two information-gathering meetings that were open to the public. The first meeting included a presentation from the sponsor and presentations on influenza antiviral effectiveness and resistance, stockpiling and distribution planning from the Centers for Disease Control and Prevention, related legal issues, and

[5]The committee notes that the terms distribution (referring to the movement of drugs, e.g., from a central location to another site) and dispensing (referring to the delivery of drugs to the patient or family member of patient) are sometimes used interchangeably outside certain circles. Strict use of the terms could lead to more confusion. Although the committee generally refers to the act of giving out medication as dispensing, the term distribution is used sometimes.

diagnosis of influenza. The second meeting focused on learning more about influenza antivirals and their use (effectiveness, resistance, surveillance), modeling of antiviral resistance, and distribution and dispensing planning from the perspective of state public health agencies. At that meeting the committee received information on the following topics: lessons from experience with large-scale distribution/dispensing of drugs or administration of vaccine; decision analysis for antiviral distribution; telephone and web-based decision support and triage; antiviral stockpile planning from the perspectives of the private and public sectors, and in a publicly funded and a private health care system; and ethical principles in planning for the distribution and dispensing of antiviral medication. The complete agendas for both meetings can be found in Appendixes C and D. The committee met in executive sessions for deliberative discussions following both information-gathering meetings. Additionally, the committee held weekly conference calls to discuss report findings and to formulate recommendations.

A website (http://www.iom.edu/antivirals/) and listserv were created to provide information to the public about the committee's work and to facilitate communication with the committee. Many of the slide presentations and audio files from both information-gathering meetings are available in electronic format on the website. The committee also received public submissions of material for its consideration at meetings and by mail and e-mail throughout the course of the study. These may be viewed in the project public access file.[6]

[6]A list of materials reviewed by the committee (in the form in which they were reviewed) including all submissions of information from the public and many items not cited in this report, can be found in the study's public access file, obtained from the National Academies Public Access Records Office at (202) 334-3543 or http://www8.nationalacademies.org/cp/ManageRequest.aspx?key=48872.

2

Antiviral Effectiveness, Safety, and Supply

Two neuraminidase inhibitors, oseltamivir and zanamivir, are the antivirals currently being stockpiled to respond to an influenza pandemic. Oseltamivir, sold under the name Tamiflu, is manufactured by Roche and Gilead and is available in capsule form and as a suspension for pediatric use. Zanamivir, sold as Relenza, is manufactured by GlaxoSmithKline and is delivered as a powder via inhaler. The two drugs are effective when used for post-exposure and extended prophylaxis for seasonal influenza, and when used for treatment to shorten the duration of both symptoms and viral shedding (European Medicines Agency, 2005).

In this chapter, the committee examines current information about the effectiveness and safety of neuraminidase inhibitors, and implications of supply issues, and emergent effectiveness and safety data for planning and implementation of an antivirals program. Supply issues include the source and the adequacy of existing drug stockpiles to meet stated planning purposes (treatment versus treatment and prophylaxis); the cost of purchasing and storing the drugs; and the drugs' shelf-life. Many of the relevant stakeholders (Association of State and Territorial Health Officials [ASTHO], state public health agencies, large health care delivery systems) consider these issues crucial to examine in the planning process and necessary to address long before an influenza pandemic begins (ASTHO, 2006; Skivington and Koscove, 2008).

EFFECTIVENESS AND SAFETY

The currently approved treatment for seasonal influenza with neuraminidase inhibitors requires a 5-day regimen[1] (one 75 mg capsule two times per day of oseltamivir, or two inhalations two times per day of zanamivir), while prophylaxis for exposure to seasonal influenza virus requires a 10-day regimen (one capsule per day or two inhalations per day). Randomized trials have demonstrated efficacy when neuraminidase inhibitors, in particular oseltamivir, were used for prophylaxis after exposure in both family and institutional settings and when used for 6 weeks as seasonal prophylaxis in nursing homes (Moscona, 2005; Hayden and Pavia, 2006). Data from a study of hospitalized adults demonstrated a strong association between oseltamivir use and decreased mortality (adjusted odds ratio 0.21) (McGeer et al., 2007). The two major gaps in the research on neuraminidase inhibitor effectiveness include lack of high-quality data in high-risk persons and lack of adequate data for H5N1.

Although neuraminidase inhibitors have not been studied or approved for prolonged use beyond 6 weeks, protecting vulnerable health care and other workers during a pandemic may require prophylaxis over several weeks or longer. Pandemic duration likely will depend on the success of non-pharmaceutical interventions in "flattening" (CDC, 2007c) the pandemic curve. This refers to decreasing and extending the plotted course of a pandemic, which in the absence of effective interventions the first wave of a pandemic is expected to have an earlier, more severe peak in the number of cases per week. Modeling and data from the 1918 pandemic suggest that effective non-pharmaceutical interventions would delay and decrease the height of the peak, but result in a longer duration of the pandemic wave (IOM, 2006). However, models have limitations, and the vastly different socio-cultural setting of historic data must be acknowledged.

Neuraminidase inhibitors are effective in treating influenza and are currently used to prevent some cases during seasonal influenza outbreaks. Randomized trials, conducted primarily among relatively healthy children and adults, have demonstrated decreased duration of symptoms, disability, antibiotic use, and decreased time to return to normal function after treatment (Moscona, 2005). However, treatment is most effective when given as early as possible after symptoms develop, and its effectiveness diminishes markedly after 48 hours. Data are limited on the efficacy in high-risk populations. The available data suggest decreased hospitalization and mortality rates with treatment; however these are derived

[1]Oseltamivir adult dose: 75 mg bid for 5 days for treatment, 75 mg qd for 10 days for prophylaxis (Roche Pharmaceuticals, 2008); oseltamivir pediatric dose (ages 1–12 years): ≤33 lbs, 30 mg/bid/5 days; >33 lbs to 51 lbs, 45 mg/bid/5 days; >51 lbs to 88 lbs, 60 mg/bid/5 days; >88 lbs, 75 mg/bid/5 days (add: same dose qd/10 days for prophylaxis).

from pooled analysis and observational studies. One study (McGeer et al., 2007) suggests a survival benefit may be seen among hospitalized patients even if treatment is started later than 48 hours from symptom onset.

In past pandemics and in seasonal influenza outbreaks, morbidity and mortality have been high among infants and pregnant women. There currently are no pharmacokinetic, efficacy, or safety data for oseltamivir in infants under 1 year of age or in pregnant women (CDC, 2007b). Because very little zanamivir is absorbed systemically, it has been considered an alternative for pregnant women (DHHS, 2005), but this is not based on adequate data. If response to a pandemic necessitates use of antivirals in populations for which the drugs have not been indicated, careful follow-up or monitoring of adverse events would be needed (see Chapter 4 for additional discussion).

Use of antivirals in the context of a pandemic will test what is known about both their effectiveness and safety. It is not known if the effectiveness of neuraminidase inhibitors against the pandemic strain will be similar to their effectiveness when used during seasonal influenza outbreaks. Wide-scale use, as well as overuse or misuse, could lead to both increased resistance and the emergence of newly identified, or at least greater numbers of known, adverse events. It also is possible that the currently recommended dosage and duration of treatment will need to be reconsidered during a pandemic. In fact, there is some evidence from studies in animals that high levels of viral replication may require higher doses and/or longer duration of treatment for effectiveness (WHO, 2008).

Safety

Neuraminidase inhibitors are generally well tolerated and have a favorable risk–benefit profile. However, serious adverse events reported in postmarketing use in individuals who took oseltamivir include skin reactions, neuropsychiatric events, and pediatric deaths (the latter two largely reported from use in Japan) (FDA, 2005; Roche Pharmaceuticals, 2008). Gastrointestinal disturbances are reported in about 10 percent of users. Adverse events experienced by people who took zanamivir include headaches, gastrointestinal problems, respiratory problems, dizziness, and musculoskeletal symptoms (GlaxoSmithKline, 2007). Postmarketing adverse events also include allergic, cardiac, neurologic, and skin reactions, as well as bronchospasm.

Oseltamivir and zanamivir have been on the market for more than 8 years and more is known about their safety profiles now than at the time of approval. However, wide-scale and prolonged use of these drugs in populations who were not well studied may lead to the recognition of rare but serious adverse events. Moreover, with the widespread use

anticipated during a pandemic, reports of possible adverse events will be much more likely and will need to be rapidly evaluated. A telling example is found in reports of neuropsychiatric adverse events from Japan where oseltamivir is used much more widely than in the United States in treating seasonal influenza (FDA, 2007b). Despite two careful reviews by Food and Drug Administration (FDA) staff and FDA advisory committees, it has not been possible to date to determine if the neuropsychiatric events are causally associated with oseltamivir.

Appropriate systems will be needed to gather, analyze, interpret, and act on the drug safety information collected (see discussion in Chapter 4). Given the challenging circumstances of a public health emergency, it is important to plan in advance for assessment of and communication about adverse events and for possible changes in antiviral dispensing strategies to keep the public's confidence in the public health effort (see discussion in Chapter 3).

Resistance

The effectiveness of adamantanes, which have been marketed for three decades, has become so limited by the spread of resistant viruses that federal and international public health authorities advise against their use in treating seasonal influenza (CDC, 2006a). Adamantane-resistant virus does not appear to have compromised infectiousness or transmissibility. The neuraminidase inhibitors are considerably newer drugs. Before 2008, rates of resistance to neuraminidase inhibitors observed in clinical trials and population surveillance were low. In clinical trials, the rate of emergence of resistance to neuraminidase inhibitors was about 1 percent among adults and approximately 5 percent among children (European Medicines Agency, 2005; Aoki et al., 2007). Among samples submitted to the Neuraminidase Inhibitor Susceptibility Surveillance Network in 2003–2004, fewer than 1 percent were resistant. Animal studies of resistant virus suggested that many, but not all, strains had compromised transmissibility and growth characteristics (or "fitness"). These clinical and laboratory data led to assumptions that resistance to neuraminidase inhibitors would emerge and spread slowly.

In the 2006–2007 influenza season, 0.5 percent of viral strains isolated (776 of 2121 H1N1) were oseltamivir resistant (Klimov, 2008). However, during the 2007–2008 influenza season, there has been some evidence of an increase in the incidence of oseltamivir-resistant strains of influenza A(H1N1) detected in Europe, Australia, Hong Kong, and North America (EMEA, 2008; Reuters, 2008). For example, 14 percent of 437 H1N1 isolates in Europe were oseltamivir resistant (Lackenby et al., 2008). This suggests that transmissible and virulent neuraminidase inhibitor–resistant viruses

may spread more readily than previously thought. It is important to note, however, that in Europe use of oseltamivir for treatment of seasonal influenza is limited, thus the emergence of resistance may not be related to use. Japan, with its higher rates of seasonal oseltamivir use has not yet reported an increase in resistant strains. The implications of increasing antiviral resistance for pandemic planning are unclear, but troubling.

The factors influencing the rate of antiviral resistance are complex. Based on what is known about the emergence of antiviral resistance in HIV, potential factors driving the emergence of neuraminidase inhibitor–resistant influenza include the structure of the circulating neuraminidase, the relationship of the susceptibility of the pandemic strain and the drug levels among the patients, and the degree of inappropriate use or partial prophylaxis in the presence of circulating resistant virus. Perhaps the most important drivers will be the number of courses of drug that are used and adherence to the drug regimen. Widespread use for post-exposure and seasonal prophylaxis as well as treatment may create selective pressure for the emergence of resistance (Lipsitch et al., 2007). However, the rate of emergence and spread of resistant viruses must be measured against the time it takes to produce an effective vaccine. If neuraminidase inhibitors remain largely effective until a well-matched vaccine can be deployed, there will be a large net benefit despite the emergence of resistance. Conversely, delays in vaccine availability could coincide with rapid development of neuraminidase inhibitor resistance, presenting a grave challenge to effective pandemic response.

Mathematical modeling of resistance in the context of treatment and prophylaxis provides some insight, albeit with a high degree of uncertainty. Lipsitch and colleagues (2007) modeled the predicted impact of four strategies for antiviral use on the number of cases and the emergence of resistance: no antivirals; antivirals for treatment only; antivirals for household prophylaxis without treatment; and antivirals for treatment and household prophylaxis. They predicted that use of antivirals exclusively for treatment led to the least emergence of resistance. Exclusive use for household and seasonal prophylaxis eventually led to significant emergence of resistant virus in the model, but only after some lag time. However, Lipsitch and colleagues predicted that combined use for both treatment and prophylaxis led to the most widespread and rapid emergence of resistant virus.

SUPPLY

The committee believes that after resistance-modified effectiveness, the second core issue in identifying the most appropriate strategies for dispensing the medication is the quantity of available antiviral drugs.

Shelf-life, manufacturing capacity, cost, and storage requirements are some of the important variables linked with quantity of antiviral supply.

Existing Stockpiles

The Division of Strategic National Stockpile (SNS) at the Centers for Disease Control and Prevention (CDC) holds a large number of courses of neuraminidase inhibitors, being purchased in a ratio of approximately 80–85 percent oseltamivir to 15–20 percent percent zanamivir. (The SNS also includes a small number of courses of rimantadine.)

The total goal for the SNS is 81 million courses of antivirals, with 50 million being stockpiled by the federal government and 31 million courses of neuraminidase inhibitors intended for procurement by states through the federally subsidized purchasing program. Of the 81 million, 6 million are intended for containment of the pandemic, and 75 million (in federal SNS and state stockpiles combined) are to be used to treat 25 percent of the population (see Table 2-1). As of March 7, 2008, the federal stockpile was nearly complete (goal of 50 million), and state stockpiles were two-thirds complete. (For more information on state plans, see Appendix B.)

Federal government documents are not yet clear on whether the goal of antiviral use will be treatment or a combination of treatment and prophylaxis. The Homeland Security Council National Strategy for Pandemic Influenza states that "current plans propose using antiviral medication stockpiles only for treatment once a pandemic is underway. Prophylactic use of antiviral medications will be reserved for initial containment efforts and other highly select circumstances" (Homeland Security Coun-

TABLE 2-1 Strategic National Stockpile Antiviral Goal and Status

	Goal	Status July 2007	Status March 2008
Federal Strategic National Stockpile	50 million courses (6 million of these are intended for domestic containment)	36 million	49.9 million
Federally subsidized, state-purchased state stockpiles	31 million courses	12 million	21.7 million
Total	81 million courses	48 million	71.6 million

SOURCES: DHHS, 2007a,c; A. Patel, personal communication, March 10, 2008.

cil, 2006:106). The Department of Health and Human Services (DHHS) *Pandemic Influenza Plan* (DHHS, 2005) provides "recommendations . . . on the distribution and use of antiviral drugs for treatment and prophylaxis throughout the pandemic phases" (DHHS, 2005:11; see Box 2-1 for a list of the groups identified to receive prophylaxis in the 2005 plan).

The DHHS draft proposed guidance on antiviral use similarly describes use of antivirals for treatment and for a potential range of prophylaxis activities (DHHS, 2007a). DHHS references to the stockpile, however, describe it as "antiviral treatment courses for 25 percent of the U.S. population or 81 million treatment courses" (Vanderwagen, 2007), and the DHHS Secretary's *Pandemic Planning Update IV* (DHHS, 2007c) refers to the stockpile as "81 million treatment courses," which "include 6 million treatment courses set aside for the early stages of an emerging pandemic." Clearly, the stockpile of 75 or 81 million courses is not suf-

BOX 2-1
Priority Groups to Receive Antiviral Treatment and Prophylaxis Identified in the 2005 DHHS *Pandemic Influenza Plan* (based on the recommendation of the National Vaccine Advisory Committee)

- Patients admitted to hospital
- Health care workers (HCWs) with direct patient contact and emergency medical services (EMS) providers
- Highest-risk outpatients—immunocompromised persons and pregnant women
- Pandemic health responders (public health, vaccinators, vaccine and antiviral manufacturers), public safety (police, fire, corrections), and government decision makers
- Increased-risk outpatients—young children 12–23 months old, persons ≥65 years old, and persons with underlying medical conditions
- Outbreak response in nursing homes and other residential settings
- HCWs in emergency departments, intensive care units, dialysis centers, and EMS providers
- Pandemic societal responders (e.g., critical infrastructure groups as defined in the vaccine priorities) and HCWs without direct patient contact
- Other outpatients
- Highest-risk outpatients
- Other HCWs with direct patient contact

SOURCE: DHHS, 2005:D-10.

ficient to both treat 25 percent of the population and provide any level of prophylaxis (at the low end of the range, post-exposure prophylaxis for certain health care and emergency workers; at the high end household post-exposure prophylaxis as described in the Community Mitigation Strategy) (CDC, 2007a). Providing any level of prophylaxis with existing drug supplies would require limiting the proportion to be used for treatment. Alternately, if the intention is to treat 25 percent of the population and provide some level of prophylaxis, a stockpile sufficient to meet those goals will be needed.

Recommendation 2-1: The committee recommends that the federal government clarify the national goals for antiviral use in an influenza pandemic. If these goals include treatment of all anticipated cases and a level of prophylaxis, fiscal appropriations will be needed to expand the national stockpile to meet these goals.[2]

Most states have purchased some or all of their portion of the federally subsidized stockpile (enough to treat 25 percent of a state's population) (ASTHO, 2007; A. Patel, personal communication, March 10, 2008). State rationale for antiviral policy differences aside, the variations in availability of antivirals for treatment across the country may result in some geographic inequities, with populations residing in one state, but not another, having potential access to antiviral treatment. Further, seasonal shifts in population density may need to be considered. The pattern of disease spread across the United States may add another layer of complexity. Ensuring equitable access to household post-exposure prophylaxis (if this were a national goal for antiviral use) within states will depend on addressing access barriers that may be faced by cultural and linguistic minorities and other vulnerable populations.

Adequacy of Supply

In thinking about the available public stockpile (at federal, state, and to a lesser extent, local levels) and the important issues listed above, the committee used three simple potential scenarios to think about antiviral dispensing. The scenarios assume different sizes of antiviral stockpile each of which is adequate for a certain level of dispensing and so, for some, but not all, dispensing goals. Scenarios A and C suggest two extremes of possible antiviral use scenarios, assuming some level of antiviral stockpil-

[2]Recommendations are numbered by the chapter where they occur and their order in the chapter. There are no recommendations in Chapter 1, so Recommendation 2-1 is the first recommendation in the report.

ing (i.e., not zero). Scenario B describes a level of stockpiling somewhere between A and C. However, the committee recognizes that decisions about the amount to stockpile and the goals of antiviral use are complex and informed by many other considerations, both related and unrelated to pandemic influenza planning.

Antiviral distribution and dispensing activities would vary with supply available (or conversely, supply would depend on the antiviral use goals selected), community circumstances, and emerging information about the severity and the epidemiology of the disease (such as what age group is most affected, who is at increased risk of death, who is transmitting the virus, etc.). With regard to severity, DHHS plans provide a 1–5 rating of severity, with <0.1 percent case fatality rate as Category 1 and ≥2.0 percent as Category 5 (CDC, 2007a).

Scenario A

In this scenario, the antiviral stockpile is 81 million courses,[3] an amount that would treat a considerable proportion of cases, or provide a considerable level of prophylaxis (depending on specific objectives), or satisfy both goals only in a limited way. Use of antivirals for prophylaxis only has been considered at least in modeling of resistance and effectiveness (e.g., McCaw and McVernon, 2006; Lipsitch et al., 2007), but short of such use to contain the pandemic in the early days of a U.S. outbreak, limiting dispensing to prophylaxis may imply denying patients the only potentially effective treatment.

Based on some of the estimates provided in the November 6, 2007, DHHS draft proposed guidance, the groups requiring prophylaxis for occupational exposure would require most of the stockpile for several courses of outbreak (or seasonal) prophylaxis, leaving little or nothing for treatment. Reserving the antivirals for treatment alone is not an option as it would leave a vast proportion of health care and emergency services personnel with certain exposure unprotected and vulnerable to becoming incapacitated by illness. Even if the intent was to provide only post-exposure prophylaxis to 10.7 million health care workers and emergency services personnel (using figures from the DHHS draft proposed guidance, which estimates that one-third of health care workers would not have direct contact with infected individuals), 2 or 3 courses for each of those workers would amount to a total of 21.4 or 32.1 million courses, which would considerably limit the supply available to treat cases.

[3]As noted earlier, this is the current goal for the Strategic National Stockpile and subsidized state stockpiles, and this total includes 6 million courses intended to be used for containment.

The best that could be achieved with this level of antivirals would be to develop dispensing strategies to treat only some cases and provide prophylaxis to a narrowly defined subset of those with occupational exposure. Once the epidemiology and virology of the disease and its agent became known, dispensing strategies could target the proportion of cases more likely to require hospitalization and more likely to die, in order to allow for the use of a portion of the stockpile for post-exposure prophylaxis of some health care workers and emergency personnel (see Chapter 4 for additional discussion). Accurate diagnosis of pandemic influenza would be crucial to ensure that antivirals are used only for confirmed cases; this may mean that remote diagnosis may be less desirable, but that could lead to later diagnosis, perhaps past the 48-hour window when antiviral efficacy may be highest. Due to the limited antiviral supply, no household post-exposure prophylaxis would be provided in this scenario, so dispensing sites and related activities for exposed individuals without occupational risk would not be needed. The risk of resistance may be smaller than in a scenario with broader prophylaxis, and resistance would spread more slowly because some of the drug courses would be used for treatment, which is less likely than prophylaxis to lead to resistance (Lipsitch et al., 2007).

A pandemic of any level of severity greater than seasonal influenza would cause some level of social and economic disruption due to higher than usual hospitalization and death rates, but a severe pandemic in this scenario of a modest antiviral stockpile would involve making the most difficult decisions, and thus, present the greatest need for a pre-developed, widely understood ethical framework. In the event that emerging information about the pandemic strain results in changing the dosage or duration of antiviral use, this would place additional demands on the limited supply of antivirals.

Scenario B

Somewhere between scenarios A and C, the committee envisioned an antiviral stockpile sufficient to provide treatment to most or all cases and prophylaxis to defined groups with occupational risk. Well more than twice the existing goal of 81 million would be needed to treat 25 percent of the population[4] and provide outbreak and post-exposure prophylaxis to broadly defined groups with occupational exposure. The draft proposed DHHS guidance on antivirals identifies about 8.7 of the 13 million

[4]This is assuming that 25 percent is sufficient, but for reasons described elsewhere in this report, such as change in dosage or higher attack rate, a greater number of courses may be needed.

TABLE 2-2 Prioritized Strategies for Antiviral Drug Use from November 2007 DHHS Draft Proposed Guidance

Population to receive prophylaxis	Estimated number of antiviral courses needed
Initial pandemic outbreaks overseas and in the United States	6 million
Exposed travelers entering the United States early in a pandemic	
Persons with pandemic influenza illness (outbreak and post-exposure)	79 million
Health care and emergency services workers	103 million
Outbreak control in closed settings (e.g., nursing homes)	5 million
Immunocompromised and not candidates for vaccine	2 million
Unique and specialized infrastructure workers	2 million
Household contacts of cases *The summary of the proposed guidance, dated November 20, 2008, revises the preliminary position on household prophylaxis: "No national recommendation is made at this time for PEP [post-exposure prophylaxis] of household contacts of an influenza case or for workers in sectors other than healthcare and emergency services."*	*88 million*
Total estimated number of courses for treatment and prophylaxis	285 million
Total excluding household post-exposure prophylaxis	*197 million*

SOURCE: DHHS, 2007a,b.

health care workers and the 2 million emergency services personnel in the United States, as needing outbreak (or seasonal) prophylaxis (DHHS, 2007a). A population of 10.7 million requiring 8 courses of antivirals (DHHS's estimate for 12 weeks of protection) would total 85.6 million courses. The draft proposed guidance also estimates needing approximately 4 courses of post-exposure prophylaxis for each of the remaining 4.3 million health care workers not identified as needing outbreak prophylaxis, for a total of 17.2 million courses. Combined, these preliminary estimates for courses needed to provide prophylaxis to health care and emergency services personnel total nearly 103 million (see Table 2-2 for additional populations and estimates provided in the summary draft

proposed guidance documents). The capacity to manufacture approximately 80 million courses of oseltamivir (plus some additional amount of zanamivir) per year may make possible an increase in the stockpile in the intermediate term (1–2 years) to provide the level of treatment and prophylaxis described above.

Scenario C

In this scenario, a large amount of courses is available for a wide range of uses.

One figure to illustrate this is 285 million courses (DHHS, 2007a), based on the estimates provided in the DHHS draft proposed guidance. An even higher total would ensure one course of treatment is available for all people in the United States at the time of the pandemic, a combination of post-exposure or seasonal prophylaxis for all health care workers and emergency services personnel, and prophylaxis for a large number of exposed household contacts (again using DHHS 2007 estimates).

In this scenario, sufficient antivirals are available for treatment and for expanded prophylaxis (both post-exposure and outbreak or seasonal, the latter requiring multiple courses of prophylaxis to protect from ongoing occupational exposure) such as that described in the DHHS draft proposed guidance. If planning for the 285 or 197 million antiviral courses (totals with and without post-exposure prophylaxis for household contacts, who would require a large portion of an antiviral supply) estimated in the draft proposed guidance, this scenario would require approximately 2.5 to 3.5 times the SNS goal of 81 million courses. The committee is not aware of plans to bring the total of federally stockpiled antivirals to that level, and as noted above, there are other considerations that inform stockpiling decisions.

Unlike a shortage scenario A, greater availability of antivirals could mean lessened concern about securing antiviral stockpiles and perhaps decreased potential for fraudulent attempts to obtain and sell antivirals. Scenario C would require the most diverse array of dispensing sites given the breadth of the prophylaxis being offered. The potential for more rapid development resistance may be greatest in this scenario, and the consequences would be most concerning in a severe pandemic. A rapid increase in resistance, facilitated by extensive prophylaxis, could undermine one of the main objectives in using antivirals: to "buy" time for the development of a well-matched vaccine. Wide-scale use in a less severe pandemic could offer early opportunities for safety signals to emerge and to be captured, assuming that health care providers are more likely to be able to report adverse events.

Additional Observations About Antiviral Supply

As noted on previous pages, pandemic influenza planners hope that antivirals will be an effective tool in reducing death and hospitalizations until a vaccine becomes available. Decision makers have been and will need to continue to consider a wide range of factors in determining what level of antiviral stockpiling is desirable, based on the goals of an antiviral dispensing program and the size of the populations to be targeted. Production capacity is one of those factors, and for oseltamivir specifically, it has increased to approximately 80 million courses per year (U.S. production alone), thanks in part to the manufacturer's ability to synthesize shikimic acid (Roche Pharmaceuticals, 2006). It is important to note an additional factor in planning for antiviral supply: the two antivirals thought to have the greatest potential for use in a pandemic remain on patent until 2016 so no generic versions are available.

The goal of stockpiling enough to treat 25 percent of the population may have been established by assuming that not all who develop influenza (with a 30 percent attack rate) will present for treatment within 48 hour after symptom onset, and also perhaps that not all cases will require some kind of medical care. Even so, there is reason to believe that additional demands will be placed on the antiviral supply. The 2005 DHHS *Pandemic Influenza Plan* includes patients hospitalized with pandemic influenza on the list of priority groups to receive antivirals, and acknowledges that hospitalized patients would include individuals presenting for care late after falling ill. Further, if the attack rate is higher than the 30 percent planning assumption, additional drugs may be needed for treatment. Also, the absence of a reliable, rapid, point-of-care diagnostic test on the one hand, and likelihood of some level of remote diagnosis (telephone or web-based) on the other hand, would lead to treating patients who do not have pandemic influenza.

With a larger quantity of available medication, a broader range of groups could be offered prophylaxis, and there would be less need to prioritize among them. However, greater financial and other resources also would be needed to purchase, distribute, and dispense the antivirals. Also, there would be opportunity costs of allocating resources to an intervention that is potentially ineffective or only partially effective against a pandemic viral strain, as well as the possibility of rapid development of resistance with widespread use. There may be other types of interventions that could be considered, for example, public health agencies and hospitals may weigh investing in antivirals against purchasing additional personal protective equipment or ventilators. Further, antivirals represent one intervention for only one kind of threat to the public's health in a context of chronic underfunding for most public health agencies and pro-

grams and inadequate federal budget allocations to address other critical areas of disease prevention (IOM, 2003; APHA News, 2008).

Shelf-Life

The expiration dating of oseltamivir capsules was recently extended from 5 to 7 years, on FDA approval of Roche's supplemental new drug application in December 2007 (Duffy, 2007). Although FDA's approval applies to oseltamivir capsules manufactured after 30 days from the approval, this extension has also been applied to state oseltamivir procurements. As an example, drugs purchased by a state in 2006 with an expiration dating of 5 years would not expire in 2011, but be considered viable until 2013. The 7-year expiration dating of oseltamivir in government stockpiles currently does not apply to current commercial product, that is, sold via commercial wholesalers or dispensed by pharmacists to individuals purchasing on their health care provider's prescription.

Aside from the change in expiration dating of oseltamivir, it is important to note that federal antiviral stockpiles are included in an FDA-overseen Shelf-Life Extension Program (SLEP) (FDA, 2007a) that is "oriented towards the testing of 'military significant' products, those that are either military-unique, possessing no commercial (non–Department of Defense) market, or drugs the Federal Government procures in such large quantities, for pre-positioned stocks, that vendors are unwilling to accept them for credit upon expiration" (DoD, 2007:2). Although states are provided a 25 percent subsidy to purchase antivirals as part of the SNS program, stockpiles built by states with partial federal funding are not included in the federal Shelf-Life Extension Program (ASTHO, 2008).

The *National Strategy for Pandemic Influenza: Implementation Plan* (released May 2006) tasked DHHS and the Departments of Veterans Affairs and Defense with exploring "the possibility of broadening SLEP [the Shelf-Life Extension Program] to include equivalently maintained State stockpiles" and with providing an answer "within 6 months" (HSC, 2006). The committee has learned that at the time of this writing, development of a SLEP for non-federal stockpiles continues to be under discussion in DHHS (D. Wawrose, personal communication, February 20, 2008).

The committee found a modest amount of information about SLEP and nothing about the feasibility, cost, and other barriers of extending the program to properly maintained non-federal stockpiles, including state and perhaps even some private-sector stockpiles. Thirty-one million of the 81 million course goal for the SNS would be held in state stockpiles. This raises the possibility that in the absence of a pandemic, large amounts of the drugs will expire and need to be discarded, an outcome that could be avoided or delayed if this considerable proportion of the nation's govern-

ment stockpile were included in SLEP. The cost of antivirals, especially given the potential of expiration before a pandemic occurs, also is an issue for states and private-sector entities seeking to build their own stockpiles. Regimens of antivirals cost approximately $70–100 for a 10-capsule treatment course when purchased commercially (compared to approximately $20 per course for government purchases for the SNS) (A. Patel, personal communication, February 28, 2008).

Considering the three scenarios described above also requires noting that the shelf-life of the antivirals in the SNS held by the federal government is unknown—information is not being disclosed about when antivirals currently stockpiled are expected to expire (according to the non-disclosure agreements signed by states, information about the SNS has the status of Sensitive But Unclassified, and as such, is not subject to the Freedom of Information Act). Furthermore, stocks of antivirals in the SNS or in state stockpiles may not be rotated to allow use of a portion of the drugs during seasonal influenza and their replacement with fresh antivirals—in fact, rotating is not permitted. Rotating stocks of antivirals may pose logistic challenges, and the amount of drug used in the United States for treatment during seasonal influenza outbreaks may be too small to enable complete rotating of stocks. Despite these issues, the fact that rotating stocks is not allowed precludes the possibility of considering alternatives that could have economic and preparedness benefits. The committee believes that use of the SNS may be constrained in ways that are counterproductive to effective preparedness and, ultimately, to an effective response.

The shelf-life of antivirals for pandemic influenza is an important factor and an economic barrier because a short shelf-life would require discarding previously purchased drugs and buying new ones. There is a need to gauge more accurately the useful life of antiviral medications, and the committee understands that there are ongoing efforts to do so. Beyond that, the exclusion of state and private-sector stockpiles from the federal SLEP presents a considerable barrier to further stockpiling.

Recommendation 2-2: The committee recommends that the federal government's Shelf-Life Extension Program be expanded to include other public- and private-sector entities that are stockpiling antivirals for use in an influenza pandemic.

In the event that no solution to this issue has been found, it is possible that a pandemic could coincide with availability of large state or private-sector antiviral supplies that have expired and would normally be discarded. It would be unacceptable to discard potentially viable medications in a scenario of scarcity.

Recommendation 2-3: The committee further recommends that the Department of Health and Human Services develop a process to use the knowledge acquired by the Food and Drug Administration in the operation of the Shelf-Life Extension Program[5] to facilitate the use of properly stored, recently expired medications that exist in supplies outside the Shelf-Life Extension Program in the event these medications are needed because of a shortage.

Role of the Private Sector

In acknowledgment of the fact that the federal government's ability to stockpile is limited by several factors, and the fact that the private sector—specifically some major employers—are exploring ways to protect some or all of their employees, DHHS has introduced the concept of "shared responsibility" and has been engaging in an ongoing dialogue with private-sector planners about their efforts (IDSA and Poretz, 2007b). The committee has learned that some private-sector employers are hesitant about assuming the cost of antivirals, a hesitation that is shaped by the many unknowns, the high cost of the medications, questions about shelf-life and the current exclusion of non-federal stockpiles in the SLEP, and by unease, expressed by some, at the possibility of government seizure of private stockpiles (Koonin, 2008). Major employers (like their counterparts in health care and in the public sector, e.g., law enforcement, fire departments, and emergency medical services personnel) also are uncertain about the desirability and feasibility of including workers' families (see discussion in Chapter 4).

The collective effort of many public- and private-sector entities will be needed to support the response to a pandemic. The goal of this coordination will be to maximize optimal distribution of limited antiviral stock consistent with key public health strategies for pandemic containment and mitigation, including a recommendation regarding prioritization. Reliance on potential private-sector resources most likely would be dictated by the private sector, but the possibility of seizing private supplies for public purposes looms. Public health agency commitments not to do this might increase private-sector stockpiling (and facilitate trust in local and state public health agencies or at least a sense that all are acting in good faith). On the private-sector side, coordination may mean a commit-

[5]As part of this program, a collaborative effort between FDA and the Department of Defense, FDA Office of Regulatory Affairs "laboratories test product samples, and in cooperation with FDA's Center for Drug Evaluation and Research, determine if the expiration date for the lot of the product can be extended and for how long" (FDA, 2007a).

ment to follow federal and state recommendations on antiviral dispensing, especially in a situation of scarcity, in which providing antivirals to low-risk employees or to those who do not perform unique and irreplaceable roles may cause public outcry and pose ethical problems. During declared states of emergency at the federal or state levels, there are legal avenues to require private-sector entities to distribute antivirals consistent with federal or state guidance. Government is sufficiently vested with emergency powers to (1) mandate that any distribution of drugs, such as antivirals, follow allocation or distribution plans; (2) change existing standards of care for practitioners of medicine, nursing, pharmacy, or public health to facilitate the rapid distribution of antivirals consistent with emergency needs; or (3) take possession of available drug supplies from private-sector entities for the purpose of ensuring adherence to allocation guidelines. Any taking of private antiviral supplies must constitutionally be compensated, although this may be determined post-emergency. Penalties for non-compliance with these potential emergency efforts may include a bevy of sanctions, such as de-licensure of medical personnel or facilities, criminal fines, and civil actions. In reality, government's capacity to enforce emergency efforts will likely be compromised, necessitating collaborative efforts between public and private sectors to make possible fair and proper allocations of antivirals to assure the public's health.

Recommendation 2-4: To promote mutual trust, collaboration, and coordination, memorandums of understanding or similar agreements should be developed between public health agencies and private-sector entities in their jurisdictions. During the pre-pandemic period and in the early stages of a pandemic such collaborations could facilitate information sharing and awareness of state and local recommendations regarding anticipated best practices in public health and standards of care in response to an influenza pandemic. (These may include prioritization schemes, guidelines for initial treatment of suspected cases, initial post-exposure prophylaxis, reporting of adverse events concerning antivirals, and coordination with state, tribal, and local officials as to who has been given medication.)

The committee understands that in a pandemic resulting in declarations of emergency or public health emergency, federal, state, or local public health authorities have the authority to take private stockpiles of antivirals to meet critical societal needs, notwithstanding such agreements.

Other potential areas of public–private collaboration include conducting joint drills and exercises, using businesses as points-of-dispensing (Khan, 2008), and sharing knowledge and expertise, for example,

private-sector logistical know-how that could strengthen a public health agency's ability to move antivirals rapidly from storage to dispensing sites to people.

Closing Observations

The federal government and state and local public health agencies have used what is known about the severe influenza pandemic of 1918 as planning devices: (1) a high case fatality rate as much as 25 times that of moderate pandemics like those that occurred in 1957 and 1968; (2) high case fatality rates among the young and healthy, in addition to the very young (with somewhat lower than expected mortality among the elderly); (3) the destabilization of vital societal infrastructure, especially health care, public safety, and utilities, threatening further loss of life and social disorder; and (4) pandemic waves separated by several months.

In the first wave of a severe pandemic, and in the absence of a vaccine well-matched to the pandemic strain (that would take several months to develop and manufacture), antivirals would have the potential to affect the course of the pandemic. They could lower mortality rates across a diverse population and could help preserve critical infrastructures by protecting key personnel and lessening the strain on the health care delivery system.

Unfortunately, confidence in the potential benefits of antivirals is tempered by the possibility of their improper use (and potentially their overuse), which could perhaps result in lessened benefit to the individual, and pose an enhanced risk that a resistant virus will emerge in the population. If more were known about how antivirals would work in a pandemic, it would be possible to make sensitive risk–benefit analyses of how to deploy antivirals, and thus answer many questions that are difficult, if not impossible, to answer in the current circumstances. Should a limited supply of antivirals be used for treatment only, or a combination of treatment and prophylaxis? If a combination of the two uses is desired, what should be the proportion of each? What types of prophylaxis should be implemented, and what groups should be targeted? Scenarios A, B, and C answer these questions in very different ways. They represent different assumptions about the available supply of antiviral drugs, as well as about the risks associated with certain of their uses. They also factor in unknowns differently. These unknowns include, What will be the effect of community mitigation in terms of attack rate and mortality rate? Will the stockpiled antivirals be effective against the pandemic virus? What is the potential that the virus will become drug resistant and how rapidly and how extensively will resistance develop? How will limited shelf-life of antivirals impact the supply at any given time? How, in the absence of

a timely and accurate diagnostic test, will demand for treatment antivirals be affected by the presence of other influenza-like illnesses? What will be the potential for restocking antivirals, should this be affordable and the best policy objective?

The greatest risk appears to be that overprescribing (e.g., to patients who do not actually have the pandemic influenza strain) and misuse of antivirals may not only deplete the supply but also may promote resistance, undermining the effectiveness of both treatment and prophylaxis. Scenario C poses the greatest risk in this regard. Scenario B runs the calculated risk that prophylaxis for workers providing critical societal functions (e.g., health care, utilities) does not risk over-use and misuse to the same extent. For the same reasons as the broad prophylaxis associated with scenario C, and because of its focus on health care and emergency services personnel, scenario B promises health care, public safety, and social order benefits for the population as a whole.

3

Ethics, Decision Making, and Communication

This chapter discusses three interrelated issues: ethics, decision making, and communication. In a severe pandemic, questions about the allocation of scarce medical resources will be inevitable. Depending on communities' levels of preparedness, responding to an influenza pandemic could be an overwhelming challenge for individuals, organizations, and government leaders. Preparing for the pandemic will require considering and communicating about contingencies in advance, developing an ethical compass to guide allocation decisions, and establishing mechanisms to ensure that antiviral use (like all other aspects of pandemic response) is rapidly adaptable to changing circumstances and new information.

ETHICS

A severe influenza pandemic poses different and far more challenging ethical dilemmas than a mild or moderate one. Chief among them is what proportions of the antiviral stockpile to commit to treatment and to prophylaxis and which groups to prioritize to receive those resources when demand exceeds supply. If medications are scarce, what ethical principles and goals should inform their allocation? For health-related resources in scarce supply, prior agreement on the ethical principles and goals that will guide strategic decisions and ground communications with the public is essential for a collaborative, coordinated response.

Judgments about the optimal allocation of scarce resources are value

judgments. Although they must be informed by science and best available evidence, they are not the responsibility of scientists or other experts alone. Ethically informed plans to allocate antivirals on grounds other than individual medical need or the principle of "first come, first served" require the considered judgment of persons with diverse experience and expertise, including the public. In this chapter, the committee indicates ethical commitments, principles, and goals to be considered in developing an ethical framework to guide decisions concerning the allocation and dispensing of antivirals in a severe pandemic.

Ethical frameworks have been offered from several sources, including the World Health Organization (WHO), the Department of Health and Human Services, several countries, and some states. A review of state pandemic influenza plans found that although most state plans acknowledged the importance of ethical considerations, they included little explanation of steps to take to ensure ethical decision making (Thomas et al., 2007). There is reason for concern that ethics may be viewed as important but secondary to programmatic activities such as planning dispensing sites and conducting exercises, rather than as the foundation for sound decision making.

The proposed federal guidance on antiviral use strategies includes four ethical principles: fairness (all equally eligible have equal access to antivirals), utility (minimize harms of the pandemic), reciprocity (minimize risks to those occupationally at risk to benefit society broadly), and flexibility (adaptability to emerging information). The federal guidance also acknowledges the importance of procedural ethics, transparency, public inclusiveness, and reasonableness (i.e., rational choices consistent with societal values, especially when science is lacking). The committee considers this a good start on an ethical framework for resource allocation in a severe pandemic, and provides some distinctions, principles, and goals to consider, and a recommendation to build on this foundation.

Many of the ethical frameworks that have been promulgated so far include ethical principles and goals, some include strategies and sample allocation plans based on detailed assumptions about the pandemic being planned for, and all of them include what might be described as "integrity factors" or ethical commitments based on respect for persons and the public (Kass, 2005, 2008). The committee finds it helpful to distinguish these three components of the ethical framework needed: (1) integrity factors/commitments, (2) ethical principles, and (3) ethical goals. It is on the basis of the ethical framework that strategies for allocating scarce resources will be determined in an actual pandemic. The committee here offers a starting point for a broadly based effort to build a national ethical framework for use of scarce health resource, and specifically antiviral, allocation in a severe pandemic. What follows is an example of a set of ethical commit-

ments, principles, and goals, as well as (in Chapter 4) a list of clinical and non-clinical characteristics potentially relevant to prioritizing groups for antiviral treatment and prophylaxis (Kass, 2008; Vawter et al., 2008).

Integrity Factors or Commitments

A number of plans have included integrity commitments for government decision makers. These might also include citizen integrity factors such as individual responsibility (e.g., neighborliness) (New Zealand National Ethics Advisory Committee, 2007). Such integrity factors can be thought of as the glue of a truly communal response rather than divisive group or individual responses in a pandemic. The committee believes a clear statement of integrity commitments is needed to accompany the ethical principles and goals that will guide allocation decisions in the United States. Integrity factors to consider include commitments to trustworthiness, accountability, transparency, public engagement in determining ethically acceptable tradeoffs, and promoting a sense of shared purpose and individual responsibility through open processes of information, consultation, and communication.

Ethical Principles

Ethical principles, the second element in an ethical framework to guide resource allocation might include safeguarding population health, protecting public safety, preserving social order, promoting fairness on the basis of morally relevant characteristics (substantive fairness), and following fair procedures (procedural fairness).

Ethical Goals

The third element of an ethical framework consists of ethical goals. The goals associated with the principles above might include (1) protect population health by minimizing mortality and morbidity; (2) protect public safety by containing disruption to health, public safety, and other critical infrastructures; (3) preserve social order by informing, involving, and practicing open communication with the public (to promote understanding and cooperation); and (4) promote fairness by protecting groups taking risks (i.e., high exposure to influenza) for the sake of others and the population as a whole (reciprocity), by giving special attention to groups with excessive mortality risks, or by removing access barriers to care, and following procedures for equitable access to a resource when supply is insufficient for all who are eligible.

It is important to understand how an ethical framework is to be

used in actual decision making. As with any ethical dilemma, allocation and prioritization decisions will require analyzing and determining the optimal way of giving balanced attention to all of the agreed-upon ethical principles and their associated goals simultaneously, not choosing among them and setting the others aside. Because information emerging in a pandemic is critical to making determinations of strategy, strategies and prioritizations can only be hypothetically chosen in advance. That is, based on detailed assumptions about how a severe, 1918-type pandemic would manifest itself today, resource allocation prioritization groups and strategies could be delineated in advance. There is the risk, however, that the public and priority groups would interpret such advance prioritization as more than the sample plan that it is, in need of adjustment to the characteristics of the real pandemic as it unfolds. For this reason, the committee does not suggest the composition of specific priority groups and only recommends a first level of prioritization (see Chapter 4 for the recommendation and additional discussion).

A broadly based effort is needed to construct an ethical framework useful to a wide range of decision makers, beginning with the consideration of the candidate integrity factors, principles, and goals indicated in this report. All resource allocation decisions involve the balancing of a number of ethically compelling objectives (e.g., population health and fairness). A broadly agreed-upon framework is needed to provide a critical grounding for decision making, justification, and communication. The proactive development of an ethical framework to guide allocation can support consistent decisions across sectors and serve as a rationale and basis of communication across the United States. Such principles and goals will provide a needed basis for flexibility in response to local circumstances and accountability in assessing and adjusting scarce resource allocation strategies as the epidemiological characteristics of the pandemic become known. Such characteristics include attack rate, case fatality rates, high-risk groups, susceptibility to antivirals of a certain dose and duration for treatment and prophylaxis, resistance, and drug safety.

The issue of resource allocation is understandably troubling to most people given the need to prioritize population rather than perceived individual interests. It is important for all levels of government to undertake efforts to engage and communicate with a diverse public about these sensitive issues and provide the public with a role in the decision-making process. Many jurisdictions, including the federal government, have worked to begin and sustain some major structured efforts of public engagement.

In 2006, a process of public deliberation sponsored by the Association of State and Territorial Health Officials and the Keystone Center, the Public Engagement Project on Community Control Measures for Pandemic

Influenza, gathered the input of organized stakeholders from various sectors and citizens-at-large (from four different areas of the United States) on five community control measures. The process led to the development of 13 priority recommendations, 1 of which related specifically to ethical decision making: Develop clear and practically useful guidance for making ethical decisions around the use of scarce resources and other difficult choices in a severe pandemic. Stakeholders shared concerns about decision making in regard to the distribution of scarce resources such as antivirals and "suggested creating ethical decision making guidance through a detailed process that begins with the federal funding of community-level conversations and deliberations on these topics. A work group would take the findings of the conversations and develop ethical guidelines to determine how scarce community resources would be dispensed" (The Keystone Center, 2007).

The committee is optimistic that these kinds of efforts will help to create a sense of shared purpose around an emerging plan and later the implementation of antiviral distribution and dispensing.

Recommendation 3-1: The committee recommends that the federal government in collaboration with state, tribal, and local governments support the development of a national ethical framework to guide the allocation of antivirals (and other scarce health resources) during a severe influenza pandemic. Developing the framework should incorporate processes to obtain input from the public and a wide array of stakeholders.

MAKING DECISIONS, CHANGING COURSE

As noted earlier in this report, preparing for an influenza pandemic requires facing uncertainty, for example, about the timing of a pandemic, its point of origin, the speed of spread, its level of virulence, its epidemiologic profile and extent of resistance, and the causative strain of influenza. In the course of responding to the pandemic, more information will become available that may require changing aspects of plans that were made with unknowns in mind, and changes will need to be made rapidly, with input from relevant experts and communication to the public.

The committee asserts that an entity and mechanism will be needed to support making national-level decisions in the course of implementing pandemic response, including the use of antivirals. There are several relevant federal advisory committees, including the Advisory Committee on Immunization Practices (ACIP); two committees that advise the Food and Drug Administration (FDA) on antiviral drug issues and drug safety issues, respectively; the National Vaccine Advisory Committee (NVAC);

and others. However, none is ideally suited, and indeed none has been constituted, to advise the government and its partners in responding to an influenza pandemic.

ACIP is a federal advisory committee that advises the federal government on all dimensions of its immunization policies. Its advice is widely regarded as the definitive expert voice on immunization issues. During the smallpox vaccination implementation program in 2003 and 2004, ACIP played an important role in making recommendations regarding the risk–benefit profile of the vaccine, and provided other guidance in the course of the program, most notably at crucial points in its implementation, such as when serious adverse events were identified. ACIP also defined priority groups during the 2004–2005 seasonal influenza vaccine shortage. FDA advisory committees such as those on antiviral drugs and on drug safety and risk management are charged with considering a wider range of drugs from a regulatory perspective, and NVAC has the role of advising the National Vaccine Program Office on policy issues related to vaccine safety and effectiveness.

There is no advisory body similar to ACIP constituted to advise the federal government and the medical and public health communities on the use of antivirals and other dimensions of a public health response during an influenza pandemic. The Infectious Disease Society of America also has called for such an entity to be established (IDSA and Poretz, 2007a). A pre-formed and on-call expert advisory body to the government is needed to address issues that arise in the course of implementation. This body could be constituted as a federal advisory committee, with meetings open to the public and to public comment, and with the charge to make recommendations to the Department of Health and Human Services and its partners at all levels of government.

Recommendation 3-2: The committee recommends that as soon as possible a federal advisory body be formed to advise the federal government and its partners on the planning and implementation of public health and medical responses to an influenza pandemic, including antiviral use. Options for establishing an advisory body include creating a subcommittee under the National Biodefense Science Board or creating a new federal advisory committee to the Department of Health and Human Services.

Scope of Work of the Advisory Body

The pandemic influenza advisory body could meet as frequently as is deemed necessary in a pandemic, but would have the mandate of convening in real-time to respond to pressing questions within 24 hours. In

addition to the scientific expertise of members and emerging pandemic data and information, the work of the group also would be informed by the national ethical framework described earlier in this chapter.

The role of the advisory body would include reviewing a variety of information and data and making recommendations about the following:

- Determinations regarding priority groups for treatment, for outbreak prophylaxis of groups with occupational exposure, and for post-exposure prophylaxis of groups with occupational exposure and household contacts of cases (on the basis of preidentified parameters vetted and expanded in public dialogue about priorities) and changes in those priorities on the basis of new information
- The nature of and systems to capture antiviral adverse events, and implications of drug safety issues for the program course of action
- Surveillance of antiviral resistance in the pandemic strain of influenza and implications for antiviral use
- New, unapproved antiviral products or use of drugs in combination for treatment or prophylaxis
- Standard protocols (including algorithms for diagnosis)
- Mobilization of private-sector stockpiles
- Professional licensure issues
- Triggers for midstream changes in algorithms and guidelines

Meetings of the advisory body also would serve as a forum for the public discussion of the issues identified above and others.

The advisory body would take a comprehensive, transdisciplinary approach that cuts across all dimensions of antiviral use (in the context of pandemic response in its entirety). Among many difficult considerations, the group would likely need to assess changing legal norms (e.g., prescribing and dispensing authority) in declared states of emergency arising during pandemic influenza. Although many emergency legal issues may be addressed in advance, legal and other actors would be working in real-time to assess potential legal barriers and implement solutions conducive to protecting the public's health during the emergency. These efforts, comprehensively referred to as "legal triage" (Hodge, 2006b) present the potential for divergent legal standards across all levels of government during the pandemic influenza emergency, which may affect the role and guidance of the advisory body. Legal triage describes "the efforts of legal actors and others to construct a favorable legal environment during emergencies through a prioritization of issues and solutions that facilitate legitimate public health responses" (Hodge, 2007).

Composition of the Advisory Body

Membership in the advisory body would be broadly constituted through a nomination process involving posting in the *Federal Register.* The advisory body would include relevant scientific expertise in disciplines including, but not limited to, virology, immunology, medicine, and epidemiology. Supplementary expertise in ethics and law may be needed at some points. Mechanisms for obtaining additional expertise would be available to the group. In order to use expertise and established lines of communication, this advisory body would ideally include members with appropriate expertise from ACIP, NVAC, the FDA Vaccine Research and Biologics Advisory Committee, and the National Biodefense Science Board (NBSB).[1] Additional members may be needed, including ex officio senior representatives from CDC, FDA, the National Vaccine Program Office, and the National Institutes of Health, as well as other relevant departments (such as the Departments of Homeland Security, Defense, and Veterans' Affairs).

COMMUNICATION

Although the health care and public health communities have been engaging in dialogue and pandemic planning for several years, preparing the public sometimes has been an afterthought (Lanard and Sandman, 2005). A well-prepared public—in all its diversity—is crucial to support the efficient and effective use of antivirals. On the pages that follow, the committee offers some overarching principles for communication about antivirals, then a communication topic relevant to providers, and finally, four areas for public communication: antiviral risk and benefit, urgency of treatment, supply and priorities for antiviral use, and the need to implement a program of antiviral use in a manner that is flexible and responsive to emerging information.

Planning the communication activities needed to support an antiviral drug program will first require initiating a dialogue with the public about antiviral medications and key issues in determining how to distribute a limited supply to achieve results that promote the greatest public good while minimizing the likelihood that individuals will be treated unjustly.

[1] "The NBSB was created under the authority of the Pandemic and All-Hazards Preparedness Act, signed into law on December 19, 2006 . . . to provide expert advice and guidance to the Secretary of the U.S. Department of Health and Human Services (HHS) on scientific, technical, and other matters of special interest to HHS regarding activities to prevent, prepare for, and respond to adverse health effects of public health emergencies. . ." (Source: http://www.hhs.gov/aspr/omsph/nbsb).

Communication during pandemic influenza will be as important to outbreak control as are other public health tools. To ensure that plans for antiviral dispensing, as directed by national guidance and shaped by state and local capabilities and needs are effective, communication needs to be timely, accurate, and conducted in a linguistically and culturally appropriate manner. Attention to the very low health literacy of many U.S. adults also should inform plans for obtaining informed consent if needed (for example, if non-approved medications are used), medication distribution and dispensing, compliance with prescription, early detection and reporting of influenza symptoms, safety reporting, and so on. Timely communication implies (1) advance preparation of the public with information that is relevant to them before a pandemic begins, and (2) advance preparation of just-in-time messages and channels for delivery in a pandemic, identification of key spokespersons, and plans for ensuring consistent communication that is based on the best available information, does not overstate what is known, or does not hide or minimize what is unknown (Janssen et al., 2006).

The committee finds it important to highlight several aspects of communication related to the antiviral distribution and dispensing component of pandemic influenza preparedness. These include the following:

Communicating About the Goals of the Antiviral Use Program and Priority Groups to Receive Antivirals (for treatment, and, if applicable, prophylaxis)

Whether or not the decision is made to identify priority groups in advance of a pandemic, the public needs to be informed about the ethical goals and other factors that will influence the decision-making process (ideally, this will be done in conjunction with a process of public engagement on the subject of prioritization for antiviral prophylaxis—see Recommendation 3-1).

Antiviral drug stockpiles currently are not sufficient either to treat or to provide prophylaxis to the entire population of the United States, so dialogue is needed in advance to develop principles that will guide prioritization during the pandemic, once more is known about the disease's epidemiologic profile. This area of communication is particularly important because the issue of scarcity raises the specter of panic. Some commentators on pandemic influenza planning express concern about the potential of widespread public panic to motivate a "run" on limited supplies and create a major problem for securing antiviral stockpiles (and maintaining order). A body of research in the social sciences indicates that the public reacts to disasters and emergencies in ways that are generally adaptive and constructive (Glass and Schoch-Spana, 2002; Auf der Heide,

2004). Although the bulk of the findings are drawn from experience with major natural or man-made disasters, there is little data to support the hypothesis of a public out-of-control.

Communication to Both Patients and Health Care Professionals About the Importance of Early Prophylaxis

Public and patient education is needed on the subject of taking antiviral drugs for treatment or prophylaxis in a way that supports peak effectiveness (e.g., taking antivirals during the 48-hour window after onset of symptoms for optimal effectiveness, compliance with prescribed instructions). Such messages could perhaps be communicated in conjunction with messages encouraging isolation to limit transmission.

Communication About Drug Risks and Benefits; Dispensing Site Instructions

It is well understood that antivirals may have considerable benefits in an influenza pandemic, but they are pharmaceutical products, and like all such products, they present risks. Also, it is important to understand that the risk–benefit profile of antivirals may change during the pandemic, if serious and unexpected adverse events emerge or if resistance develops rapidly, thus modifying the drug's effectiveness. If the pandemic strain is not as susceptible to antivirals as the seasonal strain(s), this would have implications for preparedness, and the risks posed by the drugs may outweigh the potential, but diminished, benefit.

Assuming that antivirals are reasonably effective against the pandemic strain, compliance with the regimen of treatment and prophylaxis will probably be important in helping to slow the development of resistance. Dispensing sites will need communication materials on this subject that are clear, concise, and culturally competent. Experience with some past mass distribution events indicates that patients receiving medication at a dispensing site will not necessarily retain the instructions conveyed to them in writing and verbally, and they may think of other questions after leaving the site of dispensing (Mahoney, 2008). Additional means for communicating this information may be useful to explore, including call centers for the general public (for example, the state of New York is planning a provider helpline) and perhaps some of the range of communication technologies that currently connect a large proportion of the population, such as text messaging.

Experience from previous outbreaks and influenza pandemics has shown that there is a potential for a high level of mistrust of governmental agencies and policies, as well as pharmaceutical manufacturers,

in response to this type of public health crisis. There also has been some degree of misinformation disseminated throughout the population via the mass media and rumor at these times. All of these factors can have a considerable effect on the public's willingness to use antivirals and to use them effectively. In the event of a pandemic influenza outbreak, several strategies may help to overcome these barriers to an effective response. The involvement of trusted community leaders and agencies in communicating and educating the public about the dispersal of antivirals, along with pandemic influenza public health services that are delivered by culturally and linguistically competent providers, should help to bring about greater public compliance and improved efficacy in the distribution and appropriate usage of antivirals.

Flexibility for Strategy Adjustment

Policy decisions and public communication will be closely linked in a pandemic and will ideally be thought of jointly in the planning process as well. During the pandemic, the public will need to be informed about emerging information on the course of the pandemic, data that is being collected, and decisions being considered and made. For example, epidemiologic information may emerge that indicates that a different age segment or occupational group is at higher risk than originally understood, and that could lead to changing the priority groups to receive antivirals. Information could emerge about drug effectiveness or resistance that demonstrates the need to increase the dose and/or duration of antiviral treatment or prophylaxis. This could have a dramatic effect on antiviral supplies, and the rationale for the change and likely outcomes with and without the change will need to be communicated. Timeliness of communication by public health authorities will be of the essence, especially given the vast array of information sources that likely will be available to comment on various aspects of the pandemic—this may be one of the more striking differences between the social context of the 1918 pandemic and the contemporary context. The federal advisory body recommended above would play a central role in providing the best scientific guidance to address all dimensions of the pandemic response, including the use of antiviral drugs to contain and mitigate the pandemic.

Other Public Communication Issues

Communication About Where and How Antivirals Will Be Distributed

In the event that some level of household post-exposure prophylaxis is needed, many or most jurisdictions intend to use their Strategic

National Stockpile (SNS) points of dispensing as the sites for giving out prophylaxis. Whether these or alternate sites or mechanisms will be used, targeted populations will need clear information about where to present and the process used to dispense, including screening for contraindications and dosage, and informed consent (if applicable). Additional consideration may be needed for messages about infection control at dispensing sites.

Removing Barriers to Access Through Communication

In planning the communication channels and messages related to antiviral dispensing, public health authorities and their partners should consider the needs of linguistically and culturally diverse communities and engage them in advance to identify the best ways to communicate. It is important to consider the broad spectrum of cultural variation within the United States and the impact that differing beliefs and values will have on the behaviors of the public during a modern day influenza pandemic. The overall linguistic and cultural diversity of the nation, coupled with documented gaps in overall health literacy and knowledge of public response from previous influenza pandemics, suggest that these factors should be considered when designing optimal delivery systems for antiviral distribution and conveying relevant information and education. Noting that the most important asset in any large-scale public health emergency is the public, the committee recommends the following:

Recommendation 3-3: The committee recommends that state, tribal, and local public health officials preparing for an influenza pandemic develop partnerships with (1) the media, including ethnic media; (2) leaders of local faith communities; (3) community-based clinics; and (4) other trusted organizations and community leaders to convey vital public health information clearly, simply, and in a manner that respects and reflects cultural and linguistic differences.

Communication with Health Care Providers

In the response to a pandemic, health care providers will need ongoing support from public health authorities and from the Centers for Disease Control and Prevention (CDC). CDC-provider communication was especially poor during the response to the 2001 anthrax attack (see Appendix A). The 2004–2005 influenza vaccine shortage experience presents a good example of optimal communication between CDC and some of its partners. States were involved in daily calls with CDC to discuss their strategies and share information. In a pandemic, health care providers would

benefit from daily web-based (including delivery to hand-held devices) numeric and other information about the antiviral dispensing effort.

Closing Observations

In addition to logistic and scientific considerations such as establishing and testing dispensing sites and conducting surveillance of antiviral resistance, planning antiviral dispensing for pandemic influenza requires the following:

1. Obtain public input, within a framework of agreed-on ethical principles and goals, on what is to be done
2. Create an entity with relevant scientific expertise that can be trusted to give good and timely advice to government and its partners in implementing antiviral dispensing (and other aspects of pandemic response)
3. Communicate to and with the public about how their input was included, what will inform mid-course corrections in the implementation of pandemic response, and what the public can and ought to know and do with respect to antivirals

4

Who Should Get Antivirals and Where?

In this chapter, the committee examines the two main components of plans for antiviral distribution and dispensing: decision making about the groups that will receive antiviral medications for treatment or prophylaxis (consistent with the ultimate goals of pandemic influenza plans) and about the locations where dispensing would take place.

DIAGNOSIS AND TREATMENT

The committee's discussion about diagnosis and treatment was informed by the knowledge that the federal government and states soon may reach the target of 75 (of a total of 81) million courses, an amount intended to be used for treatment (see discussion in Chapter 2). However, the committee notes that if program goals for the current antiviral supply include both treatment and some level of prophylaxis, it may become necessary to prioritize groups for treatment in addition to prophylaxis on the basis of the national ethical framework and the recommendations of the advisory body described in Chapter 3, as well as the characteristics of the pandemic.

A number of tests are available to diagnose seasonal influenza but few are sufficiently accurate (i.e., high sensitivity and specificity) for use in a pandemic in the context of antiviral scarcity and need for targeted use. Also, there are some tests available for use at the point-of-care, but they have significant limitations (WHO, 2005; CDC, 2006c).

The optimal diagnostic tool would be an accurate test that could be

used on large numbers of patients at the point-of-care, would provide rapid results (in 30 minutes or less), and would require minimal skill to administer and interpret (Griffin, 2007; Grijalva et al., 2007).

Current diagnostic tools include the following:

- Culture (of the virus) is traditionally considered the gold standard, with 100 percent specificity, but a culture also requires 48 hours or longer, so it cannot be used to determine treatment with antivirals that require prompt use for maximum efficacy.
- Real-time polymerase chain reaction (RT-PCR) is at least as, and perhaps more, sensitive than culture. It currently is expensive, of limited availability, and requires somewhat sophisticated laboratory capabilities.
- Direct immunofluorescence (or direct fluorescent antibody assay, DFA) provides results in approximately 1–6 hours and has 80–95 percent sensitivity.
- Enzyme immunoassay (EIA) rapid test gives results in 30 minutes, and has 50–90 percent sensitivity (median 70 percent) and 90–95 percent specificity.
- Serology is mostly useful for epidemiologic studies and takes more than 10 days.

Most tests available do not provide information about influenza A subtypes (CDC, 2006a; FDA, 2007b). Only PCR and culture currently can detect the H5N1 strain. Even fewer tools may be available if a different strain with pandemic potential emerges.

The performance of laboratory tests varies by the type of sample (swab versus aspirate or wash; nasal versus nasopharyngeal versus throat), the age of the patient (generally more sensitive in children because of higher viral loads), and the time since onset of symptoms (CDC, 2006b; FDA, 2007b). In addition, the operating characteristics (e.g., the sensitivity, specificity, likelihood ratio) of any laboratory or clinical diagnostic tool depend on the prevalence of influenza in the population, which influences the predictive value. For example, the positive predictive value of rapid tests is fairly good (i.e., most positives are true positives) when disease is highly prevalent, helping rule in true influenza. However, negative predictive value at the peak of a pandemic will be poor, so rapid tests would not be a good tool for denying treatment.

The clinical diagnosis of influenza is difficult because the symptoms overlap with those of other respiratory viral infections. A number of studies have examined the ability of clinical symptoms to predict which patients with respiratory infections have influenza (Call et al., 2005). The results are influenced by study design, the age of the patients, the

presence of co-morbid states and the prevalence of influenza. One of the largest studies examined 3,744 participants in clinical trials of zanamivir, who were pre-selected as having a high pre-test probability of influenza (Monto et al., 2000). The combination of fever and cough had a sensitivity of 64 percent and a specificity of 67 percent. In this setting where the prevalence of influenza was 66 percent, the positive predictive value was 79 percent and the negative predictive value was 49 percent.

Clinical diagnosis in children may be even more difficult because the symptoms vary by age, and many respiratory viral infections mimic influenza. In one study of 128 children, the triad of cough and headache by history and clinical finding of pharyngitis had a sensitivity of 80 percent (95 percent CI [confidence interval], 69–91 percent), specificity of 78 percent (95 percent CI, 67–89 percent), positive predictive value of 77 percent (95 percent CI, 61–88 percent), and a negative predictive value of 81 percent (95 percent CI, 70–92 percent) (Friedman and Attia, 2004). In another study of children ages 5–12 years old participating in a zanamivir trial, cough and fever had a positive predictive value of 83 percent (Ohmit and Monto, 2006).

Thus, clinical diagnosis in children and adults has a modest positive predictive value in high prevalence settings, but with low specificity and negative predictive value. In other settings, such as the beginning of a pandemic when disease is still rare, the positive predictive value may be considerably lower. In most settings, clinical diagnosis does not perform as well as rapid tests, which have modest sensitivity.

In a pandemic, symptom frequency in a naïve population could potentially be different than during seasonal influenza, and it is possible that severe influenza could facilitate clinical diagnosis (unusually severe and distinctive symptoms would help to differentiate it from seasonal influenza and other common respiratory illnesses). However, public perception, public health concerns, patient pressure, and ethical concerns may lead to pressure to overdiagnose (M'Ikanatha et al., 2005).

The implication of a modest positive predictive value of diagnostic tests is that a greater number of treatment courses will be needed. If the positive predictive value is 50 percent, half of those diagnosed will not have influenza and twice as many doses will be needed. Clearly, more accurate, rapid, and simple-to-use diagnostic tools would improve the efficiency of antiviral use during a pandemic. Cost would undoubtedly be an additional consideration, so inexpensive tests that meet all criteria described above would be ideal.

Many questions arise when considering the processes to be used for diagnosis and treatment. What are the criteria for prescribing? A prescribing algorithm? Should these systems be tested during seasonal influenza? Other outbreaks? What about concerns about attempts by individuals not

in a priority group to obtain drugs, or attempts to obtain or sell drugs unlawfully outside established distribution systems? In regard to the final question, the committee believes that it will be impossible to keep people from gaming the system, and that it would be a better use of time and resources to ensure that the greatest proportion of people who need antivirals actually get them.

Several options (or a combination) could be used to diagnose cases of influenza and, where applicable, link them with a dispensing site or dispensing mechanism (discussed later in this chapter). Decision making about the appropriate site for diagnosis will be influenced by several considerations, including concern about mixing infected and uninfected persons, point in time during the pandemic wave (for example, diagnosis could occur in the primary care setting early in the pandemic), ability and feasibility of dispensing at the same site, and implications of referring to another location.

Two potential sites for diagnosis are described below. Later in this chapter, dispensing sites are discussed, some of which could function as sites for diagnosis.

Remote Diagnosis: Telephone- or Website-Based Triage

The National Health System in the United Kingdom is planning to use the National FluLine as its main mechanism for providing information, and for diagnosing, triaging, and referring individuals to dispensing locations (Alcock, 2007; UK Department of Health, 2007). In the United States there are multiple locally or regionally based call centers, such as poison control centers, county extension offices, nurse advice lines, and tobacco cessation hotlines. Some jurisdictions, such as the state of Iowa, have considered or are considering use of such call centers to support response to a pandemic. A study funded by the Agency for Healthcare Research and Quality (AHRQ) and conducted by Denver Health (2007) has explored the use of call centers to support the following activities in a crisis: provision of health information, disease surveillance, triage and decision support, quarantine and isolation support and monitoring, outpatient drug information and adverse event reporting, and mental health support and referral. All or most of these functions would apply to antiviral distribution and dispensing in an influenza pandemic. Use of web-based support systems in a pandemic could be of great help, but would require careful planning including the development of an effective algorithm and clear, easy-to-understand language and format. On a more basic level, such systems would depend on functioning technology (e.g., telecommunication hubs) and a stable electrical power supply, both of which could be affected in a severe pandemic due to worker illness and absenteeism. It has been

suggested that the federal government could make advance arrangements to use the telephone- and/or web-based customer service system of a large business with an online retail presence (B. Wolcott, personal communication, December 17, 2007). However, this would require rapid and effective training (if at all feasible) of phone personnel and contingency planning for pandemic-related attrition in regional or international call centers. Existing state- or local-level call centers may be a more realistic mechanism for diagnosis and referral, although they would experience human resource demands similar to those of dispensing sites (perhaps minus the risk of infection). An algorithm for diagnosis and triage would be needed for these systems.

Clinician Examination

Diagnosis by one's own health care provider may not be possible during a pandemic, especially after the pandemic strain is known to have entered a community. Clinicians in the primary care setting could be overwhelmed (by both legitimate demand and perhaps by pressure from the worried well) during a severe or even a moderate outbreak, and there are concerns about infection control, storing and securing antivirals, linking with a data-gathering system, and other potential problems; thus it is highly unlikely that dispensing antivirals could occur in this setting (see discussion below). Furthermore, as noted earlier, clinical diagnosis would have somewhat limited predictive value, and in a severe pandemic with insufficient antiviral stockpiles, an accurate and rapid point-of-care test would be necessary (this would be most useful early and late in the pandemic).

PROPHYLAXIS

The committee believes current antiviral supplies will not be adequate for all of the uses considered. If expanding antiviral stockpiles is not feasible or desirable, a prioritization scheme developed by a transparent and inclusive national process will be needed for decision making (see recommendations in Chapters 2 and 3). The vaccine prioritization strategies (see Table 4-1) that have been developed by the federal government are the result of a process that considered different scenarios of pandemic severity, made explicit the values that guided decision making, and used input from the public in determining basic values.

Recommendation 4-1: The committee recommends that in the pre-pandemic period, the Department of Health and Human Services undertake an effort similar to that for influenza vaccine priorities—

TABLE 4-1 Groups to Receive Influenza Vaccine (from Draft Guidance on Allocating and Targeting Pandemic Influenza Vaccine, October 2007)

Four categories of target groups:

- Homeland and National Security
- Health Care and Community Support Services
- Critical Infrastructures (CI)
- General Population

Each category includes multiple target groups. The tiers cut across categories:

Tier 1	Tier 2	Tier 3	Tier 4
Critical occupations - Deployed forces - Critical health care - EMS - Fire - Police - Government leaders High-risk population - Pregnant women - Infants - Toddlers	Critical occupations - Military support - Border protection - National Guard - Intelligence services - Other national security - Community services - Utilities - Communications - Critical government High-risk population - Infant contacts - High-risk children	Critical occupations - Other active duty - Other health care - Other CI sectors - Other government High-risk population - Healthy children	High-risk population - High-risk adults - Elderly people

Tier 5 includes the remaining population not included in the target groups listed above.

national in scope, inclusive of diverse populations and viewpoints, and in keeping with a shared ethical framework[1]—to discuss and develop a prioritization scheme for antiviral treatment and prophylaxis that is capable of adjustments in real-time in response to the influenza pandemic.

The national dialogue and public engagement activities will ideally include a discussion of the goals of an antiviral dispensing program, for example, maintaining the functioning of society or mitigating death and hospitalizations, and whether the program can address some or all potential goals. As noted in Chapter 2, the amount of antivirals stockpiled will need to be commensurate with antiviral use goals.

There are two main types of prophylaxis that could be undertaken as part of an antiviral dispensing program for pandemic influenza: post-

[1]See Chapter 3.

exposure prophylaxis for those who come in close contact with infected individuals (either in an occupational setting or through household contact), and outbreak or seasonal prophylaxis that would be prolonged (i.e., for the duration of the first wave of the pandemic) and provided to groups with occupational exposure.

There are at least three factors that warrant consideration in identifying priority groups. First, there seems to be widespread consensus at the national and state levels that ethical principles are needed to inform policy and program decisions on the allocation of antiviral drugs, particularly if supplies are very limited (see discussion in Chapter 3). The epidemiologic profile of the disease is a second factor in decision making, but it will emerge from the data gathered in the early weeks of the pandemic (e.g., age groups and types of health status, including pregnancy, linked with greatest likelihood of death or severe disease requiring hospitalization). A third factor in decision making is based on both practical and ethical issues: occupations in general and work duties in particular that (1) pose greater likelihood, intensity, and frequency of exposure; and (2) are associated with situations where personal protective equipment may not be effective, usable, or available.

The most basic level of prioritization requires deciding whether a limited antiviral supply (beyond that needed for treatment) would be provided to household contacts of infected individuals, or to certain groups of front-line workers, either as prolonged or post-exposure prophylaxis, depending on the amount of drugs available. Despite the theoretical and ethical arguments for post-exposure prophylaxis among household members who participate in voluntary quarantine, there is little evidence to support the feasibility or efficacy of this approach. Moreover, this approach requires a large stockpile (more than 88 million courses according to the estimate provided in the Department of Health and Human Services [DHHS] draft proposed guidance dated November 6, 2007) and may lead to unanticipated consequences.

Recommendation 4-2: The committee recommends that pandemic influenza planners at all levels make outbreak prophylaxis for health care and emergency personnel who are in short supply and will have repeated and difficult-to-control exposure a first priority for prophylactic antiviral use. Post-exposure prophylaxis for other health care personnel and emergency responders should be a second priority. Post-exposure prophylaxis of household contacts of infected individuals should be a third priority if stockpiled antivirals are insufficient to meet all prophylaxis objectives.

In the absence of pharmacologic means of protection, alternate methods for containing disease spread in and beyond the household would be

applied, including quarantine and isolation (voluntary or not, depending on circumstances) and advance instructions for implementing household infection control.

For a 1918-type (i.e., severe) pandemic, age, occupation, and health status would be among the characteristics of note for prioritization. The differential age-based mortality risk seen in 1918, as one of several potential epidemiologic features of a pandemic, is an ethically relevant consideration for prioritization, especially if, as in 1918, healthy persons who are in the prime of life and key to infrastructure stability are at high risk of mortality due most likely to their robust immune response (the cytokine storm phenomenon). Furthermore, people who put themselves in harm's way for the sake of all in a pandemic should be given protection not only because of the utility of doing so (lessening mortality and strengthening infrastructure), but also the fairness (reciprocity) of it. Some groups may be at a disproportionately high risk of mortality, as pregnant women were in the 1918 pandemic due to their pregnancy-suppressed immune systems. If supplies are adequate and antivirals are deemed safe, these groups would be a likely high-priority group for occupational and household post-exposure prophylaxis. Likelihood, frequency, and intensity of exposure to the influenza virus are other important considerations. In a public health crisis when supplies are short, those who voluntarily assume risk on behalf of others both need and deserve first-priority status. With an indeterminate supply of antivirals, primarily prioritized for treatment in the first wave, offering prophylaxis from a limited supply to household contacts of ill individuals and to family members of those with occupational risk would likely undermine capacity for treatment and protection of health care workers and emergency response personnel. Because severe pandemic by definition involves both high mortality and infrastructure degradation, the group characteristics to be considered for prioritization can certainly be named and considered in advance, and tentative prioritizations per particular supply levels (as in scenarios A, B, and C) can be developed on the basis of national dialogue and public engagement process, subject to adjustment during the actual pandemic.

Outbreak[2] Prophylaxis

The severity and characteristics of the pandemic itself and the available supply of antivirals are key considerations in developing and adjusting a prioritization strategy. Because pandemic-specific information is so crucial to selecting group prioritization characteristics, the committee

[2]Outbreak prophylaxis refers to prophylaxis offered for the duration of an outbreak (i.e., the first pandemic wave), and is also referred to as seasonal prophylaxis, estimated by federal planners to last approximately 12 weeks.

only indicates characteristics to be considered. As described above, factors to be considered in deciding what groups will receive outbreak prophylaxis include epidemiologic information available early in the pandemic, practical and ethical considerations about occupations and duties, and availability of drugs.[3]

The following characteristics will need to be considered in determining prioritization of occupational groups for outbreak prophylaxis:

- Societal function
- Irreplaceable societal function (this will be challenging to define)
- Risk level for influenza-related mortality/morbidity
- Risk level of exposure (most current plans seem to assume that a large proportion of health care workers will experience certain exposure, without any effort to stratify them further, for example, by those who *will* be exposed and those who *may* be exposed)
- Risk of transmission
- Age
- Assumption of risk for others and society (reciprocity)

The committee affirms that notwithstanding limited supplies of antiviral stockpiles, some antiviral medication will need to be used for prophylaxis to protect essential health care workers who are providing care directly to severely ill patients in both the inpatient and outpatient settings. Antiviral use in this situation will best be done as an adjunct to other infection control measures in hospitals and clinics and within the broader community.

There are groups and individuals in certain occupations, in settings, and with duties that will have the greatest risk of infection and the least ability to control exposure (e.g., through the use of infection control and personal protective equipment [PPE]). These groups include, but are not limited to emergency department and triage personnel; direct care nurses and nurses' aides; emergency medical technicians and others who may conduct early diagnosis; respiratory therapists and other hospital personnel assigned to care for patients with influenza-like illness; critical operating room personnel; and public health workers with laboratory, epidemiology, and antiviral distribution-related responsibilities.

Depending on the pandemic's severity, effect on the health care and

[3]For a complete ethical framework including strategies for allocation of antivirals, see Vawter, D. E., J. E. Garrett, A. W. Prehn, D. A. DeBruin, C. A. Tauer, E. Parilla, J. Liaschenko, M. F. Marshall, and K. G. Gervais. *For the good of us all: Ethically rationing health resources in Minnesota in a severe influenza pandemic*. Minnesota Pandemic Project, Minnesota Department of Health, 2008.

emergency services workforce, and availability of antivirals, pandemic planners could consider strategies to minimize the need for prolonged prophylaxis (and thus decrease the amount of antiviral regimens needed, as well as minimize safety concerns about antiviral use longer than 6 weeks) by limiting health worker exposure to infected individuals. This could perhaps be done by organizing front-line workers into subsets or cohorts and deploying them in turn to care for cases of influenza. The use of personal protective equipment would constitute an additional strategy, assuming some level of availability at least during part of the pandemic.

Although the committee was not charged with examining dimensions of pandemic influenza planning outside antiviral distribution and dispensing, the committee notes that given the likely use of antiviral prophylaxis in conjunction with other strategies to reduce the risk of health care personnel and emergency responders, greater clarity is needed on official recommendations for the use of masks and respirators in health care settings, workplaces, and homes. To the extent that the lack of clarity relates to inadequate scientific evidence, it will be important to conduct studies of the efficacy of infection control methods that could be used with antiviral prophylaxis and in order to decrease the need for prophylaxis in groups with occupational exposure. Further, the committee notes that the cost and opportunity costs associated with personal protective equipment will be a consideration. Also, the recent IOM report *Preparing for an Influenza Pandemic: Personal Protective Equipment for Healthcare Workers* described maintenance and reusability as two priority areas for research given concerns that personal protective equipment supplies at the state, local, and hospital level are limited and will be depleted rapidly in an influenza pandemic.[4]

The need for the strategies described above may vary depending on local circumstances. A small emergency department in a rural area, for example, may require continuous prophylaxis for all staff members during the entire first phase of a pandemic; that may or may not be the case for a large, well-staffed, urban emergency department.

Earlier in this chapter, the committee noted the limitations of existing rapid diagnostic tests and the great need for accurate, rapid, easy-to-use point-of-care tests to ensure the most judicious use of antivirals in a scenario of scarcity. An additional argument for the development and deployment of accurate diagnostics is the ability to adequately identify health care personnel and other "front-line" workers who develop influ-

[4]"Careful consideration should be given to the trade-offs between disposable and reusable PPE [personal protective equipment], particularly given the extreme demands that would be placed on a disposable PPE supply in an influenza pandemic. Maintenance and reuse are key factors for consideration in developing performance requirements" (IOM, 2008).

enza and recover. They will be able to work safely without prophylaxis or personal protective equipment.

Identifying priority groups among emergency responders may be made more complex by the fact that other personnel and trained volunteers may play emergency response roles in a pandemic. Thus, groups other than the obvious emergency responders (law enforcement, emergency medical services, and fire department personnel) may need protection to do work that exposes them to unusually high risk of transmission. It will be necessary to identify the likely levels of exposure among all traditional emergency response workers, in addition to including other types of personnel or volunteers. Further, to target prophylaxis more accurately, it may be important to make an advance distinction between those who *will* undoubtedly be exposed and those who *may* be exposed.

The committee asserts that final determination of priority groups for outbreak prophylaxis cannot be made before the pandemic because the epidemiology of the disease is not known (e.g., who will be most likely to get sick, and who will be most likely to die). To use antivirals sparingly and strategically based on available epidemiologic data and local circumstances,

> **Recommendation 4-3: The committee recommends that efforts be made to minimize the need for outbreak prophylaxis among health care and emergency responders, and efficiently allocate scarce health resources. Necessary measures include proper and consistent use of personal protective equipment and grouping of workers in subsets to stagger their exposure to infected patients, thus reducing the numbers who need prophylaxis at any given time and shortening the duration of needed prophylaxis.**

From a communication and public relations standpoint, preidentifying a given group or groups as priority targets for prophylaxis could have unintended consequences, if it later became necessary to change their status as more information (e.g., epidemiologic pattern) becomes available or circumstances change. Labor-related concerns will also arise because protecting all personnel in the same occupational category may be impossible. This area undoubtedly will require advance dialogue with relevant labor organizations and other stakeholders. Not identifying priority groups in advance could be disruptive if likely groups have no advance warning. Also, although a great deal of attention is given to the potential benefits of antivirals in decreasing severe morbidity and mortality, antivirals also pose risks, and their risk–benefit profile may change if emerging data in a pandemic indicates that the pandemic strain is less susceptible to antivirals than anticipated in planning.

Although the exact groups that will be prioritized to receive antivirals

may not be known until a pandemic has begun, it may be helpful to identify in advance the sites best suited to dispense antiviral drugs to various potential occupational groups, which may include workplaces. Also, it may be helpful to plan basic communication tools, including a focus on supporting prophylaxis adherence. Federal planners anticipate a 12-week duration of prophylaxis for certain health care and emergency services workers, on the assumption that non-pharmaceutical interventions will lengthen the duration of the first pandemic wave.

When antiviral use guidelines are determined, it would be helpful to have national guidance (provided by the Centers for Disease Control and Prevention [CDC]) to ensure a level of consistency across state and territorial borders. From past experience (the 1998 meningitis outbreak, the 2004–2005 influenza vaccine shortage), it is known that differences among jurisdictions may cause confusion, distrust of the guidance provided, movement of citizens to areas where they think they can improve their chances of getting the drug or vaccine, and complaints to the public health authorities (GAO, 2000; Hannan, 2008) (see Appendix A). Thus, consistency on some aspects of the program across the United States (and possibly with neighboring nations), will be needed to preserve the credibility of the guidelines and of public health officials, to underscore the scientific, ethical, and practical basis for decision making, and to help encourage the greatest possible public compliance with the guidelines. However, the committee recognizes that in some circumstances, the guidelines may need to be clarified or modified somewhat by state and local authorities to address local realities. For example, there could be variation in the manifestations of the pandemic and variations in the populations served, which might potentially lead to minor differences in public health response.

The committee believes that provision of prophylaxis to health care personnel and other relevant workers during a pandemic would rely on their health care facilities' plans and existing information systems, distribution mechanisms, and procedures. However, it is important to note that some emergency response workers may not have occupational "bases" that lend themselves equally well to providing a site for dispensing medications, or the education and record keeping activities needed for the duration of the pandemic or until a well-matched vaccine is available.

A further factor in decision making relates to the assumption of risk for others and society (reciprocity). It has been suggested that health care workers' absenteeism could be motivated by concern about their families, both about infecting members of their household, and about needing to care for stricken family members (Wynia and Gostin, 2004). Some presenters at the committee's information-gathering meetings also suggested that some health care workers might take the prophylaxis intended to

them and give it to family members, thus leaving themselves vulnerable to infection. For these reasons, the possibility of providing some type of prophylaxis (or perhaps priority treatment in the event of very scarce antiviral supplies?) to family members of health care personnel has been raised. There are ethical issues of fair treatment for families of those who assume a risk for the public good and in doing so may increase their families' risk of contracting influenza (as suggested by experience during the Severe Acute Respiratory Syndrome outbreak of 2003) (Tufts, 2003; Wynia and Gostin, 2004). However, one public engagement activity revealed that although the public agrees with prioritization of workers who risk their own health and life to care for those who are stricken, the view on protecting the families of such workers with prophylaxis is less favorable (The Keystone Center, 2007). This clearly is one of many issues that warrant a broad public dialogue about antiviral use in a pandemic. There may be other means of preventing exposure of family members of health care workers, including meticulous and comprehensive infection control measures, but in-depth examination of these issues is beyond the scope of this report.

Post-Exposure Prophylaxis for Household Contacts

The ability to provide post-exposure prophylaxis for household contacts of cases is dependent on decisions made about the size of stockpiles (see scenario C, described in Chapter 2). The committee has recommended that this prophylaxis goal should be a lower priority after prophylaxis of certain types of health care workers and emergency responders. Moreover, providing this type of prophylaxis will likely be more difficult than offering prophylaxis to the occupational-exposure groups who are easier to gather, communicate to and with, dispense to, and monitor for drug adverse events and adherence.

The committee does not propose a prioritization scheme for household contacts for the same reasons outlined above. However, the committee lists some of the key considerations below:

- What groups experience the highest attack rates?
- What groups are most likely to transmit the disease (i.e., schoolchildren)?
- Who is getting sickest (requiring hospitalization)?
- Who is most likely to die?

It is possible that the same group(s) will be the answer to all these epidemiologic questions, or different groups may fit each of these dimensions of the epidemiologic profile that are expected to become evident early in

a pandemic. Additional consideration may be needed for disadvantaged or special population groups who experience barriers in accessing health care services in general, and to groups institutionalized with congregate living (e.g., long-term care facilities, correctional facilities). National pandemic influenza strategy in certain circumstances could involve asking members of households to care for ill individuals in the home in the event that health care inpatient facilities have exceeded all surge capacity. In that case, consideration will be needed for providing post-exposure prophylaxis to home-based caregivers who are being asked to remain in the home caring for a family member.

In addition to ethical and other considerations that will be needed in prioritizing groups to receive post-exposure prophylaxis, there will be logistical challenges. It will be necessary to enumerate household members of infected cases, to dispense drugs to them perhaps without a clinician actually examining them, and to provide a diagnosis if it appears they are developing symptoms (depending on the timing of the presentation of the infected household member).

Legal Considerations

During an influenza pandemic, declarations of emergency, disaster, or public health emergency at federal, state, or local levels alter the existing legal environment to allow government public health and safety officials and others sufficient flexibility and powers to respond. Though essential to emergency responses, such flexibility may also allow decisions or actions in real-time that may not be consistent with prior planning for the distribution of antivirals (Hodge, 2006b). In essence, government officials may be empowered during declared states of emergency to deviate from pre-emergency plans for the distribution of antivirals. For example, they may require household prophylaxis for specific persons, even if supplies are scarce. Public health or emergency management authorities may seek shifts in existing prioritization plans for many reasons, but ideally decisions should be grounded in what are viewed as the most effective strategies to protect the public's health. Household prophylaxis, for example, may be viewed as critical to garner the efforts of essential health care personnel or others to treat patients with influenza, or others suffering from other life-threatening conditions. Regardless of the justification, deviations from existing distribution strategies are predictable during emergencies as the extent of the impact of pandemic influenza is measured within populations and available supplies are assessed. As a result, although it may not be possible to specify legal responses to emergency circumstances arising from pandemic influenza, advance planning and real-time assessments of public health needs should heavily influence communal actions.

Enumerating and Dispensing to Household Contacts

Diagnosis of infected individuals will take place in person (depending on severity of symptoms, either in the primary care setting or in the emergency department) very early before the pandemic strain is known to have entered a community. The first cases in the United States and in a given community will be confirmed by current (or better) diagnostic tests. Thus, the availability of rapid, accurate point-of-care testing will be very important during that early phase.

In the middle to latter phases of the outbreak, diagnosis (or rather identification of cases) is more likely to be based on syndromic diagnosis. Thus, it may be more feasible to perform diagnosis and prescribing for many patients over the telephone or via a web-based interface in order to help prevent transmission and to lessen the likely effect on the health care delivery system. Thus a triage function would need to be built into the telephone or web algorithm so those who are acutely ill are channeled in a different direction (hospital, clinic, etc.). If sufficient antiviral courses are available to provide prophylaxis to household contacts, once the pandemic strain is in the community, this would trigger the points-of-dispensing (PODs)[5] or other dispensing sites to begin functioning.

In the context of diagnosis for initiating empiric treatment, voluntary isolation of cases and household prophylaxis, there are tradeoffs to remote diagnosis (e.g., via a telephone or web-based algorithm, see discussion earlier in this chapter).

There are tradeoffs between the risk of having transmission at the site of outpatient care and the potential increased accuracy of diagnosis. In the absence of abundant and accurate point-of-care diagnostics where influenza would be diagnosed based on simple clinical rules, there may be advantages to making the presumptive diagnosis remotely in persons not requiring acute care. However, if the goal is to quarantine the household and initiate prophylaxis, there is a high cost that must be acknowledged: due to the modest predictive value of clinical diagnosis, up to three times as many people will be quarantined and up to three times more drug will be used than is necessary. Thus, algorithm- or telephone-based diagnosis is very costly if voluntary quarantine and post-exposure prophylaxis of household contacts are planned.

Strategies for post-exposure prophylaxis of household contacts will need to be evaluated and reevaluated in the course of program implementation based on the following interrelated factors:

[5]Point-of-dispensing and point-of-distribution are sometimes used interchangeably in literature about state and local planning.

- The availability, accessibility, and cost of a rapid, accurate, point-of-care test to establish that a person with influenza-like illness has the pandemic strain and how readily it can realistically be deployed
- Availability of antivirals, since much of the decision making about household contact prophylaxis may occur on the basis of remote diagnosis versus in-person diagnosis
- Weighing the risk of exposing people to an infected person in the course of in-person diagnosis against the risk of misusing antivirals by dispensing them for treatment and prophylaxis of someone without confirmed pandemic influenza infection or exposure

There are a number of tasks related to household post-exposure prophylaxis that have to be resolved after diagnosis. These include enumeration; reasonable identification and screening of household members to receive prophylaxis; identification of the appropriate dispensing site for that household, whether pharmacy or POD or other site (or a delivery method); issuing a valid set of prescriptions; and recording the process. The details might vary in each jurisdiction based on the dispensing site, but the tasks will remain constant. For example, if a person is identified as being a candidate for treatment, and the strategy at the time is to offer prophylaxis to household contacts, the clinician on the telephone or interacting on the Web could have a household contact form that requests the number of household contacts, names, ages (noting children, the elderly), and known contraindications (including pregnancy), if any. Depending on the dispensing sites used in a given jurisdiction, there may be plans to have the clinician call in (or communicate in some way) the prescription for treatment of the infected individual and for post-exposure prophylaxis for household contacts to the POD, pharmacy, or other dispensing site that will be accessible to the respective household. This will require careful planning and decision making by each jurisdiction to ensure optimal placement of dispensing sites to ensure the most rapid and equitable process for giving antiviral courses to those who meet dispensing criteria.

DISPENSING SITES

Allocation and Distribution to Dispensing Sites

The importance of timely and efficient distribution of potentially life-saving drugs in responding to a pandemic cannot be overstated. All or most states have planned and tested their mechanism for taking the materiel obtained from their portion of the Strategic National Stockpile (SNS)

and placing it at predetermined locations around the state. If distribution mechanisms other than the SNS mechanism are considered to disperse some or all of a jurisdiction's antiviral supply, the respective public health agencies and their partners would benefit from considering private sector and Department of Defense expertise in supply chain science: efficiently moving product or material from point A to point B.[6] After the declaration of a pandemic, drugs need to be moved to dispensing sites smoothly and quickly to address treatment needs and, if appropriate, prophylaxis needs.

To facilitate prompt dispensing, the CDC supplemental guidance for pandemic influenza asked grantees to identify sites where antivirals may be pre-positioned when a pandemic is judged to be imminent (DHHS and CDC, 2006). A recent survey from the Association of State and Territorial Health Officials found that "21 state public health agencies plan to or have already prepositioned antivirals at hospitals, local health agencies and other locations around the state, and 26 do not plan to do so" (ASTHO, 2008).

Selecting Sites of Dispensing

Assuming adequate antiviral stockpiles are available to undertake post-exposure prophylaxis of contacts of infected individuals, the most challenging aspect of any dispensing program would be determining how to quickly and efficiently dispense antivirals on a large scale in circumstances where the pandemic influenza virus has entered a community and disease prevalence is increasing rapidly. There may be good reasons to consider using existing SNS distribution mechanisms (even for sources of medication other than the SNS, e.g., state stockpile). The vast majority of state and local public health agencies in the United States have developed considerable experience with PODs, which are the final destination of SNS supplies and are intended for the distribution of medications or vaccines rapidly and efficiently to large numbers of people. Despite potential drawbacks that may include the strict nature of the distribution channels and potentially expired supplies within the SNS, most jurisdictions are familiar with this distribution system, have invested resources, including funds and staff time for exercises, and have identified points-of-dispensing.

Once the SNS or state antiviral supplies have been delivered to the local level, there are a number of options for dispensing sites. The committee has learned about a wide array of locations (or mobile dispensing,

[6]In some states, the plan is that the state-purchased supply of antivirals will be sent out to the local agencies, freeing up the state facilities to receive the state's portion of the SNS.

in the case of visiting nurses, etc.) that could be used. Sites that could be considered, and many of which are already considered by jurisdictions around the country, include the following:

- Public health agency POD
- Hospitals
- Physicians' offices or other primary care settings
- Pharmacies
- Businesses
- Schools
- Drive-through pharmacies or other stores
- Parking lots
- Parish nurses or visiting nurses
- Homes, through mail or parcel delivery service, either pre-distributed or just-in-time
- Other private-sector delivery mechanisms employing a mail or parcel delivery service (e.g., Netflix-like system)
- Health maintenance organization systems
- Nursing homes or other long-term care facilities

Other dispensing sites could be used depending on local circumstances and needs. No one type of site will be suitable in all cases, and it is likely that if prophylaxis on a medium-to-large scale is the objective, many jurisdictions may need to plan for a combination of dispensing sites to reach all groups identified to receive antivirals. Site selection will ideally build on what has been learned about PODs and consider demographics and population density. Dispensing sites also may be characterized by a range of advantages and disadvantages, strengths and weaknesses. These include, but are not limited to the following:

- Integration of dispensing site features with other interventions in a jurisdiction's pandemic plan, such as social distancing (the SNS guidance makes this a condition for selection of points of dispensing)
- Capacity for infection control in general, including size of facility and efficiency of processing, availability of hand sanitizer and posted educational material on hygienic practices, and focus on other avenues for transmission such as sharing pens or clipboards, if applicable
- Accessibility and convenience
- Capacity and/or throughput (ability to process large numbers of people quickly and efficiently)

- Suitability for facilitating early treatment (within 48 hours of disease onset)
- Ability to implement crowd control and ensure security of drug supply (required by the SNS guidance)
- Ability to collect and report important data, including tracking who gets the drugs and a contingency pen-and-paper option in the event of technology or power failure, to (other) public health agencies
- Appropriateness for diagnosis if (1) decision is to use some/all sites for treatment in addition to prophylaxis, and if (2) exposed contacts provide information that suggests they may be infected, should there be a need to provide diagnosis at prophylaxis-only sites
- Implications for communication and education (e.g., drive-through sites offer little opportunity to educate, but how much education can be given if the goal is to process people efficiently and minimize contact? Is it useful to couple dispensing with an education component? Or should education take place through the mass media and new media [e.g., text messaging] instead?)
- Issues related to using private distributors to deliver antiviral medications to private homes

A major consideration in selecting dispensing sites is suitability for vulnerable or special-needs populations (e.g., ease of access, linguistic and cultural competence, geographic proximity so transportation does not become a barrier, perceived safety of the site, hours of operation). The choice of well-trusted community sites using personnel who have the greatest potential to deliver public health information and antiviral medications in a linguistically and culturally competent manner will be important. Examples of these sites may include community clinics, houses of worship, neighborhood (senior) centers, and other trusted community organizations. If security and other logistical concerns can be addressed, antiviral dispersal at these nontraditional sites will help to ensure that the service delivery is linguistically competent and that services are delivered by trusted agencies within communities across the nation. The provision of linguistically and culturally competent information and distribution services can help to facilitate the elimination of disparities in knowledge and avoidance of disparities in pandemic outcomes.

Below, the committee discusses the features of some of the dispensing site options, including public health agency points-of-dispensing, hospitals, homes, pharmacies, and physicians' offices.

Public health agency PODs have been exercised in most jurisdictions and are well-established mechanism for mass dispensing. A poten-

tial disadvantage is that they may not be sufficiently dispersed in some jurisdictions and therefore not accessible to all residents in a community. PODs also may include a one-size-fits-all approach that may not be optimal for hard to reach or vulnerable populations. PODs could, however, be expanded to include a wider range of setting and greater breadth of geographic distribution. Several jurisdictions have explored the use of a head-of-household model to facilitate rapid and efficient dispensing of antibiotics. For example, the Seattle and King County health departments collaborated with the University of Washington to exercise their public health POD and distribute mock medication to heads of households (Stergachis et al., 2007). In this exercise, which lasted 68 minutes, more than 600 10-day courses of "antibiotics" were dispensed to 254 heads of household in a process that included a triage element (including by age and need for pharmacist consultation). Philadelphia employed a similar process to test antibiotic dispensing and found that express dispensing to heads of household was a viable option (Agócs et al., 2007). In this exercise, 717 heads of household picked up drugs for a total of 2,120 household members in a period of 2 hours. The patients were directed to one of two lines, one of which was intended for those requiring additional screening (pediatric dosage and other issues). One noteworthy feature of this activity was that 42 of 50 point-of-dispensing staff were trained in the hour before the exercise began. The head-of-household dispensing model could perhaps be used to dispense antivirals for households with a known case of influenza. Something similar could occur in cases where individuals diagnosed with pandemic influenza are well enough to give information about their household to the health care provider who would be treating them and to return home with courses dispensed for all household members. The major advantage of the head-of-household dispensing model is that it involves only one point of contact for each household with an infected member, but that may also be a potential disadvantage if some households do not have a single member who is well enough to go and retrieve medication for the rest of the household.

Although hospitals are a typical site of diagnosis and dispensing, they are less than ideal for timely dispensing of antivirals (within the 48-hour window from symptom onset), because people may go to the hospital only when their condition is worsening. Also, hospitals may rapidly become overwhelmed in a pandemic, making them undesirable for further activities that would place strain on available human and other resources. In a pandemic, many people may try to avoid the hospital believing it to be a locus of infection. Hospitals may have security problems—including securing the antiviral supply, other hospital assets, and patient information—if they were used as community dispensing sites with large numbers of non-patients streaming through.

Pharmacies have well-established channels for acquiring, dispensing, tracking inventory, and screening for contraindications and proper dosage. However, most pharmacies sell a wide range of products that will continue to be in demand in a pandemic, making pharmacy facilities sites where the ill and the well would come in contact. Also, there may be good reasons to offer diagnosis and dispensing at the same site, and it is unclear whether pharmacies are appropriate sites for diagnosis.

The primary care setting has at least in principle the advantages of familiarity, ability to screen for contraindications and prescribe the proper dose for each individual patient, ability and duty to follow patients and refer in the event of adverse events, and so on. However, in a moderate-to-severe pandemic, primary care providers may be rapidly overwhelmed with demand. Also, providers do not typically dispense drugs, and locating antivirals in a primary care setting may present a logistic and security challenge. If tracking antiviral use is an objective, using primary care sites to dispense would greatly multiply the sites of dispensing, with implications for information technology resources. Finally, having individuals with influenza-like illness travel and congregate with others in a multitude of primary care waiting rooms may not support infection control objectives that may call for immediate self-isolation of sick persons and the avoidance of public settings.

If the home were the site or focus of dispensing, there are several models that have been explored by the Department of Health and Human Services (DHHS) and its state and local partners. One model is found in the MedKit project, which involved pre-positioning mock drugs with households and instructing household members to wait until further notice to use the contents of their kit. A second model has been tested through the Cities Readiness Initiative distribution of identical just-in-time packages containing bottles of "antibiotics" to homes in two ZIP Codes each in Boston, Philadelphia, and Seattle (Koh et al., 2008). This activity used U.S. Postal Service workers paired with local police personnel to deliver packages to homes. A third model that has been suggested is to encourage households to purchase antivirals in advance personal stockpiles. In the past, limited manufacturing capacity meant that personal stockpiling threatened the availability of antivirals for seasonal use and creating central stockpiles. This is no longer an issue. Personal stockpiling, however, is likely to be inconsistent and heterogeneous. It is unlikely to be an effective resource for public health use.

Pre-positioning of antiviral kits in homes or delivering them "just in time" to households would be a considerably more difficult endeavor than delivery of antibiotics, because given the gradual spread of the pandemic, the timing of the initiation of treatment or prophylaxis is complex. Common misconceptions about what constitutes "flu," anxiety, rumors,

and the difficulty of accurately identifying influenza using symptoms will make it difficult to ensure that antivirals are deployed appropriately. (The communication challenges are formidable, but must be addressed in advance, as noted in Chapter 3.) Some data exist for the MedKit project, but one cannot easily extrapolate from the ability to keep a blister pack of ciprofloxacin in reserve for a declared anthrax attack to the more complex requirements of antiviral use. Concerns have been raised about the risk of increased resistance from inappropriate use, but there are few data available to address this or other concerns. If pre-positioning is to be considered, the committee believes that careful exploration of these issues through extensive feasibility studies will be needed.

Legal Barriers Related to Dispensing Sites

The use of some sites for dispensing may present legal impediments. During declared states of emergency, governments may determine that public properties need to be used as dispensing sites, but interjurisdictional or other legal disagreements may interfere. For example, while the federal government may lawfully seek to use state or local property to facilitate the dispensation of antivirals, legal disputes about the selection of specific sites or other grounds can result in delays. Legal issues may include assessing responsibility for maintaining the premises, determining compensation for its use, providing adequate security to ensure public safety, and resolving liability concerns. On the other hand, state and local governments may not typically use federal properties for dispensing sites without federal approval, even during emergencies. Though the Pandemic and All-Hazards Preparedness Act (PAHPA) (PL 109-417, § 101 et seq. [2006]) and other federal laws have streamlined federal organization and responses to public health emergencies through DHHS, obtaining advance authorization to use federal sites for state or local dispensing programs will be helpful.

Political or other legal factors may interfere with dispensing site selection. Some potential dispensing sites may not be able to fully accommodate persons with disabilities, or pose risks to the health or safety of others, thus raising concerns about equal protection, disability rights, liability, and other issues. For example, local elementary schools may be deemed by public health officials in some communities as suitable sites for distributions of antivirals. However, such plans to use these facilities may be mired in legal concerns over the short- and long-term consequences of using these facilities for these purposes (e.g., potential for contamination to delay the reopening as school facilities). As discussed above, emergency laws are designed to allow government authorities to quickly resolve these types of legal issues (Hodge, 2006b). In reality,

however, competing legal norms may still interfere with plans for the use of public properties as dispensing sites. On a practical level, some of the planning issues described above may be addressed by taking steps such as engaging in dialogue with community entities about expectations and roles and drafting memorandums of understanding.

Emergency laws may also allow government to use private-sector facilities as dispensing sites (Gostin et al., 2002). In many instances, private-sector entities may collaborate with government agencies to avoid potential legal concerns while protecting the public's health. However, resistance of private-sector entities to the use of their property as dispensing sites may lead to legal disputes. Government is positioned during formal declarations of emergency to commandeer the use of private property for public health purposes. Government acquisition of private property for this purpose would likely be viewed as a constitutional taking, requiring compensation for the temporary use of the facilities and potential restoration after the emergency. Even if private-sector entities offer their properties for use as dispensing sites, they may seek assurances from government that the entity will not face claims of civil liability or increases in property insurance premiums for any harms that arise on the property for acts or ordinary negligence. Such protections are not automatically guaranteed under emergency laws. To the contrary, most emergency liability protections are designed to protect individuals, not corporate or other entities. As a result, although health care volunteers providing assistance at dispensing sites may be protected from liability claims, a private-sector entity that hosts the site or is responsible for its operation may not be entitled to similar liability protection (Gostin et al., 2002). This legal gap has been addressed legislatively in a few states, but is largely unresolved in most states and at the federal level (University of North Carolina Institute for Public Health, 2008).

Staffing

A number of jurisdictions have information available on the human and other resource requirements for setting up points of dispensing. In terms of the types of personnel that will be used, 36 states intend to use hospital staff for dispensing, 35 plan to use public health staff, 17 intend to use medical reserve corps, 15 will use other emergency response personnel, 12 will use emergency systems for the advance registration of volunteer health professionals (ESAR-VHPs), 14 intend to use pharmacy personnel, and 15 plan to dispense via local health departments, primary care providers, and community health centers (ASTHO, 2007). It cannot be assumed that adequate personnel will be available to roll this out in the time needed. Plans ideally will consider the effect of absenteeism

due to pandemic-related morbidity in personnel or family members, the dual roles of many responders, and the human resources available. The actual attack rates and epidemiologic features of the pandemic will help determine staffing decisions. One model that is used by many local jurisdictions to plan the staffing and other aspects of their point-of-dispensing is the Agency for Healthcare Research and Quality–supported Weill/Cornell Bioterrorism and Epidemic Response Model, which was designed for mass dispensing planning by hospital and health system officials.[7]

Potential Legal Issues Related to Staffing

Human resources are essential to the operation of a POD, but the participation of various persons may require the resolution of potential, significant, legal issues in advance. Government and private-sector entities responsible for their operation may seek to staff PODs with suitable, trained employees to provide essential services. The use of employees to staff nontraditional operations during public health emergencies implicates an array of legal concerns for the employees and their employers, as discussed below. As prior emergencies have demonstrated, emergency planners must also be prepared for significant staff shortages during pandemic influenza. Some employees will not be comfortable working in direct contact with the public because of the deadly threat of influenza, others will simply not report to work, and regrettably, some will be stricken with the condition they are being asked to help address.

Meeting surge capacity of persons seeking antivirals through PODs will likely necessitate the deployment and use of volunteers, specifically health practitioners who are pre-vetted, trained, and organized to provide essential public health or health care services (unlike spontaneous volunteers who may simply show up at emergency sites) (Hodge et al., 2005). To discourage spontaneity and promote organization of volunteer health practitioners during emergencies, Congress (PL 107-188, 42 U.S.C.A. § 247d-7b [*United States code annotated*, 2005]) directed DHHS to fund states and territories to develop interoperable emergency systems for the advance registration of volunteer health professionals (HRSA, 2005).[8] Virtually all states and territories have created (or begun to cre-

[7]The model may be found at http://www.ahrq.gov/research/biomodel3/toc.asp.

[8]Public health emergencies, such as pandemic influenza, have consistently featured support from volunteer health professionals (VHPs) (e.g., physicians, nurses, public health workers, lab technicians, emergency medical responders, psychologists). Emergency response planners count on VHPs to fill surge capacity and provide needed medical expertise and related support functions. Some volunteers are organized, trained, and directed to respond through governmental programs (e.g., Disaster Medical Assistance Teams [DMATs], Medical Reserve Corps [MRC]) and private-sector efforts (e.g., American Red Cross). Others

ate) these and other registration systems (e.g., Medical Reserve Corps at the local level) (Hoard and Tosatto, 2005) to organize and register skilled health practitioners who are willing to volunteer their services during emergencies.

While the need for volunteers during emergencies is essential to staff PODs or other public health or health care sites, volunteers, employees, and the entities that host or support them face an array of critical legal issues, including the following:

Liability When and under what circumstances may persons staffing PODs be personally liable for their actions during declared states of emergency? This question is critical to employees and volunteers alike, especially during emergencies when standards of care in phases of medical triage may rapidly change. However, their exposure to personal liability is highly variable. For example, some actors, such as governmental workers, may be largely immune from liability claims for acts of negligence during emergencies (HRSA, 2006). Many volunteers (who do not fit the definition of uncompensated volunteers under the federal Volunteer Protection Act [PL 105-119 (1997); 42 U.S.C.S. § 14501 et seq. (2004)] or similar state laws) may be potentially liable. Federal legislative proposals following Hurricane Katrina to better protect volunteers from liability have been introduced, but not passed (Hodge et al., 2006a). Some states' existing emergency laws may provide some liability protections for volunteers (HRSA, 2006). Other states have recently passed or are currently considering passage of a 2007 model law, the Uniform Emergency Volunteer Health Practitioners Act (UEVHPA) (National Conference of Commission-

simply show up at the site of a disaster or nearby health care facilities. These "spontaneous volunteers" are ready to help, but lack organization, identification, credentials, and, ultimately, utility. Their presence can actually impede effective emergency responses.

Prior experiences concerning complications in the deployment and use of VHPs led Congress to authorize DHHS to fund and assist states and territories to develop emergency systems for the advance registration of VHPs (ESAR-VHPs). These systems are designed to recruit and register prospective VHPs within each jurisdiction to help ensure a ready supply of trained, vetted volunteers during actual emergencies. As currently organized at the state and territorial levels, ESAR-VHP systems typically include verifiable, current information regarding a volunteer's identity, licensing, credentialing, accreditation, and privileging in hospitals or other health care facilities that might need volunteers. With the passage of the Pandemic and All-Hazards Preparedness Act in December 2006, DHHS is authorized to link ESAR-VHP systems and comparable volunteer registries organized via the MRC at the local level into a single, national verification system to better organize volunteers for federal emergency response efforts. The establishment of interoperable, state- and local-based registration systems will help federal, state, and local emergency response coordinators and others to quickly identify and better utilize VHPs during public health emergencies. However, a series of legal and regulatory questions impact their use and participation, most notably liability concerns.

ers on Uniform State Laws, 2006), to provide greater liability protection for volunteers (Hodge et al., 2007).[9] It should be noted that no laws protect persons staffing PODs from liability for their wanton, willful, or criminal acts (Hodge et al., 2006).

Workers' compensation Beyond issues of personal liability for actions causing harm to others, when may staffers be responsible for the personal injuries that they may incur during emergencies? In non-emergencies, employees who are injured or killed at work are covered through workers' compensation programs, which provide compensation regardless of fault. These same benefits should continue during emergencies for employees, but not necessarily for volunteers. By definition, volunteers are not employees, and thus may not be entitled to typical workers' compensation benefits while serving as volunteers (HRSA, 2006). Some employers may deem volunteers as covered through their workers' com-

[9]To address specific legal concerns underlying the deployment and use of volunteer health practitioners during declared states of emergency, the National Conference of Commissioners on Uniform State Laws (NCCUSL) has approved the Uniform Emergency Volunteer Health Practitioners Act (UEVHPA) as of August 2007. Among its key provisions, the Act (1) establishes a system for the use of volunteer health practitioners that is capable of functioning autonomously even when routine methods of communication are disrupted; (2) defines "volunteers" to include compensated and uncompensated individuals; (3) requires pre-deployment registration in a recognized system to facilitate subsequent deployment and streamlining of volunteers to a disaster site; (4) provides reasonable safeguards to assure that volunteer health practitioners are appropriately licensed and regulated to protect the public's health; and (5) allows states to regulate, direct, and restrict the scope and extent of services provided by volunteer health practitioners to promote disaster recovery operations. The UEVHPA also provides immunity against civil claims for negligence or other acts to volunteers enrolled in a registration system who provide services through a local host agency in cooperation with local emergency management requirements and adhere to scope of practice limitations imposed by their licensing state and host state. The Act offers two legislative options for state legislatures to determine the level of liability protection to provide volunteer health practitioners. Alternative A provides strong, comprehensive liability protections for the negligent acts of volunteer health practitioners during emergencies. Under Alternative A "a volunteer health practitioner who provides health or veterinary services pursuant to this [act] is not liable for damages for an act or omission of the practitioner in providing those services." Volunteer health practitioners are not protected against willful misconduct, or wanton, grossly negligent, reckless, or criminal conduct, intentional torts, breach of contract, or an act or omission relating to the operation of a motor vehicle, vessel, aircraft, or other vehicle. Alternative A also provides some liability protections for entities that host volunteer health practitioners, such as hospitals, clinics, or disaster response agencies. The liability protections of Alternative B, on the other hand, are more comparable to existing liability protections found in the federal Volunteer Protection Act, which provides liability protections to largely uncompensated volunteer health practitioners. As of January 2008, four states (Colorado, Kentucky, New Mexico, and Tennessee) have enacted versions of the UEVHPA. Additional legislative enactment efforts are underway in multiple, additional jurisdictions in 2008.

pensation plans, but this is atypical. As a result, unless legal protections are provided, volunteers may provide services in risky environments during emergencies without any guarantee of protections from harms except from their own personal health insurance (which may not provide similar coverage as workers' compensation plans). In response, some states' emergency laws extend workers' compensation protections to volunteers (largely those volunteers providing direct services to government). The Uniform Emergency Volunteer Health Practitioners Act, which is under consideration in multiple jurisdictions, seeks to provide workers' compensation benefits to registered volunteers as if they were state employees (Carpenter et al., 2008).

Insurance coverage limits Related to the two major issues discussed above are the limits of health, medical malpractice, workers' compensation, disability, or life insurance coverage during emergencies. Staffers, whether employees or volunteers, may have to deal with varying limits of coverage under these and potentially other types of insurance during declared states of emergency. For example, some life insurance policies may not cover individuals for deaths resulting from pandemic influenza or other public health emergencies. Medical malpractice coverage for health care practitioners may contain express limits as to liability exposures during emergencies. Since staffers may make decisions based on their perceptions of existing insurance protections, any legal change that tends to downgrade the scope or benefits of this coverage may be inimical to the staffers' participation.

Unauthorized use of personnel Staffing responsibilities for various workers or volunteers at PODs may involve legal issues inherent in the delivery of medical services or products to individuals and populations. During non-emergencies, non-licensed personnel are not authorized to distribute prescription drugs (like antivirals) to individuals in the interests of protecting public health and safety. Staffing shortages or other exigencies during a pandemic influenza may nevertheless require the use of unlicensed personnel to assure ready distribution of antivirals to persons in need. The potential illegality of this practice may be waived under federal or state emergency laws (HRSA, 2006). Federal authorities may even consider re-characterizing antivirals as non-prescription medications during declared emergencies. Absent direct waivers or federal interventions, however, non-licensed personnel and the entities organizing their service may be concerned about the legality of their actions and refuse to allow non-licensed personnel to perform certain actions. Interstate volunteer health care practitioners (assuming their availability during pandemic influenza) face a different, potential legal restraint. Since they are not

licensed in the jurisdictions in which they seek to volunteer, any medical service they may provide may be considered unlawful (Hodge, 2006a). To remedy this issue, many existing state emergency laws and the Uniform Emergency Volunteer Health Practitioners Act allow states to view out-of-state volunteer health practitioners as licensed in the jurisdiction for which they provide services during the duration of the emergency (Hodge et al., 2007).

Site Set-Up, Flow, and Infection Control

States and local jurisdictions have already done a great deal of work developing and exercising (sometimes in live events) point-of-dispensing set-up and flow. If jurisdictions select a variety of dispensing sites for post-exposure prophylaxis, they may benefit from including in their planning early communication directing people to the appropriate site (e.g., individuals without insurance, employment, or with disability, or in cases where there are multiple sites of dispensing in one's neighborhood). Effective management of flow through a dispensing site and crowd control have been studied, planned for, and exercised by most state and local jurisdictions, as part of public health preparedness exercises and drills.

Separating the well from the ill may be an objective of pandemic influenza response, or if social distancing is one of the non-pharmaceutical interventions a jurisdiction or the nation as a whole undertakes, but the benefits of doing so are unclear, given uncertainty about the rate of transmission and the limited evidence about the efficacy of various non-pharmaceutical interventions (Aledort et al., 2007). Instituting other infection control measures may be useful, for example, encouraging and supporting use of cough etiquette and hand sanitizers at dispensing sites.

INFORMATION SYSTEMS FOR MONITORING DRUG USE AND SAFETY

The committee is aware of the long-standing efforts in the governmental public health infrastructure to develop comprehensive information systems that are compatible with one another and can communicate and exchange data. Preparing for an influenza pandemic presents additional needs for information systems or functionalities that can be used to track antivirals and other countermeasures, such as vaccine.

Most states are required through their CDC grants for public health emergency preparedness to develop compatible public health information networks (PHINs). The 2002 CDC guidance noted that CDC and its state partners had the shared goal of adopting and implementing "standards-based, integrated, and interoperable information technology (IT) systems"

to support public health activities. Any information system that would be used in an influenza pandemic would ideally be integrated with or the same as a system that supports other preparedness activities. The 2008 *Pandemic Influenza Funding Announcement for Competitive Proposals (Activities)* (CDC, 2008) asks grantees to develop demonstration projects that explore ways to integrate existing state-based immunization information systems (IISs) with National Countermeasure and Response Administration (CRA) systems to track doses of pandemic influenza vaccine, facilitate electronic laboratory data exchange supporting pandemic influenza surveillance, develop statewide PHIN-compliant electronic mortality reporting systems and explore ways to distribute and dispense drugs to isolated or quarantined persons in a pandemic influenza event. Also the language of the guidance does not specifically suggest use of immunization registries or similar systems to track or gather any other information related to antiviral drugs. The committee has learned that some localities intend to use or are considering the use of immunization registries to track both influenza vaccine and antiviral use (Biedrzycki, 2007; Zucker, 2007). Also, some states intend to use immunization registries to track use of pandemic influenza vaccine (IOM Meeting Two Transcript [Williamson, 2008]). For example, Michigan has enacted legislative changes to expand the use of its immunization registry to include antivirals (American Immunization Registry Association, 2006).

For a variety of reasons having to do with efficiency (cost, staff time, training needs, etc.), it is reasonable to suggest that information systems for antivirals be the same as those used for influenza vaccines. It is unclear to what extent and what proportion of state immunization registries have the capacity and functionality to be used for tracking antiviral use. Immunization registries may not be easily adapted to include antivirals. Such registries are used largely in pediatric clinical settings, so few or none of the sites that will be used for antiviral dispensing have a link to an immunization registry, and potentially not even to a clinical setting through with data about dispensing could be linked to subsequent clinical information or health care databases. (The committee is aware that there are jurisdictions that are exploring the addition of adult immunizations to registries, perhaps beginning with health care worker immunizations.) Further, some immunization registries are still paper-based. The volume of data entered in a pandemic mass dispensing setting would be likely to place unprecedented demands on most existing public health information systems, such as registries. Finally, some jurisdictions have extremely limited information technology resources that do not meet existing public health practice needs, let alone those of an emergent pandemic response. Use of immunization registries simply may be unfeasible with existing personnel, technology, and systems. Despite all this, systems for tracking

who gets antivirals will be needed, especially in the context of a severe pandemic and with limited supplies, although it is unclear how quickly a system could be ready in cases where a usable system is not already available. Even where a usable information system is in place, a backup system that is technology-independent would be helpful to include in planning exercises and, if possible, in real-life use.[10] (Preventing "gaming" the system—i.e., fraudulent attempts to secure antivirals—would not be an objective of a tracking system, but rather the objective would be to prevent the inadvertent duplication of dispensing.)

Further, expansion of existing systems to address pandemic response functions may constitute the best use of resources in some cases. Ideally, this work will be completed before the pandemic begins.

Recommendation 4-4: The committee recommends that the Department of Health and Human Services support and fund public health agencies to develop or expand information systems for tracking dispensed antivirals. The development or expansion of these systems should make use of existing information resources or systems, consider information technology needs for other dimensions of pandemic influenza response, comply with the Centers for Disease Control and Prevention standards, and be interoperable and robust.

Any proposed system would need to be tested. One context for addressing this important area of planning may be the Cities Readiness Initiative (a CDC pilot project to enhance the capacity of cities to deliver medications and medical supplies in a public health or similar emergency).[11]

For reporting adverse events related to antiviral use, the proposed DHHS draft guidance states that the Food and Drug Administration Adverse Event Reporting System (AERS)/Medwatch should be used. This system is passive and not ideally suited to rapidly capture, interpret, and convey information needed to evaluate a course of action. It is also possible that providers will be unable to recognize and/or report adverse events in an environment of extreme surge and human resource shortages. Also, the public may not be concerned enough in the face of a life-threatening disease outbreak to report medication-related adverse events. AERS does not address the need of state and local jurisdictions to monitor and respond to adverse events, so public health agencies and their partners may need some additional measures to prepare and plan

[10]This would be needed in the event of power failure and other critical infrastructure failures.

[11]Information about the initiative is available at http://www.bt.cdc.gov/cri/.

to respond to safety signals, whether real or perceived. It also is unlikely that existing systems, for jurisdictions that have something reasonably capable in place, are sufficiently robust to be repositories of dispensing records that link data to a visit or diagnosis around an adverse event. Some health care organizations may have such a database capability, but if antiviral distribution occurs outside the medical home (i.e., people may not receive antivirals and other care from their primary care provider), health care organization and health plan data would have little to no data related to antiviral distribution.

Finally, unlike the need for complete antiviral tracking data, it is not necessary or realistic to attempt to gather comprehensive information about each antiviral drug-related adverse event. The use of sentinel sites, such as those used to conduct epidemiologic surveillance of seasonal influenza could be one solution to get some statistically meaningful data. CDC (with FDA input) could solicit specific types of adverse event reporting, or initiate a type of active surveillance based on individual reports and hypotheses about emerging safety signals. Special attention should be given to adverse events in certain vulnerable populations such as pregnant women and young children, for whom safety data is limited or non-existent. Also, planning could focus on systems to capture only serious and unexpected adverse events.

Recommendation 4-5: The committee recommends that the Department of Health and Human Services consider options in addition to the Food and Drug Administration Adverse Event Reporting System to capture adverse events resulting from use of antiviral drugs to ensure active and timely reporting. One option is a network of sentinel sites that can collect data that are representative of antiviral use nationally. (Data gathered and compiled by such a system would be provided to the advisory body described in Chapter 3 for analysis and determination of whether changes are needed in national recommendations on the use of antivirals.)

Legal Issues Related to Information Systems

What legal norms exist to protect the privacy of individuals receiving medical services or products during emergencies? In non-emergencies, a panoply of health information privacy laws at the federal, state, and local levels apply to the provision of health services. Highlighted by the Health Insurance Portability and Accountability Act (HIPPA) Privacy Rule (45 C.F.R. § 160.100 et seq. [2004]), these laws seek to assure patients that their health data are entitled to reasonable protections against unwarranted acquisition, use, disclosure, and storage (Hodge, 2004). Adhering to legal

privacy protections during emergencies may be viewed as impractical or impossible. In part, this led DHHS to briefly suspend adherence to the HIPAA Privacy Rule for patients affected by Hurricane Katrina in 2005 (Hodge et al., 2007). Still, personnel at dispensing sites may need to be sensitive to the privacy expectations of individuals seeking antivirals during pandemic influenza. Community perceptions that privacy norms are largely being ignored or intentionally breached may lead some to avoid accessing medications through PODs.

Privacy and security implications also underlie public health surveillance systems. These issues depend on whether surveillance systems tracking the use of antivirals are distinct systems or tied into existing federal, state, or local databases. Federal and state laws regulate public health surveillance systems to assure that the acquisition and use of identifiable health information are purposeful and the data are held confidential. Disclosures outside public health or other governmental authorities are often restricted, absent specific written authorization of individuals who are the subjects of the data. Security protections may require these databases to protect against unwarranted access by non-approved users. If the data to be collected through this type of public health surveillance are truly non-identifiable, privacy or security issues are not relevant, but of course non-identifiable data are of limited utility to public health practitioners seeking to intervene to protect communal health.

EXERCISES AND DRILLS

Reviews from drills and exercises find few that are specific to antiviral distribution; the bulk of the drills and exercises that have been conducted have been in the context of the Cities Readiness Initiative and dispensing materiel from the SNS (e.g., ASTHO, 2006). Most of these activities do not involve the complex assumptions and considerations required for treatment and prophylaxis. However, they do provide an experience base from which to draw. Unfortunately, many of the preparedness drills and exercises that have been conducted throughout the country do not have objective, numerical measures or outcomes associated with them. RAND Corporation's work on countermeasure distribution through the SNS has focused on the development of drills and exercises that break the complex tasks down into discreet components, and identify clear metrics for each component. Once a health department can successfully complete the key component tasks, it may conduct a more comprehensive functional exercise. It is extremely difficult to assess and improve the capability to distribute countermeasures without a robust and quantitatively focused exercise program. A primary resource is the Department of Homeland

Security Homeland Security Exercise and Evaluation Program toolkit, which includes an Exercise Evaluation Guide that can be customized.

Some jurisdictions have used actual disease outbreaks or other emergencies as opportunities to practice their pandemic influenza or public health emergency response plans. A number of local public health agencies have used seasonal influenza immunization clinics to test their preparedness for mass dispensing in the event of an influenza pandemic. During the mumps epidemic in 2006, Iowa dispensed measles–mumps–rubella vaccine to all counties and provided some special vaccination clinics to college-age adults, utilizing the state's public health emergency preparedness plans (ASTHO, 2006; McCormick, 2006). There are many other states, counties, and cities that have had similar experiences.

The CDC public health emergency preparedness and Strategic National Stockpile guidance to grantees is largely oriented toward tabletop exercises and full-scale exercises (CDC, 2006b, 2007a, 2008). It is unclear whether jurisdictions are considered to have met funding requirements when they implement plans to respond to actual events (such as an outbreak of measles or meningitis, or seasonal influenza immunization clinics), develop after action reports, and implement changes to address identified shortcomings. Some real-life activities may present more realistic challenges and constitute better tests of how well pandemic influenza plans will function in a pandemic. Also, well-planned efforts to measure performance in real-life events may contribute to an evidence base that demonstrates what works.

Recommendation 4-6: The committee recommends that federal pandemic influenza grant guidance explicitly state that jurisdictions receiving federal funding may fulfill the exercise requirement through the implementation of response to actual biologic emergency situations or similar events, if the appropriate benchmarks are used, performance is evaluated, and necessary corrective action is taken.

CLOSING OBSERVATIONS

Implementation of an antivirals program for an influenza pandemic, whether it occurs in the near or distant future will need to take into account multiple factors, many of which are evolving or cannot be known in advance, including supply of antivirals, shelf-life, resistance, and vaccine technology. The epidemiologic characteristics of the pandemic strain—e.g., age of greatest impact and/or mortality, mode of spread, rapidity of development of resistance—constitute large unknowns that will affect when, how, and which individuals are treated with antivirals. Regardless

of the final shape of the pandemic, it is clear to the committee that many of these issues need to be addressed in advance and provide a foundation for later decision making. Several overarching goals need to be kept in the forefront: developing in advance an ethical framework, communication and education of the public with clear and consistent messages, the need to reconcile actual supply and antiviral program goals, and flexibility on the one hand to react to the changes in the course of the pandemic and on the other hand to address the diverse needs of localities.

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Appendix A

Summary of Lessons Learned from Other Mass Distribution Events

Public health agencies at the federal, state, and local levels, along with their community partners, have experienced events that involved distributing medications or administering vaccines on a large scale in the context of an actual or potential public health threat (e.g., an anticipated swine flu pandemic, an anthrax attack, fear of bioterrorism with smallpox, shortage of seasonal influenza vaccine). The committee heard presentations about these events and reviewed some of pertinent literature to determine if some lessons learned could be applied to pandemic influenza. However, the distribution and dispensing of antivirals may be significantly different from some of these events because of the nature of the disease, the scarcity of the resources involved, and the characteristics of the antiviral medications.

VACCINE SHORTAGE

Before the 2004–2005 influenza season, the Food and Drug Administration was notified by vaccine manufacturer Chiron that the British regulatory agency had suspended its manufacturing license, leading to a shortfall in vaccine production and a severe shortage of influenza vaccine (FDA, 2008). Production and distribution of vaccine are normally private-sector processes, but the creation of a public health emergency (i.e., inadequate ability to protect vulnerable groups) led public health agencies to play a larger role than usual (ASTHO, 2006). Similarly, in preparing for and responding to an influenza pandemic, the production and

distribution of antiviral medications will require not only considerable public health agency involvement, but also leadership. Several aspects of the vaccine shortage are noteworthy, and some are especially relevant to antiviral distribution and dispensing.

- Vaccine delivery systems vary from state to state.
- Differences among health departments in prioritization and implementation created public confusion.
- There was a need to prioritize initially, but the range of priority groups broadened with time as successful coverage of high-need groups allowed some flexibility in the use of remaining vaccine. However, the change in priority groups was hard to implement and communicate, and in the end, some vaccine went unused.
- Some states invoked an emergency order to restrict vaccine distribution to specified groups. Some states held mass vaccination clinics for target groups; others directed the existing provider infrastructure to administer vaccine only to priority groups. One state held a lottery.
- The Health Alert Network was used in communication between the Centers for Disease Control and Prevention (CDC) and the states. States also used existing communication plans.
- The Health Alert Network was a helpful mechanism for disseminating secure information, and it would likely play a similar role in a pandemic, assuming no drastic changes in technologic capacity and availability of electrical power (Hannan, 2008).
- State public health agencies played an unusual role as facilitators of vaccine reallocation. Given some concerns about the Strategic National Stockpile scheme for allocating to states (e.g., not accounting for seasonal displacement) and some differences in states' ability to purchase and stockpile antivirals, it is conceivable that a limited process of reallocation may become necessary in a pandemic.
- A centralized CDC-based ordering system developed a few weeks after the emergency began, and there were some difficulties that having a system already in place would have prevented. This reflects the challenge of having needed information systems in place at the time of a pandemic.
- Daily CDC partner calls were a helpful component of the response to the public health emergency. This may speak to the need for such close collaboration in a pandemic, although it cannot be overstated that a pandemic could place vastly greater burdens on public health partners' time and ability to confer.

SWINE FLU

In early 1976, a respiratory disease outbreak at Fort Dix in New Jersey raised concern about an impending influenza pandemic like that of 1918. In a context of great uncertainty, government decision makers at the state and federal levels, including Army officials, notified state health departments and vaccine manufacturers about the information that was emerging.

Aspects of the swine flu immunization campaign of 1976 may be particularly instructive because they involved taking action—mass vaccination—to prepare for what was thought to be an imminent pandemic. There was uncertainty about whether what was being observed was indeed the beginning of a pandemic, and even the Advisory Committee on Immunization Practices was unable to make a definitive statement. It is important to note that there were barriers to the implementation of the program. The most formidable was the insurance industry's claim that it would be unable to provide liability coverage for the vaccination program. This led to passing of a tort claims bill (see Box A-1 for the contemporary successor to that early law).

BOX A-1
Liability Protection Provided by the Public Health Service Act (PHSA)

The PHSA (Section 319F-3) immunizes manufacturers, distributors, program planners, "qualified persons," and their employees for claims for loss concerning the administration or use of any "covered countermeasure" that is the subject of a declaration made by the Secretary of Health and Human Services. A covered countermeasure is a drug, device, or biological that is (1) subject to an emergency use authorization under the Federal Food, Drug and Cosmetic Act (Section 564), (2) used against an epidemic or pandemic and either approved or subject to an IND (investigational new drug), or (3) a security countermeasure as defined under the Project BioShield Act. "Claims" must be causally related to the administration or use by an individual of a covered countermeasure, including claims related to design, development, clinical testing, investigation, manufacture, labeling distribution, formulation, packaging, marketing, promotion, sale, purchase, donation, dispensing, prescribing, administration, or use of such countermeasure. This liability protection does not include liability protection for "willful misconduct" causing death or serious physical injury. "Section 319F-4 also allows the Secretary to, by declaration, establish an emergency fund in the Treasury which will be used to provide compensation for injuries directly caused by administration of a covered countermeasure."

Many months passed between the initial isolation of swine flu virus from hundreds of samples and the implementation of the program, with no additional evidence of a pandemic emerging anywhere around the world. The vaccination program began 7.5 months after the first isolate of swine flu, and 45 million doses were administered in 10 weeks, a public health program on an unprecedented scale.

The level of implementation of the program varied significantly, ranging from 10 to 80 percent of the population vaccinated across various jurisdictions. Approximately 85 percent of vaccine was administered in the public sector. There were communication problems, including rumors that required timely response with accurate information. Also, the commitment to vaccinate every person was not tempered by a similar commitment to re-evaluate the course of action on the basis of emerging information. In effect, there was no going back—a lesson, perhaps, about the perils of announcing a strategy that will require reconsideration due to change in circumstances (e.g., in the case of pandemic influenza, real-time data about the disease's epidemiologic profile).

One of the most important lessons to be learned from the swine flu immunization program may be that all interventions pose risk (Dowdle, 2008). Even in the face of a pandemic that could cause a high rate of deaths and severe illness, countermeasures, such as antivirals and vaccines, are not risk free. It is essential to communicate to the public that antivirals have the potential for unknown risks, to provide clear risk–benefit statements, and to ascertain and address changes in the level of public perception of risk.

ANTHRAX

The public health response to the anthrax attacks in 2001 occurred in an environment of limited preparedness. Most public health agency preparedness for bioterrorism was in the early stages, so little existed in the way of ready-to-use dispensing mechanisms (staffing schemes, clinic set-up and flow, usable information systems, and so on).

The experience of providing antibiotics to postal workers may provide some potentially helpful information as jurisdictions prepare for pandemic influenza. For example, the labor unions questioned decisions to provide medication to some workers and not others, even if some of the latter were not exposed. There may be lessons to be learned about communication with stakeholders such as labor groups and about the imperative to fully protect workers who will be at risk. Furthermore, the distribution of antibiotics after anthrax contamination illustrates, in a limited way, some issues that will arise in an influenza pandemic. The committee learned about the emergence of a black market to sell medication

obtained at dispensing sites. The dispensing sites provided some early experience with triage. There were lessons from communication activities, in the context of media attention, rumors, and mixed or unclear messages from government and community leaders. There was a shift in the type of medication and the required regimen (7 days of ciprofloxacin changed to 60 days of doxycycline), illustrating a mid-course adjustment that could be needed in a pandemic.

Dispensing to postal workers occurred at two types of sites: hospital and postal processing center. Although the hospital setting facilitated referral after triage (e.g., for acute condition), it was not necessarily convenient for affected individuals. The workplace (postal facility) was convenient for some and a familiar setting, but there were disadvantages because it was not a health care facility and so was not ideally suited to the functions of triage, education, and dispensing. The dispensing effort encountered groups with special needs, such as postal employees with hearing and visual impairments, as well as considerable proportions of workers needing mental health support, including the worried well (Bresnitz, 2008; Mahoney, 2008). Public health workers and their partners in the response to the anthrax attack also recognized adherence to treatment/prophylaxis regimens as a major challenge, requiring considerable education, as well as a high level of cultural competence.

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Appendix B

State Plans[1]

This appendix summarizes a sampling of state plans for the distribution and dispensing of antivirals. Plans or descriptions of plans were obtained from the Association of State and Territorial Health Officials (ASTHO) presentations at the committee's information gathering meetings and from the Institute of Medicine staff's search of the World Wide Web.

STATE PLANS FOR MASS DISPENSING OF PROPHYLAXIS

State public health agencies have a wide variety of plans and activities for the distribution of antivirals. Some states have plans specific to antivirals, and others are relying on their Strategic National Stockpile (SNS) plans. Most states assume they will use antivirals from the SNS and, if available, from their own stockpiles. States have already spent nearly $300 million to build their stockpiles based on the federal guideline of enough antivirals for one quarter of the population, largely targeted toward treatment. Most states have purchased all or some of their portion of the federally subsidized stockpile (enough to treat 25 percent of a state's population) (ASTHO, 2007). State representatives have expressed concern about the tradeoff states are making to purchase antivirals with a limited shelf-life and uncertain efficacy for pandemic influenza, against

[1]This appendix was compiled by Institute of Medicine staff with guidance from the committee, and it was intended to inform the committee's deliberations.

spending public health dollars for interventions for which there is probably more immediate need and that, in some cases, have better efficacy data (IOM, 2007).

Most state plans have been revised since the announcement of the federal purchasing contracts in 2006 (although not all are public), and 21 states have already or plan to pre-position antivirals around their state. This year several states will use their Centers for Disease Control and Prevention (CDC) public health emergency preparedness grants to develop antiviral distribution plans as part of their priority projects for the year (IOM, 2007).

Most state plans can be grouped into one of four models for distribution planning of antivirals. The first model is to take the existing SNS plans and add a distribution plan for antivirals. This would involve using the state as the primary distributor with pre-designated distribution sites. A second model is having a formal agreement with local health departments. The third model involves the pre-positioning of antivirals at hospitals and other health care facilities for the treatment of ill persons and the prophylaxis of certain health care workers. The fourth model being employed by states is use of pre-determined points-of-distribution/points-of-dispensing systems (PODs) (separate from their SNS plan), and distributing antivirals through those sites (some are considering drive-through distribution sites) (IOM, 2007).

Another issue that states need to address is how to work with the private sector. At the January 2008 meeting, the committee learned that eight states outsource storage and material management of their antivirals to the private sector. Virginia is incorporating retail pharmacies in its antiviral distribution plan. The Virginia Department of Health has designated a private distributor to work directly with pharmacies to fill daily orders based on maximum allotment of antivirals in the health district. The agency is working with the state pharmaceutical association to solicit participation. In Virginia's plan, the treatment course would be provided to the patient at no cost, and the health department would track patients receiving medication. A challenge is to ensure that only the target population receives treatment (IOM, 2007).

At the committee's second meeting, the ASTHO Executive Director presented a preliminary report based on a survey of seven states' activities in regard to influenza antivirals.[2] Some characteristics common to all seven plans include considerable state and local collaboration; planning for treatment of pandemic influenza, but little planning for prophylaxis; and prioritizing groups for treatment as identified in the 2005 Department

[2]The seven states are Iowa, Missouri, New Mexico, North Dakota, Virginia, Washington, and Wyoming.

of Health and Human Services (DHHS) *Pandemic Influenza Plan* (Jarris, 2008).

Examples of SNS-Associated Plans (Washington, New Mexico, Iowa, Missouri, California, Indiana, West Virginia)

Washington state's SNS drug distribution plan is designed to cover all pharmaceutical countermeasures, including antivirals for pandemic influenza. The state-level plan is integrated with 35 local plans (local jurisdictions have primary responsibility for distribution once the state delivers the allocation to them). They are considering four types of dispensing sites: (1) alternate care facilities (primary care triage sites), (2) hospitals, (3) home health agencies, and (4) drive-through sites (Jarris, 2008).

New Mexico's distribution plan is strongly associated with the SNS plan, and includes points-of-distribution. Because the majority of its population resides in Albuquerque, the state is considering alternative methods of dispensing such as drive-though clinics, large institutional settings, and Native American casinos. The population is diffuse in the rural and frontier areas, so the focus there is on points-of-distribution (Jarris, 2008).

Iowa is planning initial distribution to 23 distribution nodes; counties will pick up their pre-designated allotments at those sites. The state public health agency is discouraging the use of points-of-distribution. Given Iowa's many rural areas, local public health agencies have had success in the past with drive-through clinics. All local jurisdictions also have specific plans to reach special needs populations. Iowa has hotlines available to answer public and clinical questions. The state is not considering mail delivery of antivirals (Jarris, 2008).

Missouri is planning to distribute SNS antiviral stocks from a central site to regional locations, and then to local communities. A portion will be reserved by the state for containment, prophylaxis, and use in state-run institutions. Points-of-distribution and drive-through sites are being discouraged. Missouri is partnering with physicians, pharmacists, and other clinicians to dispense antivirals for treatment. According to the Missouri Department of Health and Senior Services (DHSS) plan (2007):

> LPHAs [local public health agencies] will identify community partners that would be appropriate and willing to dispense this medication without charge and to comply with other stipulations set forth by DHSS and the CDC regarding the distribution of subsidized medications. Partners could include hospital pharmacies, retail pharmacies, health care providers, and other facilities with appropriate storage facilities, hours of operation, and staff to dispense the medication.

Hotlines are available for people who develop adverse reactions to antivirals (Missouri Department of Health and Senior Services, 2007; Jarris, 2008).[3]

California has addressed antiviral distribution by amending its SNS plan, but has not yet addressed the dispensing aspect. Because it has not yet created a dispensing plan separate from the SNS plan, it expects to make this one of its Priority Projects for the CDC Public Health Emergency Preparedness cooperative agreement. To distribute the state stockpile of antivirals when a pandemic has been declared it plans to push them out to pre-determined local health department locations based on population. It intends to keep 10 percent of these antivirals in reserve and expects to receive antivirals from the SNS concurrently, which will be sent out to the counties (ASTHO, 2008).

Each of the 61 local health departments in California is creating its own dispensing plan, which will be based on geographic locations, demographics, and other factors. A state committee is being formed to incorporate private entities and representatives from the local health departments to discuss the various methods for dispensing (ASTHO, 2008). California local health departments are also responsible for getting antivirals to sick individuals within 24–48 hours of symptom onset as well as preventing sick persons from going to dispensing sites. They report that they do not have plans for prophylaxis, since they have no funds available to support this activity (ASTHO, 2008).

Indiana's antiviral distribution plan is part of the state's SNS plan, so is therefore classified. The state plans to provides security from local law enforcement, and it is receiving support from the state sheriffs association. Distribution of state-stockpiled antivirals will mostly be to health care facilities identified in the plan with the trigger being the first human case of pandemic influenza in the United States. Local health departments will decide what method to use for dispensing (ASTHO, 2008).

Indiana is only considering drive-through clinics at this time because they plan to implement social distancing. This model has been tested in the state and is written into its plan as an option to be considered by local health departments. Due to administrative issues, its drive-through clinics have a slower throughput than PODs, so planners are trying to address this. Indiana does not yet have a distribution plan for prophylaxis of household contacts and would like to have additional federal guidance

[3]The Missouri Antiviral Storage and Distribution plan (August 2007) calls for reporting antiviral adverse events to the "DHSS, Department Situation Room by calling 1-800-392-0272. Specific questions pertaining to medical conditions will be triaged and forwarded to nursing staff via the designated Nurse Hotline for consultation" (Missouri Department of Health and Senior Services, 2007).

on prophylaxis for critical infrastructure workers. It also does not know how many antiviral courses to expect from CDC or the trigger point for CDC to distribute them (ASTHO, 2008).

West Virginia's antiviral plan is SNS-associated. Most state-stockpiled antivirals will go to the hospitals. The state public health agency is reviewing local county plans to ensure they are feasible and to determine if antivirals should be pushed to local health departments as would be the case in the SNS plan. West Virginia has determined the state has adequate transportation resources within the state to move antivirals, but can do so using the SNS plan if needed. Prophylaxis may be used based on medication supply for priority groups that are identified by CDC and the state. This determination will not be made until the event takes place and the impact, supply, and other factors can be determined (ASTHO, 2008).

Private-Sector Distribution Model

North Dakota plans to use the existing commercial supply distribution chain. Vendors are under contract with the state and will distribute the state portion of the federal stockpile once the state's supply runs out. The private vendor will use commercial shipping such as Parcel Post and United Parcel Service. The primary recipients of antivirals will be pharmacies, hospitals, and clinics. The North Dakota backup plan would use local health agencies instead of the private sector. The state is currently looking into using a telephone triage and prescription system as well as drive-through distribution at banks (Jarris, 2008).

Pharmacy-Based Dispensing

The Virginia plan was developed under the guidance of the state Pandemic Influenza Advisory Committee/Subcommittee on Antiviral Distribution. In this state, pharmacies will be the primary dispensing sites along with community health centers, health departments, and other health care facilities. The underserved population will be supported by local health departments. Antivirals will be pre-positioned with restocking schedules. The Virginia Department of Medical Assistance Services will track antiviral dispensing to prevent misuse of the system. The major barriers that Virginia is facing are how to provide access to care and the requirement for a provider prescription (Jarris, 2008; Virginia Department of Health, 2008).

Alabama has approximately a half-million courses of antivirals in the state stockpile, and the state anticipates getting an additional 700,000 through the SNS. To distribute these drugs (in a setting with limited amounts of the drug), when the appropriate trigger is reached, the state

plans to "push" its stockpile through the drug distribution channels of the drug wholesalers, hospitals, pharmacies, and physicians, and probably would distribute state supplies directly through community health centers and county health departments. Because of concerns about infection control, the state probably will not use points-of-dispensing sites for treatment unless intended distribution sites were not adequate. However, Alabama would use points-of-distribution for prophylaxis assuming adequate supply (Jarris, 2008).

New York City

Like those of most states, the New York City planning assumptions are similar to those outlined by DHHS. The public health agency is planning for multiple waves of the pandemic with an attack rate of 30 percent, and assumes that about half of those cases would require outpatient care and about 11 percent of those infected would need to be hospitalized, with a case fatality rate of 2 percent (Category 5 of severity on DHHS's 1 to 5 scale, with 1 indicating the lowest case fatality rate). New York City's planning also assumes that antiviral supplies are limited, with the expectation that the supply chain may increase. The city expects to receive antivirals from the SNS, the federally subsidized New York state stockpile, and additional state-purchased antivirals to which the city would have access if needed. The city expects 267,000 hospitalizations and 49,000 deaths in a pandemic (Zucker, 2007). As part of its plan, the NY Department of Health and Mental Hygiene has developed draft treatment algorithms and has vetted those with health care partners. The department has identified more than 300 sites for antiviral distribution for treatment of staff, patients, and the public. These sites include hospitals, nursing homes, home health care agencies, and community health centers. The department is in the process of completing a Memorandum of Understanding for the dispensing sites (Zucker, 2007). It also plans to use existing health care resources and providers, and the fire and police departments. The city plans to distribute to its 68 hospitals on a pro rata basis by number of beds. The city also has 25 federally qualified health centers; the department intends to divert patients there if the patients do not need hospitalization to avoid overwhelming emergency departments.

The city has not decided whether to pre-position antivirals, and if it does, in what quantities. To track antiviral dispensing (and influenza vaccine), the New York City Department of Health plans to use the citywide immunization registry (94 percent accountable for the several million doses of pediatric vaccines annually). New York City public health officials do not believe they can track all individuals infected with pandemic

influenza, so it is unlikely they can provide post-exposure prophylaxis for all contacts of cases (Zucker, 2007).

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Appendix C

Meeting One Agenda

Committee on Implementation of Antiviral Medication Strategies for an Influenza Pandemic

Meeting 1
December 3–4, 2007
National Academy of Sciences Building
2101 Constitution Avenue, NW
Washington, DC

AGENDA

December 3, 2007
Auditorium

1:00 pm	Welcome, Committee Introductions, and Opening Comments *June Osborn* *Committee Chair*
	Background
1:15 pm	Charge to the Committee Guidance on Use of Antiviral Drugs and Planning Assumptions *Benjamin Schwartz* *Senior Science Advisor* *National Vaccine Program Office* *Department of Health and Human Services*
1:45 pm	Committee Questions

2:15 pm Primer on Antiviral Drug Effectiveness and Resistance
Fred Hayden
World Health Organization
Professor of Internal Medicine and Pathology
Department of Medicine
Division of Infectious Diseases and International Health
University of Virginia Health System
Infectious Diseases Society of America

2:45 pm Committee Questions

3:00 pm Antiviral Drug Stockpiling and Distribution Planning
Anita Patel
Health Scientist
Lockheed Martin Information Technology Contractor assigned to
Division of Strategic National Stockpile
Coordinating Office of Terrorism Preparedness and Emergency Response
Centers for Disease Control and Prevention

3:15 pm Committee Questions

3:30 pm Legal Issues in an Influenza Pandemic
James G. Hodge
Associate Professor
Johns Hopkins Bloomberg School of Public Health
Executive Director and Principal Investigator
Centers for Law and the Public's Health: A Collaborative
Core Faculty, Johns Hopkins Berman Institute of Bioethics

3:45 pm Committee Questions

4:00 pm Break

Panel 1: Diagnosing Influenza

4:15 pm Diagnosis in Children
John Bradley
Director of the Division of Infectious Diseases
Children's Hospital, San Diego
American Academy of Pediatrics
Infectious Diseases Society of America

4:30 pm Diagnosis in Adults
Andrew Pavia
George and Esther Gross Presidential Professor
Chief of the Division of Pediatric Infectious Diseases
University of Utah Health Sciences Center and Primary Children's of Utah
Infectious Diseases Society of America
Member of the Institute of Medicine Committee

4:45 pm Other Diagnostic Issues
Marie Griffin
Professor of Preventive Medicine
Professor of Medicine
Vanderbilt University School of Medicine

5:00 pm Infection Control in the Waiting Room
Richard Clover
Dean
School of Public Health and Information Sciences
University of Louisville

5:15 pm Committee Questions and Discussion with Panel

5:45 pm Adjourn

December 4, 2007
Lecture Room

8:00 am Welcome
June Osborn
Committee Chair

Panel 2: Treating Cases and Providing Post-Exposure Prophylaxis to Their Household Contacts

8:15 am Federal, State, and Local Laws Regarding Prescribing and Dispensing
Stephen W. Schondelmeyer
Chair
Department of Pharmaceutical Care Health Care Systems
Professor of Pharmaceutical Economics
Century Mortar Club Endowed Chair in Pharmaceutical Management
University of Minnesota

8:30 am Federal Regulatory Perspective
Barbara A. Styrt
Medical Officer
Division of Antiviral Drug Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

8:45 am Role of Pharmacies
Catherine M. Polley
Vice President
Pharmacy Services
Food Marketing Institute

9:00 am Other Issues Related to Dispensing Prophylaxis
Tammy Robertson
Operations Manager, Fedex Custom Critical

9:15 am Committee Questions and Discussion with Panel

9:45 am Break

Panel 3: State and Local Planning

10:00 am State Planning (overview, considerations, and examples)
Donald E. Williamson
Health Officer
Alabama State Department of Health

10:30 am Local Planning (overview, considerations, and examples)
Jane Zucker
Assistant Commissioner
Bureau of Immunization
New York City Department of Health and Mental Hygiene

Paul Biedrzycki
Director
Disease Control and Prevention
City of Milwaukee Health Department

Junie Delizo
Director
Emergency Preparedness
Rockland County (NY) Department of Health

11:30 am Committee Questions and Discussion with Panel

12:00 pm Lunch

Panel 4: Outbreak Prophylaxis of Health Care Workers

1:00 pm Hospital-Based Prophylaxis
Allison McGeer
Microbiologist, Infectious Disease Consultant
Mount Sinai Hospital
Toronto, Ontario
Professor
Departments of Laboratory Medicine and Pathobiology
Department of Public Health Sciences
University of Toronto

Stephen R. Pitts
Attending Physician, Emory Crawford Long Hospital
Emergency Department
Associate Professor
Department of Emergency Medicine
Emory University School of Medicine
on sabbatical as
AcademyHealth Fellow
National Center for Health Statistics

1:45 pm Prophylaxis at Outpatient Sites
Douglas Campos-Outcalt
Clinical Professor and Associate Chair
Department of Family and Community Medicine
University of Arizona College of Medicine
American Academy of Family Physicians

2:00 pm Long-Term Care Facilities
Janice Zalen
Director of Special Programs
American Health Care Association

2:30 pm Health Care Worker Labor Issues
Katherine Cox
Health Policy Analyst
American Federation of State, County and Municipal Employees International

2:45 pm Committee Questions and Discussion with Panel

3:00 pm Break

Panel 5: Outbreak Prophylaxis in Emergency Service Organizations (fire, police, emergency medical services)

3:15 pm Emergency Medical Services (EMS)
Kathy Robinson
Program Advisor
National Association of State EMS Officials

3:30 pm Fire
John Delaney
Captain
Fire Department
Arlington County, VA

4:00 pm Committee Questions and Discussion with Panel

4:30 pm Adjourn

Appendix D

Meeting Two Agenda

Committee on Implementation of Antiviral Medication Strategies for an Influenza Pandemic

Meeting 2
January 7, 2008

Keck Center of The National Academies
500 Fifth Street, NW
Room 110
Washington, DC 20001

(live audio/video feed provided in Room 105)

10:00 am	Influenza Antivirals and Their Use: Effectiveness, Resistance, Surveillance *Alexander Klimov* *Chief, Virus Surveillance and Diagnosis Branch* *Influenza Division* *Centers for Disease Control and Prevention*
10:20 am	Mathematical Modeling of Resistance in a Pandemic *Marc Lipsitch* *Professor of Epidemiology* *Department of Epidemiology* *Department of Immunology and Infectious Diseases* *Harvard School of Public Health*
10:40 am	Committee Questions and Discussion

11:00 am Antiviral Distribution Planning: More from State Public Health Agencies
Paul Jarris
Executive Director
Association of State and Territorial Health Officials

11:15 am Committee Questions and Discussion

11:30 am Lessons from Past Public Health Drug or Vaccine Distribution Campaigns: Swine Flu Immunization Program, Vaccine Shortage, Antibiotic Distribution After Anthrax Attacks

Swine Flu
Walter Dowdle
Senior Consultant to World Health Organization
Polio Eradication Program
Task Force on Child Survival and Development

11:45 am Lunch

12:45 pm Lessons from Past Public Health Drug or Vaccine Distribution Campaigns (continued)

Influenza Vaccine Shortage
Claire Hannan
Executive Director
Association of Immunization Managers

Anthrax
Eddy Bresnitz
Deputy Health Commissioner
State Epidemiologist
New Jersey

Mary Mahoney
Bioterrorism Coordinator
North Shore–Long Island Jewish Health System
New York

1:30 pm Committee Questions and Discussion

1:50 pm Decision Analysis for Antiviral Distribution
Sinan Khan
Epidemiology Analyst
Los Angeles County
Emergency Preparedness and Response Program

Telephone and Web-Based Decision Support and Triage
Barry Wolcott
Associate Professor
Uniformed Services University of Health Sciences

2:30 pm Questions from the Committee and Discussion

2:45 pm Break

3:00 pm Antiviral Stockpiling: Stakeholders' Perspectives
Lisa Koonin
Associate Director, Business Partnerships
Division of Private and Public Partnerships
National Center for Health Marketing/CoCHIS
Centers for Disease Control and Prevention

Antiviral Distribution Planning: The Public–Private-Sector Interface
Rex Archer
Director
Kansas City Health Department
Missouri

Perspectives from the Private Sector
Katherine B. Andrus
Assistant General Counsel
Air Transport Association of America, Inc.

Stephen Jones
Cluster Occupational Health Manager
Downstream and Chemicals
ExxonMobil Corporation

Michael McGuire
Vice President
Roche Laboratories, Inc.

4:00 pm Committee Questions and Discussion

4:15 pm Ethical Principles in Planning for the Distribution of Antiviral Medication
Nancy Kass
Phoebe R. Berman Professor of Bioethics and Public Health
Johns Hopkins University

Ethical Framework in Minnesota's Plans for Distribution of Antiviral Medication
Dorothy Vawter
Associate Director
Center for Health Care Ethics
Minnesota

4:45 pm Committee Questions and Discussion

5:00 pm Antiviral Distribution Planning (continued)

In a Publicly Funded Health Care System
Victoria Davey
Deputy Chief, Public Health and Environmental Hazards Officer
Veterans Health Administration
Department of Veterans Affairs

In a Private Health Care System
Skip Skivington
Vice President of Supply Chain and Director of Operations, Procurement and Supply Program Offices
Kaiser Permanente

Eric Koscove
Chief
Emergency Department
Kaiser Permanente Medical Center
Santa Clara, CA

5:35 pm Committee Questions and Discussion

5:50 pm Public Comment *(if time allows)*

6:00 pm Adjourn

Appendix E

Committee Member Biographies

June E. Osborn, M.D. (*Chair*), became the sixth president of the Josiah Macy, Jr. Foundation in New York in September 1996, and became president emerita at the end of 2007. She received a B.A. from Oberlin College in 1957 and an M.D. from Case Western Reserve University in 1961. She spent 3 years in training as a pediatric resident at Boston Children's and Massachusetts General hospitals and then 2 years as a postdoctoral fellow in virology and infectious diseases at Johns Hopkins Medical School and at the University of Pittsburgh. From 1966 to 1984 she was on the faculty of the University of Wisconsin Medical School, where she was a professor in the Departments of Medical Microbiology and of Pediatrics. In 1975 she also became associate dean for biological sciences in the University of Wisconsin Graduate School. From 1984 to 1993 she was dean of the School of Public Health at the University of Michigan. She was also professor of epidemiology in that school and professor of pediatrics and communicable diseases at the University of Michigan Medical School. In 1986 she was elected to membership in the Institute of Medicine (IOM) and from 1995 to 2000 she served as a member of its governing council. In 1994 she was also elected to fellowship in the American Academy of Arts and Sciences. Beginning in the early 1970s, she began playing advisory roles concerning virology, infectious diseases and vaccines, health care, public health, and public policy for a number of federal agencies and the World Health Organization (WHO). In addition, she has worked with private foundations in designing or advising on specific programs, and from 1990 to 1998 served as a member of the Board of Trustees of the

Kaiser Family Foundation. From 1984 to 1989 she chaired the National Heart, Lung, and Blood Institute advisory committee on AIDS, and from 1988 to 1992 was a member of the WHO Global Commission on AIDS. From 1989 to 1993 she was chairwoman of the U.S. National Commission on AIDS. In 2005 she was elected to a 5-year term on the Board of Trustees of the U.S. Pharmacopeia. She has published on topics in virology, infectious diseases, AIDS, and public policy. She received the distinguished alumna award from Case Western Reserve Medical School in 1993, and in 1994 she shared with Dr. Mathilde Krim the Scientific Freedom and Responsibility award of the American Association for the Advancement of Science. She holds honorary degrees from the University of Medicine and Dentistry of New Jersey (1990), Yale University (1992), Emory University (1993), Oberlin College (1993), Medical College of Pennsylvania (1994), Rutgers University (1994), Case Western Reserve University (1997), State University of New York–Stony Brook (1998), and the University of Wisconsin–Madison (2004).

Karen G. Gervais, Ph.D., director of the Minnesota Center for Health Care Ethics, received her B.A. from Oberlin College and her Ph.D. from the University of Minnesota. A philosophy professor for 18 years, in 1989 she transitioned her career into the field of health care ethics. She served as center associate of the Center for Biomedical Ethics at the University of Minnesota; coordinator of the Minnesota Network for Institutional Ethics Committees; Winifred and Atherton Bean Visiting Chair of Professor of Science, Technology, and Society at Carleton College; Visiting Distinguished Professor of Law and Liberal Studies at Hamline University; and Visiting Associate Professor of Philosophy at St. Olaf College. Dr. Gervais' scholarly interests include clinical and organizational ethics and health policy, public health ethics, access to health care, health disparities, resource allocation, managed care, community benefit responsibilities of nonprofit health care organizations, ethically informed decision making for persons with dementia, and the definition of death. She has served as ethics and policy consultant for the Office of Technology Assessment, Minnesota Council of Health Plans, Minnesota Medical Association, Hennepin Medical Society, Minnesota Department of Human Services, Minnesota Department of Health, Minnesota Attorney General's Office, Science Museum of Minnesota, American Association of Health Plans, National Council of State Boards of Nursing, and the National Marrow Donor Program. She also served as an ethics advisor to the Minnesota Commission on End-of-Life Care and is a member of the Minnesota Department of Health's Task Force on Health and Bioterrorism. She is currently co-investigator of the project, "Ethical and Policy Challenges in Deep Brain Stimulation for Parkinson's Disease." In 1987 Dr. Gervais published

Redefining Death (Yale University Press) and in 1999 co-edited *Ethical Challenges in Managed Care: A Casebook* (Georgetown University Press). She has published in the *Hastings Center Report*, *American Journal of Bioethics*, *IRB Vaccine*, *The American Journal of Managed Care*, *Medical Humanities Review*, and *Minnesota Medicine*, and contributed articles to several edited works, including the *Encyclopedia of Bioethics*. She is co-author of *Allocating Pandemic Influenza Vaccines in Minnesota: Recommendations of the Pandemic Influenza Work Groups Project*, a project of the Minnesota Department of Health. She is co-leader of the Minnesota Pandemic Ethics project, also a project of the Minnesota Department of Health.

Sandra R. Hernández, M.D., is chief executive officer (CEO) of the San Francisco Foundation. Dr. Hernández is a graduate of Yale University, Tufts School of Medicine, and the John F. Kennedy School of Government at Harvard University. Prior to becoming CEO of the Foundation, she served as the director of public health for the City and County of San Francisco. She is an assistant clinical professor at the University of California–San Francisco School of Medicine and maintains an active clinical practice in the AIDS clinic at San Francisco General Hospital. Dr. Hernández currently serves on the boards of the Council on Foundations, Lucile Packard Children's Hospital, Corporation for Supportive Housing, and National Alliance for Hispanic Health. She is also a trustee of the Western Asbestos Settlement Trust. Her prior affiliations include President Clinton's Advisory Commission on Consumer Protection and Quality in the Healthcare Industry; the Pew Commission on Environmental Health; the Foundation Consortium for California's Children and Youth; Grantmakers in Health; American Foundation for AIDS Research; the Volunteerism Project; the IOM Committee on the Consequences of Uninsurance; the Latino Community Foundation, a supporting organization of The San Francisco Foundation; and the California Managed Risk Medical Insurance Board, which is the governing body for California's Children's Health Insurance Program.

James G. Hodge, Jr., J.D., LL.M., is an associate professor at the Johns Hopkins Bloomberg School of Public Health, where he teaches health information privacy law and policy; public health and the law; and bioethics and the law. In addition to his primary faculty appointment at Hopkins, he is an adjunct professor of law at Georgetown University Law Center, where he lectures in public health law; bioethics; international human rights; and health law and policy. He is the executive director of the Center for Law and the Public's Health: A Collaborative at Johns Hopkins and Georgetown Universities; a core faculty member and former Greenwall Fellow of the Johns Hopkins Berman Institute of Bioethics; and

a faculty member of the Information Security Institute at the Johns Hopkins Whiting School of Engineering. Through his scholarly and applied work, Professor Hodge delves deeply into multiple areas of public health law, ethics, and human rights. The recipient of the 2006 Henrik L. Blum Award for Excellence in Health Policy from the American Public Health Association, he has drafted (with others) several public health law reform initiatives, including the Model State Public Health Information Privacy Act, the Model State Emergency Health Powers Act, the Turning Point Model State Public Health Act, and the Uniform Emergency Volunteer Health Practitioners Act. His diverse funded projects include work on (1) the legal framework underlying the use of volunteer health professionals during emergencies; (2) the compilation, study, and analysis of state genetics laws and policies; (3) historical and legal bases underlying school vaccination programs; (4) international tobacco policy for WHO's Tobacco Free Initiative; (5) legal and ethical distinctions between public health practice and research; (6) legal underpinnings of partner notification and expedited partner therapies; and (7) public health law case studies in many states. He is a national expert on public health information privacy law and ethics. He consulted with the Centers for Disease Control and Prevention (CDC) on its creation of a Health Information Privacy Office and with other federal health agencies on privacy issues. Additional areas of research include new federalism, HIV/AIDS, partner notification, legal approaches to bioethics, and human rights.

Nicole Lurie, M.D., M.S.P.H., is director of the RAND Center for Population Health and Health Disparities and co-director of the RAND Center for Domestic and International Health Security. She is also a senior natural scientist and the Paul O'Neill Alcoa Professor of Health Policy at RAND. Previously, Dr. Lurie was a professor of medicine and public health at the University of Minnesota, and most recently, medical advisor to the Commissioner at the Minnesota Department of Health. From 1998 to 2001, she served as principal deputy assistant secretary of health in the U.S. Department of Health and Human Services (DHHS). She had line responsibility for the Office of Emergency Preparedness, which included development of emergency response plans at state and local levels, including plans for events involving multiple jurisdictions and development of the pandemic influenza plan. She was involved with flu surveillance and response at a time when hospitals in multiple jurisdictions across the country were full, with multiple preparedness and response exercises, and with other efforts to directly link public health and health delivery sectors. Dr. Lurie's research has focused on health services, primarily in the areas of access to and quality of care, managed care, mental health, prevention, and health disparities. She is leading a collaborative effort, centered at RAND, to study the impact of changes in the health care safety net in the District

of Columbia, and to develop a collaborative, public–private health data infrastructure for the District and the region. Dr. Lurie serves as senior editor for *Health Services Research* and has served on editorial boards and as a reviewer for numerous journals. She was president of the Society of General Internal Medicine, is currently on the board of directors for the Academy of Health Services Research (AHSR), and has served on multiple national committees. She is the recipient of numerous awards, including the AHSR Young Investigator Award, the Nellie Westerman Prize for Research in Ethics, and the Heroine in Health Care Award. Dr. Lurie attended medical school at the University of Pennsylvania, and completed her residency and M.S.P.H. at the University of California, Los Angeles, where she was also a Robert Wood Johnson Foundation Clinical Scholar. Dr. Lurie, an IOM member, has served on several IOM committees and is currently the chair of the IOM Roundtable on Health Disparities.

Andrew T. Pavia, M.D., is the George and Esther Gross Presidential Professor and chief of the Division of Pediatric Infectious Diseases at the University of Utah Health Sciences Center and Primary Children's Hospital. He received his B.A. and M.D. at Brown University. He trained in internal medicine and pediatrics at Dartmouth and the University of Utah, held an infectious disease fellowship at the University of Utah, and trained in public health epidemiology as an Epidemic Intelligence Service (EIS) officer and a preventive medicine resident at CDC. He is involved in the care of adults, pregnant women, and children with HIV and children with other infectious diseases. His research interests include the epidemiology of influenza and other emerging infections, vaccine-preventable diseases, and HIV/AIDS, with a particular interest in the treatment of HIV in women and children and prevention of mother-to-child transmission. He is a member of the National Vaccine Advisory Committee and chairs the Vaccine Safety Subcommittee, and he is chair of the National and Global Public Policy Committee and the Pandemic Influenza Task Force of the Infectious Diseases Society of America. He is on the editorial board of *JAIDS*, he is a section editor for *Current Infectious Disease Reports*, and he is a reviewer for numerous journals. He has published more than 100 scientific articles and chapters.

M. Patricia Quinlisk, M.D., M.P.H., is a medical epidemiologist practicing at the Iowa Department of Public Health, where she functions as both the medical director and the state epidemiologist. Her background includes training as a clinical microbiologist (MT(ASCP)); training microbiologists while serving as a Peace Corps volunteer in Nepal; an M.P.H. from Johns Hopkins (with a emphasis in infectious disease epidemiology); an M.D. from the University of Wisconsin; and training as a field epidemiologist in CDC's Epidemic Intelligence Service. Yearly, for 12 years, she conducted

week-long epidemiologic training courses in Europe. She is a professor at the University of Iowa, the University of Wisconsin–La Crosse, and Iowa State University, and lectures regularly at these and other Midwestern educational institutions. She serves or has served on several national advisory committees, including the National Vaccine Advisory Committee, the Subcommittee for Vaccine Safety and Communication, the Advisory Committee of the U.S. Marine Corps Chemical/Biological Incident Response Force, the Department of Defense's Panel to Assess the Capabilities for Domestic Response to Terrorist Acts Involving Weapons of Mass Destruction (the Gilmore Commission), and the Management Committee of the Association of State and Territorial Health Officers, and as president of the Council of State and Territorial Epidemiologists. She has testified before two congressional subcommittees on public health about terrorism and participated on the IOM's Committees on Microbial Threats to Health in the 21st Century, The Psychological Consequences of Terrorism, and Modeling Community Containment for Pandemic Influenza. She was also on the National Academy of Sciences' Committee on Animal Health at the Crossroads, and Board of Scientific Counselors for CDC's National Center for Infectious Diseases. She serves on CDC's *Morbidity and Mortality Weekly Report* editorial board, and is an editor for the *Emerging Infectious Diseases Journal*. She was recently appointed to the National Biodefense Science Board established by DHHS.

Eileen Scanlon, R.N., M.S.N., is a public health nurse supervisor with New York's Nassau County Department of Health. She is a registered nurse who received her undergraduate degree from Long Island University at C.W. Post and her M.S. in emergency nursing and disaster management at Adelphi University. Her experiences as a public health nurse in the Nassau County Department of Health have included all areas of community and public health nursing. She currently directs the Office of Public Health Preparedness, which is an integrated multidisciplinary team preparing for disasters. Her office has received national recognition for the development of the Nassau County Medical Reserve Corps. Ms. Scanlon was recognized by the Nassau County Fire Commission in 2006 for the work she did with the fire service in training them to prophylax themselves for a biological event. Ms. Scanlon was honored by the New York State Office of the Assembly in August 2006 and the Town of Oyster Bay, New York, in April 2007 for the work she has done on community public health preparedness. Ms. Scanlon has presented at numerous conferences, including the Long Island Emergency Management Conference, New York State Association of County Health Officials meeting, the University of California–Los Angeles's Disaster Preparedness Conference, and the American Public Health Association Conference.