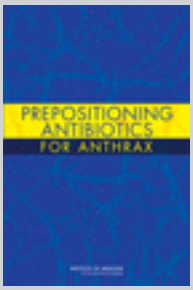

Prepositioning Antibiotics for Anthrax

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Clare Stroud, Kristin Viswanathan, Tia Powell, and Robert R. Bass, Editors; Committee on Prepositioned Medical Countermeasures for the Public; Institute of Medicine

PREPOSITIONING ANTIBIOTICS FOR ANTHRAX

Committee on Prepositioned Medical Countermeasures
for the Public

Board on Health Sciences Policy

Clare Stroud, Kristin Viswanathan, Tia Powell, and Robert R. Bass,
Editors

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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 **Brian L. Strom,** University of Pennsylvania School of Medicine, and **Kristine Gebbie,** Flinders University School of Nursing and Midwifery. Appointed by the National Research Council and the 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.

Preface

Rapid access to antibiotics can prevent people who are exposed to aerosolized *Bacillus anthracis* from developing anthrax; once symptoms of anthrax emerge, the disease progresses rapidly and can prove fatal. Since the anthrax attack in 2001, the nation's public health system has made great strides in developing plans to deliver antibiotics quickly to all potentially exposed people. However, concerns remain about the nation's ability to respond to an anthrax attack scenario of the most dire proportions—for example, a large-scale attack impacting hundreds of thousands of people and carried out in multiple cities.

Prepositioning (storage closer to intended users, before an attack occurs) is one of the mechanisms that have been discussed over the past several years for helping to ensure that all members of a community have rapid access to medical countermeasures (MCM) such as antibiotics. Antibiotics could be prepositioned in many different venues, including local stockpiles, workplace caches, caches in health care settings, and even in the home. The Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, asked the Institute of Medicine (IOM) to convene a committee to examine the potential role of these different prepositioning strategies in the overall MCM dispensing strategy. The committee was tasked to examine a wide range of factors, including benefits, costs, safety, and ethical issues.

The committee found that, under particular circumstances, prepositioning strategies can reduce the time within which individuals in a community can receive prophylactic antibiotics, and certain strategies can help alleviate the burden on the public health dispensing system. Relative to existing, more

centralized distribution and dispensing strategies, however, prepositioning provides less flexibility to change plans following an attack if necessary. For example, prepositioning may not be helpful if an attack occurs in a location other than anticipated or uses a strain of anthrax that is resistant to the prepositioned antibiotic. The committee also found that costs are likely to increase as antibiotics are prepositioned closer to the intended users.

In the current climate of dramatic cuts in public health funding, the issue of how communities use their limited resources is critically important. The committee was not asked to address the prioritization of prepositioning strategies and anthrax preparedness relative to other disaster preparedness activities, such as preparing for other kinds of terrorist attacks, natural disasters, and infectious diseases, to say nothing of the broad range of other public health efforts vying for resources and planning efforts. However, the committee recognizes that this is precisely the context in which public health officials will make decisions about which, if any, prepositioning strategies to develop. Indeed, careful stewardship of public health resources is one of the committee's guiding ethical principles.

Recognizing that communities across the nation have differing needs and capabilities, the committee believes their needs will best be served by different strategies. The decision-aiding framework presented in this report is intended to assist public health officials in considering the benefits, costs, and trade-offs involved in developing alternative prepositioning strategies appropriate to their particular communities. The committee also has attempted, wherever possible, to comment on which strategies would help strengthen public health infrastructure and capability for other purposes beyond prepositioning and which strategies would not.

We note that it was a great pleasure and a privilege to chair this IOM committee. We could not have attempted this project without the exceptional capability and dedication of the IOM staff, including Clare Stroud, Kristin Viswanathan, and Tonia Dickerson. We also offer our sincere thanks to our fellow committee members for their willingness to serve, for their hard work and dedication, and for their enthusiasm and collegiality. The members brought a remarkable range of expertise and perspectives to this study. In the face of many areas of uncertainty and significant gaps in the evidence, they diligently grappled with this extremely challenging and multifaceted topic to develop evidence-based and well-supported insights and advice that would be useful to public health authorities and others charged with developing plans to protect the health of the nation's public.

Robert R. Bass, *Chair*
Tia Powell, *Vice Chair*
Committee on Prepositioned Medical
Countermeasures for the Public

Acknowledgments

The committee gratefully acknowledges and thanks the many individuals who contributed to this study by sharing their expertise, perspectives, and time with the committee.

Funds for the committee's work were provided by the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response. The committee greatly appreciated the insightful discussions with George Korch and Lisa Kaplowitz at the first committee meeting, and the ongoing support and assistance it received from Susan Cibulsky, Chad Hrdina, and Elin Gursky.

Many individuals provided important input to the committee's work at its public workshop and other open sessions; their names and affiliations are listed in Appendix B. Many others took the time to share their expertise with committee members through interviews or more informal conversations; they are identified by name throughout the text. The committee would like to extend particular thanks to Greg Burel, Daniel Sosin, Stephanie Dulin, and others at the Centers for Disease Control and Prevention for providing important information on the Strategic National Stockpile and its interface with state and local public health systems.

The committee thanks the authors of the paper commissioned for this study—James Guyton, Robert Kadlec, Chandresh Harjivan, Shabana Farooqi, Sheana Cavitt, and Joseph Buccina of PRTM Management Consultants—which provided a critical source of information for the committee's work. The committee also thanks the many individuals who were interviewed by PRTM during the preparation of the commissioned paper; their names are listed in Appendix D.

Finally, the committee greatly appreciates the valuable contributions of Andrew Pope and Bruce Altevogt of the Institute of Medicine's Board on Health Sciences Policy; Neal Glassman of the Division on Engineering and Physical Sciences' Board on Mathematical Sciences and Their Applications; Theresa Wizemann, consultant writer; and Rona Briere, consultant editor.

Contents

Summary[1]

If bioterrorists released Bacillus anthracis (anthrax) over a large city, hundreds of thousands of people could need rapid access to antibiotics to prevent the deadly inhalational form of anthrax. Delivering antibiotics effectively following an anthrax attack is a tremendous public health challenge, however, because of the large number of people who may be exposed and the brief time window during which people exposed to anthrax spores must start taking antibiotics to prevent illness and death.

This report considers the use of prepositioning strategies to complement current plans for distributing and dispensing anthrax antibiotics, which rely heavily on postattack delivery from the centralized Strategic National Stockpile or state stockpiles. Once delivered to a state or locality, antibiotics from these stockpiles are dispensed to the public primarily via points of dispensing (PODs) located throughout the community. Prepositioning involves the storage of medical countermeasures (such as antibiotics) close to or in the possession of the people who would need rapid access to them should an attack occur. Examples of prepositioning strategies include local stockpiles, workplace caches, and home storage.

[1]This summary does not include references. Citations and detailed supporting evidence for the findings presented in the summary appear in the subsequent report chapters.

Although potentially effective for ensuring that large numbers of people have rapid access to antibiotics, prepositioning strategies require more resources than strategies relying on distribution from central locations after an attack, and some could increase health risks. Prepositioning strategies, therefore, provide the greatest value in enhancing response to large-scale attacks in high-risk areas with limited dispensing through the current POD system and in filling specific gaps in current capabilities. Conversely, prepositioning strategies may offer little added value in areas in which the risk of an attack is low or dispensing capability is sufficient.

In their planning efforts, state, local, and tribal officials should give priority to improving dispensing capability and developing prepositioning strategies such as local stockpiles and workplace caches. The committee recommends against broad use of home antibiotic storage for the general population because of concerns about inappropriate use, lack of flexibility as a response mechanism, and high cost. In some specific cases, home storage may be appropriate for individuals or groups that lack access to antibiotics through other timely dispensing mechanisms.

Because communities differ in their needs and capabilities, this report sets forth a framework to assist state, local, and tribal policy makers and public health authorities in determining whether prepositioning strategies would be beneficial for their community. The committee's recommendations also identify federal- and national-level actions that would facilitate the evaluation and development of prepositioning strategies, including the development of national guidance to enhance public-private coordination on prepositioning, distributing, and dispensing antibiotics for use in response to an anthrax attack.

If bioterrorists released aerosolized *Bacillus anthracis* (anthrax) over a large city, hundreds of thousands of people could need rapid access to antibiotics to prevent the deadly inhalational form of anthrax. Delivering antibiotics effectively following an anthrax attack is a tremendous public health challenge, however, because of the large number of people who may be exposed and the brief time window during which people exposed to anthrax spores must start taking antibiotics to prevent illness and death.

Since the anthrax attack in 2001, the nation has made much progress in developing plans for the rapid delivery of antibiotics. Nonetheless, there are ongoing concerns about the threat of anthrax, the scope of the public

health challenge of responding to such an attack, the ability to implement the plans that have been developed, and gaps in the performance of the distribution and dispensing system revealed during such recent events as the 2009 H1N1 influenza pandemic. For these reasons, all levels of government—in partnership with the private sector and community organizations—continue to explore ways to improve the nation's ability to distribute and dispense antibiotics rapidly to the public.

The backbone of current distribution plans is the Strategic National Stockpile (SNS) maintained by the Centers for Disease Control and Prevention (CDC), a national repository of medicine and medical supplies that can be deployed rapidly around the country to supplement state and local stockpiles. Following an attack, SNS supplies are delivered to state and local public health authorities, who assume responsibility for dispensing the medical countermeasures (MCM), such as antibiotics, to their populations. Currently, the primary delivery model is for the public to receive MCM at points of dispensing (PODs) located throughout the community.

This report examines the use of prepositioning strategies as a complement to the current centralized system. Prepositioning entails the storage of MCM close to or in the possession of the people who would need rapid access to them should an attack occur so as to reduce the time required to distribute and dispense initial doses. Examples of prepositioning strategies include local stockpiles, workplace caches, and home storage. Prepositioning strategies may help individuals receive antibiotics more quickly. In addition, by alleviating the burden on the POD system, some prepositioning strategies may indirectly increase timely access to antibiotics for people who will receive them from PODs, and these strategies could enable public health officials to devote additional efforts to reaching those who may have difficulty accessing MCM through the standard POD system. Discussions about prepositioning strategies over the past several years, however, have raised concern about their potential to introduce increased health risks, increased costs, legal and regulatory issues, questions of equity and fairness, and logistical burdens on public health departments.

Prepositioning is just one potential component of a larger endeavor to enhance the nation's capability to prevent illness and death from an anthrax attack. Other components include national security efforts to prevent an attack or mitigate its effects; efforts to enhance detection and surveillance capability; further development of strategies for anthrax prevention (e.g., anthrax vaccine) and treatment (e.g., anthrax antitoxin); continuing refinement of the current MCM distribution and dispensing system, including development of a model for using the postal system to deliver antibiotics; and efforts to engage the private sector in both the development and the delivery of MCM.

STUDY CHARGE

Given the potential benefits and concerns associated with prepositioning strategies, the Office of the Assistant Secretary for Preparedness and Response (ASPR), Department of Health and Human Services (HHS), commissioned the Institute of Medicine (IOM) to undertake a study to inform the use of prepositioned antibiotics for protection against anthrax (Box S-1).

In response to this charge, the committee reviewed the scientific evidence on antibiotics for prevention of anthrax and the implications for

BOX S-1
Statement of Task

In response to a request from the Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR), the Institute of Medicine will convene an ad hoc committee of subject matter experts to inform the use of prepositioned medical countermeasures (MCM) for the public. The committee will focus on prepositioning antibiotics for protection against a terrorist attack using *Bacillus anthracis* or a similar pathogen. More specifically, the ad hoc committee will produce a report that will:

- Consider the role of prepositioned medical countermeasures for the public (e.g., prepositioning at home, local stockpiles, and workplace caches) within an overall MCM dispensing strategy that includes traditional MCM dispensing and distribution strategies such as points of dispensing (PODs), taking into account both logistical and non-logistical factors (e.g., safety and ethics).
- Identify and describe key factors and variables that should be included in a strategy for prepositioning MCM for the public (e.g., population demographics, threat status, proximity to high-value targets, proximity to healthcare facilities).
- Discuss preliminary considerations for the development of an incremental and phased MCM prepositioning strategy.
- Based on available evidence, describe economic advantages and disadvantages of various MCM prepositioning strategies for the public.

The committee will develop scenarios, as needed, to illustrate the interaction of the strategic considerations, key factors, and variables in different situations and environments. The committee will base its recommendations on currently available published literature and other available guidance documents and evidence, expert testimony, as well as its expert judgment.

decision making about prepositioning; described potential prepositioning strategies; and developed a framework to assist state, local, and tribal public health authorities in determining whether prepositioning strategies would be beneficial for their communities. The committee concluded that each jurisdiction should assess the benefits and costs of prepositioning in their particular community; however, based on an analysis of the likely health benefits, health risks, and relative costs of the different prepositioning strategies, the committee also developed findings and recommendations to provide jurisdictions with some practical insights as to the circumstances in which different prepositioning strategies may be beneficial. Finally, the committee identified federal- and national-level actions that would facilitate the evaluation and development of prepositioning strategies.

ANTIBIOTICS FOR POSTEXPOSURE ANTHRAX PROPHYLAXIS

Inhalational anthrax is considered to be the most dangerous form of anthrax infection resulting from bioterrorism because aerosolized spores of *B. anthracis* can travel significant distances through the air and have a highly successful infection rate for humans, and because this is the deadliest form of the disease (compared with the more treatable cutaneous and gastrointestinal forms of anthrax). The Food and Drug Administration (FDA) has approved four antibiotics for prophylaxis (prevention of disease) following exposure to aerosolized spores of *B. anthracis*: doxycycline, ciprofloxacin, levofloxacin, and parenteral procaine penicillin G. These antibiotics protect against anthrax provided (1) the antibiotic used is effective against the particular strain of *B. anthracis* used in the attack, and (2) exposed individuals begin to take the antibiotic prior to the appearance of symptoms of anthrax. These conditions are highly relevant to decision making about prepositioning, as described below.

Antibiotic-Resistant *B. Anthracis*

Creating a strain of anthrax that is resistant to one or more antibiotics does not require a high level of microbiologic knowledge, and methodology for doing so is described in the open scientific literature. In 2006, the Secretary of the Department of Homeland Security (DHS) issued a Material Threat Determination specifically for multi-drug-resistant anthrax.

Concerns about antibiotic-resistant anthrax are relevant to any strategy for distributing and dispensing antibiotics, particularly since laboratory testing of susceptibility of a strain to antibiotics is likely to take 2 days or longer. Given the brief window of time during which people exposed to the spores must receive antibiotics to prevent disease (see section on incubation period below), antibiotic distribution and dispensing efforts would have to

be initiated before the susceptibility profile of the attack strain was known. These concerns may be amplified for prepositioning strategies, because it would likely be prohibitively expensive to stockpile a variety of antibiotics in all locations relative to stockpiling a variety of antibiotics in centralized locations.

Finding 2-1[2]: *Prepositioning of a single type of antibiotic (or class of antibiotics) would reduce flexibility to respond to the release of an antibiotic-resistant strain of anthrax, a biothreat recognized by the U.S. Department of Homeland Security. Furthermore, although some information about planned responses is already available in the public domain, prepositioning antibiotics in the home would provide a greater degree of certainty about the planned response and, therefore, could conceivably increase the probability of release of a resistant strain of anthrax.*

Incubation Period

Data on human exposure to aerosolized *B. anthracis* are limited, however, and there is a great deal of uncertainty regarding the incubation period (time from exposure to appearance of symptoms). Prophylaxis with a single antibiotic begun while an individual exposed to aerosolized anthrax is still in the incubation period can prevent symptoms from occurring. A clear understanding of the incubation period is critical for decision making about effective antibiotic distribution and dispensing strategies, including prepositioning strategies.

An exposed population will exhibit a range of times from exposure to the appearance of symptoms for the exact same exposure/dose, and the shape of the distribution curve is important for decision making about prophylaxis strategies. If, for example, there is a wide range of incubation times, then even after the development of a small number of clinically recognized anthrax cases, sufficient time may exist to distribute and dispense antibiotics to a large fraction of still-asymptomatic persons, thereby protecting a large fraction of the exposed population. On the other hand, if the distribution of incubation times is relatively narrow, then there could be much less time to distribute and dispense antibiotics to the exposed population after initially identified clinical cases. Beyond the shape of the distribution curve, the shortest incubation time that would be expected in an exposed population (i.e., the time at which the first person(s) would begin exhibiting symptoms) also is important for public health decision

[2]The findings and recommendations in this report are numbered according to the chapter of the main text in which they appear. Thus, for example, Finding 2-1 is the first finding in Chapter 2.

making about prepositioning. A longer minimum incubation period would permit more time for the distribution of MCM before symptom onset and thus would have a direct impact on decisions regarding the need for prepositioning.

Finding 2-2: *Review of the limited available data on human inhalational anthrax shows that people exposed to aerosolized anthrax have incubation periods of 4 to 8 days or longer. Much of the modeling used to derive shorter estimates is based on data from the Sverdlovsk incident,*[3] *and the assumptions made potentially lead to an underestimate of the minimum incubation period.*

With the most probable minimum incubation period being approximately 4 days (or 96 hours), there is no compelling evidence to suggest that jurisdictions must plan to complete dispensing of initial prophylaxis more rapidly than 96 hours following the time of the attack, although incremental improvements appear to be achievable and could provide additional protection against unforeseen delays.

Therefore, the current operational goal of the Centers for Disease Control and Prevention's Cities Readiness Initiative of completing dispensing of initial prophylaxis within 48 hours of the decision to dispense appears to be appropriate, as long as the ***total*** *time from exposure to prophylaxis does not exceed 96 hours. Achieving this goal depends on robust detection and surveillance systems that can rapidly detect an anthrax attack, rapid decision making, and effective distribution and dispensing systems. If detection or decision making is delayed, faster distribution and dispensing may be needed to minimize symptomatic disease in the exposed population.*

PREPOSITIONING STRATEGIES

Strategies for storing MCM lie along a continuum based on their proximity to the location of the anticipated event. At one extreme, MCM may be stored in a central warehouse that serves the entire nation (the SNS); at the other extreme, they may be stored in the homes of the intended users. Figure S-1 defines three categories of prepositioning strategies that can be used to complement the existing centralized system: forward-deployed MCM, cached MCM, and predispensed MCM. A mix of strategies along the continuum could be used—for example, some forward-deployed stockpiles near areas of high risk combined with some centrally located stockpiles to serve the remaining areas.

[3]The largest anthrax outbreak in history, the Sverdlovsk accident in 1979, is believed to have been the result of an accidental release of aerosolized anthrax from a Soviet Union biological weapons program. The incident is explained in more detail in Chapter 2.

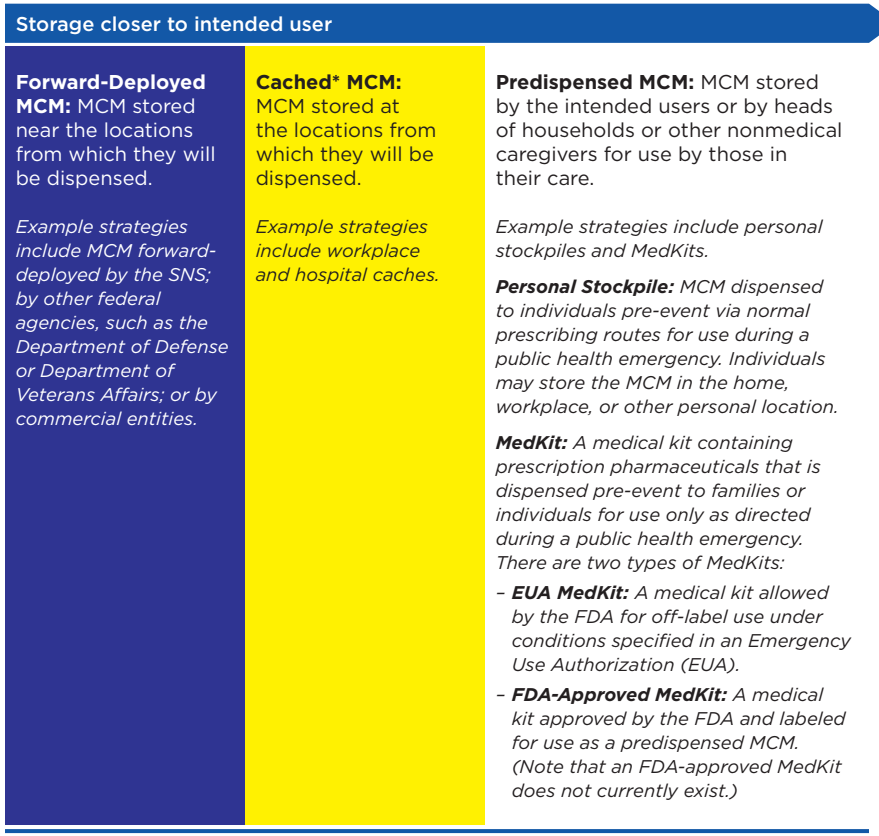

FIGURE S-1
Definitions of prepositioning strategies.

NOTE: FDA = Food and Drug Administration; MCM = medical countermeasures; SNS = Strategic Natural Stockpile.

*The term *cache* is often used broadly to describe stockpiles of MCM, whether held by state or local jurisdictions, health care facilities, or private-sector organizations, among others. For the purposes of this report, and to enable clear discussion of the different properties associated with different types of prepositioning, the committee defines *cache* more specifically as storage in the location from which MCM will be dispensed, and uses the term *stockpile* to denote federal, state, and local stockpiles.

PUBLIC-PRIVATE COORDINATION

Expanding public-private coordination has the potential to enhance MCM distribution and dispensing capability in communities. Many private-sector entities already play important roles throughout the MCM distribution and dispensing system, including managing inventory and distributing MCM for the SNS. Private-sector entities may be interested in developing or expanding systems through which they can preposition, distribute, and dispense antibiotics to help ensure the safety of employees and their families, provide for business continuity of operations, and potentially reduce insurance costs. Many large private-sector companies already have systems through which they communicate effectively with their employees, and such companies often have medical staff and other resources that could be used to enhance dispensing capability within their community during a time of crisis. As described in this report, however, potential private-sector partners face many barriers in carrying out this role, including liability, cost, legal and regulatory issues, and the complexities of working across multiple jurisdictions during the development of MCM dispensing plans.

Recommendation 4-1: Develop national guidance for public-private coordination in the prepositioning, distribution, and dispensing of medical countermeasures.
The Department of Health and Human Services should convene state, local, and tribal governments and private-sector organizations to develop national guidance that will facilitate and ensure consistency for public-private cooperation in the prepositioning, distribution, and dispensing of medical countermeasures and help leverage existing private-sector systems and networks.

A DECISION-AIDING FRAMEWORK FOR STATE, LOCAL, AND TRIBAL PUBLIC HEALTH OFFICIALS

Because communities differ in their needs and capabilities, the committee developed a decision-aiding framework to assist state, local, and tribal public health officials in determining whether prepositioning strategies would be beneficial for their community. This framework is summarized in Box S-2. This box is intended to provide an overview of the key elements of the framework; additional details on the recommended actions are provided in the recommendations that follow and in the main text of the report.

BOX S-2
Key Elements of the Decision-Aiding Framework

Communities across the United States differ in their needs and capabilities. Different communities may benefit most from different strategies for prepositioning antibiotics for anthrax, or may not benefit from prepositioning strategies at all. The committee developed a decision-aiding framework to assist state, local, and tribal jurisdictions in deciding which prepositioning strategies, if any, to implement in their community. The key elements of this framework are:

- Assessment of risk and current capabilities
  - — Consideration of the risk of an anthrax attack
  - — Assessment of current capability for timely detection of an attack
  - — Assessment of current dispensing capability, including (1) overall dispensing capability, and (2) specific gaps in dispensing capability, such as particular subpopulations not well served by current plans
- Incorporation of ethical principles and community values
- Evaluation of potential prepositioning strategies for medical countermeasures for anthrax
  - — Evaluation of potential health benefits, including evaluation of potential effectiveness in reaching specific populations or filling other specific gaps in dispensing capability
  - — Evaluation of potential health risks
  - — Evaluation of likely costs
  - — Consideration of practicality, including (1) communications needs and expected social behavior and adherence, (2) logistics, and (3) legal and regulatory issues

Assessment of Risk and Current Capabilities

To determine the potential benefits of prepositioning strategies, it is critical for jurisdictions to accurately assess their capabilities for both distribution and dispensing. The few performance measures available with which to assess dispensing capability are still nascent in their development. Existing performance data often are derived from small-scale drills rather than full-scale exercises because of limitations on financial resources and personnel, as well as on the feasibility of interrupting the daily operations of partner entities outside of the public health system. This fact, coupled with limited standardization and comparability of measurements across jurisdic-

tions, makes it difficult to evaluate the current capability of a dispensing system and in turn, the value of adopting prepositioning strategies to augment that capability. While the development of more accurate knowledge of distribution and dispensing capability would likely be more resource-intensive than continuing with current policies, it is a necessary precursor to developing and implementing expensive prepositioning strategies.

Recommendation 5-1: Enhance assessment of performance in implementing distribution and dispensing plans for medical countermeasures. **The Centers for Disease Control and Prevention should continue to facilitate assessment of state, local, and tribal jurisdictions' performance in implementing dispensing plans for medical countermeasures, in addition to assessing planning efforts. More specifically, the Centers for Disease Control and Prevention, in collaboration with state, local, and tribal jurisdictions, should facilitate assessment of the entire distribution and dispensing system by:**

- **demonstrating Strategic National Stockpile distribution capabilities to high-risk jurisdictions;**
- **facilitating large-scale, realistic exercises in high-risk jurisdictions to test dispensing capability; and**
- **continuing efforts to identify objective criteria and metrics for evaluating the performance of jurisdictions in implementing mass dispensing.**

Incorporation of Ethical Principles and Public Engagement

Jurisdictions must ensure that their dispensing plans adhere to ethical principles with respect to both general considerations in drafting public health policy and issues specific to the question of prepositioning anthrax MCM.

Recommendation 5-2: Integrate ethical principles and public engagement into the development of prepositioning strategies within the overall context of public health planning for bioterrorism response. **State, local, and tribal governments should use the following principles as an ethical framework for public health planning of prepositioning strategies:**

- **Promotion of public health—Strive for the most favorable balance of public health benefits and harms based on the best available research and data.**

- **Stewardship—Demonstrate stewardship of public health resources.**
- **Distributive justice—Distribute benefits and harms fairly, without unduly imposing burdens on any one population group.**
- **Reciprocal obligations—Recognize the professional's duty to serve and the reciprocal obligation to protect those who serve.**
- **Transparency and accountability—Maintain public accountability and transparency so that community members grasp relevant policies and know from whom they may request explanation, information, or revision.**
- **Proportionality—Use burdensome measures, such as those that restrict liberty, only when they offer a commensurate gain in public health and when no less onerous alternatives are both available and feasible.**
- **Community engagement—Engage the public in the development of ethically sound dispensing plans for medical countermeasures, including plans to preposition antibiotics, so as to ensure the incorporation of community values.**

Evaluation of Potential Prepositioning Strategies for MCM for Anthrax

The committee recommends that each jurisdiction assess the benefits and costs of prepositioning in the particular community. Recognizing that some local jurisdictions may have limited resources, the committee recommends that state, local, and tribal jurisdictions work in partnership with each other and with other stakeholders, such as the federal government, the private sector, and community organizations, to gather the necessary information and conduct the recommended assessments and evaluations.

Recommendation 5-3: Consider the risk of attack, assess detection and dispensing capability, and evaluate the use of prepositioning strategies to complement points of dispensing.

State, local, and tribal governments should, in partnership with each other and with the federal government, the private sector, and community organizations:

- **Consider their risk of a potential anthrax attack.**
- **Assess their current detection and surveillance capability.**
- **Assess the current capability of and gaps in their medical countermeasures dispensing system.**
- **Based on their risk and capability assessment, evaluate whether specific prepositioning strategies will fill identified gaps and/or improve effectiveness and efficiency. The decision-making framework should include, for a range of anthrax attack scenarios:**

- **evaluation of the potential health benefits and health risks of alternative prepositioning strategies;**
- **evaluation of the relative economic costs of alternative prepositioning strategies;**
- **comparison of the strategies with respect to health benefits, health risks, and costs, taking into account available resources; and**
- **consideration of ethical principles and incorporation of community values (see Recommendation 5-2).**

In the report, the committee presents a qualitative exploration of the potential effects of each of the key elements of the decision-aiding framework on the incremental effectiveness of prepositioning strategies. The committee also presents a first-order quantitative model for estimating health benefits associated with different prepositioning strategies; a discussion and case study of the estimation of likely economic costs; and a suggested method for using estimates of health benefits and economic costs to explore trade-offs associated with alternative prepositioning strategies and inform decision making.

While recommending that each jurisdiction conduct its own analysis, the committee offers findings and recommendations based on its analysis of the likely health benefits, health risks, and relative costs of the different prepositioning strategies to give jurisdictions some practical insights as they consider the strategies' benefits and costs.

Importance of Adequate Dispensing Capability and Timely Decision to Dispense

In the event of an attack, forward-deploying stockpiles and caches will have the potential to decrease morbidity and mortality only if the community has adequate dispensing capability, and the time from release until dispensing is initiated is brief compared with the minimum incubation period. Analytical models of existing distribution strategies show that in the event of a large-scale attack, dispensing capability—not antibiotic inventories—is likely to be the rate-limiting factor in getting antibiotics to the potentially exposed population.

The benefits of prepositioning, measured in terms of time to prophylaxis and resulting fraction of the exposed population saved, increase as the time from attack until the decision to dispense increases. This result occurs because of the distribution of the incubation period of anthrax across exposed individuals. Reducing time to prophylaxis from 48 hours to 24 hours after exposure, for example, will likely have little impact on the fraction of the exposed population saved because few individuals will develop anthrax symptoms within that period. On the other hand, reducing time to

prophylaxis from, for example, 120 hours to 96 hours after exposure can significantly improve the fraction saved because many individuals are likely to develop anthrax symptoms between 96 and 120 hours after exposure.

Health Benefits, Health Risks, and Costs of Prepositioning Strategies

Prepositioning MCM has the potential to reduce the expected time until exposed individuals in the population receive prophylaxis. If associated with closed PODs, which dispense to a defined population rather than to the general public (e.g., in a private-sector workplace), prepositioned MCM can directly benefit those who receive MCM from the closed PODs, reducing their time to prophylaxis. Moreover, by reducing demand at public PODs, prepositioning can indirectly benefit those who receive MCM from public PODs, reducing their time to prophylaxis as well.

Although potentially effective for ensuring that large numbers of people have rapid access to antibiotics, prepositioning strategies will require more resources than strategies that rely on distribution from central locations after an attack, will decrease flexibility (e.g., to redeploy based on attack location or to provide alternative MCM based on the susceptibility of the strain), and may increase potential health risks. Therefore, prepositioning strategies will provide the greatest value in enhancing response to large-scale attacks in high-risk areas with limited dispensing through the current POD system and in filling gaps in coverage of subpopulations that could be addressed effectively through prepositioning. Conversely, prepositioning strategies may offer little added value in areas in which the risk of an attack is low or dispensing capability is sufficient.

Table S-1 summarizes factors that affect the appropriateness of each strategy and the consequences of its implementation. The table consists of a set of suggested "if-then" rules, stored in its rows: if a situation is well described by the entries in a row under "Factors Affecting the Appropriateness of Strategies," then the strategy or strategies in that row might be appropriate to consider. The right side of the table describes qualitatively the consequences of implementing such a strategy.

Recommendation 5-4: Give priority to improving dispensing capability and developing prepositioning strategies such as forward-deployed or cached medical countermeasures.

In public health planning efforts, state, local, and tribal jurisdictions should give priority to improving the dispensing capability of points of dispensing and push strategies and to developing forward-deployed or cached prepositioning strategies.

The committee does not recommend the development of public health strategies that involve *broad* use of predispensed medical

TABLE S-1
Appropriateness and Consequences of Alternative Prepositioning Strategies: Qualitative Summary

Continuum of MCM Storage Locations	Strategies to Consider[a]	Factors Affecting Appropriateness of Strategies			Consequences of Strategies			
		Risk Status[b]	Public Health Dispensing Capability[c]	Gaps in Sub-populations Covered[d]	Cost to Public Health[e]	Time to Prophylaxis[f]	Inventory Flexibility[g]	Potential for Misuse[h]
No Pre-positioning	– Centralized stockpiles (SNS, other)	Low	Adequate	None	Limited	Baseline	Greatest	None
Forward-Deployed MCM	– SNS forward-deployed – Other federal forward-deployed (e.g., DOD, VA) – Private forward-deployed	High	Adequate	n/a	Moderate	Shorter	Medium	None
Cached MCM	– Hospital/ pharmacy caches – Workplace caches	High	Limited	Some	Moderate	Shorter	Less	Some/little
Predispensed MCM	– Personal stockpiles	Extremely High	Inadequate	Many	Limited	Shortest	Least	Moderate/ high
	– MedKits				High			

NOTE: DOD = Department of Defense; MCM = medical countermeasures; n/a = not applicable. SNS = Strategic National Stockpile; VA = Department of Veterans Affairs;

[a] Combinations of strategies may be appropriate.

[b] Likelihood of an attack and likelihood of an attack of a given type or size.

[c] MCM dispensing capability in the event of a large attack.

[d] Subpopulations that may not be covered by MCM dispensing capacity in the event of an attack.

[e] The cost incurred by public health authorities to store and maintain inventories of MCM. Other costs may be borne by other entities, such as private-sector workplaces (e.g., storage, training, and maintenance of workplace caches) and individuals or private insurers (e.g., personal stockpiles). Research and development costs for MedKits may be borne by the federal government, by a private-sector company, or by some combination of these.

[f] The time from the decision to dispense until MCM can be delivered to all exposed and potentially exposed individuals.

[g] Inventory flexibility includes the potential for use of multiple drugs, the potential for redeployment of inventories based on need, and the ease with which stockpiles can be rotated.

[h] Potential for misuse of the prepositioned MCM (e.g., individuals taking the antibiotics for other conditions or not in the event of an anthrax attack).

countermeasures for the general population. In some cases, however, *targeted* predispensed medical countermeasures might be used to address specific gaps in jurisdictions' dispensing plans for certain subpopulations that lack access to antibiotics via other timely dispensing mechanisms. These might include, for example, some first responders, health care providers, and other workers who support critical infrastructure, as well as their families.

Personal stockpiling might also be used for certain individuals who lack access to antibiotics via other timely dispensing mechanisms (e.g., because of their medical condition and/or social situation) and who decide—in conjunction with their physicians—that this is an appropriate personal strategy. This is allowed under current prescribing practice and would usually be done independently of a jurisdiction's public health strategy for dispensing medical countermeasures.

The available evidence and reasoning leading to the committee's conclusions and recommendations with respect to predispensed MCM are summarized below.

Predispensed Medical Countermeasures

Predispensing of MCM is unique relative to other potential prepositioning strategies because it puts the MCM directly into the hands of the intended end-users. Potential health risks are thereby introduced that are not entailed in prepositioning strategies such as forward-deployed and cached MCM. As noted above, predispensing also increases costs and decreases flexibility to alter the MCM provided based on the specifics of an attack. The committee considered two potential predispensing strategies: predispensing to the general public in a community and predispensing for targeted subpopulations. The committee also considered the likely relative risks, benefits, and costs of different forms of predispensing (e.g., MedKits and personal stockpiling).

The use of predispensing as a broad public health strategy for the general public is unlikely to be cost-effective and carries significant risks. The most extensive body of relevant evidence (statistics about the misuse of antibiotics prescribed for routine medical care) suggests that if predispensing were implemented broadly for the general public, the rate of inappropriate use could be high, resulting in increased health risks to individuals and the community. Concerns include inappropriate use in routine settings (e.g., using the antibiotics to treat a cold) and widespread inappropriate use in response to events such as a distant anthrax attack, a false alarm caused by a nonanthrax white-powder event, or another public health emergency for which antibiotics are not indicated.

Based on a community's comprehensive assessment of risk and current dispensing capability, predispensing could prove to be an appropriate strategy for specific groups and individuals who would not have access to prophylactic antibiotics via other timely dispensing mechanisms. For these groups and individuals (examples of which are given in Recommendation 5-4 above), the risk of not getting antibiotics following an anthrax attack may outweigh the potential health risks associated with inappropriate use. In addition, with a more limited, targeted strategy, or a strategy that involves a direct relationship between patient and physician, it may be easier to provide patient education about proper antibiotic use, institute systems to decrease inappropriate use and manage costs, and/or develop an alternative dispensing mechanism in case of an attack with antibiotic-resistant anthrax.

With regard to the *form* of the MCM that might be predispensed to these targeted groups and individuals, the intent of special MedKit packaging (relative to personal stockpiling with standard prescription vials) is to decrease misuse, but the committee found no direct evidence of this benefit. Future studies may be able to demonstrate that special packaging for MedKits could decrease the rate of inappropriate use.

Recommendation 5-5: Do not pursue development of a Food and Drug Administration–approved MedKit unless this is supported by additional safety and cost research.

The committee does not recommend the development of a Food and Drug Administration–approved MedKit designed for prepositioning for an anthrax attack until and unless research demonstrates that MedKits are significantly less likely to be used inappropriately than a standard prescription and can be produced at costs comparable to those of standard prescription antibiotics.

RECOMMENDED ACTIONS FOR MOVING FORWARD

To provide a plan for moving forward, the committee organizes its recommendations into those addressed to state, local, and tribal public health officials and those intended for implementation at the federal/national level. Recognizing that implementation of these actions should involve partnerships among all levels of government and nongovernmental stakeholders, this division is intended to indicate the entity or entities recommended to take the leading role, not the sole actor(s). Box S-3 lists the committee's recommendations in these two categories. The committee notes that, although these actions are proposed in the context of the selection, development, and implementation of prepositioning strategies, many also would help enhance the nation's overall ability to distribute and dispense antibiotics

BOX S-3
Recommendations at the State/Local/ Tribal and Federal/National Levels

State/Local/Tribal

Different communities may benefit most from different strategies for prepositioning antibiotics for anthrax, or may not benefit from prepositioning strategies at all. The following recommendations are intended to assist state, local, and tribal public health officials in evaluating the potential benefits, health risks, and costs of developing prepositioning strategies in their community:

- Integrate ethical principles and public engagement into the development of prepositioning strategies within the overall context of public health planning for bioterrorism response. *(Recommendation 5-2)*
- Consider the risk of attack, assess detection and dispensing capability, and evaluate the use of prepositioning strategies to complement points of dispensing. *(Recommendation 5-3)*
- Give priority to improving dispensing capability and developing prepositioning strategies such as forward-deployed or cached medical countermeasures. *(Recommendation 5-4)*

Federal/National

- Develop national guidance for public-private coordination in the prepositioning, distribution, and dispensing of medical countermeasures. *(Recommendation 4-1)*
- Enhance assessment of performance in implementing distribution and dispensing plans for medical countermeasures. *(Recommendation 5-1)*
- Do not pursue development of a Food and Drug Administration–approved MedKit unless this is supported by additional safety and cost research. *(Recommendation 5-5)*
- Perform additional research to better inform decision making about prepositioning strategies. *(Recommendation 6-1)*

rapidly following an anthrax attack regardless of specific decisions made about prepositioning.

Finally, throughout the report, the committee highlights areas of uncertainty in the evidence and research that would help inform decision making on prepositioning strategies.

Recommendation 6-1: Perform additional research to better inform decision making about prepositioning strategies.

Results of such research would strengthen the decision-aiding framework proposed in this report for determining whether prepositioning strategies would be beneficial within a community. The Department of Health and Human Services should conduct additional research in the following broad areas: epidemiological and medical issues regarding anthrax and postexposure prophylaxis for anthrax, operations and logistics, behavior and communications, safety, and cost-effectiveness.

1

Introduction

Rapid access to antibiotics is critical for preventing and treating illness and death due to a bioterrorism attack with a bacterial agent such as *Bacillus anthracis* (anthrax). Yet the logistics of effectively delivering antibiotics to prevent anthrax infection pose a tremendous challenge because such an attack could potentially expose a large number of people who would require antibiotics within a relatively brief time window. For example, if aerosolized anthrax were released over a large, densely populated area, hundreds of thousands of people could need prophylactic antibiotics to prevent deadly inhalational anthrax (Danzig, 2003; U.S. Congress, 1993). The goal of current planning efforts is to be able to dispense prophylactic antibiotics to all exposed and potentially exposed individuals within 48 hours of the decision to dispense (CDC, 2011a). Although the nation has made much progress in developing plans for the delivery of antibiotics over the last decade, this public health goal continues to be recognized as difficult to achieve because of the challenges involved in implementing and executing these plans.

STUDY CHARGE

Given the challenges noted above, interest currently is focused on supplementing existing centralized strategies for the delivery of prophylactic antibiotics with so-called *prepositioning* strategies, whereby antibiotics are stored at or near locations in which they are anticipated to be needed. Accordingly, the Office of the Assistant Secretary for Preparedness and Response (ASPR), Department of Health and Human Services (HHS), com-

missioned the Institute of Medicine (IOM) to undertake a study that would inform the use of prepositioned antibiotics for the public for protection against an anthrax attack (Box 1-1).

To respond to this charge, the IOM appointed the Committee on Prepositioned Medical Countermeasures for the Public, bringing together 16 experts with a broad spectrum of expertise, including state and local public health preparedness, emergency medicine and response, infectious disease, pediatrics, toxicology, systems analysis and operations research, materials management and supply chains, economics, health systems, the

BOX 1-1
Statement of Task

In response to a request from the Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR), the Institute of Medicine will convene an ad hoc committee of subject matter experts to inform the use of prepositioned medical countermeasures (MCM) for the public. The committee will focus on prepositioning antibiotics for protection against a terrorist attack using *Bacillus anthracis* or a similar pathogen. More specifically, the ad hoc committee will produce a report that will:

- Consider the role of prepositioned medical countermeasures for the public (e.g., prepositioning at home, local stockpiles, and workplace caches) within an overall MCM dispensing strategy that includes traditional MCM dispensing and distribution strategies such as points of dispensing (PODs), taking into account both logistical and non-logistical factors (e.g., safety and ethics).
- Identify and describe key factors and variables that should be included in a strategy for prepositioning MCM for the public (e.g., population demographics, threat status, proximity to high-value targets, proximity to healthcare facilities).
- Discuss preliminary considerations for the development of an incremental and phased MCM prepositioning strategy.
- Based on available evidence, describe economic advantages and disadvantages of various MCM prepositioning strategies for the public.

The committee will develop scenarios, as needed, to illustrate the interaction of the strategic considerations, key factors, and variables in different situations and environments. The committee will base its recommendations on currently available published literature and other available guidance documents and evidence, expert testimony, as well as its expert judgment.

private sector, the social sciences, risk management and communication, bioethics, pharmacy, and faith and civic organizations. Biosketches of the committee members are included in Appendix E. The committee developed this report to assist federal policy makers and state, local, and tribal public health officials, as well as their private-sector and community partners, in evaluating the potential health benefits, health risks, costs, and practical considerations of implementing strategies for prepositioning antibiotics in their communities as a complement to existing, more centralized dispensing strategies.

STUDY CONTEXT

In the fall of 2001, the United States experienced its first—and thus far only—bioterrorism attack involving *B. anthracis*, in which the bacterium spores were spread via mail sent through the U.S. postal system. These attacks resulted in 22 cases of documented anthrax; 11 of these cases were inhalational anthrax—the most deadly form of the disease—and resulted in 5 deaths (Jernigan et al., 2002).

Despite relatively limited experience with anthrax in the United States, it is considered one of the most serious threats to national security and the health of the nation for a variety of reasons, including the following:

- *B. anthracis* occurs in nature and is relatively inexpensive and easy to obtain and grow (CDC, 2009a; Inglesby et al., 2002).
- Inhalational anthrax can result from exposure to a relatively small number of spores and typically is lethal without effective treatment, and prophylaxis or treatment must be initiated within a relatively brief window of time following exposure (Inglesby et al., 2002; Turnbull, 2008).
- Although no nation publicly acknowledges having an offensive biological weapons program, it is estimated that a dozen countries have such programs (Kerr, 2008). The largest anthrax outbreak in history, the Sverdlovsk accident in 1979, is believed to have been the result of an accidental release of aerosolized anthrax from a Soviet Union biological weapons program (e.g., Meselson, 1988). There is also evidence that some terrorist groups have attempted to develop the capability to use anthrax, including the unsuccessful attempts by Japanese cult group Aum Shinrikyo to release anthrax in Tokyo in 1993 and evidence that Al Qaeda has pursued the development of anthrax as a biological weapon (Carus, 2002; Danzig et al., 2011; Mowatt-Larssen, 2010). The actual capability to conduct an attack using anthrax as a weapon is unknown for both national programs and terrorist groups.

- Among terrorist attacks, those involving anthrax may be among the easiest to carry out simultaneously in multiple locations or repeatedly over time (Danzig, 2003).
- Naturally occurring *B. anthracis* strains sometimes are resistant to certain antibiotics, and *B. anthracis* can be engineered to be resistant to multiple available antibiotics (Athamna et al., 2004; Brouillard et al., 2006; Inglesby et al., 2002; Price et al., 2003).

In 2004, the Secretary of the Department of Homeland Security (DHS) determined that anthrax presents a threat to the U.S. population of sufficient severity to affect national security (GAO, 2009). In 2006, the Secretary of DHS also determined that multi-drug-resistant anthrax was a material threat to the nation (DHS, 2008; GAO, 2009). The Centers for Disease Control and Prevention (CDC) classifies anthrax as a Category A bioterrorism agent/disease, a designation that indicates the greatest potential to adversely impact public health and result in mass casualties (CDC, 2011b; Rotz et al., 2002).

Concerns About the Current Dispensing System for Medical Countermeasures

All levels of government—federal, state, and local—and the private sector are involved in plans to distribute and dispense antibiotics to the public for protection against an anthrax attack. The backbone of current distribution plans is the Strategic National Stockpile (SNS), a national repository of medicine and medical supplies that can be deployed rapidly around the country to supplement state and local stockpiles (CDC, 2011c). Once medical countermeasures (MCM) from the SNS arrive, state and local public health authorities assume responsibility for distributing and dispensing them to their population.

Because of the scope of the challenge and the resources required, many public health authorities and other policy experts fear that most communities still lack adequate mechanisms and capacity to dispense antibiotics rapidly to all exposed and potentially exposed populations following a large anthrax attack (HSPD-21, 2007). This concern is driven by several factors, briefly outlined in the remainder of this section.

First, the anthrax attack of 2001 represents the nation's only domestic experience with response to an anthrax attack; the available real-world evidence with which to assess the nation's ability to dispense MCM following an anthrax attack is limited. Similarly, the number of exposed individuals in 2001 was small compared with estimates of the number of people who could potentially be exposed and infected in a large multicity aerosolized release of *B. anthracis*. Danzig (2003) predicts 200,000 expected infections

within a 40-mile radius of a small commercial sprayer from a single point source; DHS Planning Scenario 2 uses 328,484 infections from a concealed improvised spraying device in a densely populated urban city (DHS, 2006). Even though the scope of the attack in 2001 was much smaller than these estimates, the response to that event highlighted the challenges and time pressure associated with responding to anthrax and revealed "an unacceptable level of fragility in systems now properly recognized as vital to national defense" (Gursky et al., 2003, p. 97).

Second, there are sparse data from large-scale exercises and few measures of dispensing performance (not just planning), making it difficult to assess the system's capacity to dispense antibiotics to all potentially exposed individuals within the required time window after a large attack. CDC and other entities have developed criteria and metrics with which to evaluate the development of state and local preparedness plans for the distribution and dispensing of MCM, including CDC's Technical Assistance Review (TAR) tool and the recently published *Public Health Preparedness Capabilities* (CDC, 2009b, 2010, 2011d). However, there are few criteria and metrics with which to assess the actual implementation of dispensing plans (TFAH, 2010; Willis et al., 2009).

Third, concerns were fueled by the challenges encountered during efforts to dispense vaccine in response to the 2009 H1N1 influenza pandemic. Lessons learned from response to the influenza pandemic do not transfer directly to an anthrax response because of differences in geographic scope, time window for response, and required countermeasures. However, the distribution, dispensing, and communications challenges that occurred, particularly in the early months of the vaccine program, made concrete for many the immense difficulties of conducting a large antibiotic-dispensing campaign within a time window of approximately 48 hours, as would be required to respond to an anthrax attack (IOM, 2010a).

Finally, observation of responses to other, non-bioterrorism-related disasters have highlighted the tremendous challenges of responding to disasters. Recent examples include the earthquakes in Haiti and Japan and Hurricane Katrina. The aftermath of these disasters underscored the challenges of disaster response, the catastrophic consequences of gaps in preparedness, and the many areas in which improvements could be made. There is little evidence to suggest that mounting a mass MCM dispensing campaign after a major bioterrorism attack would not reveal challenges of a similar magnitude.

Prepositioning and Other Novel Dispensing Strategies

In response to the concerns outlined above, the past few years have seen a burgeoning interest in exploring novel dispensing strategies to complement

the existing system. In 2004, the U.S. Postal Service (USPS) began working with selected large cities to develop plans to use the postal service to distribute antibiotics to residents in their homes after an attack. Drills of the plan were conducted in Boston, Philadelphia, and Seattle in 2006 and 2007, and a pilot program of this model has been developed in Minneapolis-St. Paul (IOM, 2010b). A Presidential Executive Order issued in 2009 instructed the federal government to pursue the development of a national postal model in which postal carriers would distribute antibiotics to residents in their homes for self-administration (Obama, 2010). In response, a National Postal Model was developed by HHS, DHS, the Department of Defense, the Department of Justice, and the USPS (HHS et al., 2011).

Another strategy under exploration is user-managed inventory, in which materials are stockpiled in hospitals, to be used regularly for routine health care purposes and continually replaced to maintain the quantity of stockpiled materials but to avoid expiry (HHS, 2011). In addition, the response to the 2009 H1N1 influenza pandemic saw a great increase in private-sector mechanisms for dispensing of MCM, particularly via pharmacies and private practices (ASTHO, 2010; Merchant Medicine, 2010; ORISE, 2009).

As a supplement to established strategies, federal, state, and local public health authorities and the private sector also are interested in strategies that would preposition MCM closer to their intended users prior to an incident—the topic of the current report (see, for example, Kadlec [2011] for results of a survey of opinions on prepositioning among editors and readers of the journal *DomPrep*). Prepositioning strategies are being considered because they could potentially help ensure access to MCM for more people within an appropriate time window, decrease stress on the existing dispensing and health care systems, and help ensure fair and equitable access to MCM. Despite the promise of prepositioning strategies, however, prepositioning involves many complex issues that need to be carefully considered before decisions are made about the wide implementation of these strategies (IDSA, 2008; NBSB, 2008). These issues include questions about effectiveness, cost-effectiveness, logistics, the legal and regulatory framework, safety, equity, and sustainability.

Prepositioning and other novel dispensing strategies, as described above, are just one potential component of a larger endeavor to enhance the nation's capability to prevent illness and death from an anthrax attack. Other components include national security efforts to prevent an attack or mitigate its effects, efforts to enhance detection and surveillance capability, further development of anthrax vaccine and antitoxin strategies, continuous refinement of the current MCM distribution and dispensing system, and efforts to engage the private sector in both the development and the delivery of MCM.

METHODS AND DEFINITIONS

The committee's work was accomplished over a 12-month period commencing in October 2010. The committee held four meetings between January and June 2011 that included both closed-session deliberations and open-session information-gathering dialogues with subject matter experts and stakeholders. The second committee meeting was held in conjunction with a 2-day public workshop whose objectives were to identify gaps and challenges in current dispensing systems; assess current prepositioning efforts; discuss a range of potential prepositioning strategies; examine ethical, legal, regulatory, and safety issues; and discuss methods, metrics, and available data for evaluating the cost and effectiveness of prepositioning strategies. A shorter open session also was held at the third committee meeting; this open session focused specifically on vulnerable populations, ethical issues, and public engagement. The agendas for both the workshop and the shorter open session are available in Appendix B. Box 1-2 presents a glossary of key terms used in this report.

In addition to the workshop and other information-gathering sessions, the committee surveyed the relevant peer-reviewed literature and other available guidance documents and publications, gathered information through personal contacts, and commissioned a paper on the economic costs and time savings associated with prepositioning strategies (Appendix D). During the study period, the committee also was able to garner relevant insights into public behavior relevant to MCM stockpiling in response to the earthquake, tsunami, and resulting nuclear disaster in Japan in March 2011.

The committee did not review any classified information, including classified information about the risk of an anthrax attack. The committee's recommendations were informed by the members' overall understanding of the threat and risk of anthrax today, 10 years after the 2001 anthrax attack. In its approach to this study and the formulation of its recommendations, however, the committee focused on how public health officials should use assessment of the current risk of an anthrax attack in their individual communities to inform decisions about prepositioning.

Strategies for positioning MCM lie along a continuum based on proximity to the location of the anticipated event. At one extreme, for example, MCM from the SNS and commercial stockpiles may be centrally located and distributed postevent to locations throughout the nation; at the other extreme, stockpiles are kept in individual homes for use immediately postevent. This continuum is depicted in Figure 1-1.

BOX 1-2
Glossary of Key Terms

Critical infrastructure personnel, first responders: For this report, the committee broadly defines *critical infrastructure personnel* and *first responders* as including those persons who will be expected to report to and stay at work during an attack in order to respond and maintain critical functions within the community. This definition is not meant to counter or supersede definitions of critical infrastructure personnel or first responders used by federal, state, and local planners.

Dispensing: The act of providing medical countermeasures (MCM) to individuals who will take them immediately or at some future defined/declared time of need. Dispensing also includes providing MCM to heads of households or other nonmedical caregivers for use by those in their care.

Dispensing capacity: The number of individuals to whom a public health dispensing system can dispense MCM per day, whether the MCM are provided directly to individuals or via heads of households or other nonmedical caregivers.

Distribution: The delivery of MCM from stockpiles to receiving, staging, and storage (RSS) sites, as well as delivery from RSS sites to dispensing sites. Distribution may be triggered by an event, or MCM may be distributed to a local storage site or point of dispensing (POD) in anticipation of a potential future need.

Emergency Use Authorization (EUA): An authorization by the Commissioner of the Food and Drug Administration (FDA) for "the use of an unapproved medical product or an unapproved use of an approved medical product during a declared emergency involving a heightened risk of attack on the public or U.S. military forces, or a significant potential to affect national security" (FDA, 2010).

Jurisdiction, community: For this report, the committee uses *jurisdiction* to refer to state, local, and tribal governments. The committee uses *community* to refer to these governmental entities in conjunction with private-sector entities, community organizations, and members of the public within the jurisdictional boundaries.

Medical countermeasures (MCM): A drug, biological product, or device that diagnoses, mitigates, prevents, or treats harm resulting from a biological, chemical, radiological, or nuclear agent that causes a public health emergency (PAHPA, Public Law 109-417, Sec403a2(Aii), 2006).

Points of dispensing (PODS): Locations where MCM are dispensed to potentially exposed individuals. PODs may be *open* or *closed*, depending on the populations served:

- Open PODs: Locations where MCM are dispensed to all potentially exposed members of the public.

- Closed PODs: Locations where MCM are dispensed to a predefined population, such as employees of a company and their family members. Closed PODs may dispense MCM from a variety of sources, including the Strategic National Stockpile (SNS), state stockpiles, commercial supplies, and on-site workplace caches.

Prepositioning: The storage of MCM at or near the anticipated event location where they will be needed so as to reduce the time required to distribute and dispense initial doses. The placement of MCM lies on a continuum with respect to their physical proximity to the anticipated event location. *Prepositioning* refers to all potential placements of MCM along this continuum, from forward deployment of MCM through placement of stockpiles in the hands of individuals, as described below. Prepositioned MCM may remain in the control of federal, state, and local governments or may be managed by others, such as health systems, businesses, and individuals.

- Forward-Deployed MCM: MCM stored near the locations from which they will be dispensed.
- Cached MCM[a]: MCM stored at the locations from which they will be dispensed.
- Predispensed MCM: MCM stored by the intended users or by heads of households or other nonmedical caregivers for use by those in their care. Example strategies include personal stockpiles and MedKits:
  - **Personal Stockpile:** MCM dispensed to individuals pre-event via normal prescribing routes for use during a public health emergency. Individuals may store the MCM in the home, workplace, or other personal location.
  - **MedKit:** A medical kit containing prescription pharmaceuticals that is dispensed pre-event to families or individuals for use only as directed during a public health emergency.
    - **EUA MedKit:** A medical kit allowed by the FDA for off-label use under conditions specified in an Emergency Use Authorization (EUA).
    - **FDA-approved MedKit:** A medical kit approved by the FDA and labeled for use as a predispensed MCM. (Note that an FDA-approved MedKit does not currently exist.)

Prepositioning strategy: The specification of locations where MCM will be stored, and for each location, the amount of antibiotics stored and dispensing methods and protocols for their use in the event of a confirmed or suspected attack (e.g., for general use at public PODs, for use at a specific closed POD, for home use).

Public: All members of a community who are not already adequately covered by separate specialized programs, such as programs for federal mission-essential personnel.

continued

BOX 1-2 Continued

Strategic National Stockpile (SNS): "A national repository of antibiotics, chemical antidotes, antitoxins, life-support medications, IV administration, airway maintenance supplies, and medical/surgical items. The SNS is designed to supplement and re-supply state and local public health agencies in the event of a national emergency anywhere and at anytime within the U.S. or its territories" (CDC, 2011c).

Subpopulation: "An identifiable fraction or subdivision of a population" (Merriam-Webster, 2011).

[a]The term *cache* is often used broadly to describe stockpiles of MCM, whether held by state or local jurisdictions, healthcare facilities, private sector organizations, among others. For the purposes of this report, and to enable clear discussion of the different properties associated with different types of prepositioning, the committee defines cache more specifically as storage in the location from which they will be dispensed, and uses the term *stockpile* to cover federal, state, and local stockpiles.

STUDY APPROACH AND SCOPE

Focus on Anthrax

ASPR asked the IOM committee to focus specifically on the dispensing of antibiotics for anthrax because (1) as noted above, the threat of anthrax currently is considered to be among the highest-priority threats; and (2) the brief time window within which antibiotics must be dispensed to protect effectively against anthrax infection is among the greatest challenges facing the MCM distribution and dispensing system as a whole. In accordance with the committee's charge, then, the decision-aiding framework, analysis, findings, and recommendations presented in this report are specific to prepositioning of antibiotics for anthrax. The committee hopes that this report will provide a starting point and potential model for evaluating whether and how to preposition MCM to prevent, mitigate, and treat illness and death caused by other biological, chemical, and radiological/nuclear threats. The committee cautions, however, that the analysis presented herein does not translate directly to such other situations because of differences in the nature of the threat, the time course of the threat, the time within which the MCM must be taken to be effective, and whether the MCM require administration by a health care professional. The find-

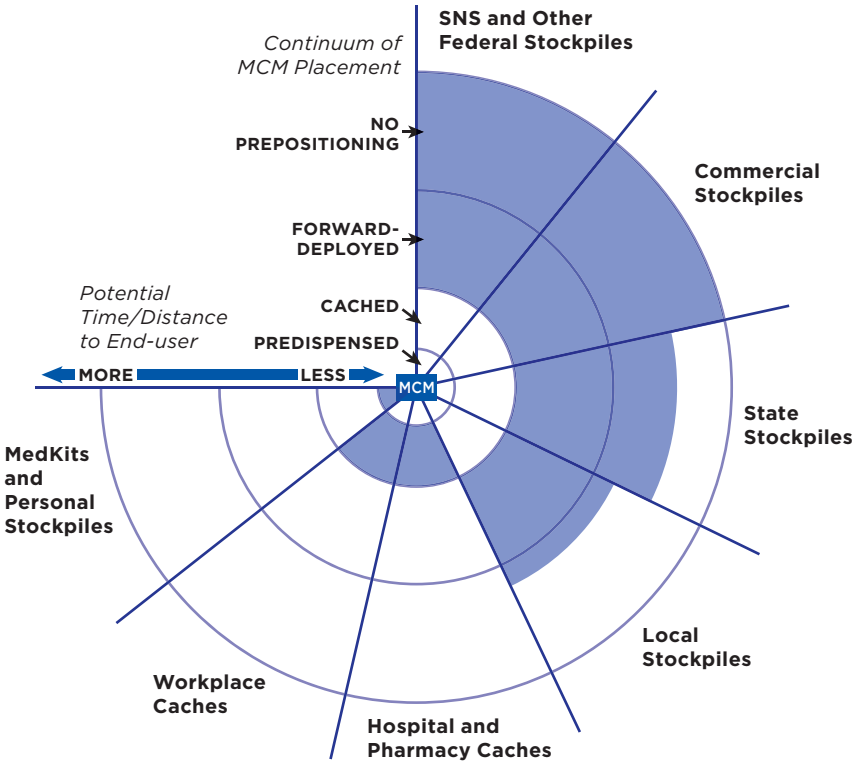

FIGURE 1-1
Strategies for positioning medical countermeasures: Centralized stockpiles distribute medical countermeasures (MCM) to a wider area but may take longer to reach people. Workplace caches and personal stockpiles may allow for more immediate access, but far more MCM are needed.

NOTE: The Strategic National Stockpile (SNS) and other entities may use a mix of placements along this continuum—for example, some forward-deployed stockpiles near areas of high risk combined with some centrally located stockpiles to serve remaining areas.

ings and recommendations presented here will be more closely applicable to other threats in which the characteristics of the threat and the associated MCM are similar to those for anthrax (e.g., another noncontagious disease with a similar time course that is prevented by an MCM that does not require administration by a health care professional). It is important to emphasize, however, that additional analysis will be needed for each threat and associated MCM.

The committee was asked to focus primarily on the response to an attack using a strain of anthrax that is susceptible to the antibiotics currently approved by the Food and Drug Administration (FDA) for anthrax prophylaxis. An attack using a strain of anthrax that is resistant to one or more antibiotics would, however, further challenge all aspects of current dispensing strategies because the majority of stockpiled antibiotics would be ineffective regardless of how early they were administered. In this event, jurisdictions and U.S. Government leaders would need to communicate with the public about alternative treatments, if any, and a massive surge of patients into the health care system would be difficult to avoid. The implications for prepositioning are discussed in more detail in Chapter 2.

Anthrax Vaccine and Anthrax Antitoxin

The committee recognizes two major issues that would significantly affect decisions about prepositioning: widespread use of anthrax vaccine, and the further development and stockpiling of anthrax antitoxin. These issues are briefly discussed here, but because the committee's charge focused specifically on the distribution and dispensing of antibiotics, they were not a primary emphasis of its deliberations.

Widespread pre-event anthrax vaccination could potentially impact the selection and design of strategies for postexposure prophylaxis using antibiotics, including strategies for prepositioning the antibiotics, because it could decrease the size of the population needing postexposure prophylaxis with antibiotics. Currently, the use of anthrax vaccine adsorbed (AVA) is limited. CDC's Advisory Committee on Immunization Practices has said that pre-exposure vaccination for emergency responders is not routinely recommended, but "may be offered on a voluntary basis under the direction of a comprehensive occupational health and safety program" (CDC/ACIP, 2010, p. 20). AVA is commercially available in certain travel clinics (Passport Health, 2010). Vaccination of potentially exposed people is recommended after an attack, in conjunction with a 60-day course of antibiotics (CDC/ACIP, 2010). However, pre-event vaccination is not recommended for the general public, and it is impractical for widespread use because it requires multiple initial doses followed by annual boosters (CDC, 2009c; CDC/ACIP, 2010; Roos, 2011).

The second issue is the development and stockpiling of anthrax antitoxin. Toxins produced by *B. anthracis* bacteria, not the bacteria themselves, cause death (Inglesby et al., 2002). Antibiotics kill the bacteria before they can produce lethal quantities of toxins but are unable to prevent death once the toxins, and the systemic damage they cause, accumulate. Anthrax antitoxin, on the other hand, functionally inhibits one or both of the toxins produced by anthrax, although debate remains as to whether the antitoxin would be as effective when given in a later (fulminant) stage of symptomatic disease, compared with early- or intermediate-stage symptomatic disease (FDA, 2009; Migone et al., 2009). The SNS stockpiles anthrax antitoxin, but not in a quantity sufficient to treat the population that could be exposed in a large anthrax attack, and the drug is not approved by the FDA for the treatment or prophylaxis of anthrax (FDA, 2011; HHS, 2010). In the future, should antitoxin be approved by the FDA and available in sufficient quantities, this MCM could assume a greater role in plans to protect the health of the potentially exposed population. The use of either vaccine or antitoxin also avoids concerns about antibiotic-resistant anthrax, discussed in Chapter 2.

Populations Considered

The committee defined *the public* to be all members of a community who are not already adequately covered by separate specialized programs, such as those for federal mission-essential personnel (Box 1-2). The committee was prompted to make this distinction because Section 4 of the Executive Order on providing MCM, issued in 2009, identifies federal mission-essential personnel as a specialized group whose work ensures the continuity of operations, and it mandates the specific provision of MCM to these individuals (Obama, 2010). State and local first responders and critical infrastructure personnel are not included in the Executive Order, since it focuses on federal mission-essential personnel. In its second information-gathering session (agenda included in Appendix B), the committee heard testimony about DHS's internal plan to stockpile and dispense MCM to its employees around the country (Brinsfield, 2011). This information provided context for the committee's definition of *the public* (Box 1-2). Some communities should take into account that federal mission-essential personnel stationed in their area will not be part of the public MCM dispensing system.

The committee's interpretation of the term *public* in this report includes consideration of entities that are perhaps not perceived as part of *the public*, such as civic entities and corporations. The committee, however, found that it was impossible in practice, and potentially inadvisable, to draw clear lines separating the public from civic entities and corporations. For example,

most plans to dispense MCM to first responders also include sufficient quantities for their families, the latter being considered members of the general public. Similarly, employees of corporations are most likely to be considered members of the public, especially if they are not directly involved in emergency response activities (e.g., employees of large retail stores). Therefore, most plans to dispense MCM via civic entities or corporations would also entail dispensing to "the public" and, moreover, would impact the capacity needed to dispense MCM via more standard public strategies such as open points of dispensing (PODs). A major benefit of dispensing through corporations, for example, is alleviating the burden on public PODs by reaching concentrated populations who would otherwise use these traditional PODs. For this reason, the committee defined the public broadly as "all members of a community who are not already adequately covered by separate specialized programs, such as those for federal mission-essential personnel." This usage recognizes the interrelated nature of all programs to dispense MCM within a community while avoiding interfering with any specialized dispensing programs that a jurisdiction may already have.

Additionally, the committee wishes to highlight the importance of giving specific attention to the needs of children and other vulnerable or at-risk populations, including those who, by virtue of socioeconomic status and/or demographic characteristics, may be at systemically increased risk for lower access to disaster mitigation response. These populations would include, for example, people with low incomes/limited transportation, people with no or limited English proficiency, historically underserved ethnic/racial groups, people with disabilities (especially the vision impaired, hearing impaired, or mobility impaired), people who are homeless, and people who are homebound.

Limitations of the Data

During the course of this study, the committee noted gaps in the available evidence in three particular areas that are critical to its charge. These gaps are introduced briefly here because of their importance to the committee's overall approach to the study; they are discussed in greater detail in subsequent chapters.

First, the committee found that reliable evidence on human inhalational anthrax, particularly on the incubation period and the relationship of dose to that period, is limited and uncertain. Data come from two primary sources: the accidental release in 1979 of *B. anthracis* spores from a military microbiology facility in Sverdlovsk, Union of Soviet Socialist Republics (now Yekaterinburg, Russia), and the anthrax attack in the United States in 2001 (Jernigan et al., 2002; Meselson et al., 1994). The committee's review of the Sverdlovsk data revealed sufficient uncertainties and problems with

data quality to make the data of limited utility. The data and their implications for MCM distribution and dispensing, including prepositioning, are discussed in Chapter 2.

Second, knowledge is insufficient as to the period of time that would likely lapse between the release of anthrax spores and the start of dispensing of MCM. This period includes the time to detection and the time to decision. The former depends on how the attack is detected: environmental detection through a BioWatch sensor, for instance, could take a minimum of 24 hours, while clinical identification of a sick patient could occur days after the release as a result of both the incubation period of the bacteria and the time required for clinical recognition and definitive laboratory testing (Jernigan et al., 2002; Shea, 2003). No data exist to support predictions of the length of time that would lapse prior to the decision to dispense once detection had occurred; this period likely would be somewhat dependent on the U.S. government's and the jurisdiction's level of confidence that the detection was not a false positive.

Third, the committee found a dearth of data, and even sparser publicly available data from realistic exercises, on the performance and implementation of current state, local, and tribal dispensing plans. This lack of data made it difficult for the committee to identify gaps in the current system. In addition, the committee recognizes that tremendous variability exists in state and local dispensing plans and capabilities and in the specific characteristics and needs of communities across the nation.

Development of a Decision-Aiding Framework for State, Local, and Tribal Jurisdictions

Many factors associated with decision making vary significantly across communities, including the risk of attack, capabilities, resources, and current public health infrastructure. Therefore, the committee concluded that it would not be possible, or advisable, for it to prescribe a specific set of prepositioning strategies to complement the traditional POD system. Similarly, it was infeasible to attempt to categorize, identify, or address specific gaps present in individual communities across the nation. Instead, the committee has outlined a decision-aiding framework for jurisdictions to use in assessing their existing capabilities to meet the 48-hour goal for completion of MCM dispensing to the population. This approach is intended to provide state, local, and tribal jurisdictions with the framework and knowledge required to select and develop the most effective prepositioning strategies given their current capabilities and the specific needs of their communities.

In the report, the committee presents a qualitative exploration of the potential effects of each of the key elements of the decision-aiding framework on the incremental effectiveness of prepositioning strategies. The com-

mittee also presents a first-order quantitative model for estimating health benefits associated with different prepositioning strategies, a discussion and case study of the estimation of likely economic costs, and a suggested method for using estimates of health benefits and economic costs to explore trade-offs associated with alternative prepositioning strategies and thereby inform decision making.

Identification of Federal/National-Level Actions

Beyond a decision-aiding framework for individual jurisdictions, the committee's recommendations identify federal/national-level actions that would facilitate the evaluation and development of prepositioning strategies. While all preparedness and response is ultimately local, the federal government has the unique ability to help coordinate regional and national dispensing strategies and provide resources, research, and technical expertise to enhance preparedness. Recognizing that implementation of the actions recommended by the committee should involve partnerships among all levels of government and nongovernmental stakeholders, the committee divides its recommendations into those aimed at the state/local/tribal level and those aimed at the federal/national level to indicate the entity or entities recommended to take the leading role, not the sole actor(s).

ORGANIZATION OF THE REPORT

Chapter 2 provides an overview of the use of antibiotics for post-exposure anthrax prophylaxis, with particular focus on the uncertainties associated with the time window within which antibiotics must be taken to prevent the deadly inhalational form of the disease. Chapter 3 gives an overview of current distribution and dispensing strategies for MCM for anthrax. Chapter 4 presents an overview of the three categories of prepositioning strategies for anthrax antibiotics: forward-deployed MCM, cached MCM, and predispensed MCM. These chapters provide the foundation for Chapter 5, which sets forth a decision-aiding framework to assist federal, state, and local policy makers and public health officials in evaluating the potential benefits and costs of implementing prepositioning strategies to complement existing dispensing strategies and to address specific gaps or overall capacity limitations. This framework encompasses the assessments that jurisdictions should perform to provide the evidence base to inform decision making about prepositioning, the need for ethical principles and public engagement, and a modeling approach that can be used to weigh health benefits and economic costs associated with the alternative prepositioning strategies. Chapter 5 also presents the committee's findings and recommendations on the costs, benefits, and suitability of alternative prepositioning

strategies. Finally, Chapter 6 presents a summary of the recommended actions for moving forward that includes actions at the state, local, and tribal levels and at the federal/national level, as well as areas in which additional research is needed to provide a more solid evidence base to inform decisions about prepositioning strategies.

The report also includes five appendixes: Appendix A is a list of acronyms used in the report; Appendix B contains agendas for the committee's public meetings; Appendix C presents a first-order model developed by the committee to estimate health outcomes for any prepositioning strategy; Appendix D is a paper commissioned for this study containing a cost and speed analysis of prepositioning strategies; and Appendix E provides biosketches of the committee members.

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2

Antibiotics for Anthrax Postexposure Prophylaxis

The symptoms, treatment, and prognosis for a person with anthrax—the disease caused by *Bacillus anthracis*—depend on how the disease was contracted: *gastrointestinal* anthrax is acquired through ingestion of contaminated (undercooked) meat from animals that have ingested naturally occurring spores from the ground; *cutaneous* anthrax requires physical contact with the spores or vegetative bacteria; and *inhalational* anthrax is the result of breathing in bacterial spores (Inglesby et al., 2002). Inhalational anthrax is considered the most severe bioterrorism threat of the three because the spores can travel significant distances through the air while remaining infectious, and it has the highest mortality rate (approaching 100 percent if untreated) (Inglesby et al., 2002).

This chapter reviews the use of antibiotics for postexposure prophylaxis (PEP) for inhalational anthrax, focusing specifically on factors that impact the design of distribution and dispensing plans, including prepositioning. The chapter begins by briefly examining two issues related to *what* is dispensed: first, the antibiotics that have been approved by the Food and Drug Administration (FDA) for prevention of anthrax and second, the threat of an attack using a strain of *B. anthracis* that is resistant to one or more classes of antibiotics. The remainder of the chapter examines two issues related to *when* antibiotics should be dispensed: first, the incubation period of inhalational anthrax (time from exposure to appearance of symptoms) and second, the delay from the time of an attack until the attack is detected and the decision to begin dispensing antibiotics is made.

ANTIBIOTICS APPROVED FOR POSTEXPOSURE PROPHYLAXIS OF INHALATIONAL ANTHRAX

Four antibiotics are FDA-approved for use for PEP following exposure to aerosolized spores of *B. anthracis*: doxycycline, ciprofloxacin, levofloxacin, and parenteral procaine penicillin G.[1] Levofloxacin was approved for PEP for anthrax in 2004 for adults and in 2008 for children (FDA, 2004, 2008a). Controlled human efficacy studies involving anthrax are not possible, so FDA approval of the inhalational anthrax PEP indications was based on animal efficacy studies and the large safety database for these antibiotics in humans (FDA, 2000b, 2002, 2008b, 2009).[2]

For adults ages 18 to 65 who have potentially been exposed to aerosolized spores of *B. anthracis*, the Centers for Disease Control and Prevention (CDC) recommends 60 days of treatment with either ciprofloxacin or doxycycline plus a three-dose series of anthrax vaccine adsorbed (AVA) starting as soon as possible after exposure (CDC, 2010; Stern et al., 2008).[3] CDC recommends that levofloxacin be reserved as a second-line agent, as safety data on its use in treatment for longer than 28 days are limited (Stern et al., 2008). Levofloxacin should be used only when treatment with first-line therapies is hampered by patient drug tolerance issues or antimicrobial resistance patterns (Stern et al., 2008). For children, ciprofloxacin or doxycycline also is used for first-line antimicrobial PEP. Because of the potential for serious adverse events, however, CDC recommends off-label use of amoxicillin as the preferred PEP agent if the anthrax strain is proven to be susceptible to that drug (CDC, 2005, 2010). Additional challenges of administering anthrax PEP to children include limited data on appropriate dosing and palatability of drug formulations. There is currently no recommendation for use of AVA in children; however, its use for those under age 18 is currently being considered (CDC, 2010).[4]

[1]Note that no oral penicillin-class of antibiotic is currently FDA-approved for postexposure prophylaxis (PEP) for anthrax. Current drug information, including PEP dosing for adults and children, is available on the FDA website at http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm063485.htm. For certain patient groups, including children and pregnant women, the Centers for Disease Control and Prevention (CDC) recommends off-label use of amoxicillin if susceptibility testing proves that the anthrax strain is susceptible (CDC, 2005).

[2]See Meyerhoff and Murphy (2002) for a detailed presentation of the antibiotics that were approved by the Food and Drug Administration for anthrax postexposure prophylaxis as of 2001.

[3]See CDC (2010), Table 1, for a summary of the current CDC recommendations for PEP with antimicrobial agents and AVA, available online at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5906a1.htm.

[4]On July 7, 2011, the National Biodefense Science Board (NBSB), at the written request of the Department of Health and Human Services' Assistant Secretary for Preparedness and Response (ASPR), convened an initial meeting to discuss vaccine to protect children from anthrax. The NBSB reported to the ASPR in October 2011. See http://www.phe.gov/Preparedness/Legal/boards/nbsb/recommendations/Documents/avwgrpt1103.pdf.

For security reasons, CDC does not disclose the quantities of the different types of antibiotics that are available from the Strategic National Stockpile (SNS), either through the initial Push Packages or through vendor-managed inventory.

THE THREAT OF ANTIBIOTIC-RESISTANT ANTHRAX[5]

A material threat determination (MTD) was issued by the Secretary of the Department of Homeland Security on September 22, 2006, specifically for multi-drug-resistant (MDR) anthrax (DHS, 2008; GAO, 2009). Multiple papers on the development of *B. anthracis* strains resistant to one or more antibiotics have been published in the open literature (e.g., Athamna et al., 2004; Brouillard et al., 2006; Price et al., 2003; Stepanov et al., 1996). Laboratory generation of antibiotic-resistant anthrax involves relatively straightforward methodology that does not require a high level of microbiologic knowledge. (Key points and additional concerns regarding antibiotic-resistant anthrax are summarized in Box 2-1.)

Polymerase chain reaction (PCR) analysis of tissue samples (meninges, spleen, lymph node) from 11 autopsy-proven inhalational anthrax cases from the 1979 accidental release of anthrax in Sverdlovsk, Russia,[6] revealed at least four strains of *B. anthracis* (Jackson et al., 1998). The existence of multiple strains has been hypothesized to suggest efforts to develop an antibiotic-resistant form of anthrax (Hugh-Jones, 2011).

Given the current focus on doxycycline (a tetracycline-class antibiotic) as a first-line PEP treatment, an explicit analysis of the potential impact of doxycycline-resistant *B. anthracis* is warranted. Postal workers voluntarily participating in a pilot program for the postal model[7] of distribution of medical countermeasures (MCM), for example, were provided with MedKits that contained only doxycycline for storage in their homes. A large-scale attack with doxycycline-resistant anthrax could result in many

[5]Because of cross-resistance of antibiotics within the same class, it is prudent to define drug resistance by antibiotic *class* and not by a single antibiotic within a given class (e.g., *B. anthracis* resistant to ciprofloxacin will likely also be resistant to levofloxacin, another quinolone-class antibiotic) (Athamna et al., 2004). Drugs from three classes of antibiotics are currently approved by the FDA for anthrax PEP: penicillins; fluoroquinolones (e.g., ciprofloxacin, levofloxacin); and tetracyclines (e.g., doxycycline) (FDA, 2011). For the purposes of this report, the committee applied the following definitions of antibiotic-resistant anthrax: *single-drug (class)-resistant B. anthracis (SDR-anthrax)* is resistant to a drug in any one of these three class of antibiotics; *multi-drug (class)-resistant B. anthracis* (MDR-anthrax) is resistant to drugs in any two of these three class of antibiotics; and *extremely drug (class)-resistant B. anthracis (XDR-anthrax)* is resistant to drugs in all three classes of antibiotics. (Note that SDR-, MDR-, and XDR-anthrax may or may not be resistant to other classes of antibiotics that are not currently FDA-approved for anthrax PEP.)

[6]Discussed in more detail below.

[7]The postal model and other MCM dispensing strategies are discussed further in Chapter 3.

BOX 2-1
Antibiotic-Resistant Anthrax

Key Points

- A Material Threat Determination (MTD) was issued by the Secretary of the Department of Homeland Security on September 22, 2006, specifically for multi-drug-resistant (MDR) anthrax.
- The level of microbiologic knowledge needed to create MDR anthrax is not high, and descriptive methodology is available in the open scientific literature.
- While visibility of a response mechanism often functions as a deterrent (e.g., visible military strength), in the case of prepositioning, increased public certainty about the plan could conceivably increase the probability of efforts to circumvent the response (i.e., adversarial development of strains resistant to prepositioned antibiotics).

Additional Concerns

- There may be a loss of public trust if the antibiotic dispensed (whether prepositioned or dispensed via points of dispensing, the U.S. Postal Service, or some other mechanism) is ineffective in preventing anthrax as the result of an attack with a strain resistant to that antibiotic.
- As laboratory testing of antibiotic susceptibility is likely to take more than 2 days, antibiotic distribution and dispensing efforts in response to an anthrax attack would be initiated before the susceptibility profile of the attack strain was known.
- Anthrax vaccine and antitoxin will likely be in even greater demand following an attack with an antibiotic-resistant anthrax strain as compared with a susceptible strain.
- Prioritization of potential response plans for resistant anthrax strains is needed. This includes analysis of all oral antibiotics that were effective against the *B. anthracis* isolate from the 2001 anthrax attack and other antibiotics studied since that time.

more deaths if doxycycline were the primary (or only) antibiotic dispensed pre-event via prepositioning strategies.

Prepositioning is a less *flexible* approach than more centralized dispensing strategies. Inventory flexibility includes the potential for use of multiple drugs, the potential for redeployment of inventories based on need, and the ease with which stockpiles can be rotated. With regard to the threat of antibiotic-resistant anthrax, a distribution and dispensing strategy that enables the dispensing of multiple drugs may be advantageous because it could allow selection of the antibiotic dispensed based on the susceptibility

of the strain.[8] Although it will likely never be possible to have complete coverage against all potential strains using PEP antibiotics—given that specific antibiotics must be manufactured and stockpiled in advance and given the threat of MDR or extremely drug-resistant anthrax—increased flexibility to provide alternative antibiotics or other MCM would provide coverage against a broader range of attacks.

Currently the SNS provides more flexibility than prepositioning strategies would be likely to provide because it contains several antibiotics (some of which are known to be stockpiled in larger quantities and others available through vendor-managed inventory), whereas only one antibiotic would likely be included in most prepositioning strategies. It would be possible, moreover, to purchase and store a greater variety of antibiotics in the centralized SNS stockpiles than is currently the case. Gaining this level of coverage using prepositioning strategies would involve purchasing much larger quantities of these different kinds of antibiotics, and any new antibiotics are likely to be more expensive than doxycycline. In addition, while strategies based on points of dispensing (PODs) would allow the dispensing of additional MCM if the initially dispensed antibiotic were determined not to be effective against the anthrax strain used in an attack, a predispensing strategy would not provide a postattack mechanism for dispensing an alternative MCM. The issue of flexibility is raised here because of its relevance to the threat of antibiotic-resistant anthrax, but it is examined in greater detail in Chapter 5.

Some information about the current U.S. MCM distribution and dispensing system is already readily available online (e.g., that doxycycline is a major component of the SNS and that the FDA has issued an Emergency Use Authorization [EUA] for the use of doxycycline for PEP[9]). However, neither the specific quantities of the various antibiotics nor the types of antibiotics available through vendor-managed inventory are disclosed. Furthermore, it would theoretically be possible to avoid disclosure of the future contents of the SNS and state and local stockpiles (e.g., by increasing the number of public health officials with security clearances and/or by further using secured websites rather than public pages for formulary information). In contrast, prepositioning strategies—and predispensing in the home in particular—involve a higher level of public messaging and storage by a large number of people without security clearances. The result could be a much

[8]As laboratory testing of antibiotic susceptibility is likely to take more than 2 days, antibiotic distribution and dispensing efforts in response to an anthrax attack would be initiated before the susceptibility profile of the attack strain was known. If the strain were ultimately determined not to be susceptible to the antibiotic dispensed, an alternative MCM would have to be dispensed, provided one was available in the quantities needed.

[9]Discussed in Chapter 3.

greater degree of certainty about the planned response, potentially signaling an adversary to engineer a specific type of antibiotic-resistant anthrax.

Finding 2-1: *Prepositioning of a single type of antibiotic (or class of antibiotics) would reduce flexibility to respond to the release of an antibiotic-resistant strain of anthrax, a biothreat recognized by the U.S. Department of Homeland Security. Furthermore, although some information about planned responses is already available in the public domain, prepositioning antibiotics in the home would provide a greater degree of certainty about the planned response and, therefore, could conceivably increase the probability of release of a resistant strain of anthrax.*

INCUBATION PERIOD OF INHALATIONAL ANTHRAX: EXISTING DATA AND AREAS OF UNCERTAINTY

Data on human exposure to aerosolized *B. anthracis* are limited, and there is a great deal of uncertainty regarding the incubation period (time from exposure to appearance of symptoms). A clear understanding of the incubation period is critical for decision making about MCM distribution and dispensing strategies, including prepositioning.

An exposed population will exhibit a range of times from exposure to the appearance of symptoms for the exact same exposure/dose, and the shape of the distribution curve is important for decision making about prophylaxis strategies. If, for example, there is a wide range of incubation times, then even after the development of a small number of clinically recognized anthrax cases, sufficient time may exist to distribute and dispense antibiotics to a large fraction of still-asymptomatic persons, thereby protecting this fraction of the exposed population. On the other hand, if the distribution of incubation times is relatively narrow, much less time may be available in which to distribute and dispense antibiotics to the exposed population after initial identification of clinical cases. Beyond the shape of the distribution curve, the shortest incubation time that would be expected in an exposed population (i.e., the time at which the first person[s] would begin exhibiting symptoms) also is important for public health decision making about prepositioning. For ease of reference, this time is referred to as the *minimum incubation period* throughout the report. The minimum incubation period for inhalational anthrax is often stated to be 1 to 2 days; however, a review of the available data suggests that it is likely to be longer. A longer minimum incubation period, such as 4 days, would permit more time for the delivery of MCM before the onset of symptoms, and thus would have a direct impact on decisions regarding the need for prepositioning.

The committee examined the current knowledge base on the incubation period for inhalational anthrax, including data from several historical

human exposure incidents, from animal studies, and from incubation and dose-response theoretical modeling.[10] This review was informed by a search of the literature and by discussions with invited experts at open sessions during committee meetings.[11] As noted in Chapter 1, the committee did not review any classified information.

United States 1900-2000: Occupational and Environmental Exposures

Eighteen cases of inhalational anthrax were reported in the United States in the 20th century, the most recent (prior to 2001) occurring in 1976 (Brachman, 1980; Jernigan et al., 2001). In most cases, an unequivocal single-point-in-time exposure was not reported. Many of these cases were associated with chronic exposures (e.g., the five-person outbreak at a goat-hair processing mill in Manchester, New Hampshire, in 1957 [Plotkin et al., 1960]). One case reviewed by Brachman was that of a 46-year-old man who presented with symptoms 6 days after his last possible exposure to spores (the man had recently been employed at a metal shop adjacent to a goat-hair processing mill before the shop closed for a 2-week summer break). Brachman notes that "the projected incubation period of six days resembled those of previous cases" (Brachman, 1980, p. 90).

United States 2001: Intentional Attacks by U.S. Mail

In the fall of 2001, 11 people on the East Coast contracted inhalational anthrax, the source of which was determined to be anthrax-laced letters and packages sent through the U.S. mail (additional individuals contracted cutaneous anthrax). Nine of the 11 patients experienced an incubation period of 4 to 8 days, or possibly longer (Cole, 2003; Jernigan et al., 2001; see Table 2-1).[12] For 2 of the 11 patients (in New York and Connecticut), the exposure is presumed to have occurred via cross-contaminated letters, and the date of exposure is unknown.

[10]The often-cited systematic review of 82 inhalational anthrax cases from 1900 to 2005 by Holty and colleagues (2006) does not mention the incubation period for any of those cases. Moreover, this review "excluded 74 cases from the Sverdlovsk outbreak because symptoms, treatment, and disease progression variables were not reported" (p. 272).

[11]A list of invited speakers/presentations is provided in Appendix B.

[12]An account of the 2001 attacks was published by Jeanne Guillemin at the same time as the release of the prepublication copy of this IOM report (Guillemin, 2011). She relies on a September 25 scenario for the opening of an anthrax letter in Florida and therefore for the exposure of the two Florida victims (referenced in Table 2-1). She also identifies September 30 and September 28 as the dates of onset of symptoms of the two Florida victims. Traeger et al. (2002) identifies September 19 and 25 as the potential dates of exposure for the Florida victims and September 30 and 28 as the dates of onset of symptoms.

TABLE 2-1
Known and Estimated Inhalational Anthrax Incubation Periods Following the 2001 Anthrax Attacks

Patient Location	Individuals Infected	Incubation Period (days)	Date of Exposure	Onset of Symptoms
Washington, DC	4	4[a]	Oct. 12	Oct. 16
New Jersey	1	5[a]	Oct. 9	Oct. 14
New Jersey	1	6[a]	Oct. 9	Oct. 15
Florida	1	8–10[b]	Sept. 19	Sept. 27 or 29
Florida	1	9[c]	Sept. 19	Sept. 28
Virginia	1	5–10[d]	Oct. 12–17	Oct. 22

[a] Brentwood (DC) and Hamilton (New Jersey) postal facility workers with known exposure dates.

[b] Individual presented on October 2 with anthrax meningitis. Investigators assume exposure occurred via a letter containing a white powder he was witnessed examining at his desk on September 19.

[c] Estimated. The letter handler was admitted to a hospital on October 1, and likely infected by the same letter as the other Florida patient on September 19.

[d] Estimated. A State Department postal worker was exposed to an unopened letter to Senator Leahy that passed through the Brentwood and State Department postal facilities.

SOURCES: Cole, 2003; Jernigan et al., 2001.

United States 2006, Scotland 2006, England 2008, and United States 2011: Exposure to Animal Hides and Unknown Source of Exposure

Three recent cases were identified in which the likely source of exposure to aerosolized anthrax spores was determined to be imported African animal hide drums (Anaraki et al., 2008; CDC, 2006b; Norris, 2009; Walsh et al., 2007). None of the three individuals infected had a clear-cut incubation period that could be calculated definitively.

One additional case of inhalational anthrax was identified in Minnesota shortly before the release of this report (Minnesota Department of Health, 2011a). This case is considered to be naturally occurring inhalational anthrax, and exposure is believed to have occurred during travel in areas where anthrax is found in the soil and has been known to cause infections in animals (Minnesota Department of Health, 2011b). The exact time, location, and source of this patient's exposure remain unknown, and thus an incubation period has not been determined.

Sverdlovsk, Russia 1979: Accidental Release

Much of what is assumed about the incubation period of inhalational anthrax is based on data from what is believed to have been an accidental aerosolized release of anthrax spores from a military research facility in Sverdlovsk, Russia, in 1979. Considerable controversy persists around the exact nature and date of the release. The issue of the date of the exposure is worth examining as it pertains directly to the question of the duration of the incubation period for affected patients.

Initially, the official Soviet explanation of the incident, supported by a published epidemiological analysis, was that it had been an outbreak of gastrointestinal anthrax due to meat contaminated with *B. anthracis* (Bezdenezhnykh and Nikiforov, 1980; Meselson, 1988). Subsequent statements (in the 1990s) by Russian officials and others support an accidental aerosolized release of spores from the military research facility as the probable cause (Meselson et al., 1994; Walker et al., 1994). Analysis by international investigators was hampered significantly by the confiscation of clinical, laboratory, and epidemiological data by the KGB (Russian national security agency) following the incident. To this day, it remains impossible to verify precise and comprehensive specific clinical and epidemiological data, including incubation periods, for many of the individuals suspected to have contracted inhalational anthrax. Most of the analyses that have been published have pieced together data from a variety of sources (e.g., the Abramova, Meselson, and Brookmeyer publications discussed below). To make the present study as comprehensive as possible, a committee member spoke with members of the U.S. team that traveled to Sverdlovsk in June 1992 to investigate the 1979 incident.[13]

Patient Exposure

Compelling evidence supports Monday, April 2, as a date of an aerosolized spore release in Sverdlovsk, including plume modeling consistent with the wind direction recorded at nearby locations on that date, and the infection of five military reservists who were only present in the area on but not before that date (Guillemin, 1999; Meselson et al., 1994). Various times have been proposed for spore release on Monday, April 2, including afternoon (1:30-4:00 PM [Guillemin, 1999; Meselson et al., 1994]) and

[13]A member of the IOM committee contacted each of the members of the U.S. team that went to Sverdlovsk in 1992—by phone, in person, and/or by email communication—to discuss the 1979 Sverdlovsk incident. Note that the committee's conclusions throughout this report are drawn from the totality of the evidence. The conclusions of the committee do not necessarily reflect the views of any of the five members of the U.S. team.

early morning (6:15-7:45 AM[14] [FDA, 2000a]; 6:00-8:00 AM [Mangold and Goldberg, 1999]). However, Friday evening on March 30 has also been proposed as a date of spore release, based on information provided to Ken Alibek, a former Soviet biological warfare expert, by one of his colleagues (Alibek and Handelman, 1999). In addition, there is no known evidence to exclude the possibility of multiple releases or a prolonged multiday release that encompassed April 2. As noted above, there are great uncertainties surrounding this incident.

The committee reviewed three key analyses of inhalational anthrax patients in Sverdlovsk. Microbiology and histopathology are viewed as the diagnostic gold standard for inhalational anthrax in this outbreak. The two pathologists who performed the autopsies in 1979—Faina Abramova and Lev Grinberg—published a report with the U.S. pathologist David Walker on 41 confirmed cases, 30 of which have known dates of onset of symptoms (Abramova et al., 1993). The data show a range of onset of symptoms from 5 to 40 days after the putative release date of April 2, 1979, with a mean incubation period of 16 days (Walker, 2000). Thus, if the anthrax spore release was a single event that occurred on April 2, then the shortest incubation period for any of the 41 autopsy-proven cases was 5 days; if the release date was March 30, then the incubation period may have been as long as 8 days for this patient. Importantly, in its analysis of previous anthrax incidents, the committee required either microbiologic or histopathologic confirmation of infection with *B. anthracis* when determining the minimum incubation period of patients with inhalational anthrax.

Using a variety of sources, Meselson and colleagues (1994) assembled data on a set of 77 patients with presumed or confirmed inhalational anthrax, including 66 fatalities. These fatalities include 41 of the 42 autopsied patients described by Abramova and colleagues (Abramova and Grinberg, 1993; Abramova et al., 1993),[15] which are, to the committee's knowledge, the only cases confirmed by microbiology or histopathology in the paper by Meselson and colleagues (1994). Of the 60 patients with known date of symptom onset, 58 had a reported incubation period of 4 to 43 days, using April 2 as the incident date. For one patient, onset of symptoms is given as 3 days, and for the other remaining patient, onset

[14]FDA (2000a), augmented by personal communication by Martin Hugh-Jones in April and June 2011.

[15]Later analysis of autopsy material showed that one case was not inhalational anthrax; that case was omitted in Meselson et al. (1994) and Guillemin (1999).

of symptoms is given as 2 days.[16] Of note, no autopsy histopathology or microbiologic evidence of anthrax infection was reported for either of these patients, and both had an atypically long time interval from reported onset of symptoms until death (6 and 7 days, respectively, compared with the 3 days noted by Meselson et al., [1994] as the typical time interval between onset and death).

Brookmeyer and colleagues (2001) present a statistical analysis of the outbreak, using April 2 as the exposure date and taking into account "truncated data" in which the disease course of at least some exposed persons was potentially impacted by public health interventions, such as a short course (about 5 days or possibly longer) of PEP with tetracycline and a live-spore anthrax vaccine. The analysis included 70 cases, all fatal (including the 41 autopsy-confirmed patients described by Abramova and colleagues [1993]). The 29 patients who were not autopsied were presumed to have inhalational anthrax, although microbiologic or other confirmation was lacking (data for these analyses were provided by coauthor Hugh-Jones). Brookmeyer and colleagues (2001) reported median and mean incubation periods of 11.0 and 14.2 days, respectively. Sixty-seven of the 70 fatalities were reported to have an incubation period of 4-40 days. Three of the 70 were reported to have an incubation period of 2-3 days, but again, there was no autopsy or microbiologic confirmation of the diagnosis of anthrax for these patients.

Despite the uncertainties and the challenges of obtaining data, there are valuable lessons to be learned from the Sverdlovsk incident. Examples are the apparent rapid progression to death after symptom onset without effective treatment, the existence of a wide range of incubation periods, and the consistent finding of large volumes of pleural fluid that contributed to respiratory failure and death (Walker, 2000).

Potential Impact of Anthrax Dose on the Incubation Period in Humans

In addition to host factors, the incubation period for inhalational anthrax is impacted by the quantity of spores to which individuals are exposed (Brookmeyer et al., 2001; Inglesby et al., 2002). Estimates of the anthrax dose released in the 1979 Sverdlovsk aerosolization vary widely:

[16]One patient is listed in Meselson et al. (1994) as having symptom onset on April 5; however, this date was changed to April 4 in a book by Guillemin (1999) based on interviews of surviving family members in 1992.

- a few milligrams to less than a gram (Meselson, 2001; Meselson et al., 1994),
- 500 grams (Martin Hugh-Jones cited in FDA, 2000a),
- "pounds" of anthrax (William Patrick III cited in Miller et al., 2001), and
- "as much as 22 pounds (10 kg)" (DIA, 1986, p. 4).

Assumptions about the incubation period have been made presuming a low-dose exposure at Sverdlovsk—in accordance with the estimates of Meselson and colleagues (1994)—including the assumption that the incubation period would be shorter if the dose were higher.

In theory, the incubation period and/or lethality of aerosolized spores could also be impacted by qualitative aspects of the spores released. For example, small particle aerosols of spores (1-5 microns) are more likely than larger particle aerosols to reach the lower respiratory tract (Thomas et al., 2010). Chemical substances added to the spores may increase their ability to remain aloft and travel farther (animals as far as 50 km downwind from the Sverdlovsk release site reportedly developed anthrax) (Meselson et al., 1994). Alibek and Handelman (1999) state that the highly virulent anthrax strain 836 was used in the former Soviet Union, including at Sverdlovsk in 1979, and that the anthrax released contained chemical additives.

Theoretical Modeling of the Incubation Period for Human Inhalational Anthrax

As discussed above, some of the data on the incubation period for inhalational anthrax considered by the committee were based on statistical analyses. The committee heard multiple presentations from both committee members and invited experts regarding theoretical modeling of the incubation period of anthrax in humans.[17] Key points are summarized in Box 2-2.

The review by Hupert and colleagues (2009), summarized in Box 2-2, highlights that the estimate of a 2-day incubation period, commonly used in planning documents and the shortest among the various anthrax models, derives in part from data for military planners by Rickmeier and colleagues (2001) that were used later in the model by Baccam and Boechler (2007). The Rickmeier et al. model derives in part from dose-response studies involving Seventh Day Adventist volunteers and using infectious diseases other than anthrax, such as Q-fever and tularemia. Such dose-response studies in humans using anthrax were never performed because of the unacceptable risk of severe disease or death.

[17]A list of invited speakers/presentations is provided in Appendix B.

BOX 2-2
Notes on Theoretical Modeling of the Incubation Period for Human Inhalational Anthrax

- Modeling of the incubation period for human inhalational anthrax has been based primarily on data from the Sverdlovsk release (Hupert et al., 2009).
- Some of the models presume that a low dose of anthrax spores (a few milligrams to almost a gram) was released in Sverdlovsk (Meselson et al., 1994). This assumption has significant implications for when antibiotics should be started and how long prophylaxis should last if a "high-dose" release were to occur (e.g., modeling by Brookmeyer et al. [2003] predicts the need for PEP for at least 4 months following a high-dose exposure).
- Hupert and colleagues (2009) state that the 2001 Brookmeyer analysis "fit the timing of hospitalization of 70 cases of inhalational anthrax to a lognormal distribution . . . [and this] Brookmeyer curve forms the basis for other AMWG [Anthrax Modeling Working Group] models" (Hupert et al., 2009, p. 426).
- In the statistical analysis of Brookmeyer and colleagues (2001), 16 of 70 fatal cases included did not have a known incubation period; instead, the end of the incubation period for these 16 patients was estimated by subtracting 3 days from the date of death. This paper was published prior to the 2001 U.S. anthrax attack and was not designed to address antibiotic prepositioning issues.
- Using a "discrete-time state transition model" (p. 425), Hupert and colleagues (2009) conclude that: "A CRI [Cities Readiness Initiative]-compliant prophylaxis campaign starting 2 days after exposure would protect *from 86% to 87%* of exposed individuals from illness. . . . Each additional day needed to complete the campaign would result in, on average, 2.4% to 2.9% more hospitalizations in the exposed population; each additional day's delay to initiating prophylaxis beyond 2 days would result in 5.2% to 6.5% additional hospitalizations" (Hupert et al., 2009, p. 424).
- Hupert and colleagues (2009) summarize anthrax modeling approaches and assumptions of eight key modeling papers published from 2005 through 2008, including those of Baccam and Boechler, 2007; Braithwaite et al., 2006; Brookmeyer and Blades, 2002; Brookmeyer et al., 2003, 2004, 2005; Fowler et al., 2005; Hupert et al., 2009, p. 427, Table 1; Wein and Craft, 2005; Wein et al., 2003; Wilkening, 2008; and Zaric et al., 2008. The shortest incubation period is that used by Baccam and Boechler (2007) at "2.3 to 12.7 days (dose dependent)" (Hupert et al., 2009, p. 427). Baccam and Boechler cite Rickmeier et al. (2001) as the source of the data used for the model (Baccam and Boechler, 2007, p. 27). In the absence

continued

BOX 2-2 Continued

of human studies of anthrax, Rickmeier et al. reason by analogy using data from human studies of tularemia and Q-fever. This methodology may have contributed to the shorter incubation period reported as compared with the other seven studies summarized.

- Wilkening (2006, 2008) assesses the accuracy of four models of inhalational anthrax dose-response and incubation period distribution using the Sverdlovsk data. He concludes that:
  - "Dose-response functions that exhibit a threshold for infectivity are contraindicated by the Sverdlovsk data" (Wilkening, 2006, p. 7589).
  - Two models are consistent with the Sverdlovsk data. One model "predicts that 50% of the victims received less than approximately two spores"; the other model "predicts that 50% of the victims received </≈ 360 spores" (Wilkening, 2006, p. 7591).
  - "The victims at Sverdlovsk either received on the order of 1-10 spores . . . or between 100-2,000 spores . . . , which is in good agreement with Meselson's estimates" (Wilkening, 2006, p. 7591).
- In sharp contrast to the above conclusions by Wilkening, Coleman and colleagues (2008) reexamine the idea that a dose-response threshold does not exist, arguing that: "The present lack of clarity regarding what is scientific fact and what is more speculative opinion about *B. anthracis* dose-response relationships has promoted the misunderstanding that a single *B. anthracis* spore is fatal" (Coleman et al., 2008, p. 148).

Animal Models of Inhalational Anthrax

While animal models have provided much of the data on anthrax disease pathology, no one such model exactly simulates the human experience (Goossens, 2009). The two animal species currently considered most acceptable for anthrax studies from a regulatory point of view under the FDA's "animal rule"[18] are nonhuman primates and rabbits (FDA, 2010).

While useful for studying various aspects of anthrax (e.g., characteristics of the organism, pathogenesis of disease, impact of interventions),

[18]The "animal rule" (21 Code of Federal Regulations [CFR] 314.600 for drugs; 21 CFR 601.90 for biological products) provides for FDA approval of certain new drugs and biologics based on animal data when efficacy studies in humans cannot ethically be conducted and field trials are not feasible. See *Guidance for Industry, Animal Models—Essential Elements to Address Efficacy under the Animal Rule* (Draft Guidance), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078923.pdf.

animal models of inhalational anthrax have not been designed to determine the minimum incubation period, the distribution of incubation times in humans, or the relationship between dose and incubation period in a precise, well-controlled manner. In addition, the majority of experiments in animals are designed to maximize the efficacy of the study through ensured infection, not to determine the incubation period (e.g., Vasconcelos et al., 2003). Most importantly, the time frame from exposure to illness and death is shorter in animal models of anthrax than in humans.

In a presentation to an FDA Advisory Committee regarding animal models and anthrax, Arthur Friedlander stated that mean survival for rabbits is 2.4 days *postexposure* and for rhesus monkeys is 4.8 days *postexposure* (Friedlander, 2000). In contrast, he stated that mean survival for humans is 4.7 days *post-onset of symptoms* (not postexposure). In other words, the time from exposure to death in rhesus monkeys is similar to the time from onset of symptoms to death in humans, consistent with the view that the incubation period is longer in humans than in these commonly employed animal models.

In the landmark study by Friedlander and colleagues (1993) on PEP antibiotics to prevent inhalational anthrax, 9 of the 10 control rhesus monkeys (nonhuman primates) exposed to inhaled anthrax spores died within 3 to 8 days postexposure. (This study, urgently undertaken because of military events in the Persian Gulf in 1990-1991, provided the foundation for PEP with antibiotics in humans following the anthrax attack in 2001.) In a dose-response study of survival in rabbits, Friedlander and colleagues report that the mean survival time of the rabbits was 2.4 days postexposure and that "although there was a trend for a decreased survival time with increasing dose, the effect was minimal" (Zaucha et al., 1998, p. 984).

In summary, studies in animals (such as those by Weiss and colleagues [2011] in guinea pigs and rabbits) confirm the importance of PEP in preventing fatal disease and may inform the development of PEP strategies in humans. Given the differences in incubation period between animals and humans, however, it is not appropriate to extrapolate an exact hour-to-hour correspondence from animal models to humans (e.g., for when to initiate PEP with antibiotics in humans). Studies using nonhuman primates could be designed to explore the distribution of incubation periods across a range of plausible exposures and to determine to what degree exposure influences the incubation period. These studies might better inform strategies for PEP than the existing modeling data.

Impact of the Anthrax Incubation Period on PEP Strategies

Antibiotics are not active against the spore form of *B. anthracis*; however, when the spore germinates into the vegetative form of the bacteria, the antibi-

otic kills the bacteria and prevents the onset of symptoms (Friedlander et al., 1993; Inglesby et al., 2002). Treatment with a single antibiotic begun while an individual exposed to aerosolized anthrax is still in the incubation period can prevent symptoms from occurring (Friedlander et al., 1993). If a person is no longer in the incubation period and thus is symptomatic from anthrax, two or more antibiotics are recommended as therapy (given intravenously at the beginning of treatment) (Inglesby et al., 2002; Meyerhoff and Murphy, 2002).

No human or animal data exist to support the notion that starting antibiotic treatment earlier in the incubation period is necessary to prevent symptomatic anthrax disease from occurring. In contrast, therapy for a person who is symptomatic from inhalational anthrax is more likely to be successful if given in the early-prodromal or intermediate-progressive stage of disease rather than in the late-fulminant stage (Holty et al., 2006; Lucey, 2005, 2007).

The effectiveness of antibiotics begun later in the incubation period is supported by some data from the 2001 anthrax attack, although notably not from a prospective, controlled experiment:

- *Brentwood postal facility in Washington, DC*[19]—More than 2,000 postal workers were potentially exposed to spores reportedly aerosolized from the letter-sorting machine after two letters passed through the facility on Friday morning, October 12, until the facility was closed on Sunday morning, October 21 (Dewan et al., 2002). Although four Brentwood workers had already developed inhalational anthrax with symptom onset on October 16, no PEP antibiotics were given to the other 2,000+ postal workers during the 9 days from October 12 to 21 because the risk was not recognized (Dewan et al., 2002). Despite the delayed initiation of PEP, however, no additional cases of inhalational anthrax were known to have occurred.
- *Hamilton, New Jersey, postal facility*—The same two anthrax letters addressed to U.S. senators passed through Hamilton after being postmarked October 9. Two postal workers experienced onset of symptomatic inhalational anthrax on October 14 and 15, and the facility was closed on October 18. More than 1,000 postal workers were offered PEP antibiotics beginning on October 20, 11 days after the spores had been released in the facility, and none developed inhalational anthrax (Greene et al., 2002).

[19]When it reopened in 2003, the Brentwood mail processing facility was renamed the Joseph Curseen, Jr., and Thomas Morris, Jr., Processing and Distribution Center, in honor of the two postal employees who worked there and died of inhalational anthrax in October 2001.

- *American Media Inc. (AMI) Building, Boca Raton, Florida*—Suspicious letters were opened on September 19 and 25. Two cases of inhalational anthrax occurred with onset in late September. PEP antibiotics were not offered to the 1,114 "workplace-exposed" persons until October 8 (13-19 days after the potential exposure); however, no further cases of inhalational anthrax occurred (Traeger et al., 2002).

Environmental sampling showed that anthrax spores had been widely dispersed in each of these large buildings. Brookmeyer and Blades (2002) estimated that in these three locations, "sensitivity analyses to a range of incubation distributions all indicated that fewer than 50 cases were prevented by AP [antibiotic prophylaxis]" (Brookmeyer and Blades, 2002, p. 1861). Importantly, however, the analysis did not include potential cases prevented by antibiotic prophylaxis on Capitol Hill.

Using a highly sensitive anthrax antibody test, CDC found that "a mild form of inhalational anthrax did not occur, and that surveillance for moderate or severe illness was adequate to identify all inhalational anthrax cases resulting from the Washington, DC, bioterrorism-related anthrax exposures" (Baggett et al., 2005, p. 991). In other words, it is unlikely that there were exposed individuals with unrecognized infection. Those who presented with mild, anthrax-like symptoms, who subsequently did not progress clinically and for whom blood cultures and immunohistochemistry were negative for anthrax, were in fact not infected, at least according to this CDC study.

IMPACT OF TIME TO DETECTION ON DISPENSING OF PEP ANTIBIOTICS

The time from exposure to prophylaxis encompasses three stages: time to detect the anthrax attack, time to decide to dispense antibiotics, and time to distribute and dispense initial doses to the potentially exposed population. To ensure that potentially exposed people receive antibiotics during the time window in which the antibiotics effectively prevent the appearance of anthrax symptoms, the total time for these three stages should be less than the minimum incubation period (approximately 4 days, as discussed above). As the time for detection and decision increases, the time available for distribution and dispensing decreases, and vice versa. Thus, estimates of the time to detection and time to decision impact public health decisions about the need to adopt prepositioning strategies and, more generally, decisions about an operational goal for dispensing the initial doses of antibiotics.

Mechanisms of Detection of an Aerosolized Anthrax Attack

An aerosolized bioterrorism agent, such as anthrax, may initially be detected by environmental monitoring (e.g., BioWatch sensors, discussed below) or by the identification of one or more symptomatic or fatal human infections (e.g., by syndromic surveillance, by clinical or laboratory diagnosis, or upon autopsy) (IOM, 2011). The relative timeline of these activities is shown in Figure 2-1; however, the actual timing is variable—from days to weeks depending on the nature of the event and the functionality of the systems. CDC's Cities Readiness Initiative (see Chapter 3) has set a goal for state and local health departments to have systems in place to complete dispensing of the initial course of PEP antibiotic(s) within 48 hours of the decision to dispense. The potential mechanisms for detection are briefly described here; a more complete review is presented in IOM (2011).

BioWatch Environmental Sensor Detection

Detection of a biological threat agent via the Department of Homeland Security's BioWatch air sampling and monitoring system is estimated to take 10 to 34 hours from exposure to discovery (Figure 2-2) (IOM, 2011). Filter units are collected daily; thus, a filter could be collected from 0 to 24

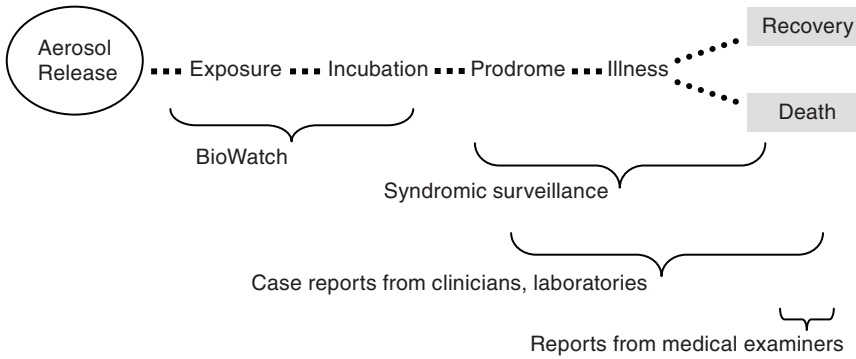

FIGURE 2-1
Schematic illustration of the temporal relation among potential mechanisms for detecting an aerosolized biological threat. The brackets span the interval over which a particular mechanism would have the potential to detect the presence of a pathogen (e.g., via BioWatch) or illness or death caused by the pathogen. This illustration represents the initial detection of a bioterrorism event. The timeline for detection of subsequent events that are part of the same attack may be compressed because an initial detection is likely to increase attention to the potential threat.

SOURCE: IOM, 2011, p. 34. Originally adapted from Sosin, 2008.

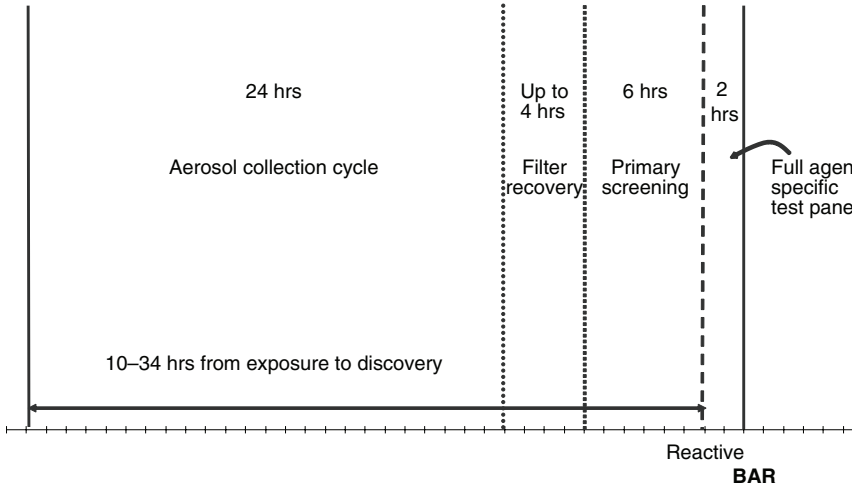

FIGURE 2-2
Event-to-detection timeline for BioWatch Generations 1 and 2. Filter recovery and transport can take up to 4 hours, and primary laboratory screening takes about 6 hours. If the primary screening indicates a positive result, confirmatory testing requires an additional 2 hours.

SOURCE: IOM , 2011, p. 54. Originally adapted from Runge, 2008.

hours after release of a biological agent. Following collection, it may take up to 10 hours for initial testing to be completed (up to 4 hours for filter recovery from the unit, 6 hours for primary screening, and 2 hours for full agent-specific testing). A BioWatch Actionable Result (BAR) is declared if the filter tests positive for genetic material from a targeted biological agent. BioWatch covers only certain metropolitan statistical areas (MSAs); for security reasons, these locations are not disclosed.

A BAR signifies simply that genetic material has been detected on a Biowatch filter, not necessarily that a bioterrorism attack has occurred or that people have been exposed to viable organisms. Factors that might immediately be considered include, for example, the number and locations of the BioWatch filters testing positive, intelligence and law enforcement information, evidence of human or animal illnesses consistent with the biological agent detected, and additional environmental testing apart from the BioWatch filters. Thus, it is difficult to predict in advance of a specific event the time period that would be required before the decision to dispense PEP antibiotics could be made by government officials. In the future, detection time could be considerably reduced (to a total of 4 to 6 hours from the current 10 to 34 hours) if "Generation 3" BioWatch sensors, equipped

to conduct automated assays for pathogens, should prove accurate (Garza, 2011).

Note that because anthrax is spread environmentally as spores, the rather singular potential exists to determine viability by laboratory culture of spores retrieved from BioWatch filters. If spores are viable and if a pure culture of the organism can be established, antibiotic susceptibility profiles can be determined. (As noted above, however, the decision to respond to the BioWatch signal will likely have been made long before the antibiotic susceptibility profile is available.)

Detection by Case Reports from Clinicians or Laboratories

As described above, symptoms of inhalational anthrax emerge 4 to 8 days or more after exposure. Therefore, detection of an anthrax attack by clinical diagnosis or laboratory report of inhalational anthrax would come many days following an attack. However, the incubation period of cutaneous anthrax (exposure via skin) is significantly shorter, approximately 1-3 days (CDC, 2002, 2006a; Freedman et al., 2002; Jernigan et al., 2002). The 1979 Sverdlovsk release and the 2001 anthrax attack caused both inhalational and cutaneous forms of the disease (Jernigan et al., 2002, Meselson et al., 1994). This probably would be replicated in any attack using aerosolized anthrax spores. Therefore, detection of an attack based on cases of cutaneous anthrax could occur days before detection based on cases of inhalational anthrax. The typical skin lesions caused by cutaneous anthrax in the initial 1 to 2 days could be caused by a number of different diseases; therefore, in small numbers, they might not be diagnosed immediately as anthrax. In the case of a large-scale attack, however, patients with these lesions might appear in large numbers in emergency departments, raising suspicions and making appropriate diagnosis and detection more likely. Detection of an attack by diagnosis of cutaneous anthrax could enable public health authorities to begin efforts to dispense antibiotics to prevent the more deadly form of the disease and to begin testing the strain for susceptibility to antibiotics.

The committee did not review in great detail the processes and timing related to making the decision to begin dispensing antibiotics, which fell outside the scope of its charge. Nevertheless, this is an important issue for MCM planning because delays in decision making due to uncertainty related to the detection mechanisms, political considerations, issues associated with the interaction among multiple levels of government or multiple agencies, or other factors could delay the initiation of dispensing and therefore result in fewer exposed people receiving prophylaxis prior to the onset of symptoms. Improvements in detection capability (either through technological enhancements or through additional clinical familiarity and

training) and in decision-making processes would allow more time for distribution and dispensing and, ultimately, shorten the time from exposure to prophylaxis.

Finding 2-2: *Review of the limited available data on human inhalational anthrax shows that people exposed to aerosolized anthrax have incubation periods of 4 to 8 days or longer. Much of the modeling used to derive shorter estimates is based on data from the Sverdlovsk incident, and the assumptions made potentially lead to an underestimate of the minimum incubation period.*

With the most probable minimum incubation period being approximately 4 days (or 96 hours), there is no compelling evidence to suggest that jurisdictions must plan to complete dispensing of initial prophylaxis more rapidly than 96 hours following the time of the attack, although incremental improvements appear to be achievable and could provide additional protection against unforeseen delays.

Therefore, the current operational goal of the Centers for Disease Control and Prevention's Cities Readiness Initiative of completing dispensing of initial prophylaxis within 48 hours of the decision to dispense appears to be appropriate, as long as the ***total*** *time from exposure to prophylaxis does not exceed 96 hours. Achieving this goal depends on robust detection and surveillance systems that can rapidly detect an anthrax attack, rapid decision making, and effective distribution and dispensing systems. If detection or decision making is delayed, faster distribution and dispensing may be needed to minimize symptomatic disease in the exposed population.*

SUMMARY

To be maximally effective in preventing morbidity and mortality, PEP for inhalational anthrax should be administered during the incubation period (before the onset of symptoms). There is, however, great uncertainty around the minimum incubation period for inhalational anthrax. Precise, confirmed data from human infection from the Sverdlovsk incident are incomplete, and data from animal models are of limited relevance as animals exhibit symptoms and succumb to the disease more rapidly than do humans. Many assumptions regarding minimum incubation time in humans are based on modeling. Most anthrax modeling has used data from the Sverdlovsk aerosolized anthrax release and presumes a low-dose exposure. Yet little is known about the details of that release (including the true size of the dose), and the actual date(s) of exposure remain unconfirmed. Most of the available data and modeling suggest that the minimum incubation period for inhalational anthrax in humans is longer than the often-cited 1 to 2 days. Individuals exposed during the 2001 anthrax attack in the

United States had actual or estimated incubation periods of 4 to 10 days, and the PEP experience following this incident suggests that asymptomatic employees who were exposed to an uncertain number of spores and who began prophylaxis with antibiotics 9, 11, and 19 days after exposure (in Washington, DC; New Jersey; and Florida, respectively) were protected.

Finally, in considering potential prepositioning strategies, it is critical to take into account the significant material threat posed by antibiotic-resistant strains of anthrax. Timely administration of PEP also hinges on prompt detection and confirmation of the threat through environmental monitoring systems and astute clinical diagnosis and surveillance.

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3

Current Dispensing Strategies for Medical Countermeasures for Anthrax

All levels of government (federal, state, and local) and the private sector are involved in the distribution and dispensing of medical countermeasures (MCM) to the public in an emergency.[1] This chapter reviews current plans and existing infrastructure for the distribution and dispensing of MCM necessary for public protection against a terrorist attack with *Bacillus anthracis* (anthrax). The first section provides an overview of the current MCM distribution and dispensing system, from the national to the local level. The chapter then reviews concerns about the current dispensing system, as well as salient legal and regulatory issues.

CURRENT MCM DISTRIBUTION AND DISPENSING SYSTEM

Figure 3-1 depicts the basic MCM distribution and dispensing system currently in place in the United States. In practice, distribution and dispensing activities will vary depending on the type of public health emergency and on state and local resources, infrastructure, and needs. Stores of MCM currently are housed around the country in the federally managed Strategic National Stockpile (SNS), state stockpiles, and smaller local caches (CDC, 2010a). Stocks of MCM also are maintained by the manufacturers. In the event of a public health emergency, these stockpiles and caches are accessed as appropriate. If state and local resources are insufficient or if a specific

[1] *Distribution*, *dispensing*, and other key terms used in the report are defined in Box 1-2 in Chapter 1.

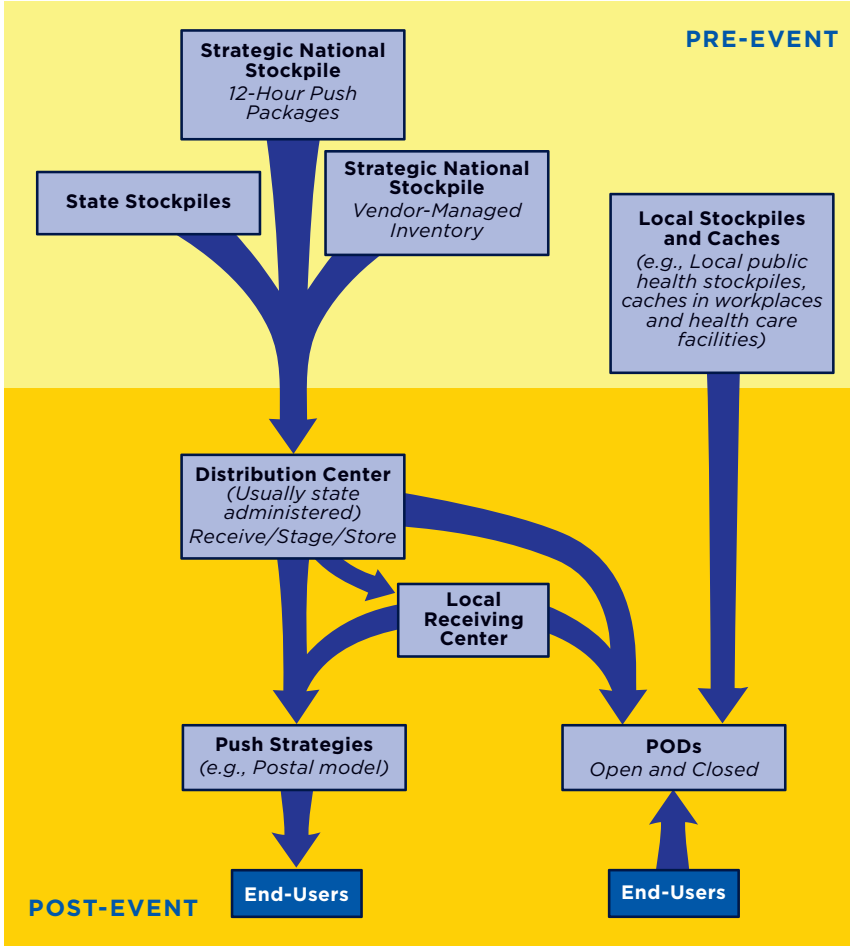

FIGURE 3-1
Basic medical countermeasures (MCM) distribution and dispensing strategy currently in place in the United States.

NOTES: Actual pathways may vary depending on the location and nature of the public health emergency. MCM are released from secure stockpiles around the country to regional or state centers, which facilitate the distribution of MCM to where they will be dispensed to the public. Note that caches may also be the sites of points of dispensing (PODs) (e.g., workplace caches). Vendor-managed inventory may be shipped to distribution sites or directly to PODs.

pharmaceutical is needed, the state governor may request supplementary supplies from the SNS or directly from preidentified vendors.

Supplies released from the stockpiles generally are sent to a state-administered regional distribution center, which receives the shipment, breaks down the packages, stages the MCM in a fashion that allows for rapid distribution, and inventories and stores them as appropriate (CDC, 2010a).[2] From this central point, the MCM are distributed to where they will be dispensed to the public, either directly or through intermediate receiving, staging, and storage (RSS) centers. These intermediate RSS centers can be at the state, county, and/or local level depending on the state, but they are referred to collectively as the RSS stage through the report. Currently, the primary distribution model is for the public to receive MCM at points of dispensing (PODs) located throughout the community. Efforts also are under way to develop plans to use the U.S. Postal Service (USPS) to dispense MCM to individual homes (HHS et al., 2011). In addition, many states and localities have plans to dispense MCM via "closed PODs," in which the MCM are dispensed to preidentified groups—such as employees, their families, and patients—rather than to the public at large. Not shown in Figure 3-1 is prepositioning of MCM for anthrax in homes since there have been only pilot studies of this strategy.

Strategic National Stockpile

The SNS, managed by the Centers for Disease Control and Prevention (CDC), is a national repository of medicine and medical supplies that can be rapidly deployed in the event of a public health emergency that is severe enough to exhaust local supplies (CDC, 2010a). The repository is intended to provide a minimum level of federal coverage as a supplement to state and local resources, and it could be called upon during such events as a natural disaster (e.g., earthquake), an infectious disease outbreak (e.g., influenza), or an act of terrorism (e.g., biological attack with anthrax). SNS resources were deployed, for example, to New York State during the September 11, 2001, terrorist attacks and to most states during the 2009 H1N1 influenza pandemic (CDC, 2009; TFAH, 2005). Established in 1999 as the National Pharmaceutical Stockpile and renamed the SNS in 2003, the repository now contains antibiotics, chemical antidotes, antitoxins, life-support medications, intravenous (IV) catheters and administration

[2]Some SNS stores of chemical/nerve agent antidotes are an exception to this traditional distribution mechanism. The CHEMPACK Program, discussed in greater detail in Chapter 4, forward-deploys SNS materiel to state and local warehouses (HHS, 2009). The Centers for Disease Control and Prevention retains control of the materiel until release, while the participating state is responsible for materiel security, the storage facility, and distribution after an attack.

sets, airway maintenance supplies, and medical/surgical supplies (CDC, 2010a). The SNS contains products that have been approved or cleared by the U.S. Food and Drug Administration (FDA) for use as MCM, as well as investigational products that can be used only as specified under an Investigational New Drug (IND) application (or Investigational Device Exemption, as applicable) or under an Emergency Use Authorization (EUA) issued by the FDA (HHS, 2007).[3]

In response to an emergency, the state governor's office can make a request for SNS resources to the Department of Health and Human Services (HHS) or CDC (CDC, 2010a). Once federal and local authorities have decided to deploy resources from the SNS, the supplies can be delivered to a designated RSS site in any state within 12 hours. To facilitate this rapid response, Push Packages containing a predefined set of pharmaceuticals, antidotes, and medical supplies are housed in secure warehouses in (undisclosed) strategic locations around the country, ready for immediate release. The packages are stored in such a way that they can be loaded immediately onto trucks or aircraft. These Push Packages are designed to deliver a broad range of supplies that would be most useful during the early stages of an event when a specific threat to health might not yet be well defined.

The contents of the SNS are determined by HHS and CDC based on such factors as current threats, the medical vulnerability of the civilian population to those threats, currently available medical products, and the ability to disseminate those products (CDC, 2010a). Since many, if not most, medical products have a defined shelf life, SNS stock routinely is rotated and replenished, and required quarterly quality assurance/quality control (QA/QC) checks and annual content inventories of all Push Packages are conducted.

In addition, some manufacturers may make available vendor-managed inventory (VMI) that can be called upon to supplement the Push Packages or to provide pharmaceuticals that are specific to a suspected or confirmed agent. VMI is shipped from preselected manufacturers and is expected to begin arriving within 24 to 36 hours (CDC, 2010a).

The federal government oversees distribution of the SNS supplies to the designated RSS sites. State and local public health authorities then assume responsibility for distributing and dispensing the MCM to their populations.

[3]As amended by the Project BioShield Act of 2004 (Public Law 108-276), Section 564 of the Federal Food, Drug, and Cosmetic Act "permits the FDA Commissioner to authorize the use of an unapproved medical product or an unapproved use of an approved medical product during a declared emergency involving a heightened risk of attack on the public or U.S. military forces, or a significant potential to affect national security" (FDA, 2007). Such an emergency must be declared by the Secretary of Health and Human Services before an EUA can be issued.

Cities Readiness Initiative

The Cities Readiness Initiative (CRI) is a CDC-administered initiative that provides technical expertise and funding to state and local public health departments to improve their ability to dispense MCM to their entire populations within 48 hours (CDC, 2010b). CRI funding is available to the nation's largest metropolitan areas. The core CRI planning scenario focuses on distribution and dispensing of antibiotics in response to an aerosolized anthrax attack. When the program first was established under the auspices of the SNS in 2004, a total of 21 cities were funded. Now, 72 metropolitan statistical areas (MSAs) receive funding and technical assistance through the CRI (at least one in each state and the District of Columbia). An MSA is defined by the U.S. Office of Management and Budget (OMB) as a geographic region with "a core urban area of 50,000 or more population . . . and includes the counties containing the core urban area, as well as any adjacent counties that have a high degree of social and economic integration . . . with the urban core" (OMB, 2010).

An evaluation of the CRI conducted by RAND at the request of CDC concluded that the "CRI appears to have improved regions' readiness to rapidly dispense lifesaving medications and other medical supplies on a large scale" (Willis et al., 2009, p. xiii). This improvement has been achieved through increased staffing, the purchase of key equipment, strengthening of partnerships, development of detailed MCM dispensing plans and streamlined dispensing models, and training and exercising. The RAND report also highlights several factors that impact the effectiveness of programs, including the degree of health system decentralization, state-local relationships, and staff turnover. However, available evidence did not allow for assessment of a jurisdiction's ability to implement mass dispensing plans under emergency conditions. Actual events are rare, and although some data were available from operational exercises, the lack of standardized performance metrics limited use of those exercises for capacity analysis. Additionally, the RAND evaluation focused on CRI program accomplishments but did not assess the cost-effectiveness of the program.

State and Local Dispensing

States purchase and maintain their own MCM stockpiles in addition to the supplies that come from the SNS or directly from the commercial supply chain. MCM also may be forward-deployed in local community-based stockpiles near planned POD sites or may be cached in the intended POD site itself, such as in a hospital or workplace cache.

Mass dispensing can be accomplished through both *pull* and *push* mechanisms (IOM, 2008). Pull mechanisms involve the public coming to

a specified site, such as an open POD, to pick up MCM. Push mechanisms involve delivering the MCM to end-users, such as through the U.S. mail (the postal model, discussed later in this chapter); workplace dispensing; or door-to-door delivery via school buses, as has been tested in Virginia (also discussed below). The more push strategies can be identified in a community and successfully implemented, the more the burden on the open POD system can be alleviated. Many state and local health agencies currently are working to expand the number of push or closed POD sites in their dispensing plans.

Points of Dispensing

Most current state and local strategies rely on the POD model for the dispensing of MCM to the public. This model allows for local customization of dispensing plans to meet the needs of the population and accommodate the local infrastructure. Key features of an effective POD include the ability to accommodate large numbers of people; location in an easy-to-find, accessible site; provisions for secure storage of MCM; areas for each stage in the process (e.g., arrival, triage, dispensing); trained personnel to handle administration and documentation; and support personnel (Lien et al., 2006; Lindner, 2006). MCM generally are distributed to PODs in response to a public health emergency. In some cases, MCM may already be on-site as a result of being forward-deployed for future dispensing (e.g., a workplace cache that is also the site of a POD).

POD Sites

Traditional open POD sites include schools, armories, and other large public facilities, but many other kinds of sites are being explored, including hotels, mobile-home parks, churches, businesses, residential institutions (e.g., nursing homes), and airports (Willis et al., 2009). Certain facilities also lend themselves to a drive-through POD model whereby people do not need to exit their cars, such as in parking lots, underpasses, and fairgrounds. The state of Utah has tested dispensing through the drive-up windows of banks (UDOH, 2009). The use of fast-food restaurant drive-up windows also has been suggested (Lindner, 2006). Results of a 2005 survey of a small set of retail executives indicated that private-sector retail stores that already dispense vaccines and medicines should be considered as potential sites for open PODs (Lien et al., 2006). These would include chain pharmacies, as well as those located in grocery stores and wholesale clubs, which generally have the infrastructure for and expertise with running large influenza vaccination clinics. The survey results suggest that retail leaders are willing to participate, the stores have the physical space for mass distribution, trained

staff are on-site, and the public has existing relationships with the stores that foster trust.

POD Operating Structures

As noted earlier, PODs may be open to the general public or closed, serving only pre-identified individuals. Both types of PODs may be medical or nonmedical. A medical POD is staffed with medical personnel who are able to conduct individualized medical assessments in addition to dispensing MCM. A nonmedical POD is staffed primarily with nonmedical personnel who are trained only to triage and dispense MCM (IOM, 2008). Medical PODs, while offering more individualized dispensing and education, are unlikely to be feasible in an emergency situation. Medical staff are needed to handle incident-related injuries or illness and probably would not be available to staff PODs. In addition, implementation of the medical POD process likely would be too slow to meet the time frame for dispensing required by the CRI. The nonmedical POD offers greater efficiency than the medical POD, but as it does not offer patients individual medical assessments, its use may necessitate altered standards of care and suspension of certain practice requirements. Moreover, while the nonmedical POD model leaves professional medical staff free to tend to victims of an incident, staffing issues still arise as some jurisdictions rely heavily on volunteers.

PODs may be set up to dispense MCM only to individuals who present at the POD or to heads of households for themselves and their family/household members. A head-of-household dispensing model was field-tested in Philadelphia in 2005 as part of the city's CRI planning activities (Box 3-1). The exercise was highly successful in dispensing MCM to a large number of people in a short time using a limited number of medically trained staff (Agócs et al., 2007). A key advantage of dispensing to heads of households is that vulnerable populations (e.g., children, the elderly, the infirm) need not come to the site. Agócs and colleagues suggest that rapid public availability of MCM lessens the tendency for people to seek out medication in desperation or to buy black market (or possibly counterfeit) MCM on the street. Also noted is the rate of adverse events due to drug allergy (4 percent) seen during the exercise, which is a concern for all dispensing strategies given that the time and logistical constraints of a mass prophylaxis campaign make it infeasible to screen individuals rigorously. Finally, the authors note that total dispensing was limited to 15 members per household to curtail hoarding, but such a strategy would not stop people from lying about their total number of household members to obtain extra medication.

A 2005 exercise in Seattle and King County in Washington State was similarly streamlined for timely dispensing and did not include a formal

BOX 3-1
Head-of-Household Point of Dispensing (POD) Exercise in Philadelphia

Exercise

- The exercise involved an inhalation anthrax exposure scenario.
- Eight pretrained POD staff trained an additional 42 POD staff during the hour prior to the opening of the POD.
- Volunteer heads of households were provided with scenarios to refer to as they filled out intake forms and participated (e.g., children in household, limited English proficiency, acting distressed, trying to steal extra medication).
- Patient education was limited to handouts provided while in line.
- Medical countermeasures (MCM) for a maximum of 15 household members could be obtained by one head of household (to limit the potential for hoarding).
- Six POD staff with medical training reviewed intake forms and referred the head of household to either:
  - express dispensing when only adult dosing of ciprofloxacin was needed for all household members, or
  - screening to collect further information about household members before dispensing (e.g., children, drug allergies).
- Security was provided by local police.

Results

- MCM were dispensed to 717 heads of households, for a total of 2,120 household members.
- The POD was open for 2 hours, with an average rate of dispensing of 1,060 household members per hour.
- Express line dispensing (median 3 minutes per head of household) was more than twice as fast as dispensing that required screening (median 8 minutes per head of household).
- Ninety-seven percent of people were prescribed antibiotics appropriate for their individual situation.
- Four percent of those with true antibiotic allergies were prescribed a drug to which they were allergic.

SOURCE: Agócs et al., 2007.

health education step (Stergachis et al., 2007). While health educators were available to answer questions as needed, patients who had no questions went directly to triage and dispensing. Exit surveys following the exercise found that 80 percent of volunteer patients felt they knew how to take the medication that had been dispensed. Seventy-three percent of

head-of-household volunteers said they understood the instructions for how the medicine should be used by others in their household. All patients received wallet cards listing an informational website and hotline phone number, yet only 68 percent reported that they knew where to obtain further information.

Closed PODs

Closed PODs may be hosted by private-sector entities, as well as government offices and nonprofit organizations (e.g., hospitals and health care providers). The state of Georgia, for example, has established a collaboration between state and local public health officials and Georgia members of Business Executives for National Security (BENS) to develop and test an SNS dispensing model. BENS is a national, nonpartisan organization working to bring private-sector expertise to bear on national security issues. In this dispensing model, company-managed PODs provide MCM to employees and their families. Once dispensing has been completed at the company, employees volunteer to assist with dispensing at public health PODs. Beyond the Georgia example, data are sparse on the prevalence of closed PODs as a component of state and local plans for dispensing MCM. Closed PODs and workplace caches are discussed in greater detail in Chapter 4.

Following an exercise of the Georgia partners model, Buehler and colleagues (2006) conducted interviews with government, business, and academic participants to identify lessons learned (Buehler et al., 2006).

The review found that such collaboration benefits both sides. Public health PODs face a reduced dispensing burden since large numbers of people are served by company PODs and more volunteers are available (as company volunteers become available once private dispensing has been completed). Companies benefit because they can offer employees and their families access to MCM and are more connected to the community in the event of an emergency.

An initial challenge to the collaboration was the underlying cultural differences between business and government (e.g., values, metrics, resources, constraints, management styles, accountability, terminology). There also were few established relationships between the sectors to call upon. In establishing the model, operational constraints, such as confidentiality, liability, and reliance on volunteerism, were encountered. Buehler and colleagues concluded that the partnership has led to essential new relationships and a sense of trust between partners; engagement of private resources and expertise; and a tested collaborative SNS dispensing model, with a commitment from partners to expand the model.

Push Strategies

In contrast to pull strategies, such as PODs, that require the public to acquire MCM proactively, push strategies take MCM to the public. Many states have been experimenting with potential push strategies; the example from Virginia described below illustrates one potential model. Along with states, the federal government also has explored the use of push strategies through a partnership with the USPS to implement the postal model.

Virginia: Distribution and Dispensing via Push Strategies

A key component of Virginia's distribution and dispensing plan is contracts with private-sector partners. In particular, Virginia contracts with UPS for distribution of antibiotics in case of an emergency. Virginia already contracts with UPS to deliver office supplies and has made emergency delivery of MCM a required part of that overall agreement. UPS can deliver to PODs for subsequent dispensing or directly to end-users through home delivery (Mauskapf, 2011).

Virginia also has tested a push dispensing model that involves using public school buses carrying Medical Reserve Corps volunteers and city employees to deliver MCM to residences (NACCHO, 2008). Exercises in Chesapeake, Virginia, demonstrated that 90,000 residences (the entire population of 230,000 people) across 350 square miles could be reached within 5 hours. Bags of MCM were hung on front door knobs or, with the approval of the USPS, placed in the mailboxes of rural residents.

Analyses of these exercises suggest that advantages of this push mechanism include rapid dispensing, thus meeting CRI requirements; reduced traffic congestion as there is no need to travel to PODs; enhanced ability to maintain social distancing (recommended during some infectious disease outbreaks, although not relevant for anthrax); and reduced time for which volunteers are needed (one shift for delivery versus multiple shifts to staff PODs). Disadvantages include reliance on vehicles being available and volunteers showing up, the potential need for security, and reduced effectiveness of this dispensing mechanism in densely populated or very rural areas. A review of the exercises also noted that any communications disseminated by the media must clearly convey the areas covered (as those communications may reach residents beyond the covered areas). Costs included purchase of the bags, paper and printing for educational materials, and fuel (NACCHO, 2008).

Postal Model

The USPS has the capability to deliver mail to every residential address in the country. In association with the CRI, the USPS has been evaluating

the potential for using its existing infrastructure to dispense oral antibiotics from the SNS to residences in response to an act of biological terrorism. This postal model is designed to deliver a short-term supply of MCM within hours of an attack, supplementing local capacity and reducing surge at PODs while they are being set up (IOM, 2010). An advantage of this push dispensing mechanism is that a large segment of the population can be served rapidly. Like the Virginia home delivery strategies, moreover, the postal model facilitates social distancing, which as noted is helpful in public health emergencies involving certain infectious diseases, as well as sheltering in place, which is useful in cases of increased environmental risk. Proof-of-concept exercises of the postal model were conducted in 2006 and 2007 in Boston, Philadelphia, and Seattle, where mock medications were delivered to 20,000 to 50,000 residents in each city in 6 to 9 hours (IOM, 2008). A pilot program was subsequently undertaken in Minneapolis-St. Paul (described below), and San Diego is beginning to undertake preparations to implement the postal plan as well (Global Security Newswire, 2011).

Minneapolis-St. Paul pilot program In 2008, a pilot postal model dispensing program was initiated for an estimated 575,000 people in 205,000 residences in the Minneapolis-St. Paul area (ASPR, 2010; IOM, 2010). An analysis by the Minneapolis Postal Service concluded that 179 volunteer carriers, each covering two regular postal delivery routes, could service this population in 8 to 9 hours. Postal carriers volunteered for the program (participation was not required). Under a special EUA,[4] all volunteers were provided with home antibiotic kits, or MedKits, containing MCM for anthrax and personal protective equipment (including an N-95 respirator) to keep at home to help ensure that they would be protected should they be called upon to serve the public in an emergency (discussed further in Chapter 4). The MedKits contained enough MCM for family members as well. All the postal volunteers were also provided with a MedKit to maintain at work so they would be able to take their own antibiotics and immediately begin dispensing antibiotics to community members following an attack, regardless of whether they were at home or at work. In the event of an attack, one law enforcement officer would accompany each carrier on the delivery route. (Law enforcement partners are not covered under the postal EUA and were not issued MedKits or personal protective equipment. Instead there is a local MCM cache dedicated to police and emergency

[4]An EUA is submitted to the HHS Secretary for approval by the FDA after a declaration of emergency. It specifies the intended use and effective time period of the MCM to be dispensed, the population for which and geographic area in which MCM dispensing is allowed, and which stockpiles of MCM are granted liability protection under the Public Readiness and Emergency Preparedness (PREP) Act. EUAs are discussed in detail in the section on legal and regulatory issues for MCM dispensing later in this chapter.

responders.) Testimony by Jude Plessas of the USPS at a November 18, 2009, workshop of the Institute of Medicine's (IOM's) Forum on Medical and Public Health Preparedness for Catastrophic Events indicated that 385 qualified volunteers were part of the program at that time, 80 percent more than the calculated need (IOM, 2010).

Executive order and national postal model The pilot program begun under the auspices of the CRI has now been developed into a national dispensing model as a result of an Executive Order issued by President Obama on December 30, 2009. Addressing the need to supplement the capabilities of local jurisdictions to provide MCM to their populations in a timely fashion, the order states:

> The Secretaries of Health and Human Services and Homeland Security, in coordination with the U.S. Postal Service … shall establish a national U.S. Postal Service medical countermeasures dispensing model for U.S. cities to respond to a large-scale biological attack, with anthrax as the primary threat consideration. (Obama, 2010)

The order also calls for the development of a plan to provide security escorts to postal workers as they deliver MCM, including supplementing local law enforcement as necessary, and plans to ensure that MCM are provided to personnel who perform mission-essential federal agency and executive branch functions so those functions would be maintained in the wake of an attack. In response to the Executive Order, HHS, the USPS, and the Departments of Homeland Security, Defense, and Justice have published plans for a National Postal Model for the Delivery of Medical Countermeasures (HHS et al., 2011).

On January 28, 2011, the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) issued a Funding Opportunity Announcement for postal model proposals (ASPR, 2011). It is expected that six awards of $50,000 each will be made to assist metropolitan areas in developing and testing postal model MCM dispensing programs.

Implementation A 2009 evaluation of the CRI by RAND found that acceptance of the postal model as a dispensing option has been limited. A key challenge has been the security aspect: law enforcement officials have raised concern that the large numbers of officers needed to accompany each postal worker would not be available in an emergency because of the need to fulfill other priority responsibilities (Willis et al., 2009). A bioterrorism attack would exacerbate the limited surge capacity many law enforcement departments face on a daily basis. Other law enforcement concerns include the fact that officers can guard only the carrier, not the MCM supplies; they cannot act on any other criminal activity they observe while escorting the

carrier; and they are not issued MedKits or personal protective equipment (IOM, 2010; Willis et al., 2009). Beyond these security concerns, the postal model as piloted raises logistical overhead issues and concerns about a lack of flexibility that could impede its incorporation into preexisting local MCM dispensing plans and/or divert MCM and planning and response efforts from POD operations.[5]

The Role of Clinicians and First Responders

Clinicians and first responders are important to many aspects of a response to a bioterrorism attack, from detection to mass prophylaxis. Both professional groups have skills that could be further leveraged through enhanced partnerships with public health and with improved education about their potential roles. This section briefly describes several roles for clinicians and first responders within the overall strategy for responding to an anthrax attack; although further work in this critical area is warranted, it is beyond the scope of the committee's task. Specific roles for clinicians and first responders in prepositioning strategies are discussed in Chapter 4.

First responders and clinicians could help ensure timely detection of an anthrax attack. Because they would likely see patients on the front line of an attack, providing them with additional training to recognize disease symptoms and to alert appropriate public health officials could help with early detection. As discussed in Chapter 2, the time to detection is crucial: the longer it takes to determine that an attack has occurred, the greater is the time from exposure to prophylaxis.

Clinicians and first responders could also play important roles in the overall MCM dispensing strategy, working alongside nonmedical volunteers in PODs or in other dispensing strategies. Prior education and training for these groups would help ensure that they could effectively participate in a response.

Finally, clinicians could play an important role in counseling their patients on the proper use of antibiotics, in general, and in the context of an anthrax attack, in particular. Additional education and training for clinicians would help them provide appropriate information for their patients, including those who would be worried about how they would receive MCM after an attack. Clinicians may be best positioned to identify some vulnerable individuals who lack timely access to antibiotics through other mechanisms, and to help address this gap. This is discussed in Chapter 4.

[5]David Starr, Director of Countermeasure Response, Office of Emergency Preparedness and Response, New York City Department of Health and Mental Hygiene, raised similar concerns in his testimony to the committee on February 28, 2011, focusing specifically on the impracticability of implementing the postal model in New York City.

CONCERNS ABOUT THE CURRENT DISPENSING SYSTEM

Concerns about the current system for dispensing MCM include the dispensing capacity of state and local jurisdictions, security, workforce issues, the need for effective communication and public education, adherence, and transportation and site selection issues. These concerns have led to increased interest in prepositioning strategies. The costs associated with the current POD model of dispensing are discussed in detail in Chapter 5.

Dispensing Capability of State and Local Jurisdictions

As noted earlier, initial supplies are delivered from the SNS to designated RSS sites within 12 hours of the decision to deploy (CDC, 2010a). The timing of distribution from the RSS sites to the PODs and end-users, however, is dependent on the local jurisdictions and is highly variable (Burel, 2011). Although evidence and metrics are lacking, the scope of the challenge and the resources required have raised concern that most U.S. communities still lack adequate capability to dispense MCM quickly to all exposed and potentially exposed populations (see, for example, HSPD-21, 2007). This concern is amplified by recent and ongoing cuts to funding for state and local public health departments (TFAH, 2010). The Executive Order mandating a national USPS MCM dispensing model was issued based on the need to supplement state and local capabilities (Obama, 2010).

Security

Although all PODs have security plans that anticipate the participation of law enforcement, there is concern that during a terrorist attack, local law enforcement personnel would be unable to guarantee the safety of stockpiles and staff because of other priorities during and after the attack (IOM, 2010). In a field test of a head-of-household POD dispensing model in Philadelphia, discussed above, participants who were scripted to try to steal extra antibiotics were successful in doing so (Agócs et al., 2007). While anecdotal evidence from recent disasters provides a spectrum of potential population reactions to a crisis, from relative calm to concentrated looting and potential rioting, there nonetheless exists a perception that safety is a significant concern for MCM dispensing plans. As discussed below, personal safety at potentially overcrowded PODs was one reason respondents in a survey gave for choosing not to go to a POD when advised to do so by public health officials (SteelFisher et al., 2011). Concern also has been raised specifically with respect to the security requirements of the postal model, as discussed previously (Willis et al., 2009).

Workforce Issues

Participants at a 2008 workshop of the IOM Forum on Medical and Public Health Preparedness for Catastrophic Events raised several potential workforce issues associated with the POD dispensing approach, including large numbers of staff required to operate the PODs, the need for training of volunteer staff pre-event and supervision during an event, and protection of volunteers' health while working at the PODs (IOM, 2008). Some jurisdictions have opted to redirect government employees to staff the PODs, reducing the reliance on volunteers. Use of community health centers and hospitals as dispensing sites could disrupt the provision of both routine and critical medical services and draw medical staff away from caring for patients (although hospitals and other health care facilities could serve as closed PODs for staff and existing patients; see Chapter 4). While many jurisdictions developed more sophisticated staffing plans during the response to the 2009 H1N1 influenza pandemic, concerns may remain (particularly in jurisdictions with fewer resources) about staffing during a more sudden response, such as would be required for an anthrax attack.

Communication/Public Education

In the event of a public health emergency, effective communication is critical to ensure that the public knows when and where to go to obtain MCM, regardless of which dispensing mechanisms are employed. Communications are likely to be one of the major challenges following an anthrax attack because of uncertainties and because of how quickly the attack and response are likely to unfold. Although official direction and information can influence individual decision making, the main determinants of behavior include risk perceptions and appraisals, trust and concerns about the safety and effectiveness of MCM, and the ease of implementing the recommended behavior (Vaughan, 2011).

State and local officials could use existing knowledge from both emergency and nonemergency public health messaging campaigns to develop a plan tailored to their population and response strategies. Tailored plans are needed because responses to a public health emergency are inconsistent across vulnerable populations and are not related exclusively to health literacy (Vaughan, 2011). Effective risk communication to a sociodemographically diverse audience will need to involve the use of multiple communication strategies (e.g., traditional media, unofficial Internet sites, social media, social interactions). Social media, with their ability to inform millions of people instantly, can be a viable source of communication in disasters, but they are unlikely to reach the entire population.

Public engagement also can inform communication plans. During a

potassium iodide prepositioning campaign in a jurisdiction within 10 miles of a New Jersey nuclear reactor, for example, researchers were able to determine which communication channels (Internet, television, radio) the public was most likely to use to obtain information and directions (Blando et al., 2008).

Adherence

Adherence to the recommended course of prophylactic antibiotics following an anthrax attack is a major concern. Survey data and evidence from the 2001 anthrax attack suggest adherence is likely to be quite poor. Following that attack, a mass anthrax postexposure prophylaxis campaign was implemented in six areas where exposures had been confirmed. Approximately 10,000 people were recommended to undergo at least 60 days of antibiotic treatment. Follow-up interviews with more than 6,000 of these individuals revealed that while 97 percent had obtained their initial supply of antibiotics, 10 percent had not initiated therapy (Shepard et al., 2002). Only 44 percent of those obtaining the antibiotics had completed the 60-day regimen. Adherence was highest at the Brentwood mail facility in Washington, DC (64 percent), and lowest at the Morgan postal facility in New York City (21 percent). A variety of reasons for nonadherence were cited, including experience with adverse reactions and a perceived low risk of having been exposed. In a separate survey of 245 of the more than 2,000 workers exposed at the Brentwood facility, only 40 percent reported full adherence to their 60-day antibiotic regimen, while 18 percent had completely discontinued the antibiotic at some point, and 42 percent reported stopping and restarting therapy one or more times, skipping days, reducing dosage, or otherwise deviating from the prescribed regimen (Jefferds et al., 2002).

A national opinion poll conducted by researchers at the Harvard School of Public Health raised the concern that while people may obtain MCM at a POD, they may delay starting therapy (SteelFisher et al., 2011). In response to a fictional anthrax attack in their own town, 89 percent of respondents said they would follow recommendations from public health authorities to obtain antibiotics from a local POD within 48 hours. However, 34 percent of individuals who said they would obtain the MCM said they would most likely wait to take them until they knew whether they really had been exposed to anthrax, and 6 percent would wait "for the foreseeable future." Of those who would most likely not go to the POD, primary reasons included concerns about public officials not being able to control crowds, exposure to anthrax while going to the POD, insufficient supply of antibiotics, and safety of the antibiotics.

Transportation and Site Selection Issues

Transportation and site selection issues—including ensuring functioning and safe public transportation and a public understanding of what to expect upon arriving at a POD—are prominent for those jurisdictions that utilize primarily pull strategies. A study of traffic and access to PODs found that during an emergency, "it is unrealistic to expect the public to arrive at the PODs in a uniform and steady rate" (Baccam et al., 2011, p. 147). The authors' model predicted that the total time to process an individual through a POD would be anywhere from 1 to 6 hours under these conditions. Therefore, it is important for state and local jurisdictions to anticipate and mitigate the consequences associated with transportation to and through PODs, especially for vulnerable populations, and to consider their impact on the total time to prophylaxis for the population. Transportation to and from PODs is further complicated when there is a need to shelter in place to avoid traversing highly contaminated areas. Also important to consider is that personnel designated to staff PODs may be overwhelmed simply by providing for the basic needs (e.g., food and water) of a large population.

Depending on the attack scenario (e.g., release at an indoor stadium versus widespread dispersion over a city with a crop duster), the decision about where to establish PODs might depend on environmental sampling results, which could further delay the time between exposure and prophylaxis. Many methods can be used for environmental sampling, depending on the type of environment in which exposure is thought to have taken place. The length of time required for each sampling technique varies: tests can take as little as a few hours or as long as days to be confirmed (CDC, 2006). Communication and public engagement prior to and during an anthrax attack (see above) will play a significant role in identifying potentially exposed populations and directing them to prophylaxis sites (e.g., open PODs).

LEGAL AND REGULATORY ISSUES IN MCM DISPENSING

This section highlights the legal and regulatory issues of primary concern to MCM dispensing, including prescription laws, EUAs, liability and the Public Readiness and Emergency Preparedness (PREP) Act, and expiration of medications and the Shelf Life Extension Program (SLEP). A more detailed discussion of each issue as it pertains to specific prepositioning strategies can be found in Chapter 4.

Prescription Laws

The Federal Food, Drug, and Cosmetic Act (FFDCA) requires that prescription medications be dispensed only with a prescription, and such medications must be appropriately labeled for the individuals for whom they are prescribed. The FDA may deem approved products to be misbranded under the FFDCA if their intended use involves, for example, dispensing without a prescription, absence of required labels, partial dosing, home crushing instructions, SLEP products (see below), or manufacturing that deviates from current good manufacturing practice (cGMP) (Sadove, 2011).

Emergency Use Authorization

As noted earlier, an EUA is submitted to the HHS Secretary for approval by the FDA after a declaration of emergency. It specifies the intended use and effective time period of the MCM to be dispensed, the population for which and geographic area in which MCM dispensing is allowed, and which stockpiles of MCM are granted liability protection under the PREP Act (see below). An EUA is contingent upon the declaration of an emergency by the Secretary of HHS, and such declarations must be renewed yearly. There are currently two EUAs in effect, described below.

The FDA recently issued an EUA for oral formulations of doxycycline products "for the purposes of stakeholder pre-event planning and preparedness activities, and, in a post-event scenario, implementation of post-exposure prophylaxis for inhalational anthrax for individuals who have been exposed, or who may have been exposed, to aerosolized *B. anthracis* spores" (FDA, 2011, p. 3). This EUA will allow public health authorities to prepare to dispense doxycycline under emergency conditions. Although doxycycline is FDA-approved for anthrax postexposure prophylaxis, the EUA is necessary to allow state and local public health officials to prepare for and implement a mass prophylaxis campaign within an entire community. This is because in the absence of the EUA, dispensing doxycycline through an open POD, for instance, could violate provisions of the FFDCA involving, for example, "[the requirement of distributing and using] emergency use information sheets . . . ; dispensing doxycycline without a prescription and without all of the required information on the prescription label . . . ; dispensing a partial supply of the full 60-day dosage regimen, i.e., initial start-up 10-day supply; pre-event storage or distribution of doxycycline packaged or repackaged for emergency distribution; and waiver of current good manufacturing practice requirements during an event, under certain circumstances" (FDA, 2011, p. 2). While this EUA does provide officials with flexibility in a postattack environment, it does

not allow the pre-event dispensing of doxycycline (as would be required to authorize MedKits).

In 2008, the FDA issued an EUA authorizing distribution of MedKits to the postal carrier volunteers in the pilot postal program in Minneapolis-St. Paul (the EUA was amended in 2009) (FDA, 2009). This EUA does not cover dispensing of MedKits to any individuals or groups beyond postal workers who volunteer to participate in the postal program and the members of their households.

Liability and the PREP Act

The HHS Secretary is authorized to issue a "PREP Act Declaration" that provides immunity from tort liability (except for willful misconduct) for claims of loss associated with the administration or use of MCM for threats that are deemed by the Secretary to constitute a public health emergency to those involved in the development, manufacturing, testing, distribution, administration, and use of covered MCM (Public Law 109-148).[6] The statutes of the PREP Act come into effect only after a declaration of emergency by the HHS Secretary. Covered persons include individuals involved in planning and administering the distribution and dispensing of a specified MCM (whether FDA-approved or covered under an event-specific EUA), as well as those individuals authorized under state law to prescribe, administer, and dispense the MCM to end-users. Each MCM required for the response is specified in the emergency declaration, along with the disease the MCM will prevent/treat, the period of time for which the MCM will be used, the populations (demographically and geographically defined) in which it will be used, and the means of its distribution. It is important to note that PREP Act protections are not limited to government officials and programs; the HHS Secretary can expand or limit the groups identified for liability protection. In the PREP Act declaration for anthrax, for instance, the Secretary defines "qualified [or covered] persons" to include a variety of nonmedical individuals operating under the supervision of an authorized person following the declaration of an emergency. This provision extends PREP Act protection to postal carriers, for example, operating under a postal dispensing program (Binzer, 2008; HHS, 2008). Liability continues to be a concern for some private-sector companies that become involved in distributing and dispensing MCM, despite the provisions of the PREP Act, as discussed in Chapter 4.

[6]See http://www.hrsa.gov/gethealthcare/conditions/countermeasurescomp/covered_countermeasures_and_prep_act.pdf and http://www.phe.gov/preparedness/legal/prepact/Pages/default.aspx (accessed March 25, 2011).

Expiration of Medications/Shelf Life Extension Program

Expiration of antibiotics could be a considerable issue for pre-event dispensing of MCM, particularly for household MedKits for the public (the manufacturer-defined shelf life of doxycycline is 2 years, and that of ciprofloxacin is 3 years). For instance, in accordance with the EUA that authorized the pilot postal program in Minnesota, the USPS must survey the volunteer participants in the program every 6 months to check on the status of the kits, including expiration of the medications. Expired product must be collected, recorded, disposed of, and replaced. These requirements add substantial costs and logistical challenges to this dispensing mechanism compared with the SNS, which has access to unique mechanisms to decrease replacement costs.

First, the SNS has an extensive QA/QC and stock rotation/replacement program to ensure that the medications in 12-hour Push Packages have not expired. This type of large-scale rotation may not be available to smaller local or private-sector stockpiles. Second, the SNS can participate in the federal SLEP, which extends the expiration of some of its MCM. The expiration of pharmaceutical products is specified by the manufacturer based on the results of stability testing. However, many medications may have a considerably longer shelf life under ideal storage conditions. Prior to the advent of the SNS, expiration of stockpiled medications had been a particular concern for the military given its need to stockpile very large quantities of certain products or to have highly specialized products with limited commercial use (e.g., antidotes for nerve agents). To address this issue, the SLEP was established in 1986 though an interagency agreement between the FDA and the Department of Defense (Courtney et al., 2009). Under the program, the FDA tests samples from individual lots of an expiring stockpiled drug to determine stability and quality. Ninety-five percent of the product must still be chemically available if the expiration date is to be extended. Shelf-life-extended products are retested every 6 months to 1 year. Although the SLEP originally pertained primarily to military stockpiles, it also has been used for the SNS since 2002. At this time, the SLEP cannot be applied to nonfederal antibiotic stockpiles or caches, resulting in significant replacement costs for state, local, and private-sector (i.e., workplace) stockpiles.

SUMMARY

Current MCM distribution plans rely on distribution from the federally managed SNS and state and local stockpiles. Following an attack, MCM generally are sent to state-administered regional distribution centers and from there to the locations from which they will be dispensed. State, local, and tribal dispensing plans rely primarily on dispensing to the public

at open PODs. In many cases, the open PODs are supplemented by other strategies, such as closed PODs at workplaces and hospital caches. Concerns about the current dispensing system have led to the exploration and development of other dispensing strategies, including the postal model; enhanced involvement by the private sector; and other novel strategies, such as Virginia's efforts to use school buses to dispense MCM to the public. These concerns also have led to increased interest in prepositioning strategies, which are examined in the next chapter. Finally, in considering any dispensing strategy, including those that involve prepositioning, it is important to take into account the legal and regulatory issues involved.

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4

Prepositioning Strategies

Policy makers are considering prepositioning to complement existing more centralized strategies because prepositioning strategies may serve to:

- increase the number of potentially exposed people who are able to access antibiotics within an appropriate time frame following an anthrax attack;
- decrease the burden on existing strategies for dispensing medical countermeasures (MCM), especially the use of points of dispensing (PODs), and reduce surge demand on the health care system; and
- enhance fairness and equitability in access to antibiotics.

As discussed in this chapter and further in Chapter 5, however, these strategies also can be associated with higher levels of inappropriate use and health risks, higher costs, and additional practical burdens relative to existing strategies.

Antibiotics may be prepositioned in many different venues using many different strategies, including:

- **forward-deployed MCM—**MCM stored near the locations from which they will be dispensed,
- **cached MCM—**MCM stored at the locations from which they will be dispensed,[1] and

[1]The term *cache* often is used broadly to describe stockpiles of MCM held by state or local jurisdictions, health care facilities, and private-sector organizations, among others. For the

- **predispensed MCM—**MCM stored by the intended users or by heads of households or other nonmedical caregivers for use by those in their care.

This chapter describes these three categories of prepositioning strategies. For each category, several example strategies, the potential roles for those strategies within a jurisdiction's overall dispensing strategy, and potential health risks, if any, are discussed. Also discussed for each category are practical considerations, including logistics, communication needs, expected behavior and adherence, and legal and regulatory issues. Table 4-1 summarizes key features of the three categories of prepositioning strategies. This table is not intended to be comprehensive; other push and pull strategies (such as those described in Chapter 3) also could be employed to enhance distribution and dispensing.

In this chapter, the committee discusses the individual properties of different prepositioning strategies to highlight the specific uses of each and the associated advantages, disadvantages, and other considerations. However, these strategies are likely to be used in combination not only during initial prophylaxis, but also later when it is necessary to provide the exposed population with vaccine and a prolonged antibiotic course. This chapter focuses primarily on the qualitative considerations that should factor into jurisdictions' decisions about whether to develop strategies for prepositioning prophylactic antibiotics in their communities. Chapter 5 outlines a decision-aiding framework and a model for quantifying and comparing health benefits and economic costs across the various prepositioning strategies and presents the committee's recommendations on this topic.

FORWARD-DEPLOYED MEDICAL COUNTERMEASURES

Forward-deployed MCM are stored near the locations where they will be dispensed. The primary purpose of forward-deploying MCM is to decrease the transportation time associated with distributing the MCM from stockpiles to PODs. Several entities could potentially maintain forward-deployed stockpiles of antibiotics, including the Centers for Disease Control and Prevention (CDC)/Strategic National Stockpile (SNS); other federal agencies, such as the Department of Veteran Affairs (VA) and Department of Defense (DOD); state and local authorities; and commercial pharmaceutical distributors. These strategies are described below.

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purposes of this report, and to enable clear discussion of the different properties associated with different types of prepositioning, the committee defines *cache* more specifically to denote storage of MCM in the locations from which they will be dispensed and uses the term *stockpile* to cover federal, state, and local stockpiles.

TABLE 4-1
Practical Considerations for Developing Prepositioning Strategies

	Example Prepositioning Strategies	Potential Uses for Strategy	Primary Entities Involved and Partnerships Needed*	Infrastructure and Other Practical Requirements	Related Strategies to Consider/Notes
Forward-Deployed MCM	SNS forward-deployed	Decrease time to initiate dispensing, and hence increase the overall number of people receiving prophylaxis within an appropriate time frame following exposure	CDC	To benefit from forward-deployed strategies, PODs must be capable of being set up quickly enough to take advantage of the time savings associated with distribution from forward-deployed stockpiles	An issue is how far along the continuum (centralized → forward-deployed) to place the MCM stockpiles
	Other federal forward-deployed (VA, DOD)		CDC; VA and/or DOD; state/local/tribal public health authorities		
	State, local, tribal forward-deployed		State/local/tribal public health authorities		
	Commercial forward-deployed to supply public health open PODs		Commercial pharmaceutical distributor(s); state/local/tribal public health authorities		
	Commercial forward-deployed to supply private-sector closed PODs		Commercial pharmaceutical distributor(s); private-sector entities with closed PODs		
Cached MCM	Caches in hospitals and other health care facilities—for example, community health centers, clinics, skilled nursing facilities, subacute care facilities	– Protect health care workers expected to work during the response and their families – Maintain functioning of the health care system – Protect patients and long-term residents from anthrax	– Health systems, hospitals, and other health care facilities* – ASPR, through the Hospital Preparedness Program	Infrastructure and staff needed to store and dispense MCM already exist in health care facilities	

continued

TABLE 4-1 *Continued*

	Example Prepositioning Strategies	Potential Uses for Strategy	Primary Entities Involved and Partnerships Needed*	Infrastructure and Other Practical Requirements	Related Strategies to Consider/Notes
Cached MCM	Retail pharmacy caches	Protect pharmacy staff expected to work during the response and their families	Pharmacies*	Infrastructure and staff to store and dispense MCM already exist in retail pharmacies	Pharmacies may serve as open PODs dispensing MCM delivered postevent
	General private-sector workplace caches	– Enhance dispensing capability for the general population by off-loading demand from the public health distribution and dispensing system – Help ensure business continuity and the well-being of employees and their families	Private-sector entities*	Most workplaces do not already have the infrastructure and staff to store and dispense MCM; this capacity would have to be developed or alternative arrangements made	Private-sector workplaces may serve as closed PODs dispensing MCM delivered postevent
	Workplace caches for those who will be expected to work during a response	Protect first responders, critical infrastructure workers, and other groups of workers expected to work during a response; workers' families may also be included	Private and public employers with employees who are expected to work during a response*		Predispensed MCM could be used for those for whom workplace caches are not a feasible option (see below)

	Caches in agencies serving vulnerable populations	Enhance access for vulnerable populations	Agencies serving vulnerable populations, including community- and faith-based organizations, such as food banks and home health care providers*	Most agencies do not have the infrastructure and staff to store and dispense MCM	Agencies may be better suited to serve as PODs, to use other existing service delivery systems to dispense MCM delivered postevent, or to help enable and encourage their clients to go to open PODs
Predispensed MCM	Individual supplies for those expected to work during a response	– Protect first responders and critical infrastructure workers who lack access to antibiotics via other timely dispensing mechanisms (e.g., workplace caches); workers' families may also be included – Help ensure business continuity and the well-being of employees and their families	Certain employers with employees who are expected to work during a response, as well as their health plans	Employers would work with employees to develop plans to store, screen, dispense, and replace MCM when expired; employers should consult with their health plan administrator to assess whether the medication will be covered	Workplace caches might be used; see above

continued

TABLE 4-1 *Continued*

	Example Prepositioning Strategies	Potential Uses for Strategy	Primary Entities Involved and Partnerships Needed*	Infrastructure and Other Practical Requirements	Related Strategies to Consider/Notes
Predispensed MCM	Individual supplies for selected patients	Enhance access for selected patients who lack access to antibiotics via other timely dispensing mechanisms	These individuals should work with their prescribers to determine ability to safely store and appropriately use antibiotics	Prescribers would work with patients to develop plans to store, screen, dispense, and replace MCM when expired	

NOTES: ASPR = Office of the Assistant Secretary for Preparedness and Response; CDC = Centers for Disease Control and Prevention; DOD = Department of Defense; MCM = medical countermeasures; POD = point of dispensing; SNS = Strategic National Stockpile; VA = Department of Veterans Affairs.

*Private and other nongovernmental entities could implement prepositioning strategies independently, but in many cases, federal, state, local, and tribal governments will play a key role in facilitating the adoption of such strategies through initiatives, planning assistance, financial and other incentives, and/or efforts to address legal and other barriers.

Forward-Deployed by the Strategic National Stockpile

SNS stockpiles currently are held in large, strategically placed warehouses throughout the nation. For security reasons, the locations of SNS stockpiles are not disclosed. Therefore, it is possible—and perhaps likely—that certain SNS warehouses are located near high-risk areas, such as major cities, and therefore would already be considered forward-deployed. The SNS could be further forward-deployed by establishing additional SNS warehouses. This might be done, for example, by prepositioning MCM in SNS-managed warehouses in the 11 Tier 1 cities of the Urban Areas Security Initiative, which are the metropolitan areas that the Department of Homeland Security (DHS) has determined to be at highest risk of a terrorist attack (Burel, 2011; DHS, 2011).

The primary motivation for forward-deploying SNS stockpiles is to decrease the time associated with transportation from the SNS warehouse to state receiving, staging, and storing (RSS) warehouses, which then redistribute the MCM to the jurisdictions' PODs. This strategy would enable PODs to begin dispensing antibiotics more quickly, thereby increasing the number of people receiving prophylactic antibiotics within the time window in which they can prevent anthrax. Decreasing the transportation time from SNS warehouses to state RSS sites will be effective, however, only if the RSS sites and PODs can be set up and staffed quickly enough to take advantage of the reduced delivery time (Burel, 2011). If MCM are delivered from the SNS before the RSS sites are ready to redistribute them or are redistributed from RSS sites to PODs before the PODs are ready to begin dispensing, the reduced delivery time from SNS warehouses will have no impact on the time at which dispensing of the MCM begins. Although data are sparse on the time currently required for state and local authorities to commence POD operations, and this time is likely to show great variability across jurisdictions, the limited data available suggest that 8 hours or more may be needed (Burel, 2011). Therefore, decreasing the SNS transportation time to under 8 hours is unlikely to be cost-effective unless jurisdictions can set up PODs more quickly. For those states and localities that already have the ability to set up RSS sites and PODs rapidly, reducing the SNS delivery time to 8 hours or less might induce some state and local entities to consider eliminating or reducing the quantity of antibiotics in their caches as a cost-saving measure.

Forward-deploying MCM that remain under the control of the SNS (rather than transferring them to state, local, or private entities) would decrease transportation time while still enabling central coordination by the SNS; some flexibility to use the SNS infrastructure to redeploy MCM to other areas of need; and the use of the Shelf Life Extension Program (SLEP, described in Chapter 3), which is available only to selected federal stockpiles (Courtney et al., 2009).

Forward-deploying SNS stockpiles would require storing MCM in more locations compared with storage in fewer, more centralized warehouses; therefore, forward-deployment would impose a higher management burden and require a greater quantity of medication, with associated costs. This strategy also would decrease flexibility to reallocate antibiotics if an attack occurred in a location with lower perceived risk.

CDC's CHEMPACK project is an example of forward-deployed SNS materiel (Box 4-1). The most significant difference between an attack with

BOX 4-1
CHEMPACK:
Forward-Deployed Strategic National Stockpile (SNS) Antidotes for Nerve Agents

- Nerve agents (e.g., ricin, sarin gas) can be absorbed through the eyes or skin, ingested by eating or drinking contaminated food or water, and inhaled; they can cause death by disrupting normal cellular mechanisms, causing muscles to tire, which results in cessation of breathing (CDC, 2006).
- Antidotes for nerve agents can prevent death, but are most likely to do so only when administered immediately after exposure (CDC, 2006).
- During the 1991 Gulf War, the Israelis distributed the nerve agent antidote atropine to all citizens based on the potential threat of a chemical attack; an order to administer the antidote never was given, and the program has since been discontinued for budgetary reasons (Stoil, 2010).
- The only known attack using a nerve agent was carried out by members of the Aum Shinrikyo cult in 1995 in the Tokyo subway system; the sarin gas attack injured approximately 3,800 people and killed 12 (Danzig et al., 2011; Olson, 1999).
- Since 2004, the Centers for Disease Control and Prevention (CDC) has stockpiled nerve agent antidotes as a part of the SNS, forward-deploying them in volunteer states because of the speed with which the antidotes must be administered postexposure to be effective (HHS, 2009).
- CDC has partnered with at least 39 states to stockpile nerve agent antidotes at locations in state (e.g., warehouses, hospitals) as part of the CHEMPACK project (CDC, 2007a; Delaware Health and Social Services, 2009).
- CDC retains control of the CHEMPACK stockpiles, monitors the proper storage of the materiel at all times, and collects and replaces expired antidote (HHS, 2009).
- Participating states are responsible for CHEMPACK security, the storage facility, and distribution after an attack (HHS, 2009).

a nerve agent and anthrax is the time frame postexposure within which MCM are effective: antidotes for nerve agents must be administered within minutes to hours, compared with several days for anthrax antibiotics. CDC also forward-deploys DTPA (diethylene triamine pentaacetic acid) in states to reduce response time in the event of a radiological incident. In 2010, CDC reported that "as of March 2010, 89% of the 62 [Department of Health and Human Services–funded] state, locality, and U.S. insular area public health departments received 78,880 doses of [DTPA] from CDC's [SNS]" (CDC, 2010d, p. 28).

Forward-Deployed by Other Federal Agencies

MCM also could be forward-deployed at VA hospitals or DOD medical treatment facilities, which are located throughout the country. Although these activities are beyond the normal scope of the VA and DOD mandates, the potential to use this health system infrastructure should not be overlooked. These facilities already maintain pharmaceutical caches for their staff and patients and have the medical staff and infrastructure required to monitor and store medications properly (VA, 2010; see Appendix D). The SNS already partners with the VA and DOD, and the VA currently provides the SNS with acquisition support (CDC, 2010a; VA, 2011). Therefore, instead of using resources to establish new SNS warehouses, it might be possible to expand VA or DOD caches to include antibiotics for the public. These MCM would be distributed to open PODs for dispensing; VA or DOD facilities would be unlikely to serve as open PODs since they would be occupied with providing health care following an attack. Stockpiles at VA or DOD facilities would allow use of the SLEP to minimize costs associated with expiration, and potentially could even be cycled through regular health care uses to avoid expiration entirely.

Forward-Deployed by State Authorities

MCM could be forward-deployed by states to locations at high risk instead of being kept in a single central location within the state. For example, Minnesota maintains 11 caches of MCM throughout the state, distributed according to population density and proximity to major cities (Minnesota Department of Health, 2006).

In 2005, the New York State Department of Health's Office of Health Emergency Preparedness established all-hazard medical emergency response caches (MERCs) in multiple locations throughout the state (NYSOHS, 2007). The MERCs contain pharmaceuticals and devices (e.g., doxycycline and ciprofloxacin, Mark I Autoinjector Kits with antidotes to nerve agents) and other medical supplies and equipment that can be deployed rapidly in

an emergency, reaching any area in the state within 4 hours (compared with 12 hours in the case of SNS Push Packages). The state-owned assets in the MERCs are the first supplies available to move into an affected area. Depending on the incident, if these state supplies are committed or expended, the state requests assistance from the SNS. The MERCs also eliminate the need for multiple local stockpiles that are not cost-effective. The MERCs are intended to bridge the supply gap between the time of an incident and the arrival and distribution of SNS resources.

Like the SNS forward-deployed strategy, this strategy offers the advantage of decreased transportation time to POD sites. It also has similar drawbacks, including increased costs associated with supporting more facilities and potentially greater quantities of MCM, and decreased flexibility to reassign MCM should an attack occur at a location other than those predicted. Unlike forward-deploying at SNS warehouses or in VA or DOD facilities, however, state stockpiles cannot take advantage of the SLEP (Courtney et al., 2009). Although this is a limitation for centralized state stockpiles as well, it could have a greater impact on disbursed forward-deployed stockpiles since they would likely require a greater quantity of antibiotics overall, and the administrative burden of monitoring, discarding, replacing, or cycling medications through regular health care uses would increase as the number of stockpile locations increased. In the past, states attempting to contract with pharmaceutical distributors to rotate the antibiotics in their stockpiles have faced the challenge of a low market demand for the MCM, and thus little benefit in terms of decreasing replacement costs due to expiring medications (Courtney et al., 2009). This might be an area for which national guidance would be beneficial, as discussed in detail later in this chapter.

Several studies have suggested that state and local planning efforts should focus first on increasing dispensing capacity because increasing local inventory is cost-effective and effective in reducing mortality if the community already has a highly robust dispensing capacity (Bravata et al., 2006; Zaric et al., 2008). This issue is examined further in Chapter 5.

Forward-Deployed by Commercial Entities

MCM could be forward-deployed by commercial pharmaceutical distributors, including both companies that specialize primarily in supply chain management and pharmaceutical distribution (e.g., McKesson, Cardinal Health, AmerisourceBergen) and companies that distribute pharmaceuticals to supply their retail stores (e.g., Target, Walmart). Commercial pharmaceutical distributors could forward-deploy MCM on behalf of either public health authorities to supply open PODs or private-sector entities to supply closed PODs for employees and their families. Under this strategy, a

jurisdiction or private-sector entity would contract with a pharmaceutical distributor to maintain stockpiles of antibiotics in a warehouse near the anticipated POD location(s). This strategy would limit the time needed for transportation (relative to relying on pharmaceutical warehouses located far away) and would take advantage of these distributors' expertise in supply chain management and medication storage. The challenge for public health authorities would be to identify pharmaceutical distributors that were interested in participating in such a program and would find it worthwhile from a business perspective. While distributors may be willing to store MCM in bulk, they are likely to find it more challenging to store MCM in prelabeled unit-of-use quantities because of storage space requirements and costs. CDC currently is exploring the use of pharmaceutical distributors to distribute antiviral drugs from the SNS (CDC, 2011a).

During the 2009 H1N1 influenza pandemic, the state of Virginia employed this model, contracting with a private vendor (AmerisourceBergen) to store and distribute its supply of antivirals at the direction of the state health commissioner (Virginia Department of Health, 2009). Virginia is pursuing additional partnerships with chains and pharmacies based on the system set up in response to the 2009 pandemic.

CACHED MEDICAL COUNTERMEASURES

Cached MCM are positioned in the locations from which they will be dispensed. The caches may be located in health care facilities (e.g., hospitals and pharmacies) or non–health care facilities (e.g., non–health care workplaces) and may be maintained by public or private entities. The specific purposes, advantages, and challenges involved depend on the type of cache and are described below.

Caches in Health Care Settings

The primary purpose of MCM caches in health care settings is to distribute the MCM to health care workers and their families. Health care workers, considered critical infrastructure personnel, are then available to treat victims of a terrorist attack and maintain the level of medical support needed for a community. In addition to the benefits to patients needing care, communities may be more resilient if health care systems remain intact in the face of an attack. This prepositioning strategy also enhances equitable access to MCM by providing an alternative dispensing method for health care workers who will be expected to report to and stay at work during the course of the response to an attack, and who therefore will be unable to stand in line at PODs to receive MCM for themselves and their families. MCM caches in health care settings also could be designated to protect

existing patients or residents of long-term care facilities from anthrax exposure, although these populations may be at lower risk for exposure.

Health care settings, especially hospitals and acute care facilities, generally are not well suited to serve as open PODs that dispense MCM to the public because serving this function likely would overwhelm the facility and distract from its essential function of providing health care during an emergency. Nonetheless, hospitals are viewed by many in their communities as a repository for essential resources for surviving a disaster or terrorist attack, and some hospitals could be overwhelmed with community members during a response to an anthrax attack. Communications and public education about where people should go to receive prophylaxis would be crucial in the event of such an attack (see Chapter 3).

Caches in Hospitals and Acute Care Medical Facilities

Hospitals and acute care medical facilities are part of the critical infrastructure for combating an anthrax attack and maintaining the health status of a community. Ensuring timely prophylaxis to this community, in particular, has a multiplicative effect: incapacitating one health care worker could negatively impact the care of dozens or more patients. If no other strategy for getting MCM to these facilities quickly is in place, prepositioning may be an appropriate strategy for protecting this infrastructure, particularly in high-risk areas.

The current emergency management standards of the Joint Commission do not specify that hospitals should have pharmaceutical caches for use in disasters (Live Process, 2011). However, many hospitals and health systems have developed pharmaceutical caches through the Hospital Preparedness Program (HPP), which was established in 2002 to enhance surge capacity and preparedness for public health emergencies among hospitals and health systems.[2] HPP funding is provided to states, territories, and eligible counties, which in turn work with hospitals and health systems in their jurisdiction and pass along to them a portion of the funding for preparedness planning and exercising (ASPR, 2011a). During the first few years of the HPP, the development of pharmaceutical caches was a focus of the program, along with other capacity-building activities such as decontamination, development of bed surge capacity, and training for providers in diagnosing diseases caused by bioterrorism (ASPR, 2011b). Awardees were required to develop regional

[2]Since the passage of the Pandemic and All-Hazards Preparedness Act in 2006, the HPP has been administered by the Office of the Assistant Secretary for Preparedness and Response (ASPR). The program was originally administered by the Health Resources and Services Administration (HRSA), during which time it was called the National Bioterrorism Hospital Preparedness Program (ASPR, 2011a).

pharmaceutical caches containing a 3-day supply of antibiotics for hospital personnel, first responders associated with the hospitals, and their families (HRSA, 2004, 2005). These pharmaceutical caches did not necessarily have to be on-site at the hospitals; strategically placed regional caches also met the requirement. Although data on national prevalence are sparse, some major health systems maintain on-site pharmaceutical caches for staff in addition to state, regional, or local health care caches.[3] Based on data from the HPP 2006 midyear progress report, 20 states reported that all their participating hospitals had pharmaceutical caches that could provide a 3-day supply to cover hospital personnel, associated first responders, and their families. Another 6 states reported that 90 to 99 percent of participating hospitals could meet this requirement (GAO, 2008).

After the first few years of the HPP, however, the focus shifted from capacity building to a capabilities-based approach. Hospitals now must demonstrate the capability to perform core response functions and no longer can meet requirements simply by purchasing equipment and supplies (ASPR, 2011b). Pharmaceutical caches became a *level two subcapability*, meaning that funding can be used for this purpose only if all capabilities designated as *level one* have been adequately addressed (ASPR, 2007, 2008, 2009, 2010, 2011c; HRSA, 2006). The grant guidance notes that most awardees should already have pharmaceutical caches because of the emphasis in earlier years, but a review of the first 5 years of the HPP notes, "Continued funding for hospitals is needed to pay for training of hospital staff, employment of hospital disaster coordinators, and maintenance or replacement of stockpiled supplies and pharmaceuticals purchased through the HPP" (Toner et al., 2009, p. 61). This report goes on to warn, "Although the [new] emphasis on coalition development is critical, it is clear that progress will be lost and individual hospitals will drop out of the HPP if they do not continue to receive some support for stockpiling, replenishing caches, and training" (Toner et al., 2009, p. 61). The new 2011-2012 effort to align the required capabilities of two major federal preparedness grants, the HPP and CDC's Public Health Emergency Preparedness (PHEP) Cooperative Agreement, is intended to promote coordination and efficient use of resources (Lurie, 2011). It should be noted that the ability to maintain hospital caches will be sensitive to the availability of ongoing funding.

Caches in Nonhospital Health Care Facilities

Antibiotics may also be cached in nonhospital health care facilities, such as community health centers, clinics, skilled nursing facilities, and

[3]Personal communication, John Hick, medical director for emergency preparedness, Hennepin County Medical Center, MN, June 15, 2011.

subacute care facilities. Some of these facilities may be part of the same health network as larger hospitals with more fully developed caches, in which case hospital plans could be leveraged and extended. Prepositioning MCM for health care workers in a range of institutional facilities outside of hospitals and acute care facilities not only would help ensure that those workers could continue to care for patients and residents, but also would expand the pool of health care workers available to engage in a broader community response should an emergency overwhelm the internal surge capacity of hospitals. MCM caches in locations such as skilled nursing facilities also would provide protection for the patients and long-term residents, many of whom would be unable to stand in line at open PODs to receive their antibiotics.

Community health centers (CHCs) are somewhat different from skilled nursing facilities because they serve community members who are more likely to be out and about and, therefore, potentially at higher risk of anthrax exposure. CHCs have the ability to reach difficult-to-serve and vulnerable populations, including the medically underserved, people of low income and limited resources, people without insurance, migrant workers, and the homeless (Muccio, 2011). CHCs also may have the ability to tailor medication sheets and messaging to the multilingual populations they serve every day; they may have mobile assets to assist with further dissemination; and, like other health care facilities, they already have qualified, experienced staff to handle medications. However, CHCs may ultimately not be appropriate places to cache medications for use in open PODs serving their usual populations. First, CHCs and associated workers may be called upon to provide surge health care and would be distracted from this function by providing an open POD for the public. Second, CHCs may lack adequate storage space and security for the cache and may have concerns about the costs and time associated with maintaining it (Muccio, 2011).

Caches in Retail Pharmacies

As a routine component of the health care system, retail pharmacies are potentially appropriate sites for MCM caches. While incorporating them into the overall MCM dispensing system would require public-private coordination, discussed in the next section, they offer the benefit of trained staff and experience in storing and dispensing pharmaceuticals. Like hospitals, they can minimize costs associated with drug expiration by rotating cached antibiotics through regular use. However, caching antibiotics on-site does represent a variation from current pharmacy practice. Retail pharmacies usually stock medications only in the quantities needed to meet immediate needs, and they rely on pharmaceutical distributors and vendors to provide

"just-in-time" inventory on a continuous basis. Additional costs also are associated with storing and maintaining excess inventory. In addition, the stock at a pharmacy likely would be in bulk, not unit-of-use packages, complicating the process of dispensing to the public. These factors make it unlikely that retail pharmacies would cache a sufficient quantity of antibiotics to supply an open POD. Instead, a retail pharmacy open POD would most likely dispense antibiotics supplied postevent by the SNS, state or local stockpiles, or vendors. On the other hand, the obstacles of stockpiling antibiotics to act as an open POD would be less of a challenge for pharmacies maintaining small caches of antibiotics just for pharmacists and other staff members and their families. The presence of such caches might encourage staff to report to work quickly and stay there throughout the response to a terrorist attack.

Public-Private Coordination and Workplace Caches

Private-sector entities may be interested in developing systems through which they could dispense antibiotics to employees and their families to help ensure their well-being, provide for continuity of business operations, and potentially lower insurance costs. In some cases, private-sector entities also have demonstrated willingness to assist in distributing and dispensing MCM for the general public (Lien et al., 2006). Many large private-sector companies have infrastructure and expertise for supply chain management and logistics, systems for communicating with employees, occupational health clinics and medical staff, and other resources that could be used to enhance dispensing capacity within their community during a time of crisis. By providing prophylaxis for employees and their families, private-sector entities also could alleviate the burden on the public health system and enable public health officials to focus more on dispensing to vulnerable populations that might not be reached by large employers. At the same time, however, potential private-sector partners face many barriers, including liability, cost, legal and regulatory issues, and the complexities of working across multiple jurisdictions during the development of MCM dispensing plans.

This section first considers private-sector participation in MCM distribution and dispensing in general, including current examples, advantages, and barriers. It then addresses the issue of the need for national-level guidance to inform public-private coordination on MCM prepositioning, distribution, and dispensing. Finally, the section examines the specific case of workplace caches, in which private-sector entities preposition MCM on-site. As discussed in more detail below, although many companies have expressed willingness to dispense SNS or state antibiotics via closed PODs, many have significant concerns about caching the MCM on-site.

Private-Sector Participation in MCM Distribution and Dispensing

Many private-sector entities played important roles in the response to the 2009 H1N1 influenza pandemic, demonstrating a willingness to partner with public health entities throughout the MCM distribution and dispensing system. The programs developed at that time greatly enhanced public-private coordination and demonstrated the expertise and capacity of the private sector, but they also brought to light some significant barriers to increased private-sector participation.

The *SNS: Supply Chain Dashboard* was developed in the fall of 2009 as part of the response to the 2009 H1N1 influenza pandemic to provide timely information about MCM in the commercial supply chain and public-sector stockpiles. This information assisted federal and state officials and other decision makers in responding to the pandemic (CDC, 2010b). Commercial partners submitted information each week on the available supply of MCM, their ability to fulfill orders, and upcoming production. Participants at a 2009 Institute of Medicine (IOM) workshop noted that this project involved an unprecedented degree of data sharing on the part of private-sector partners and a new level of coordination and communication among public and private stakeholders in addressing a public health emergency (IOM, 2010b). CDC plans to maintain the *Dashboard* as part of its Countermeasure Inventory Tracking program (CDC, 2011b).

Retail pharmacies played an important role in providing vaccine and, in some states, antiviral medications during the response to the 2009 H1N1 influenza pandemic (ASTHO, 2009; IOM, 2010a). Facilitated by the Association of State and Territorial Health Officials, many private and public entities came together quickly to create a framework for state and territorial health officials to partner with pharmacies to administer H1N1 vaccine. The organizations involved included the American Pharmacists Association, CDC, the National Alliance of State Pharmacy Association, the National Association of Chain Drug Stores, the National Association of County and City Health Officials, the National Community Pharmacists Association, the Office of the Assistant Secretary for Preparedness and Response (ASPR)/Department of Health and Human Services (HHS), DHS's Office of Health Affairs, and Pharmaceutical Research and Manufacturers of America's (PhRMA's) Rx Response (ASTHO, 2009). This model extends public health capacity to reach large numbers of people because privately employed pharmacists are a large workforce, pharmacies already have the staff and infrastructure to store and dispense MCM, and pharmacies generally are in well-known and accessible locations throughout communities. For these same reasons, this model also could be highly effective for dispensing antibiotics in response to an anthrax attack. However, it is critical that a framework for cooperation among public health officials and

retail pharmacies be in place prior to an anthrax attack as the timeline of the response would not allow for this to be accomplished postevent.

Some private-sector entities have volunteered to serve as closed PODs that would dispense SNS or state MCM to employees and their families. The committee is unaware of data on how many private-sector entities have developed plans to serve as closed PODs after an anthrax attack, but this is a major component of the overall dispensing strategy in some jurisdictions. Speaking at a 2008 IOM workshop, Pamela Blackwell, Director of the Center for Emergency Preparedness and Response for the Cobb and Douglas Boards of Health, estimated that the closed PODs planned at that time for the metropolitan Atlanta area would serve enough people to reduce demand on the open POD system by 40 to 50 percent (IOM, 2008). At the same workshop, Teresa Bates of Tarrant County, Texas, reported that several large employers in the county have partnered with public health authorities to plan closed PODs (IOM, 2008). Some private-sector entities that plan to serve as closed PODs, dispensing only to employees and their families, also plan to provide volunteers to public health open PODs once the closed POD has completed dispensing (Buehler et al., 2006). A 2005 survey of private retailers suggested their willingness to serve as PODs. These respondents included many retail pharmacies—chain and independent pharmacies operating as stand-alone stores or through supermarkets—that, as noted earlier, already possess the physical space for staff training and dispensing and have an existing relationship with the public (Lien et al., 2006).

At the same time, participants representing the private sector at 2009 and 2010 IOM workshops cited several barriers that could discourage private-sector entities from becoming more involved. These included concerns about liability; compliance with federal and state laws and regulations; payment and reimbursement issues; communications; and, especially, working with multiple jurisdictions across the nation (IOM, 2010a,b).

Public-Private Coordination

No federal/national-level guidance currently exists on private-sector participation in an antibiotic prophylaxis campaign. Private-sector entities interested in prepositioning, distributing, and dispensing antibiotics must work directly with state and local public health authorities to coordinate on distribution and dispensing plans, and they must comply with varied state and local laws and regulations in addition to federal laws and regulations. Companies with multiple facilities nationwide must implement multiple policies and procedures instead of adopting a single corporate dispensing protocol. This fragmented approach has been cited as a significant challenge to increased participation by large national corporations, in presentations to this IOM committee and during previous workshops hosted by the IOM

on MCM distribution and dispensing and on the 2009 H1N1 vaccination campaign (IOM, 2010a,b; Stargel, 2011; Turnbull, 2011).

Many states and localities already have developed their own memorandum of understanding (MOU) or memorandum of agreement (MOA) templates for private-sector entities interested in serving as a closed POD, specifying the respective roles, rights, and obligations of the public health agency and the private-sector entity. No central repository of existing MOUs or MOAs exists, and the committee is unaware of data on how many states and localities have developed them, but it believes that most states and many localities have done so.[4]

National guidance for public-private coordination in prepositioning, distribution, and dispensing would facilitate private-sector participation in these activities by promoting consistency across the nation. The federal government should convene state, local, and tribal governments and private-sector entities to develop such national guidance. The latter group should include representatives of businesses of different sizes, from different geographic locations, from both critical infrastructure and noncritical infrastructure industries, and from both health care and non–health care sectors. The federal government should also ensure that the plans developed in the national guidance include Public Readiness and Emergency Preparedness (PREP) Act coverage, without which private-sector entities are unlikely to participate. CDC should serve the convening role since it has primary responsibility for MCM distribution and dispensing at the federal level, has existing relationships with all public health authorities and many large private-sector entities, and already has been involved in developing public-private models for public health preparedness and response. This national guidance would be informed by the relationships already forged between the private sector and state and local agencies in response to real-life events (e.g., the 2009 H1N1 influenza pandemic).

Although the federal government may play a convening role, the guidance developed must ultimately be *national*-level guidance, and MOUs and MOAs must still be signed at the state level (even if the template is consistent across states). State and local public health authorities are responsible for dispensing MCM to the general public. Furthermore, most disasters are local rather than national, and therefore the declaration of a disaster will be at the state level. For example, there was no federal Stafford Act declaration of emergency for the 2001 anthrax attack.

[4]Some MOU and MOA templates are available online. Examples include Sonoma County, California (http://www.sonoma-county.org/health/ph/phpreparedness/pdf/cds_mou.pdf); Franklin County Board of Health, Ohio (http://centralohioready.org/files/Mass%20Prophylaxis%20Dispensing%20Contract.pdf); and New Mexico (http://nmhealth.org/HEM/SNS/documents/ClosedPODMOUforReceiptandUseofMedicalCountermeasures-Federal-031210.doc).

The national guidance should address the range of roles that private-sector entities might play in the MCM distribution and dispensing system, including logistical support for distribution and dispensing, retail pharmacies dispensing to the general public, closed PODs in all kinds of workplaces, workplace caches of MCM, and private-sector rotation of state and local stockpile material to decrease replacement costs. Although the proposed national guidance (and the process for its development) would include consideration of prepositioning and workplace caches—the topic of this study—it is critical that these strategies be considered within the overall context of enhancing private-sector participation rather than being addressed in isolation. Box 4-2 outlines key components that might be included in national-level guidance for public-private coordination in prepositioning, distributing, and dispensing MCM.

Across the various components of the national guidance, plans should leverage private-sector partners' existing systems and networks wherever possible. This would likely increase private-sector entities' willingness to participate since it would entail a lesser burden in terms of both cost and effort while also taking advantage of private-sector expertise and design efficiencies.

BOX 4-2
Key Components of National Guidance for Public-Private Coordination in Prepositioning, Distribution, and Dispensing of Medical Countermeasures

The national guidance might include (but should not be limited to):

- mechanisms for sharing threat assessments among all partners;
- a model memorandum of understanding;
- security requirements;
- roles and responsibilities of each partner;
- processes for communication both between public and private entities and within the participating private-sector entity;
- guidance on who would have authority to initiate dispensing;
- processes for inventory control and liability protection;
- processes for implementing workplace caches;
- strategies to reduce the costs associated with obtaining, maintaining, and replacing expired product; and
- mechanisms to encourage a uniform state approach to reducing legal and regulatory barriers to prepositioning, distribution, and dispensing.

Finding 4-1: *Private-sector entities may be interested in developing systems through which they can preposition, distribute, and dispense antibiotics to help ensure the safety of employees and their families and to provide for business continuity. Many large private-sector companies already have systems through which they communicate effectively with their employees, and they often have medical staff and other resources that could be used to enhance dispensing capacity within their communities during a time of crisis. However, potential private-sector partners face many barriers, including liability, cost, legal and regulatory issues, and the complexities of working across multiple jurisdictions during the development of MCM dispensing plans.*

> ***Recommendation 4-1: Develop national guidance for public-private coordination in the prepositioning, distribution, and dispensing of medical countermeasures.***
> **The Department of Health and Human Services should convene state, local, and tribal governments and private-sector organizations to develop national guidance that will facilitate and ensure consistency for public-private cooperation in the prepositioning, distribution, and dispensing of medical countermeasures and help leverage existing private-sector systems and networks.**

Workplace Caches

As discussed above, workplace caches are one potential way in which private-sector entities could participate in MCM distribution and dispensing. Here the committee examines the specific strategy of private-sector prepositioning of MCM on-site in the workplace or storage of MCM on the company's behalf in a nearby pharmaceutical distributor warehouse.

Most existing plans to dispense antibiotics in workplaces via closed PODs rely on postevent supplying of the MCM by the SNS or a state or local stockpile. However, closed PODs could dispense MCM from several potential sources:

- SNS or state or local stockpile (distributed postevent),
- manufacturers or pharmaceutical distributors (distributed postevent),
- a cache on-site at the workplace (prepositioned), or
- dedicated caches at nearby pharmaceutical distributor warehouses (prepositioned).

Potential advantages As noted earlier, closed PODs at workplaces could decrease the burden on public health open PODs regardless of the source of the MCM. Prepositioning MCM in on-site workplace caches or in

dedicated caches in nearby pharmaceutical distributor warehouses also would alleviate the burden on the SNS or state or local RSS system. On-site caching may be particularly advantageous for employers that already have occupational health personnel on staff, mitigating many of the logistical and legal challenges involved (discussed in detail below). Especially in the case of large companies with many employees, closed PODs served by prepositioned caches could therefore alleviate the burden on the entire public health distribution and dispensing system and enhance the overall dispensing capacity in a jurisdiction while also potentially reducing costs by relying on private-sector efficiencies.

For employers, having an on-site MCM cache could minimize absenteeism due to incident-related concerns, allowing the company to maintain critical operations or to recover from a resulting business interruption more quickly. In a public health emergency, this capability is especially critical for hospitals, health care providers, and public and emergency services, as well as for critical infrastructure (e.g., public utilities). With on-site MCM caches, employers could provide prophylaxis to employees even if the public health distribution system became overwhelmed following a large-scale anthrax attack. However, additional costs and complications are associated with moving from a closed POD model with MCM supplied by the SNS or a state stockpile to a prepositioned workplace cache model, as described in more detail below.

Current prevalence of workplace caches The committee is unaware of examples of private-sector companies that have developed workplace caches of MCM for their employees and families. Many companies have expressed willingness to dispense SNS or state MCM via closed PODs but have significant concerns about caching the MCM on-site. These concerns include storage space, liability, pharmacy laws, internal and external command and control, and replacement costs, as described below.

Companies have shown more interest in stockpiling antiviral medications, and in 2008, CDC issued guidance to advise employers that are interested in stockpiling antiviral medications for pandemic influenza (CDC, 2008a). In 2009, the H1N1 influenza pandemic greatly increased private-sector interest in MCM distribution and dispensing (IOM, 2010a). It is not clear, however, whether the systems developed to administer influenza vaccine would transfer directly to a response to threats such as anthrax because in the latter cases, MCM would have to be administered much more rapidly than would influenza vaccine.

Logistics As mentioned above, most existing workplace (closed POD) dispensing plans rely on the MCM being supplied by either the SNS or a state stockpile. Logistical arrangements are outlined in an MOA and include

the responsibilities of state and local governmental health agencies and the closed POD sponsor. The MOA addresses liability issues, particularly those associated with the PREP Act and Food and Drug Administration (FDA) Emergency Use Authorization (EUA) requirements, as well as required risk communication and any reporting requirements. Prepositioning MCM in these types of sites would be relatively simple administratively. The relationship already exists, legal issues have been addressed, and roles and responsibilities have been defined. Prepositioning would, however, entail two additional logistical issues: secure and climate-appropriate storage, and MCM replacement upon expiration and disposal of the expired MCM.

Workplaces considering a prepositioning strategy face the challenge of finding space to house a stockpile and maintaining it under appropriate climatic conditions to ensure that the medication remains potent and to comply with prescription laws. The average dimensions of a pharmaceutical pallet are 48 by 48 inches (Missouri Department of Health and Senior Services, 2008); for workplaces with large numbers of employees, identifying physical space for storage could be an obstacle. Both antibiotics currently stockpiled for anthrax prophylaxis must be stored in a dry climate at approximately room temperature (ciprofloxacin must be stored below 86°F [FDA, 2011], while doxycycline can be stored at room temperature, at 68-84°F [NLM, 2008]). In addition, workplaces would need a permit from their state pharmacy regulatory agency to store MCM (or any other prescription medication) on-site (NABP, 2010).[5]

Medical professionals might not be necessary to staff a closed POD after an emergency since the emergency declaration could authorize nonmedical personnel to dispense MCM, but medical professionals would be needed to purchase MCM and store them in a workplace cache in advance of an emergency declaration. Businesses that employ medical professionals or that have occupational health programs may be particularly well suited to developing workplace caches since the required staffing already exists.

Appropriate security measures would be needed to safeguard the cached MCM and to ensure their secure transportation if storage and dispensing were carried out at different locations. Organizations also would have to plan for the safety of the personnel securing and dispensing the medications. If dedicated personnel were required for this task, that cost would have to be factored into the overall cost of maintaining a cache.

Private-sector entities would be responsible for monitoring the expira-

[5]Section 104 of the Model Pharmacy Act, a version of which has been adopted by most states, defines the practice of pharmacy to include "proper and safe storage of Drugs and Devices" (among other things). Private organizations caching antibiotics on-site would fall within this definition in the absence of an emergency declaration and issued EUA, and therefore be required to obtain a permit/license to "practice" pharmacy.

tion dates of cached MCM, disposing of expired MCM, and replenishing the cache. These processes increase the logistical burden and costs of maintaining a cache. Currently, no mechanisms are available to defray the costs of replenishing expired stock, as only federal stockpiles are eligible for the SLEP (see Chapter 3) (Courtney et al., 2009). Unlike caches at health care locations, workplace caches cannot be rotated through routine health care delivery using a first-in/first-out approach to avoid expiration.

Legal considerations Private-sector entities serving as closed PODs would have to consider many applicable federal and state laws and regulations. The Public Health Law Network has outlined the following legal issues relevant to private-sector entities that serve as closed PODs:

- impact of an official declaration of emergency, disaster, or public health emergency;
- MOU between a public health agency and an entity;
- ownership of medical supplies;
- medical personnel;
- authorization to dispense medications;
- EUAs;
- liability;
- workers' compensation;
- privacy (Health Insurance Portability and Accountability Act [HIPAA] Privacy Rule and state privacy law compliance); and
- reporting and documentation requirements (Public Health Law Network, 2011a).

In addition, employers caching medications on-site would have to consider some other legal issues, including compliance with state laws for pharmaceutical distribution, prescription, and storage; liability concerns associated specifically with the cached medications; liability if MCM were dispensed outside of a declared emergency; the possibility of the government's taking the MCM; and concerns about setting up an entitlement for employees. As noted above, laws and practices vary significantly from state to state, which greatly complicates the situation for large national companies.

The primary legal obstacle for non–health care entities is identifying and complying with state and federal laws governing prescription medications and the purchase of medications (CDC, 2008a). Private-sector entities seeking to cache antibiotics for anthrax would first have to identify someone licensed to have them and therefore allowed to purchase them. Companies that employ medical professionals, such as in an occupational health program, might be able to use those individuals to fill this role.

Without such a licensed staffer, however, organizations would have to look to other mechanisms for obtaining MCM within the confines of the law. One remedy would be for the organization to contract with a physician organization. The physicians would write the prescriptions for the MCM to be stockpiled, and a mail-order pharmacy would deliver the MCM to the organization (Shulman, 2011).

Once a cache had been established, private entities or other workplaces would have to monitor the expiration date of the MCM and ensure that expired medications were disposed of and replaced. Federal laws regulate expiration dates placed on medication in its original packaging (usually in mass containers of hundreds of doses that must be separated to be dispensed), while states often establish the expiration of individual prescriptions at 1 year from the time the prescription is filled.[6]

Regardless of whether antibiotics were prepositioned or received from the SNS or a state stockpile, non–health care entities dispensing MCM would face certain liability issues. Under noncrisis conditions, dispensing prescription medications outside of the traditional health care system (at the workplace) exposes organizations to significant legal liability for any adverse events that might be experienced. During a federally declared emergency, however, the provisions of the PREP Act extend liability protections to all entities and individuals involved in the distribution and/or dispensing of approved MCM—including nongovernmental entities and persons (see Chapter 3 for further discussion; Public Health Law Network, 2011b). As noted in Chapter 3, however, some private-sector representatives continue to cite liability concerns as a barrier to increased participation in MCM distribution and dispensing plans (IOM, 2010b).

Entities that prepositioned antibiotics would face specific legal concerns that could increase their risk of liability compared with those acting as a postevent POD. First, if an organization were to dispense MCM prior to an approved EUA, it would be operating outside of its legal authority and the protection offered by the PREP Act. In contrast, SNS materiel is likely to be covered automatically by the PREP Act by the time it reaches PODs. Second, organizations could be liable for MCM cached on-site that were stolen and then used in a way that caused harm. This concern might be decreased by storing the medications securely and developing processes for access. Third, even during an emergency, PREP Act coverage does not limit an organization's liability if the MCM was stored improperly. Constant

[6]Federal Law: Food, Drug, and Cosmetic Act (21 U.S.C.). Rockville, MD: FDA, http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct ucm 086299.htm#chapV (accessed August 5, 2011). State Law: NABP*LAW*® database search of state "prescription labeling requirements," conducted in November 2008 and provided to the committee by E. Lewalski, National Association of Boards of Pharmacy, July 18, 2011.

monitoring of cached materiel could pose both a logistical challenge and a financial burden. Fourth, in developing a workplace cache, employers could be perceived to be establishing a contract to provide employees with MCM after an attack.[7] If they were unable to meet that obligation, perhaps because of extenuating circumstances arising from the aftermath of the attack, the organization could be held liable.

Finally, while there are no federal laws allowing or prohibiting public officials from reallocating private stockpiles during an emergency (known as "taking"), there is concern that the breadth of emergency powers granted to many governors might make public seizure of private stockpiles a reality (Gostin et al., 2002). This scenario was voiced as a barrier to private-sector prepositioning at the committee's public workshop (Turnbull, 2011). The PREP Act does afford private businesses some reassurance because it denies liability protection to assets that have been seized. The private and public sectors also can enshrine private ownership of private caches through independent legal agreements (MOUs or MOAs) that complement or supersede states' emergency powers; however, local governments may want to retain the right to take a private stockpile if the crisis should require doing so (Mathias, 2011). Public-private coordination in an overall dispensing system would decrease the incentive for governments to seize private stockpiles because those stockpiles would be seen as part of a single system, benefiting the entire population by off-loading demand on public PODs.

Caches in Other Non–Health Care Settings

Caches also could be established in community- and faith-based organizations and educational institutions.

Community- and Faith-Based Organizations

Service networks that serve vulnerable populations could play an important role in enhancing access to MCM for vulnerable populations, including people with low incomes and/or limited transportation, people with no or limited English proficiency, historically underserved ethnic/racial groups, people with disabilities, people who are homeless, and people who are homebound. These service groups include, for example, mutual association groups based on language or cultural commonalities; member organizations of the National Voluntary Organizations Active in Disaster; and service organizations such as Meals on Wheels, the Red Cross, local agencies on aging, and home health care services (Janis, 2011; Silver, 2011). Some vulnerable populations may not be best served by traditional public

[7]Personal communication, J. Hodge, Public Health Law Network, June 22, 2011.

PODs because of issues of lack of trust of government services, mobility, and other demographic factors (Janis, 2011). However, community agencies could help provide better MCM access to the populations with whom they already interact by serving as PODs or by dispensing MCM via their usual service delivery systems.

Similarly, houses of worship often participate in the traditional MCM dispensing system by serving as open PODs and channels of reliable public health communication. The availability of staff and volunteers, status as a trusted place of gathering, and ability to accommodate the influx of a large number of people make houses of worship suitable to assist in dispensing MCM. In addition, houses of worship frequently are organizations with the ability to reach vulnerable groups such as non-English-speaking populations. Community groups that focus on disaster response, such as Community Emergency Response Teams (CERT), could also potentially play a role in dispensing MCM in their neighborhoods.

However, most community- and faith-based organizations lack the infrastructure and staff required to preposition MCM. These organizations may be better suited to serve as PODs or use other existing service delivery systems to dispense MCM delivered postevent. Some agencies—for example, food banks with their climate-controlled warehouses—may already have the capacity to provide appropriate storage conditions (Smith, 2011). However, these agencies would be unlikely to have medical staff permitted to purchase and store MCM.

Certain faith-based and other nonprofit human service organizations may have internal expertise in storing and dispensing medications and could be identified as potential prepositioning partners. These organizations might include, for example, home health care services and houses of worship with established health programs, such as faith community nursing, which promotes holistic and preventive care within faith communities. Prepositioning MCM with these agencies could alleviate the postattack burden on the traditional distribution system if the agencies were willing and able to meet the regulatory requirements of maintaining caches.

Educational Institutions

Schools have been suggested as logical venues for prepositioning, especially considering the need to address concerns that children have equal access to MCM (Anderson, 2011). Primary and secondary schools have both an infrastructure for and experience with interacting with children and their families, sometimes employ nurses, and often have the space required for MCM storage. Yet as large, trusted gathering places, schools usually are already involved in the local dispensing system as public (open)

PODs, making it difficult to rely on them as closed PODs for students and staff as well.

Universities, on the other hand, might be better equipped to preposition and dispense MCM without the previous commitment to act as open PODs. They employ health care personnel and experienced staff, have the space for MCM storage, often are the place of residence for large numbers of students, and in some cases are the largest local employer (Turner, 2011).

PREDISPENSED MEDICAL COUNTERMEASURES

Predispensing occurs when MCM, such as antibiotics, are stored by the intended users or by heads of households or other nonmedical caregivers for use by those in their care. Predispensing MCM is unique relative to other potential prepositioning strategies because it puts the MCM directly into the hands of the intended end-users. This introduces potential health risks to both individuals and the community that do not exist for prepositioning strategies such as forward-deployed and cached MCM. Predispensing MCM also involves a different set of logistical, communications, behavioral, and legal considerations compared with prepositioning strategies in which the MCM are not stored by the end-users.

The development of a strategy for predispensing MCM involves consideration of both *function* and *form*. *Function* refers to the role of the strategy within a jurisdiction's overall MCM dispensing plan. For example, predispensing could be used to dispense MCM broadly to the general public in a community, or it could be used only to target specific subpopulations or individuals, such as those who lack timely access to MCM through other mechanisms. *Form* refers to the specific manner in which the MCM is predispensed, including the following:

- *Personal stockpile*: MCM that is dispensed to individuals pre-event via normal prescribing routes for use during a public health emergency.
- *MedKit*: A medical kit containing prescription pharmaceuticals that is dispensed pre-event to families or individuals for use only as directed during a public health emergency.
  - —*EUA MedKit*: A medical kit approved by the FDA under its EUA for off-label use.
  - —*FDA-approved MedKit*: A medical kit approved by the FDA for labeling and use as a predispensed MCM.

An over-the-counter MedKit is a theoretical possibility, but the committee did not consider this to be a feasible option since the FDA has never approved any antibiotics for over-the-counter use, and this strategy also

would run counter to current public health efforts to restrict the widespread use of antibiotics, as discussed in greater detail below.

This section of the chapter is organized primarily by *function*: it first examines predispensing MCM to the general public in a community and then examines predispensing to targeted subpopulations within a community. This latter strategy is illustrated using two examples: certain first responders and critical infrastructure workers and their families, and selected patients. For each function, the committee discusses potential benefits; concerns about inappropriate use; concerns about the flexibility and adaptability of the strategy; storage and stability issues; and practical considerations such as logistical burdens, legal issues, and communications. The discussion of each function also includes the potential impact of the form in which the MCM is predispensed. First, however, an overview of the available evidence on predispensing strategies is presented.

Overview of Available Evidence

The evidence base available for assessing the use of predispensing strategies is limited. The predispensing of antibiotics for anthrax has been tested in one pilot study in St. Louis, Missouri, and has been implemented for a limited group of postal carriers who volunteered for the Minneapolis-St. Paul pilot of the postal model. These examples are summarized below and provide some insight into predispensing of antibiotics for specific subpopulations; however, significant limitations hinder generalization to the general public and to circumstances beyond those in the St. Louis study and the Minneapolis-St. Paul pilot program. Predispensing of antibiotics has never been tested in an actual emergency or tried with the general population.

The committee also considered evidence from other potential models, including the misuse of antibiotics prescribed during routine medical care; the predispensing of potassium iodide (KI) to those living within 10 miles of a nuclear power plant; and the general public's response to crises in which MCM are indicated only for a narrowly defined potentially exposed population, such as during the 2001 U.S. anthrax attack and the 2011 nuclear accident in Fukushima, Japan.

Some examples of predispensing MCM exist in other countries, such as a previous program to preposition antidotes for nerve agents in homes in Israel (suspended because of a lack of cost-effectiveness) (Stoil, 2010). Because of the different political and cultural environments and the differences in health care systems and regulations, however, the committee did not think these examples would provide reliable evidence to inform the use of predispensing in the United States.

The sources of evidence considered by the committee are introduced here, with brief discussion of how each source informs (or does not inform)

the evaluation of predispensing strategies for anthrax, in both function and form. The specific findings from each source are discussed throughout the following sections on predispensing for the general public and for targeted subpopulations.

Misuse of Antibiotics for Routine Medical Care

Antibiotics are commonly prescribed during routine medical care, and their misuse also is common, including failing to complete the recommended regimen, skipping doses, and reusing leftover doses (e.g., Kardas et al., 2005). The committee considered available data on misuse of routinely prescribed antibiotics to inform conclusions about the likelihood that the general public will use predispensed antibiotics—intended for use during an anthrax attack—outside of a declared emergency. The committee found no data on antibiotic misuse that would inform predispensing for particular targeted subpopulations. In terms of the form of predispensing, this example aligns most closely with personal stockpiling of antibiotics for anthrax, since both involve standard prescription vials. However, provision of a regular prescription bottle specifically as a predispensing method for anthrax has never been studied, and no evidence is available to help determine whether antibiotics dispensed for protection against anthrax would be treated the same as those dispensed during routine medical care. In the absence of research examining this question, the committee judges that the two situations would likely show comparable rates of misuse.

MedKit Pilot Study: St. Louis, Missouri

In 2006, the Missouri Department of Health and Senior Services, in collaboration with CDC, placed prototype MedKits containing a blister-packed 5-day supply of doxycycline in more than 4,000 homes in St. Louis (CDC, 2007b, 2008b). The study population comprised three cohorts: clients and some employees of a community health clinic, employees from 10 major corporations, and first responders. To ensure compliance with state and federal regulations, the prototype MedKit was classified as an Investigational New Drug (IND), and the prospective pilot study was conducted under an IND protocol. The pilot study was the first effort to test the ability of households to store and maintain the MedKits properly, including saving them for emergency use only, and to assess attitudes and perceptions regarding the kits and factors that might influence how participants maintained or used them. Limitations of the study that were discussed at a 2009 IOM workshop included that it did not test whether participants were able to follow the enclosed instructions for preparing and using the antibiotics accurately and safely (a general challenge for any dispensing

mechanism), nor did the study test how the medication was impacted by actual storage conditions in participants' households (a significant challenge for predispensing as therapeutic effectiveness can be affected by improper storage) (IOM, 2010b).

Households were randomly assigned to follow-up after 2, 4, or 8 months, at which point an exit interview was conducted and the MedKit was collected. A monetary incentive was offered to participating households, consisting of a $25 gift card provided at the time of the initial interview and another $25 gift card upon completion of the follow-up interview.[8]

Participants were not necessarily representative of the general population of St. Louis or of the United States (e.g., with regard to level of education or incentive to participate). However, the three study cohorts did have varied characteristics:

> Clinic Cohort generally had lower levels of educational achievement, employment, and household income than the other two cohorts, was more likely to be African American, and was less likely to have health insurance coverage. The Business Cohort respondents were two-thirds female, and one[-]third reported an annual household income of greater than $80,000. They also accounted for 50% of the study population's graduate-level education. The First Responder Cohort respondents were predominately male (67%) and the majority were married (68.5%). First responders were also more likely to have health insurance coverage (96.9%). (CDC, 2008b, p. 6)

Although the study participants were not representative of the general public, these variations in their characteristics—for example, a cohort with a lower level of education than average and two cohorts with higher education than average—mean that this study could potentially provide some sense of the range of behaviors that might be expected if predispensing were implemented for the general public. Given the sparseness of available data on predispensing, the committee carefully considered the results of this study but ultimately concluded that it has limited utility as a model for predispensing for the general public because some design features could have biased participants toward greater adherence to instructions than would be expected outside of the study environment. Specifically, the study offered a financial incentive for participation, there was a selection bias toward those interested in volunteering, the follow-up periods were short, and the level of supervision and screening might not be possible if the strategy were used on a much larger scale over a longer period of time.

The committee did, however, consider the evidence from the first responder cohort to be useful as a model for predispensing in targeted sub-

[8]Personal communication, Linda Neff, lead study author and senior epidemiologist, CDC, June 17, 2011.

populations. In this case, (1) the study population was more aligned with the subpopulation under consideration, (2) the level of supervision and screening provided in the study could similarly be provided in the first responders' workplaces, and (3) the financial incentive to participate in the study could have an effect comparable to that of an employer directive to adhere to instructions. Concerns about selection bias still do somewhat limit the applicability of this evidence, however.

With regard to the form of predispensing, this model informs the use of a MedKit (either through an EUA or FDA-approved) in terms of the range of potential rates of inappropriate use. This model also aligns most closely with the committee's definition of an EUA MedKit in terms of costs.

MedKits for Postal Workers in Minneapolis-St. Paul

As discussed in Chapter 3, postal carriers who volunteered to participate in the Minneapolis-St. Paul pilot of the postal model for MCM distribution were provided with MedKits to keep in their homes, containing sufficient quantities of antibiotic for themselves and their families. The MedKits would help ensure that postal carriers would be protected as they delivered MCM to the community. The provision of the MedKits to volunteers was a condition of participation negotiated by the postal workers' union and the U.S. Postal Service (USPS) (IOM, 2010b). The MedKits contained a short-term supply of the antibiotic doxycycline; postal carriers with a contraindication for doxycycline (e.g., an allergy) could not participate in the pilot program. Under the program, individual MedKits also were kept in the participants' workplaces for use should an attack occur when the postal carriers were already at work.

To ensure compliance with state and federal regulations, an EUA was obtained to authorize the distribution of the MedKits—referred to as a "household antibiotic kit" in the EUA (FDA, 2009). According to the conditions of the EUA, the USPS must survey participants every 6 months regarding the status of their MedKits (e.g., storage conditions, expiration of antibiotic, use of antibiotic). The USPS also is responsible for collecting expired antibiotic and turning it over to the designated public health authority for disposal and accountability record keeping. Upon termination of the EUA, the USPS must collect all MedKits and turn them over to public health authorities. This program did not assess participants' ability and willingness to take the MCM as instructed.

As with the household MedKit pilot study in St. Louis, the participants in the Minneapolis-St. Paul pilot are not necessarily representative of the general population. Volunteers were generally white, male, older, highly educated, and likely to comply with guidance (Griffith, 2011). In addition, they volunteered to participate, and the MedKit program was developed

in exchange for postal workers' agreement to participate in the pilot of the postal model for dispensing MCM to homes throughout the community. It could be argued that the families of postal workers can be considered representatives of the "general public" because, for example, they may not necessarily have the higher education levels of the family members who work for the USPS. However, postal workers' family members likely have a financial and social incentive to comply with instructions of the workers' employer regarding adherence and saving the kit for emergency use. Therefore, the committee judged that the evidence from the postal pilot informs primarily predispensing to targeted subpopulations.

Examples Involving Potassium Iodide

The only example of widespread MCM prepositioning in homes that has been employed in the United States is the dispensing of KI to those living within 10 miles of a nuclear power plant (Box 4-3). This example has limited use as a model for predispensing of antibiotics because of key dif-

BOX 4-3
Prepositioned Potassium Iodide for People Residing Near Nuclear Power Plants

- Potassium iodide (KI, provided in tablet form) prevents the thyroid gland from absorbing radioactive iodine that can cause cancer and death.
- Several thousand people across the United States live close enough to nuclear power plants to be affected in the event of a containment breach.
- For this reason, in 2001 the U.S. Nuclear Regulatory Commission (NRC) suggested that states consider prepositioning KI pills in the homes of those potentially affected by a nuclear containment breach.
- As of February 2005, 20 states had requested—and the NRC had provided—KI for their populations living within 10 miles of a nuclear power plant.
- Once the KI is received, states direct its prepositioning within their borders.
- Studies suggest that significant public education, outreach, and effective risk communication are necessary for preemptive distribution of KI to be effective.

SOURCES: Blando et al., 2007; NRC, 2009.

ferences between KI and antibiotics. First, there is no reason for the public to take KI other than for protection following a radiological/nuclear emergency, while some people could be tempted to take predispensed antibiotics to treat a perceived infection. Second, KI is not a prescription medication, meaning that it is not subject to the same legal and regulatory requirements as antibiotics. And third, KI is a stable salt, unlike antibiotics, which degrade and require regular collection and replacement potentially every year (in light of current prescription law), although the packaging does still have a printed expiration date as required by the FDA.

2001 U.S. Anthrax Attack and 2011 Japanese Nuclear Crisis

Some useful insights into social behavior may be gleaned from the public's response during the 2001 U.S. anthrax attack and the reaction in the United States following the nuclear accident in Fukushima, Japan, in March 2011 (for an overview of the former, see Jernigan et al., 2002, and of the latter, see IAEA, 2011).

Two research groups have reported that during and after the 2001 U.S. anthrax attack, there was a significant increase in patient requests for anthrax-related antibiotics in areas of the country not affected by the attack (i.e., areas outside of New York; Washington, DC; and Florida) (Belongia et al., 2005; M'ikanatha et al., 2005). The physicians surveyed reported not only an increase in patient requests but also an increase in their own prescribing of such antibiotics as a result of these requests. M'ikanatha and colleagues (2005, p. 1) conclude that "public fears may lead to a high demand for antibiotic prophylaxis during bioterrorism events."

Likewise, the nuclear meltdown in Fukushima in the aftermath of the 2011 Japanese earthquake engendered some panic in the United States, despite messaging from the federal government that no risk of harmful radiation exposure existed to U.S. residents; some Americans still perceived the risk of harmful radiation exposure to be significant. The media reported that pharmacies around the country sold out of KI, that all three manufacturers and suppliers of FDA-approved KI treatments sold out just a few days after the earthquake and tsunami hit Japan, and that a surge in prices occurred for KI products sold online (Aleccia, 2011; Lazaruk, 2011). Reports also cited customers purchasing what they thought were KI pills, only to find later that the product was fake or of an inadequate dosage (Lazaruk, 2011). Unfortunately, no research has been done on the breadth of public concern and the extent to which the panic was fanned and exaggerated by the media. The only data the committee could find on how many people actually took KI in the United States after the meltdown in Japan come from an MSNBC.com article, which stated that the American Association of Poison Control Centers said seven adverse reactions to KI

had been reported among its 57 poison control centers across the United States; two of these reactions were reported to be serious, including vomiting, racing heart rates, and vertigo (Aleccia, 2011).

Despite the extremely limited evidence, the committee considered these examples in its deliberations on predispensing of anthrax antibiotics for the general public because they are the only source of evidence that provides insight into how people might behave with predispensed MCM during an actual emergency. With regard to the form of predispensed antibiotics, however, KI does not align specifically with either personal stockpiles or MedKits since it does not require a prescription.

Table 4-2 provides an overview of the available evidence relevant to two functions of predispensing (for the general public and targeted subpopulations) and several potential forms of predispensed antibiotics. The table clearly shows the gaps in the available evidence. In particular, it highlights the complete absence of evidence on personal stockpiling and the lack of evidence with which to compare and select among the potential forms of predispensing: personal stockpiles and MedKits—EUA, IND, and FDA-approved. The results of these studies and the implica-

TABLE 4-2
Overview of Available Evidence to Inform Predispensing Strategies

Evidence Source	General Public	Targeted Subpopulations[a]
General Antibiotic Use	Extensive evidence	*No available evidence*
Personal Stockpile	*No available evidence*	*No available evidence*
MedKit—FDA-Approved[b]	*No available evidence*	*No available evidence*
MedKit—Investigational New Drug (IND)	Limited evidence: St. Louis study[c]	Limited evidence: first responder cohort from the St. Louis study
MedKit—Emergency Use Authorization (EUA)	Extremely limited evidence: families of some postal workers in Minneapolis-St. Paul[c]	Limited evidence: some postal workers in Minneapolis-St. Paul
Potassium Iodide (KI)	Extremely limited evidence: U.S. public response to the nuclear accident in Japan	*No available evidence*

[a] For example, first responders, critical infrastructure workers, postal workers, and their families; patient populations.

[b] A Food and Drug Administration–approved MedKit did not exist at the time this report was written.

[c] Limitations include participants not necessarily being representative of the general public, financial incentive or employer instructions, selection bias, and high degree of screening and supervision.

tions of these evidence gaps are discussed throughout the remainder of this chapter.

Predispensing to the General Public

Predispensing has the potential to significantly benefit members of the general public after an anthrax attack by reducing the time to prophylaxis for those individuals possessing the predispensed antibiotics and potentially alleviating the burden on the public PODs, which in turn would reduce the time to prophylaxis for individuals receiving their antibiotics from those sites. These potential health benefits and the costs associated with this strategy are discussed below; a framework for assessing the trade-offs between these benefits and costs is presented in Chapter 5. As described below, however, the decision to employ predispensing as a general public health strategy also should take into account the significant concerns about potential health risks, the inflexibility of this strategy, and associated practical burdens.

The major determinants of the magnitude of the risks associated with predispensed antibiotics are the maximal acceptable delay in prophylaxis following exposure and the risk of an attack. With a shorter acceptable time to initiate prophylaxis and a higher risk of attack, the risks of adverse events and inappropriate use become more tolerable. With a longer acceptable time to initiate prophylaxis and a lower risk of attack, the risks of adverse reactions and inappropriate use become less tolerable. Likewise, as discussed further below, the less well defined the exposed population, the more people will self-treat inappropriately, thus increasing that risk.

As discussed in Chapter 2, the available scientific evidence indicates that dispensing of MCM should occur within approximately 4 days of the time of exposure. If an attack were detected within the first 48 hours or so, jurisdictions might be able to use other dispensing strategies to reach the exposed population without incurring the potential health risks and practical burdens associated with predispensing (discussed below). However, if the window to treat were briefer, communities might determine that the potential health benefits associated with predispensing would outweigh the potential health risks, costs, and practical burdens. Chapter 2 raises the possibility of a shortened time window for effective prophylaxis delivery due to the uncertainties inherent in the available scientific data on the incubation period for anthrax and the concern that detection of an anthrax attack could be delayed. In addition, the committee acknowledges that risk data could be available at the classified level that would indicate a shorter time frame for prophylaxis.

This section examines issues related to predispensing MCM to the general public: concerns about inappropriate use; storage and disposal issues;

concerns about the flexibility of the strategy; and practical considerations such as communications, behavior and adherence, logistics, and legal issues. The discussion indicates how the form in which the MCM is predispensed would impact these issues.

Inappropriate Use

Safety is a primary concern associated with predispensing of antibiotics, particularly if predispensing targets the general public. This concern includes the potential for inappropriate use in routine settings (e.g., using the antibiotics to treat a cold) and the potential for widespread inappropriate use in response to a distant anthrax attack, a false alarm caused by a non-anthrax white-powder event, or some other public health emergency for which antibiotics are not indicated. In her testimony to the IOM committee, Nadine Shehab of CDC outlined several potential areas of concern: misuse, which could result in adverse reactions and increased antibiotic resistance; unintentional ingestion; dosing and dose delivery; drug interactions; stability and storage; and adherence (Shehab, 2011).

This section first outlines what evidence can be brought to bear to estimate the prevalence of misuse if antibiotics were predispensed among the general public, including a discussion of the potential impact of the MedKit's special packaging and emergency-specific instructions. The section then outlines the anticipated consequences of inappropriate use, including adverse reactions and the potential to contribute to increased community and antibiotic resistance.

Estimated prevalence A meta-analysis of antibiotic misuse found that in North America, mean adherence to antibiotic regimens was 57.4 percent (95 percent confidence interval [CI]: 44.0-70.8 percent); failure to adhere included not completing the entire course, missing doses, and reusing leftover doses (Kardas et al., 2005). A survey of more than 1,300 patients conducted in 2001 found that 17 percent had "self-prescribed" antibiotics left over from another illness (Richman et al., 2001). Most of the latter patients responded that they had used the antibiotics to treat a cough or sore throat without consulting a physician. This body of evidence suggests that the rate of misuse of predispensed antibiotics is likely to be high.

The example of KI use in the United States after the Japanese nuclear accident demonstrates the potential for misuse during a perceived emergency even when there is little or no risk of exposure. As noted earlier, in addition to the rush to purchase KI, limited evidence suggests some people actually took it, with seven adverse reactions being reported. Although it cannot be confirmed, these adverse reactions likely were related to KI prophylaxis among individuals concerned about the Japanese accident since

KI is not a recommended treatment for any other indication. The data on inappropriate use of KI are extremely limited; this is the only example of MCM use during an actual emergency. Given that the emergency occurred on the other side of the world, it appears likely that misuse of predispensed antibiotics would rise across the nation following a localized anthrax attack somewhere within the United States.

In contrast to the above two sources of evidence, misuse among participants in the St. Louis pilot study was very infrequent (CDC, 2007b, 2008b). There were 4,076 households in the final analysis:

- 97 percent returned their MedKit (blister packs intact, although some outer bags had been opened out of curiosity);
- 3 percent could not locate the kit (or refused to return it, in the case of five households); and
- 0.1 percent of households (four total) admitted to having used the medication.

The clinic cohort was more likely to report having used the MedKit (4 of 1,443 households, 0.3 percent) than the business and first responder cohorts, which reported no usage (out of 1,077 and 1,556 households, respectively). No analysis was presented as to whether this difference among groups was statistically significant. Although the overall rate of having taken the medication was low, the differences between the study conditions and the conditions under which MCM would be predispensed broadly to the general population make it difficult to extrapolate from these results to the expected rate of misuse in a *broad* predispensing strategy for the general public. As described above, the financial incentive to participate, selection bias, and the short follow-up periods limit the conclusions that can be drawn from this study to inform predispensing of MCM to the general public in a community.

Similar rates of return without opening were seen in the 6-month survey of participants in the Minneapolis-St. Paul pilot postal program. The first status check survey, conducted 6 months after initiation of the pilot program, found that the vast majority of volunteers had maintained their kit unopened (Griffith, 2011). One year into the program, 367 of the 377 kits held by active volunteers were returned, unopened, for scheduled replacement. As discussed above, however, the committee found that the postal workers could not be considered the "general public," and it would be a stretch to consider their families as such. Because of these limitations, the committee does not view this pilot program as compelling evidence in favor of dispensing MedKits for the general population.

The St. Louis MedKit study and the MedKit component of the Minneapolis-St. Paul pilot program suggest that misuse of predispensed

MCM would not be highly prevalent, but these examples have significant limitations, as described above. The overall prevalence of misuse of antibiotics and the recent experience with KI in the United States cast doubt on the likelihood of the general population's adhering to the requirements for a safe and effective home storage program for MCM, and therefore increase concerns about adverse outcomes and cost-effectiveness (cost-effectiveness is discussed in detail in Chapter 5).

Impact of form of predispensing It is not known whether the relatively low rates of misuse in the St. Louis study and the postal pilot are attributable to the special packaging used in MedKits or to other study features, such as the financial or other incentives to participate or the short follow-up period. Certainly the intent of the MedKit packaging is to decrease misuse, but no direct evidence exists linking low misuse rates to the form of packaging (e.g., a comparison of misuse rates from two cohorts, one of which is given a routine antibiotic prescription bottle and the other a MedKit). The most extensive body of evidence suggesting a high rate of misuse (of antibiotics generally) is aligned more closely with the committee's definition of a personal stockpile. However, no evidence exists as to whether antibiotics dispensed specifically for protection against anthrax would be treated in the same way as those dispensed during routine medical care, although it appears possible that the two situations would be comparable. These uncertainties call for a larger, more comprehensive study to test the impact of the form of predispensed MCM on rates of inappropriate use and to better test the feasibility of predispensing by omitting features that could artificially increase the rate of adherence to instructions, such as financial incentives for participation.

Finding 4-2: *The most extensive body of relevant evidence (statistics on the misuse of antibiotics prescribed for routine medical care) suggests that inappropriate use would be high if predispensing were implemented broadly for the general public. There are no appropriate data to bring to bear on the question of whether the rate of inappropriate use of MedKits (as currently designed) would be lower than that for personal stockpiles. However, future studies may be able to demonstrate that special packaging for MedKits (or similar products) could decrease the rate of inappropriate use.*[9]

Adverse events All antibiotics are associated with significant rates of adverse drug events (ADE), even when used appropriately. FDA-approved package inserts for most prescription medications list many ad-

[9]Along with other findings presented in Chapter 5, Finding 4-2 leads to Recommendations 5-4 and 5-5 in Chapter 5.

verse reactions.[10] In a systematic review of 24 doxycycline clinical trials (N = 3,833), the range of incidence of ADEs was 0 to 61 percent (Smith and Leyden, 2005). Although many of these ADEs were relatively minor (usually gastrointestinal), antibiotics also are associated with ADEs severe enough to result in an emergency department visit; indeed, 7 of the top 15 medications implicated in emergency department visits for ADEs in 2004-2005 were antibiotics (Budnitz et al., 2006). Data from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project, 2004-2006, showed that ADEs from antibiotics accounted for nearly one in five emergency department visits for ADEs, corresponding to approximately 140,000 visits annually in the United States (95 percent CI: 116,506-168,504) (Shehab et al., 2008). Although these ADEs were severe enough to lead people to visit the emergency department, 94 percent of the visits did not require admission (Shehab et al., 2008). Of the antibiotics indicated for the treatment and prevention of anthrax, doxycycline was associated with an estimated 5.8 (95 percent CI: 3.9-7.7) annual emergency department visits per 10,000 outpatient prescription visits; ciprofloxacin with 6.4 visits (95 percent CI: 4.5-8.4); and amoxicillin and penicillin with 15.5 visits (95 percent CI: 12.3-18.7) (Shehab et al., 2008).

Of 5,343 people who took at least one dose of antibiotics following the 2001 anthrax attack, 57 percent (N = 3,032) reported ADEs, but hospitalizations and severe ADEs were rare (Shepard et al., 2002). Of the 2,631 persons (49 percent) who failed to complete the recommended 60-day course of antibiotics, 43 percent indicated that the reason for discontinuation was ADEs.

Similar rates of ADEs could be expected for those who misused predispensed MCM. Broader and less targeted predispensing of MCM would

[10]FDA-approved labeling for doxycycline outlines the following adverse reactions: "Due to oral doxycycline's virtually complete absorption, side effects of the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines: **Gastrointestinal:** anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of the drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. . . . **Skin:** maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. . . . **Renal toxicity:** Rise in BUN has been reported and is apparently dose related. . . . **Hypersensitivity reactions:** urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus. **Blood:** Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported. **Other:** bulging fontanels in infants and intracranial hypertension in adults. . . . When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid gland. No abnormalities of thyroid function studies are known to occur" (Pfizer, 2011, pp. 12-13).

likely increase the numbers of ADEs. These rates of ADEs would likely be acceptable following an anthrax attack, when the potential benefits of the antibiotics would outweigh the potential risks, but might not be acceptable at other times.

Contraindications and warnings Some people are allergic to doxycycline and other antibiotics; of the estimated 140,000 emergency department visits for ADEs attributed to antibiotics, approximately 80 percent were due to an allergic reaction (Shehab et al., 2008). Doxycycline also can cause permanent tooth discoloration if taken during tooth development, and therefore it is not recommended during the last half of pregnancy or for infants or children under the age of 8 (Pfizer, 2011). Widespread availability of doxycycline in homes, combined with some evidence that family members often "share" prescription antibiotics, could conceivably increase the likelihood that a pregnant women or child would take doxycycline (Larson et al., 2003).

Antibiotic resistance Infectious disease experts have expressed concern that misuse of antibiotics in home MedKits could contribute to the growing problem of antibiotic-resistant microorganisms (IDSA, 2008; Navas, 2002; NBSB, 2008). Again, this issue would be of particular concern if predispensing were carried out on a large scale for the general public instead of for targeted subpopulations since the potential for large-scale misuse would be greater. Public health experts view antibiotic resistance as a major public health concern. The concept of predispensing runs counter to major educational efforts by CDC, the Alliance for the Prudent Use of Antibiotics (APUA), and others regarding the rational and limited use of antibiotics. CDC's national Get Smart campaign aims to reduce antimicrobial resistance by promoting more appropriate antibiotic use (CDC, 2010c). Comparable campaigns are conducted at the state level (e.g., Get Smart Colorado, 2011). APUA has similar aims (APUA, 2010).

Overuse of antibiotics not only increases selective pressure for the development of antibiotic-resistant organisms in the community but also leads to carriage of antibiotic-resistant organisms in individual patients. An additional concern is that selection for resistance to one antibiotic can result in resistance to multiple antibiotics because genes mediating resistance often travel together on transmissible genetic elements, such as plasmids or transposons (Bennett, 2008). Therefore, overuse of doxycycline could also lead to resistance to other, more commonly used antibiotics, such as penicillin, cephalosporins, and fluoroquinolones (e.g., ciprofloxacin). Again, impact depends on the extent of use: if an antibiotic is used broadly, the potential for resistance is greater than if use is more targeted and restricted. It is unclear, however, whether use of antibiotics predispensed as MCM would

be a significant contributor to resistance relative to other known factors, such as prescribing for nonbacterial infections, failure to adhere to dosage and length-of-administration instructions, and the use of antimicrobials in animal feed (Levy, 2001; Rambhia and Gronvall, 2009).

Storage and Disposal Issues

Storage and disposal issues include stability and storage conditions, the potential for unintended ingestion, and safe disposal.

Stability and storage conditions Prepositioning antibiotics in homes raises a number of concerns about storage conditions. First, are the products stable under home conditions? Most expiration testing is conducted in a dark, cool, dry place, but many people store their medications in a warm, moist bathroom. In the St. Louis MedKit study, 56.2 percent of participants stored the kit in a bedroom, 75.4 percent stored it in a closet, and 99.4 percent stored it out of the reach of children and pets. In this study, participants were given careful instructions to store the MedKits in a cool, dark, dry place out of the reach of children and pets; it appears likely that if predispensing were implemented broadly for the general public, storage conditions might more closely approximate those found for most medications. The St. Louis study did not test the impact on the medication of the storage conditions in which participants kept their MedKits (IOM, 2010b).

Having degraded drugs would give the individuals storing them a false sense of security. If the MCM were replaced every year, they would likely be stable enough to provide adequate protection against anthrax, regardless of the storage conditions (Injac et al., 2007). However, this strategy would impose substantial cost and logistical burdens (cost issues are discussed in Chapter 5). Finally, there are concerns that the stored MCM could be lost or stolen.

Potential for unintended ingestion If predispensed MCM were not stored out of the reach of children, the potential for unintentional/unsupervised ingestion by children would arise. Poison control centers receive approximately 1.5 million calls annually for pediatric overexposures, the majority of which are through ingestion (Bronstein et al., 2007). Approximately 58,000 emergency department visits annually are for unsupervised medication ingestion by children, and 1 of every 180 visits made annually by 2-year-olds to an emergency department is for a medication overdose (including unsupervised ingestion) (Schillie et al., 2009; Shehab, 2011).

Safe disposal of antibiotics Expired antibiotics stored at home must be disposed of safely. Improperly disposed antibiotics and other drugs in the

normal waste stream reach water supplies (Karthikeyan and Meyer, 2005). Expired antibiotics in a government-sponsored predispensing program would need to be collected and disposed of by a company with appropriate expertise, again adding to logistical and cost burdens. If predispensed MCM were available solely through an individual purchase and maintain system, they likely would frequently be stored long past their expiration date or disposed of improperly.

Impact of form of predispensing No data are available comparing how individuals would store and dispose of MedKits versus personal stockpiles and the effect on the stability of the MCM. The committee judges that the use of MedKits might encourage better storage conditions since the kits could be designed using a dark box to protect the antibiotics from light and with large-font instructions about avoiding storage in a bathroom. Rates of unintended ingestion would likely be similar since MedKits would be sealed, while standard prescription vials have child-safety features. The concerns and burdens associated with safe disposal would be similar unless a special dispensation were obtained to allow an extended expiration date for MedKits relative to the usual state prescription law.

Flexibility

In addition to misuse (discussed above) and cost-effectiveness (discussed in detail in Chapter 5), the primary concern associated with predispensing to the general public is the strategy's lack of flexibility. There are several specific concerns, described below: lack of ability to quickly provide alternative MCM; access to household stockpiles during an attack; dosing, dose delivery, and screening for contraindications and drug interactions; and inability to serve multiple purposes relative to PODs. Flexibility is examined in this section as it applies to predispensing strategies in isolation. The committee recognizes that if predispensing is used in conjunction with more flexible strategies (e.g., open PODs), the impact of potential challenges can be mitigated. As discussed in Chapter 5, however, this approach is costly because it requires the establishment and maintenance of multiple dispensing mechanisms.

One of the greatest concerns with predispensing strategies targeting the general public is the possibility that the anthrax used in an attack could be resistant to the predispensed antibiotic. This is a major concern for the entire dispensing enterprise, but particularly for predispensing strategies because, unlike the use of PODs, these strategies involve no infrastructure that could be used to rapidly dispense a different MCM, the communication challenges would be immense, and the loss of public trust would likely be great. As currently conceptualized, predispensing would involve a

single antibiotic, such as doxycycline. One conceivable way to mitigate the concern about drug-resistant anthrax would be to develop a predispensing model involving multiple MCM. After an attack occurred, public health authorities would give instructions such as "take the blue pill." This strategy would be somewhat similar to the current Australian Flying Doctors model, in which a series of common medications, including antibiotics, are prepositioned in medical chests in rural towns throughout Australia. When residents become ill, they call a hotline to speak with a health care professional and are told which medications to take from the chest and how often (RFDS, 2011a,b). However, safety risks increase with multidrug models, and cost would increase as well since this strategy would likely entail adding medications beyond the current least expensive antibiotics, ciprofloxacin and doxycycline.

Another concern associated with predispensing antibiotics to be stored in the home is that people may not be at home or may not be able to get there in the event of a bioterrorism attack. This possibility degrades the presumed reduction in time to prophylaxis that is the driving force behind predispensing strategies. Moreover, while any dispensing strategy carries the risk that exposed individuals will commute outside of areas in which they will be able to receive timely prophylaxis, predispensing MCM may convey a false presumption of lower demand at public PODs, which will not be the case if many or most individuals are unable to reach their MedKits. As discussed above, postal carriers who volunteered to participate in the Minneapolis-St. Paul postal model pilot were provided with two MedKits: one to keep in their home and one for their workplace. Although providing more flexibility to adapt to the situation, this solution decreases cost-effectiveness and increases waste and disposal needs.

Special dosing and forms of dose delivery may be required for children, pregnant and lactating women, older adults, people with renal impairment, and adults who cannot swallow tablets. Concern has been raised about the lack of evidence on palatability and the ability of parents and other adults to follow instructions for preparing child doses (NBSB, 2008; Robbins, 2011). The committee concludes, however, that (unlike with the issue of antibiotic-resistant anthrax raised above) this is a surmountable issue. First, challenges of accurate dosing are common to all dispensing strategies and are not unique to predispensing. Deviations from proper dosage for children are minimized through a combination of increasing parents' health literacy, providing parents with easy-to-use dosing instruments (e.g., oral syringes versus cups), and utilizing color coding (Frush et al., 2004; Yin et al., 2010). Another concern regards screening for contraindications and drug interactions. Although screening could be performed when the antibiotic was predispensed, individuals' health situations could change; for example, women could become pregnant. The committee also concluded

that this issue would be surmountable by using clear instructions in the packaging. Nevertheless, the committee notes that it may be easier to address these issues in a POD than in a predispensing strategy.

Lastly, POD infrastructure can be used for many public health functions other than postexposure prophylaxis against anthrax, such as influenza vaccination and postexposure prophylaxis following exposure to hepatitis. In contrast, predispensing likely would not serve multiple purposes, which suggests that PODs may be more cost-effective and a better use of planning resources.

The form of predispensing does not impact concerns about lack of flexibility related to antibiotic-resistant anthrax, lack of access to MCM stored at home during an attack, and inability to serve multiple purposes. MedKits may be able to mitigate some of the concerns related to dosing by, for example, providing specific instructions for child dosing.

Finding 4-3: *Predispensing provides no flexibility to dispense alternative MCM in case of an attack using a strain of anthrax that is resistant to the predispensed antibiotic. In addition, unlike POD strategies, the development and implementation of a predispensing strategy for the general public would be unlikely to strengthen public health infrastructure and the capability to accomplish other public health goals beyond dispensing antibiotics for anthrax.*[11]

Communications, Behavior, and Adherence

Predispensing MCM to the general public raises many issues related to communications, behavior, and adherence—both outside of an emergency situation and during a public health emergency. Many of these issues apply to all dispensing strategies but may be exacerbated with predispensing.

Communications In the event of a public health emergency, effective communications are critical to ensuring that the exposed and potentially exposed populations receive prophylactic antibiotics. This will be one of the major challenges of the response, regardless of the particular dispensing strategies used. Potential communications-related advantages of predispensing include a sense of individual preparedness that could promote postevent calm, although this has not been corroborated by population-level evidence. In addition, this strategy provides increased time before an event to communicate with and educate the population on using the MCM safely and appropriately. Predispensing also presents specific communications chal-

[11]Along with other findings discussed in Chapter 5, Finding 4-3 leads to Recommendations 5-4 and 5-5 in Chapter 5.

lenges for several reasons. First, in addition to telling people when to take their antibiotics, communications would be needed to tell people when *not* to take their antibiotics, such as in the case of a local public health emergency for which antibiotics were not indicated or an anthrax attack elsewhere in the country. The response to the nuclear accident in Japan highlights that even consistent and pervasive messaging may not be sufficient to achieve this goal. Second, if the anthrax turned out to be resistant to the antibiotic(s) in the home, this would need to be communicated, along with instructions on what to do instead—for example, instructions to go to a POD to receive a different antibiotic. If people felt that they were protected because they had taken their home antibiotics and therefore did not seek additional care, mortality could increase greatly. Finally, MedKits would likely contain only a 10-day supply, so communications would still be needed about how to obtain the remaining doses.

Instructions, health literacy, and limited English proficiency Comprehensible instructions would be necessary to explain how to take predispensed antibiotics for both children and adults who cannot swallow pills. The study by Stergachis and colleagues (2007) discussed in Chapter 3 raised concern about improper medication use due to a misunderstanding of the instructions provided during rapid dispensing in a nonmedical POD exercise. Similar misunderstandings would likely arise with home prepositioning.

In theory, MedKits may be better suited than personal stockpiles to providing clear, emergency-specific instructions. This advantage is dependent, however, on the FDA's authorizing or approving such instructions. The drug fact sheets included in the EUA MedKits distributed in the Minneapolis-St. Paul postal model pilot are lengthy and written at a high reading level, and translations to other languages are not available (Griffith, 2011). The content of these fact sheets is specified by the EUA and may not be altered for readability or comprehensibility. Similarly, drug product labels are FDA-approved materials that may not be altered. Using MedKits or personal stockpiling effectively and safely as a strategy for a cross-section of the population would require instructions that could be understood by people with low health literacy, as well as translated instructions for non-English speakers.

Social behavior Little behavioral research has identified the factors that affect individual motivation to participate in preparedness (e.g., perceived risk of attack, cost, at-risk family members); to acquire a home stockpile (e.g., ability to store the MCM); to understand and follow MedKit labeling and instructions; and to self-administer medication from emergency caches without explicit direction that there is a public health emergency (IDSA, 2008; NBSB, 2008). As noted in Chapter 3, communications would have to

be developed to effectively reach a sociodemographically diverse audience and would have to involve multiple communications strategies, including both traditional media outlets and social media.

Adherence Adherence to the recommended course of prophylactic antibiotics following an anthrax attack is a major concern, regardless of the dispensing method used, as discussed in Chapter 3. No data are available with which to determine whether adherence would be better or worse with predispensed MCM than with PODs. It is conceivable, however, that adherence could be worse for predispensed MCM since there would be no POD staff member specifically emphasizing the importance of taking the full course of antibiotics. In addition, the POD system prevents people from taking MCM during an emergency in which antibiotics are not indicated (since the PODs would not be set up).

Logistics

Predispensing of MCM has not been tested or used at a scale that would provide the experience needed to fully understand its impact on state and local MCM dispensing plans. A strategy of predispensing MCM for the general public could be government sponsored or could rely on individuals to obtain and own the MCM. The form of the predispensed MCM (e.g., personal stockpile or MedKit) would not greatly impact the logistics of this strategy.

For a government-sponsored predispensing strategy, state and/or local jurisdictions would likely be responsible for the initial distribution, registry, and tracking of the MCM. Jurisdictions would be responsible for ongoing communication with households participating in the plan. Expiring MedKits or personal stockpiles would need to be replaced regularly, imposing another logistic and cost burden on state and local health agencies. Since many states require a 1-year expiration date on prescriptions (regardless of the date indicated by the manufacturer), replacement could be required every year unless a special dispensation could be obtained to allow replacement every 2 or 3 years. A registry would have to be used for notifying households that they should or should not take the MCM; this registry also would need to be maintained.

Privately obtained and owned personal stockpiles or MedKits would shift the responsibility for maintenance to the head of the household. State and local health agencies would not know how many privately obtained predispensed MCM were in the community. Households possessing the kits would not need to use the POD system initially, which would likely alleviate the initial stress on that system. Nevertheless, local jurisdictions still would have to plan for the entire community because (1) they would not know

how many households had predispensed MCM; (2) PODs would be needed to provide antibiotics for days 11-60; and (3) if the anthrax attack involved a strain resistant to the predispensed antibiotic, PODs would be needed to provide an alternative antibiotic.

Legal Issues

The legal issues associated with predispensing depend entirely on the form of predispensing used. Personal stockpiles currently are allowed under normal prescribing practices. An EUA MedKit was authorized for dispensing to postal workers participating in the Minneapolis-St. Paul postal model pilot. However, the use of this MedKit is highly restricted. As noted earlier, for example, the first responders accompanying the postal workers did not receive MedKits (FDA, 2009). While HHS, DHS, and others have been discussing a potential EUA covering MedKits for first responders and emergency care providers, this idea has not yet been implemented (IOM, 2010b; NBSB, 2008). A central impediment is that while the USPS is a federal agency and the EUA can be tailored specifically to postal workers, the first responder community varies widely across and within federal, state, and local jurisdictions and has no centralized organizational structure. Given these legal issues, it is unlikely that an EUA MedKit could be implemented for the general public, except, perhaps, for the general public in a limited geographic area if there were intelligence information about a specific, imminent threat.

Currently, no MedKit has been approved by the FDA. The discussion on predispensing below includes the steps that may be required to obtain FDA approval for such a kit.

Predispensing to Targeted Subpopulations

An alternative to using a predispensing strategy for the general public within a community is for predispensing to target specific groups and individuals who would lack access to prophylactic antibiotics via other timely dispensing mechanisms. For these groups and individuals, the risk of not obtaining prophylactic antibiotics following an anthrax attack may outweigh the potential health risks associated with inappropriate use. In addition, with a more limited, targeted strategy, it may be easier to institute systems to decrease inappropriate use, manage costs, and/or develop an alternative dispensing mechanism in the case of an attack with antibiotic-resistant anthrax.

The use of predispensing for some first responders and critical infrastructure workers and for selected patients is discussed here for illustrative purposes, but the benefits and risks of predispensing for specific groups and

individuals will vary across communities. In particular, because the committee recommends this strategy primarily for those who lack other means of obtaining MCM in a timely manner, the benefits of this use of predispensing in a community will depend heavily on the coverage of the other dispensing mechanisms in place. State and local public health officials likely already know about groups and individuals that are likely to face challenges in accessing MCM, and they could work with health care providers, local community organizations (e.g., faith-based), and constituent advocacy groups to identify other vulnerable subpopulations and evaluate their access to current dispensing mechanisms.

First Responders and Critical Infrastructure Workers

Certain first responders and critical infrastructure workers (including health care personnel) will be expected to report to work as soon as an attack is detected and/or remain at work for extended periods during the response. Therefore, they will be unable to stand in line at PODs. The HHS et al. (2011) proposal for implementing the postal model includes providing prophylaxis to postal workers' families as well as the workers themselves based on the assumption that workers may not report to work until their family members have been taken care of. While workers may consider other factors in deciding whether to participate in the response, ensuring that these workers have a means of obtaining MCM in a timely manner both yields a multiplicative effect, impacting others in society through the services they provide, and ensures that they have equitable access while fulfilling responsibilities that prevent them from waiting in line at open PODs. Communities can determine how to define these subpopulations and how best to dispense to them.

Most communities will likely find that workplace caches, where feasible, are a better strategy than predispensing for these workers. Workplace caches avoid the risks of inappropriate use described above, provide a better (but not seamless) infrastructure for distributing an alternative MCM if needed, and are more cost-effective (see Chapter 5; note also that in the postal pilot program, MCM were kept in both homes and workplaces, thus increasing costs). However, communities may find that in some cases, workplace caches would not provide timely access while still enabling workers to begin working immediately and to stay at work. These cases might include, for example, first responders and critical infrastructure workers who do not muster in a workplace or workers for whom it would not be feasible to bring MCM from the workplace cache to their family members in a timely fashion. This section outlines considerations for predispensing to these selected groups.

Inappropriate use There is no available evidence to suggest that first responders and critical infrastructure workers are inherently less likely to misuse antibiotics than members of the *general* public. However, the results for the St. Louis first-responder cohort and the Minneapolis-St. Paul pilot program suggest that these *subpopulations* would be unlikely to misuse the MCM during nonemergency times given circumstances similar to those used in the study and pilot program. Of the 1,556 first-responder households in the St. Louis study, 98.7 percent returned their MedKit; 1.3 percent could not locate it (two had thrown it away, and seven had lost it); and one refused to return it (CDC, 2008b). No household in the first responder cohort used the medication. And as noted earlier, 1 year into the postal pilot program, 367 of the 377 kits (97.3 percent) held by active postal volunteers were returned, unopened, for scheduled replacement (Griffith, 2011). Unlike predispensing programs for the general public, programs set up through employers may provide more screening, supervision, and incentives not to misuse the medication, thus being more aligned with the St. Louis study and postal pilot program.

Although the data suggest that these groups may not misuse the MCM in nonemergency situations, no data are available on whether these groups would misuse them in an emergency situation in which antibiotics were not indicated—for example, a nonanthrax public health emergency, a false alarm caused by a nonanthrax white-powder event, or an anthrax attack far away. As with the general public, there also is no appropriate evidence with which to address the question of whether the form of predispensing would impact the rate of inappropriate use among first responders.

Flexibility Predispensing for some first responders and critical infrastructure workers raises concerns about flexibility similar to those described above for the general public, particularly with regard to what would happen if the anthrax used in an attack were resistant to the predispensed MCM. However, this issue may be somewhat mitigated since it may be possible to develop a plan through which employers would communicate with employees about the issue (e.g., through a phone tree) and distribute an alternative MCM in the workplace.

Legal considerations Jurisdictions, in partnership with public and private employers as applicable, could implement a home-based predispensing strategy using personal stockpiling, which currently would be allowed under normal prescribing laws. Such a strategy also could be implemented with an FDA-approved MedKit if one were to be developed and licensed. As noted above, however, there is limited evidence to suggest that the use of such a kit would decrease the rate of inappropriate use in these subpopulations; therefore, it is not clear whether the considerable expense of develop-

ing an FDA-approved MedKit would be worthwhile. The costs associated with developing an approved MedKit are touched on below.

As an intermediate solution, it might be possible to use a MedKit authorized under an EUA (as was done in Minneapolis-St. Paul), although accomplishing this may not be straightforward. During a discussion at a 2009 IOM workshop, it was noted that although an EUA could be obtained for postal workers who volunteered to participate in the postal pilot, obtaining similar consideration for the first responders who would accompany the postal workers as they delivered MCM postattack was challenging (and has to date not been accomplished) (IOM, 2010b). In particular, speakers observed that all postal workers have a single employer (the USPS), whereas first responders are employed by jurisdictions at many different levels and privately. Adding critical infrastructure workers to the mix would only increase the challenges.

Selected Patients

Certain patients may have social situations and/or medical conditions that preclude them (or are a significant barrier) from accessing medications through the public health system. For example, some patients might be unable to travel to PODs or might have a compromised immune system that would make it unadvisable to stand in line with a crowd. In many cases, such patients could rely on another household adult or a neighbor to obtain MCM, and some jurisdictions might develop plans through which home health care workers or other service delivery agencies would deliver MCM. For patients without access via these mechanisms, the potential risk of not having antibiotics following an anthrax attack may outweigh concerns about health risks from inappropriate use, lack of flexibility, and cost.

Kent Sepkowitz, Vice Chairman of Clinical Affairs at Memorial Sloan-Kettering Cancer Center, suggested to the committee that oncology patients and possibly HIV patients might appropriately receive predispensed antibiotics. These patients would not be well suited to standing in POD lines, and they have a long history with prepositioned antibiotics and their use with appropriate physician control (Sepkowitz, 2011). Little available published evidence exists on whether patients with complex medical conditions are less likely to misuse antibiotics relative to the general population, and there is likely to be a great deal of individual variation in this regard. Physicians considering prescribing antibiotics for protection against anthrax would need to take into account individual patients and their demonstrated level of adherence to medication instructions. For such patients, predispensing also would make it possible to adapt to their individual needs. For example, alternatives to doxycycline could be provided for those allergic to that drug,

and the time would be available to provide thoughtful solutions to those at risk of drug interactions or with complex physiology.

Predispensing for these selected patients is most likely to entail personal stockpiling through normal physician-patient contact and prescription routes, as an independent activity. Thus it would be done on an ad hoc basis and would likely be covered by health insurers.

The committee is not recommending predispensing for those who have other ways of obtaining access to postexposure prophylactic antibiotics given the concerns discussed above about potential health risks, lack of flexibility, and cost. Predispensing is warranted only if the alternative (i.e., no access to antibiotics postevent) is worse. Specifically, the committee is not recommending predispensing for those who are anxious about an anthrax attack but who could, for example, obtain MCM at a POD, although the committee recognizes that this is currently allowed legally under normal prescription laws. The committee acknowledges that public health officials have not done a very good job at communicating what plans are in place, and therefore it may be challenging for physicians and their patients to determine whether and how a patient would access antibiotics in case of an anthrax attack. Improving communication on existing dispensing plans may be a safer and more effective means of decreasing anxiety than promoting widespread availability of predispensed MCM. Table 4-3 provides a summary and comparison of the different potential forms of predispensing of MCM: the general safety-related advantages, the potential for inappropriate use among the general population and target subpopulations, and associated costs.

TABLE 4-3
Comparison of Potential for Inappropriate Use Among Different Potential Forms of Predispensed Antibiotics

		Potential for Inappropriate Use		
Form	**Advantages**	General Population	Target Subpopulation(s)	**Costs (to whom)**
Personal Stockpile	Physician screening for contraindications, allergies, and drug interactions	Misuse is likely to be high	Unknown whether they differ from general population	Baseline for predispensed MCM
EUA MedKit[a]	Include screening out of people allergic to the MCM; specific instructions and tamper-evident packaging; provision of instructions on how to prepare for children and adults who cannot swallow pills; special packaging to distinguish from routine prescriptions	Extremely limited data restricted to families of postal workers suggest that misuse is decreased relative to historical prescription data	Two studies, with substantial limitations, that used target subpopulations show decreased misuse relative to historical prescription data (no head-to-head comparison) (CDC, 2008b; IOM, 2010b)	Administrative costs at FDA; cost to assemble packages (customized to household); limited economies of scale
FDA-approved MedKit[b]	Same as above, but broader availability than EUA MedKit, and screening by physician or pharmacist	Very limited evidence to suggest it would be different from prescription medications	Two studies, with substantial limitations, that used target subpopulations show decreased misuse relative to historical prescription data (no head-to-head comparison) (CDC, 2008b; IOM, 2010b)	Most expensive (requires approved MedKit, physician screening, pharmacist dispensing)

NOTE: EUA = Emergency Use Authorization; FDA = Food and Drug Administration; MCM = medical countermeasures.

[a] Screening currently is performed by nonmedical personnel.

[b] Could be prescribed during normal patient-physician contact. Another possibility is that a public health professional or occupational health physician could write a standing order and set up a screening system.

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5

A Decision-Aiding Framework

As highlighted throughout this chapter, the benefits of prepositioning strategies will depend on the particular community in which they are implemented. Different communities differ in their likelihood of experiencing an anthrax attack; in their existing surveillance, detection, and dispensing infrastructure; in their population and geographic characteristics; in their values and preferences; and in their available resources. These differences affect which prepositioning strategy or combination of prepositioning strategies, if any, will be most effective in meeting a community's prophylaxis goals.

To assist state, local, and tribal jurisdictions in evaluating whether their community would benefit from implementing prepositioning, the committee has developed a decision-aiding framework. The key elements of this framework are presented in Box 5-1. The framework is intended to assist each community in evaluating the strategies described in detail in Chapter 4—forward-deployed, cached, and predispensed—according to its own needs, objectives, value trade-offs, and constraints. This chapter details the elements of the framework listed in Box 5-1. It then presents a recommended modeling approach for communities to use in applying the quantitative elements of the framework (evaluation of potential health benefits versus likely costs) to make decisions about the use of prepositioning strategies. The final section presents the committee's findings and recommendations on the benefits, costs, and sustainability of the various strategies.

BOX 5-1
Key Elements of the Decision-Aiding Framework

Communities across the United States differ in their needs and capabilities. Different communities may benefit most from different strategies for prepositioning antibiotics for anthrax, or may not benefit from prepositioning strategies at all. The committee developed a decision-aiding framework to assist state, local, and tribal jurisdictions in deciding which prepositioning strategies, if any, to implement in their community. The key elements of this framework are:

- Assessment of risk and current capabilities
  - Consideration of the risk of an anthrax attack
  - Assessment of current capability for timely detection of an attack
  - Assessment of current dispensing capability, including (1) overall dispensing capability, and (2) specific gaps in dispensing capability, such as particular subpopulations not well served by current plans
- Incorporation of ethical principles and community values
- Evaluation of potential prepositioning strategies for medical countermeasures for anthrax
  - Evaluation of potential health benefits, including evaluation of potential effectiveness in reaching specific populations or filling other specific gaps in dispensing capability
  - Evaluation of potential health risks
  - Evaluation of likely costs
  - Consideration of practicality, including (1) communications needs and expected social behavior and adherence, (2) logistics, and (3) legal and regulatory issues

ASSESSMENT OF RISK AND CURRENT CAPABILITIES

To evaluate whether alternative prepositioning strategies would be appropriate for their communities, jurisdictions must consider the risk of an anthrax attack in their community and assess their current capability to detect such an attack in a timely manner and to distribute and dispense postexposure prophylactic antibiotics to their population. This section describes these assessments.

Risk of an Anthrax Attack

A community's risk assessment for an anthrax attack is important for prioritizing funding for dispensing capabilities within the context of

overall public health needs, and it helps inform decisions about the specific dispensing strategies that would protect the community most effectively. For example, a community facing a low risk of an anthrax attack might decide to rely on the Strategic National Stockpile (SNS) and not assume the additional costs associated with implementing local prepositioning strategies. Conversely, a community facing a high risk of an anthrax attack might decide that the additional cost was a valuable use of public health resources. This section reviews the factors included in risk assessment, identifies sources of risk information to which jurisdictions already have access and that can be used in decision making about prepositioning, and briefly addresses how this information can be used to inform prepositioning decisions (a topic discussed in greater detail below in the section on evaluation of potential prepositioning strategies).

The Department of Homeland Security (DHS) outlines three components of risk: the *threat* (the likelihood of an attack), the *vulnerability* of a community to that attack, and the *consequences* of a successful attack (DHS, 2008a). For assessment of specific terrorism scenarios, factors that impact the assessment of *threat* may include intent and capability of adversary, weapon availability, attack simplicity, historical information, and intelligence information (FEMA, 2007). The following factors related to *vulnerability* and *consequences* are also taken into account in assessment of risk: "population and population density, the presence of critical infrastructure and key resources, location in high terrorist or high risk natural disaster areas, and capabilities to prevent, protect against, or mitigate a threat" (FEMA, 2007, p. 10).

State, local, and tribal jurisdictions rely primarily on the federal government to provide information about the **threat** of a terrorist attack. The Secretary of DHS has issued material threat determinations (MTDs) for anthrax and multi-drug-resistant anthrax (DHS, 2008b; GAO, 2009). Many public health officials, particularly those from states or larger cities, have access to additional classified intelligence information that, if available, could be used to inform decisions about prepositioning.

The committee has focused primarily on long-term planning for prepositioning and recognizes that the federal government and public health officials in jurisdictions may not have detailed, long-term information about specific anthrax threats to jurisdictions (beyond what is conveyed by the MTDs), including detailed information about the relative likelihood of specific attack scenarios. Nevertheless, jurisdictions should use this information if they have it (or can make reasonable assumptions about it) to inform policy and decision making about prepositioning. In contrast, the federal government may, on occasion, have specific information about an imminent credible threat to a specific jurisdiction(s). In such circumstances, the risk of an attack might be considered very high, and rapid decisions

might be made to forward-deploy medical countermeasures (MCM) to that jurisdiction(s). The committee focused less on this type of prepositioning in response to a potentially imminent attack.

Vulnerability and **consequence** are largely independent of specific intelligence information about a threat. Jurisdictions do not need classified, detailed intelligence information about specific threats to consider their vulnerability to an anthrax attack and the potential consequences to the community.

Jurisdictions already have access to several sources of information about risk in their community. Some are provided by the federal government, and jurisdictions generate others as part of the process for applying for federal funding.

First, DHS funding allocations are based on DHS-developed risk assessments (FEMA, 2011). DHS's Urban Areas Security Initiative (UASI) grant identifies 31 metropolitan areas at the highest risk of a terrorist attack (FEMA, 2011). A designation of UASI Tier 1, assigned to the 11 highest-risk areas, or Tier 2, assigned to the remaining 20 areas, is itself a generalized risk assessment. DHS funding reflects this differential risk, assigning Tier 1 cities 81.6 percent of the program's total funding.

Jurisdictions funded by DHS's UASI and State Homeland Security Program (SHSP) grants (another terrorism response-related grant program) have access to the information from their specific Threat and Hazard Identification and Risk Assessment (THIRA), a required part of their grant application (FEMA, 2011). THIRAs assess all threats and hazards facing the jurisdiction, including terrorism threats, and are submitted to DHS as part of the overall State Mitigation Plan, which is intended to foster collaboration among the disaster response plans of all jurisdictions within a state.

Awardees of the Office of the Assistant Secretary for Preparedness and Response's (ASPR's) Hospital Preparedness Program (HPP) grant are required to use the results of a Hazard Vulnerability Analysis—which identifies, analyzes, and prioritizes potential threats to a jurisdiction—to inform their planning efforts (ASPR, 2011). This is another existing information source for state and local jurisdictions to use in assessing the value of prepositioning strategies in meeting their prophylaxis goals.

The use of risk-related information in decision making about prepositioning is addressed in greater detail later in the chapter, including how a community's relative risk of an anthrax attack and the likelihood of specific attack scenarios impact the potential benefits and cost-effectiveness of different prepositioning strategies. The committee recognizes, however, that detailed information about threat and the likelihood of specific attack scenarios may not exist. Jurisdictions should use the best risk assessment information available to inform decision making about prepositioning.

In the absence of such information, jurisdictions can also explore the potential benefits and costs of prepositioning given different assumptions about threat and specific attack scenarios. In some cases, jurisdictions may ultimately rely more heavily on the *vulnerability* and *consequences* aspects of risk assessment. For example, a remote county with low population density, no high-profile potential critical infrastructure targets, and a high risk of flooding may decide to rely on the SNS instead of implementing prepositioning strategies, instead devoting more public health resources to flood preparedness. On the other hand, a community with high population density and infrastructure that is thought to be a potential terrorism target might decide to implement several prepositioning strategies. These tradeoffs are discussed in greater detail in a later section.

Finally, in further recognition of the fact that some local jurisdictions may lack resources to conduct an in-depth assessment of the risk of an anthrax attack, the committee recommends below partnerships among state, local, and tribal governments and with the federal government in working through the key elements of the decision-aiding framework presented in this chapter. In many cases, federal and state governments may have greater access to classified information and resources for conducting risk assessment and could provide guidance on this element of the framework to local jurisdictions.

Assessment of Current Capability for Timely Detection of an Attack

Along with assessing the risk of an anthrax attack, jurisdictions need to assess their current surveillance and detection capability in order to evaluate their ability to meet prophylaxis goals and the potential usefulness of prepositioning in achieving those goals. The various mechanisms for detecting an attack were discussed in Chapter 2. Minimizing the time between the decision to dispense and antibiotic administration becomes increasingly crucial as the delay in detecting an attack increases. Therefore, prepositioning strategies may be particularly beneficial in jurisdictions that lack robust detection and surveillance systems. Jurisdictions should assess their community's detection and surveillance capabilities and take into account the possibility of delayed detection of an attack when deciding whether prepositioning strategies would be beneficial.

The committee does not intend to imply that if a jurisdiction's capability for rapid detection is low (for example, a rural jurisdiction without BioWatch sensors), this should automatically be addressed through the addition of rapid detection technology; many considerations beyond the scope of this report are involved in such a determination. The point is simply that low detection capability is one potential indicator that prepositioning would be beneficial.

Assessment of Current Distribution and Dispensing Capability

Jurisdictions also need to understand the capability of their current distribution and dispensing system in order to evaluate whether prepositioning strategies would benefit the community. If a community's distribution and dispensing system is already capable of covering the entire population within an appropriate time window, the development of prepositioning strategies is unnecessary. Conversely, if a community has inadequate overall capability or gaps in reaching particular subpopulations, prepositioning strategies may be beneficial. The effort required to gain an accurate understanding of distribution and dispensing capability will likely be more resource-intensive than current practices are, but that understanding is necessary before decisions are made about developing and implementing expensive prepositioning strategies.

Jurisdictions should assess their overall distribution and dispensing capability and determine whether there are any gaps. A gap analysis can reveal whether certain portions of the population, by virtue of socioeconomic status and/or demographic characteristics, are at a systemically increased risk of reduced access to disaster mitigation response. Some people may not be well served by traditional points of dispensing (PODs)—for example, people with low incomes or limited transportation options, people with no or limited English proficiency, historically underserved ethnic/racial groups, people with disabilities (especially the vision impaired, hearing impaired, and mobility impaired), people who are homeless, and people who are homebound. Identifying such gaps is important in determining whether strategies are appropriate to augment current distribution and dispensing mechanisms and, if so, which strategies are likely to be most appropriate.

It is difficult, however, to obtain an accurate assessment of jurisdictions' current distribution and dispensing capability for three primary reasons. First, the full capability of the SNS has not been demonstrated. Second, the extent to which distribution and dispensing plans have been developed is used as a proxy for understanding how those plans will be implemented. Although this may be a useful first step, it does not capture the realities and potential obstacles associated with implementing a distribution and dispensing plan in a real emergency. Where performance metrics exist, they are scattered across different grant requirements and often simply measure whether a task was performed or not, rather than the quality of performance. Third, full-scale drills have not been required until now, so information on how distribution and dispensing systems function has been obtained from piecemeal exercises. These data cannot provide a complete and accurate picture of the overall capability of a jurisdiction's distribution and dispensing system.

Distribution from the Strategic National Stockpile

Jurisdictions need to know how quickly SNS assets will reach them so they can calculate their capability to complete dispensing of initial prophylactic MCM to their population within the appropriate time window. SNS Push Packages (described in Chapter 3) are deployed rapidly in response to an ill-defined threat within no more than 12 hours of the federal decision to deploy and are unlikely to include the full quantity of MCM necessary for initial prophylaxis (CDC, 2011a). Current estimates of the time to deliver the initial Push Packages to the Tier 1 UASI cities after the decision to dispense varies between approximately 4 and 8 hours for the first shipment to arrive (Burel, 2011). The committee is unaware of any large-scale exercise of the vendor-managed inventory (VMI) portion of the SNS, which is expected to begin arriving within 24-36 hours and contains the supplies needed beyond the original Push Package quantities. It is also unknown whether the SNS has the capability to distribute MCM to multiple locations simultaneously and over a sustained period of time (as would be necessary in the reload scenario envisioned by Danzig [2003]). The gap in knowledge surrounding distribution from the SNS prevents jurisdictions from understanding the capability and capacity of the current prophylaxis system. If the current system can provide prophylaxis to the exposed population within the specified time window, the disadvantages of prepositioning discussed in Chapter 4 and later in this chapter (e.g., increased cost) may outweigh any marginal benefit from a decrease in time to prophylaxis. If, on the other hand, significant challenges exist in the centralized distribution system, prepositioning at the state and local levels may be highly beneficial.

Existing Performance Measures and Metrics

Four primary sources measure state and local MCM dispensing capability and capacity: the Centers for Disease Control and Prevention's (CDC's) *Public Health Preparedness Capabilities*, the SNS Technical Assistance Review (TAR) tool, the RAND-CDC Performance Metrics Project, and the CDC-administered Public Health Emergency Preparedness (PHEP) grant (CDC, 2009a,b, 2011b; Nelson et al., 2009). This section describes the performance metrics associated with each of these four sources, highlighting the need for more and better measures and metrics for accurately assessing a dispensing system's performance.

Public Health Preparedness Capabilities: National Standards for State and Local Planning CDC's *Public Health Preparedness Capabilities* (CDC, 2011b) catalogs the fundamental capabilities that all jurisdictions should

have to mount a successful mass prophylaxis campaign. These capabilities are broken down into five core dispensing functions:

- identify and initiate MCM dispensing strategies;
- receive MCM;
- activate dispensing modalities;
- dispense MCM to identified populations; and
- report adverse events.

For each function, the document lists associated tasks, performance measure(s), and resource elements required.

This effort is a significant step forward because it highlights the importance of performance measures for each MCM dispensing function and identifies gaps in existing measures. Those gaps remain substantial, however: three of the five core functions as yet have no associated performance measures. Performance measures for specific functions are part of the Medical Countermeasures Distribution and Dispensing (MCMDD) composite measure, introduced in the 2011 PHEP cooperative agreement grant guidance (CDC, 2011c). The composite measure, discussed in greater detail below, was designed to describe comprehensively the capability of a jurisdiction (state or Cities Readiness Initiative [CRI] area) to meet Public Health Preparedness Capability 8: MCM dispensing (CDC, 2011c).

Technical Assistance Review (TAR) tool for states and localities The SNS TAR entails a detailed evaluation of state and local jurisdictions' planning efforts for receiving, distributing, and dispensing SNS MCM (CDC, 2009a,c). At both the state and local levels, the TAR assesses 12 core distribution and dispensing functions, similar to but more detailed than the five core functions of CDC's *Public Health Preparedness Capabilities* (the state TAR measures the additional function of capability to repackage). The SNS TAR does not emphasize performance measures: of the local TAR tool's 85 metrics, only 7 are performance measures. TAR scores are based primarily on an "all or nothing" scale: a full score is awarded if an item can be identified in the plan or if an exercise has been conducted. The score does not depend on the quality of performance during the exercise.

The TAR, like *Public Health Preparedness Capabilities*, represents progress in assessing state and local preparedness to mount a mass prophylaxis campaign, but it evaluates jurisdictions primarily by how well they plan. Adding more performance metrics and measures of the ability to achieve preset prophylaxis goals to the SNS TAR would enable jurisdictions to chart their progress quantitatively and determine persistent weaknesses.

RAND-CDC Performance Metrics Project (Nelson et al., 2009) The 2009 RAND report *New Tools for Assessing State and Local Capabilities for Countermeasure Delivery* is intended to provide detailed performance metrics that build on and are compatible with the TAR (Nelson et al., 2009). RAND's ongoing project has yielded the most detailed performance metrics to date. They measure the capability of system elements to meet their goal, as well as the time required to complete various tasks. Because a primary motivation for prepositioning is to decrease the time to prophylaxis, measurement of the time to completion is critical for determining the potential benefit of prepositioning strategies. If the current distribution and dispensing system were capable of providing prophylaxis to a population within the appropriate time frame, prepositioning strategies would be redundant.

On the other hand, like the performance measures in the *Public Health Preparedness Capabilities* and the TAR, the RAND metrics are not comprehensive. Specifically, they do not assess the distribution system (SNS to states), a potentially rate-limiting process in a mass prophylaxis campaign. There also are no performance metrics designed to collect data from realistic full-scale exercises rather than piecemeal drills.

Public Health Emergency Preparedness (PHEP) cooperative agreement program Beginning in fiscal year 2011, jurisdictions receiving funding through the CDC-administered 2011-2016 cooperative agreement program are required to report on the MCMDD composite measure described above and must achieve a minimum benchmark score that will increase gradually over time (CDC, 2011c). The measure is meant "to serve as a collective indicator of [MCM distribution and dispensing] preparedness and operational capability" (CDC, 2011c, p. 24). In the first year (i.e., required by July 15, 2012), a jurisdiction's composite score will comprise the state and local 2011 TAR scores and the results of a minimum of three different drills (from the eight described by previous PHEP guidance) (CDC, 2009b, 2011c). Within the 5-year grant cycle (by 2016), each jurisdiction must participate in a full-scale exercise, the results of which will then contribute to its composite score. These requirements apply to both states and CRI areas, with potentially different requirements for each (specific guidance on conducting and reporting the results of full-scale exercises is expected at a later date). Adoption of this composite measure will enhance intrastate planning and will represent a significant step toward standardizing performance measurement across jurisdictions. Beyond the composite measure, the 2011 PHEP grant will require funded jurisdictions to provide more detailed reporting on capability-based performance measures for MCM dispensing; those details are also forthcoming (CDC, 2011c).

Data from Full-Scale Exercises and Real Events

Along with performance metrics, data on a distribution and dispensing system's performance are needed to assess how the system will function during a real event. If the data identify system inadequacies, prepositioning of antibiotics may be a means to fill identified gaps. Performance data may be gathered in two ways: from exercises and drills and from real-world experiences.

Data from full-scale exercises Full-scale exercises have been included as an acceptable method of collecting data for fulfilling PHEP reporting requirements in previous years, although these exercises often have not been performed. Instead, other acceptable exercises and drills have been used in their place, including tabletop exercises, drills, and functional exercises (CDC, 2009b). As noted above, the most recent PHEP cooperative agreement (2011-2016) requires each state and CRI area to participate in at least one full-scale exercise over the course of the 5-year grant period (CDC, 2011c). While the details of the exercise requirements are forthcoming, current guidance explains that a CRI area's full-scale exercises "must include all pertinent jurisdictional leadership and emergency support function leads," along with all planning and operational staff who will have a response role in a crisis (CDC, 2011c, p. 33).

However, the cost and resources required to conduct a full-scale exercise remain significant barriers for public health departments, which already face limited funding. Full-scale exercises also require partnership and significant coordination with non–public health elements of the distribution and dispensing system, such as schools, community centers, and private businesses. These entities may not be willing or able to interrupt their daily operations to participate in such exercises. Yet without the data from full-scale exercises, jurisdictions are left to extrapolate how quickly the entire system would work in a real emergency, what obstacles they might face (e.g., logistics or communications), and what mechanisms could be used to circumvent those obstacles.

In addition, the data collected in other types of exercises are not standardized, limiting the ability to compare neighboring distribution and dispensing systems and, in turn, making it difficult to identify and apply best practices across a region. Recognizing these issues, CDC has continued to develop and refine templates and guidance, making significant strides with the 2011 PHEP grant requirements for collecting data and interpreting metrics more efficiently and cost-effectively at the state and local levels (Neff, 2011). Ongoing efforts by CDC to facilitate large-scale exercises, whether through funding or through technical support and guidance, will

enable state and local jurisdictions to assess the performance of their MCM distribution and dispensing system.

In addition to large-scale exercises conducted in the context of the PHEP program, other efforts to assess large-scale performance could be useful. DHS, for example, sponsors an annual nationwide exercise that could be a potentially useful venue for assessing the performance of the entire system—from the federal government to state and local entities. In addition, the use of computer simulations or models could be explored to assess a community's ability to dispense MCM in a timely manner without having to conduct large-scale exercises in each high-risk jurisdiction. Such models would need to be anchored in real-world data to the maximum extent possible and be flexible enough to represent the unique attributes of a wide range of different communities with reasonable fidelity.

Data from real events: the 2009 H1N1 vaccination campaign The 2009 H1N1 influenza pandemic was the most recent real-world test of emergency preparedness plans, offering insights into the working of the entire emergency response system (ASTHO, 2010; FICEMS, 2009; HHS and DHS, 2009; IOM, 2010; NACCHO, 2010). However, the differences between pandemic influenza and anthrax limit the utility of these data for informing anthrax preparedness policy. A response to pandemic influenza takes place over many weeks or even months, whereas the current goal for initial antibiotic prophylaxis after an anthrax attack is 48 hours after the decision to begin dispensing is made (see Chapter 2). Additionally, the 2009 H1N1 influenza pandemic saw an ebb and flow of the number of patients seeking immediate treatment, whereas an anthrax attack could necessitate offering medication to an entire city at once, creating a sudden massive demand on the public health system. The performance of the distribution and dispensing system can also be assessed using more routine real-life distribution events, such as annual influenza vaccination campaigns.

Finding 5-1: *To determine the potential benefits of prepositioning strategies, it is critical that jurisdictions accurately assess their distribution and dispensing capability. The few performance measures available for assessing prophylaxis capability are still nascent in their development. Existing performance data often have come from small-scale drills rather than full-scale exercises because of limited financial resources and personnel and the infeasibility of interrupting the functioning of non–public health entities such as schools, community centers, and private businesses. This fact, coupled with limited standardization and comparability of measurement across jurisdictions, makes it difficult to evaluate the current capability of a distribution and dispensing system and, in turn, the value of adopting prepositioning strategies to augment that capability.*

Recommendation 5-1: Enhance assessment of performance in implementing distribution and dispensing plans for medical countermeasures. **The Centers for Disease Control and Prevention should continue to facilitate assessment of state, local, and tribal jurisdictions' performance in implementing dispensing plans for medical countermeasures, in addition to assessing planning efforts. More specifically, the Centers for Disease Control and Prevention, in collaboration with state, local, and tribal jurisdictions, should facilitate assessment of the entire distribution and dispensing system by:**

- **demonstrating Strategic National Stockpile distribution capabilities to high-risk jurisdictions;**
- **facilitating large-scale, realistic exercises in high-risk jurisdictions to test dispensing capability; and**
- **continuing efforts to identify objective criteria and metrics for evaluating the performance of jurisdictions in implementing mass dispensing.**

INCORPORATION OF ETHICAL PRINCIPLES AND COMMUNITY VALUES

Many authors have addressed the question of which values and principles ought properly to serve as the basis for policies in public health, both in general and for the prevention of and response to disasters (Childress et al., 2002). Addressing ethical principles specifically for the public health emergency of a pandemic, the University of Toronto Joint Centre for Bioethics produced a list of substantive and procedural ethical principles to guide policy making for disasters (Joint Centre for Bioethics, 2005). Similarly, in its letter report on crisis standards of care, the Institute of Medicine (IOM) proposed an ethical framework that included such elements as fairness, the duty to care and to steward resources, transparency, and proportionality (IOM, 2009).

In these reviews of public health ethical principles, distinguishing features include a concern with both outcomes and processes. Utilitarian goals, such as saving the greatest number of lives, clearly play a part in shaping ethical priorities. Just as important to note, however, is that utilitarian goals *never* supply the entire ethical framework for public health policy. Rather, utilitarian goals within democratic societies are balanced by the need to uphold additional substantive and process principles. A desirable outcome, such as saving many lives, if attained by unethical means, such as discrimination against a vulnerable class within the population, does not reflect an ethically viable policy.

Ethical Framework

Among the various possible ethical frameworks, which substantive and procedural principles are most relevant for the current context of providing MCM for an anthrax attack? The committee believes an ethically sound policy for this context should include the following elements:

- **Promotion of public health—**Strive for the most favorable balance of public health benefits and harms based on the best available research and data.
- **Stewardship—**Demonstrate stewardship of public health resources.
- **Distributive justice—**Distribute benefits and harms fairly, without unduly imposing burdens on any one group in the population.
- **Reciprocal obligations—**Recognize the professional's duty to serve and the reciprocal obligation to protect those who serve.
- **Transparency and accountability—**Maintain public accountability and transparency so that community members grasp relevant policies and know from whom they may request explanation, information, or revision.
- **Proportionality—**Use burdensome measures, such as those that restrict liberty, only when they offer a commensurate gain in public health, and no less onerous alternatives are both available and feasible.
- **Community engagement—**Engage the public in the development of ethically robust MCM dispensing plans, including plans for prepositioning antibiotics, to ensure the incorporation of community values.

This section addresses each of the above elements of an ethical framework in turn, starting with the need for **promotion of public health**. First, it is necessary to acknowledge that sound ethical policies are based on the best available evidence regarding public health interventions. To promote public health effectively, public health authorities must assess a wide range of possible interventions and carefully weigh their possible impact. Good policy rests on good science. Thus the most challenging aspect of evaluating different prepositioning strategies may well be the lack of conclusive data. Acknowledging this uncertainty and working to obtain better data are ethical obligations that emerge from this first element of the framework. Failure to adhere to established public health practices and to acknowledge uncertainty can have dire consequences, such as when the Environmental Protection Agency (EPA) too speedily pronounced air quality safe in the immediate vicinity of the World Trade Center after the terrorist attack of

September 11, 2001, arguably increasing both exposure and health consequences for workers and residents of the area (EPA, 2003; Schorn, 2009).

Stewardship, the next element of the framework, is especially crucial now, when public health dollars are severely limited in many jurisdictions. Any expenditure or intervention will mean that other possible public health measures can no longer be funded. Communities today face significant health challenges from threats as diverse as obesity, diabetes, *E. coli* in the food supply, tobacco use, and influenza. Public health authorities must scrutinize the level of every risk and the benefit of every dollar. Public health measures against terrorism cannot be viewed in isolation, but they form part of the total context of public health priorities and interventions.

The next element in the framework calls for **distributive justice**. Health care access and health outcomes are highly variable within communities and often are unevenly distributed according to levels of income and education, insurance status, and ethnicity. We cannot hope to correct these inequities in the moment of a public health disaster, but policies for such events should not exacerbate existing inequities. Ethically sound public health policies must provide equivalent benefits to different groups within the population, while harms such as the inconvenience and risk of picking up MCM at a distant site should not be borne disproportionately by vulnerable groups.

The next element addresses the **reciprocal obligations** of professionals and those they serve. Professionals have an ethical obligation to use their skills and training in times of crisis, while communities in turn have an obligation to offer appropriate protection to those who take risks on their behalf. In the context of prepositioning MCM for anthrax, this principle is relevant to options that ensure that families of first responders have access to MCM when the first responders must work and cannot avail themselves of standard means of obtaining MCM used by the general public (see the discussion of the postal model in Chapters 3 and 4).

The next three elements of the ethical framework focus on the role of ethics in relation to the community. **Transparency and accountability** are crucial elements of any important public policy in a democracy, especially policies related to disasters. A natural disaster or terrorist attack creates fear and turmoil, which, in turn, place extraordinary pressure on the bonds of trust between public servants and communities. A perception that authorities are less than candid or inadequately responsive can further erode a community's ability to function just when full and efficient cooperation is most needed.

The principle of **proportionality** instructs us to preserve liberty and human rights as crucial aspects of our democracy even when under severe duress. To some extent, a command-and-control orientation must exist in the early stage of a disaster while damage is being assessed and first

responders are caring for those in acute need. It is equally important, however, to preserve the legal structure of democracy in a way that does not impede disaster response yet limits incursions on liberty to those necessary to protect public health and safety. Any limit to individual freedom that is imposed must be the only viable means of promoting an important public health goal.

The final element of the ethical framework calls for **community engagement**. This crucial step can mean the success or failure of attempts to create viable public health policy. When disaster strikes, if people are either uninformed or unwilling to accept disaster plans, they will not carry them out effectively. Expert opinion and review of data are important components of planning but never can be the sole determinants of what is appropriate for an individual community. During planning for pandemic influenza, for example, experts gave priority to the needs of medically vulnerable adults. A community engagement project revealed that the public believed that children should be given higher priority than those vulnerable adults (Keystone Center and University of Nebraska, 2008). Indeed, a consistent message that flows from public engagement processes is that the needs of children should receive greater attention than is currently the case in public health planning (Keystone Center and University of Nebraska, 2008; Li-Vollmer, 2010; Vawter et al., 2010). Public engagement is necessary to ground planning in public values.

At the same time, however, community values that may serve as the basis for ethically sound policy are not without limits. One could imagine, and perhaps find, a community that wished to prevent members of a locally reviled group from receiving scarce benefits in a disaster. Various laws enshrine ethical principles that prevent discrimination and would likely render unworkable a plan that prevented access to emergency resources for vulnerable groups. For instance, a community could not legally enact a preference to exclude prisoners in the local jail from access to scarce resources, even though doing so might accurately reflect the community's values. A responsible process for community engagement will include adequate transparency and educational information to make clear that not all options are ethically and/or legally viable. Nonetheless, there is room for flexibility and for addressing specific concerns related to values and preferences. The demand for greater emphasis on the needs of children is one example of how successful community engagement can improve alignment between community values and public policy. An effective community engagement process will facilitate deliberation of ethically and legally viable choices, building consensus and transparency in the process.

Public engagement should not be limited to a focus on planning strategies, but should also include attempts to provide an overall picture of the bioterrorism and other public health threats to the community and the op-

tions for protective measures. Thorough efforts at education and dialogue are critical for building community resilience.

Ethical Issues Specific to Prepositioning of Medical Countermeasures

Various ethical challenges arise in planning for different sorts of public health responses. In the case of a pandemic, the tension between isolation/quarantine and individual liberty may be of primary concern. Since inhalational anthrax is noncommunicable, isolation is not a useful response and thus is not a relevant ethical challenge in this context. In the case of an anthrax attack involving a well-defined area of known contamination with anthrax spores, public health and public safety authorities might consider quarantining the area or confining people to their homes so they would not come in contact with the contaminated area.

One question relevant to prepositioning of anthrax MCM is whether public health resources should function as the primary source for distribution of emergency MCM or as a safety net for individuals unable to meet their needs in another way. In areas prone to natural disasters, all community members are encouraged to maintain supplies such as drinking water, emergency food rations, and means to provide warmth and light. Public shelters also supply these critical items and will offer them to any member of the community, but there is no ethical objection to individuals' maintaining private stores of these items in case of disaster. Indeed, those who are able to access their own supplies during a disaster lessen the strain of providing for those in desperate need.

Antibiotics likely to be of use in response to an anthrax attack, including doxycycline and ciprofloxacin, are widely available and not prohibitively expensive. In the event of an anthrax attack, these antibiotics could nevertheless be temporarily scarce if exposed citizens needed rapid access to greater supplies than were immediately available. Still, this scarcity would be temporary and related to the disaster context rather than absolute, as is the case, for example, with solid organs for transplantation.

The lack of absolute scarcity changes the ethical viability of certain proposals for the distribution of anthrax antibiotics. For instance, if some people secured their own supply of antibiotics in advance of an attack, this would not diminish the overall supply of antibiotics available for the rest of the community. When there is an absolute limit to a scarce resource, such as kidneys for transplant, distribution to any one individual precludes distribution to someone else. In the case of rapid distribution of MCM after a disaster, prior distribution to some individuals would potentially reduce wait times for others and thus could provide a benefit to both groups (win/win) rather than a gain for one group at the expense of the other (win/lose). Community members who wished to maintain their own supplies of

antibiotics might argue that they were merely keeping emergency supplies at hand, much as others might wish to keep a supply of clean water or canned goods ready in case of a flood or power outage. Further, such individuals could argue that the state should have a compelling reason to prevent them from taking this step to protect their families. Of course, families could not simply purchase antibiotics as they would emergency food supplies; they would first need to obtain a prescription from a physician who supported their plan. As discussed above, the procedural principle of proportionality indicates that public health policy should not limit individual freedom unless compelling and proportionate public health goals cannot be met in a less restrictive fashion. This line of argument results in a favorable appraisal of the *ethical* aspect of proposals to permit individual citizens to keep initial supplies of anthrax antibiotics in their home, independently from publicly held supplies. A final decision on whether individuals *should* maintain home stockpiles requires a full assessment of the other factors discussed in this report, such as the local risk of attack, the well-documented risks associated with taking antibiotics in inappropriate doses or for the wrong indication, cost, effectiveness, and flexibility (see Chapter 4 and below).

At the same time, while there is no strong ethical argument to prevent community members from obtaining MCM in advance of an anthrax attack, neither is there an ethical basis for public authorities relying on this method in lieu of other modes of distribution, particularly if individuals, not public health entities, are intended to bear the costs. Many community members lack sufficient funds to meet their current daily medical needs. If individuals bore the cost of home stockpiling, the impoverished, uninsured, and underinsured would effectively be prevented from relying on this strategy. A lack of stable housing or of knowledge of the danger of terrorist attack, or a host of other factors, would likely prevent large groups of individuals within the community from purchasing MCM privately in advance. For these vulnerable groups, home stockpiling poses excessive challenges, and additional distribution measures are needed.

Other features specific to distribution of MCM in an anthrax attack have ethical implications. For instance, the POD system requires that people arrive at a distribution center to receive antibiotics. For those with substantial cognitive or mobility impairments, finding and getting to a POD, let alone waiting in a lengthy line, may prove an insurmountable burden. For these vulnerable individuals, different distribution systems may be more viable and therefore ethically appropriate. Current proposals include a head-of-household model in which a single person collects MCM for a family or for groups of vulnerable community members, such as residents in a group home. Community engagement should include specific efforts to engage members of vulnerable populations. Such efforts are important to maintain transparency and earn trust, but they are also critical to help en-

sure that strategies developed for MCM dispensing will function effectively for vulnerable members of the community. This idea has been expressed by the disability community, and has since adopted by others, as "nothing about us without us" (e.g., Carlin, 2011; Charlton, 1998).

Taking into consideration both the general ethical considerations that should be involved in drafting public health policy and issues specific to the question of prepositioning anthrax MCM, the committee makes the following recommendation.

Recommendation 5-2: Integrate ethical principles and public engagement into the development of prepositioning strategies within the overall context of public health planning for bioterrorism response. **State, local, and tribal governments should use the following principles as an ethical framework for public health planning of prepositioning strategies:**

- **Promotion of public health—Strive for the most favorable balance of public health benefits and harms based on the best available research and data.**
- **Stewardship—Demonstrate stewardship of public health resources.**
- **Distributive justice—Distribute benefits and harms fairly, without unduly imposing burdens on any one population group.**
- **Reciprocal obligations—Recognize the professional's duty to serve and the reciprocal obligation to protect those who serve.**
- **Transparency and accountability—Maintain public accountability and transparency so that community members grasp relevant policies and know from whom they may request explanation, information, or revision.**
- **Proportionality—Use burdensome measures, such as those that restrict liberty, only when they offer a commensurate gain in public health and when no less onerous alternatives are both available and feasible.**
- **Community engagement—Engage the public in the development of ethically sound dispensing plans for medical countermeasures, including plans to preposition antibiotics, so as to ensure the incorporation of community values.**

EVALUATION OF POTENTIAL MCM PREPOSITIONING STRATEGIES FOR ANTHRAX

As discussed in the preceding chapter, various strategies for prepositioning MCM are available, including

- forward-deployed MCM (e.g., local stockpiles),
- cached MCM (e.g., hospital caches, workplace caches),
- predispensed MCM in all or some homes in a community, and
- combinations of these.

The committee defines a *prepositioning strategy* as the specification of locations where MCM are stored and, for each location, the amount of antibiotics stored, associated dispensing methods, and protocols for their use in the event of a confirmed or suspected attack (e.g., for general use at public PODs, for use at a specific closed POD, for home use).

The primary purpose of prepositioning is to provide individuals who have been exposed or potentially exposed to anthrax more rapid access to MCM. (Potentially exposed individuals include those who are not known to have inhaled enough spores to become sick but who nonetheless require antibiotics.) All of these individuals are referred to here as members of the *population at risk*.

Each potential prepositioning strategy can have advantages and disadvantages, depending on where and how it is implemented and the characteristics of potential anthrax attacks. This section refers to the characteristics of an attack (the type of locale, number and concentrations of spores released, method of release, weather conditions, location indoors or outdoors, local population density, etc., combined with the nature and distribution of the exposure within the population at risk) as an *attack scenario,* or *scenario*.

This section focuses on two of the most critical factors impacting the ultimate decision about whether and how to preposition: the potential health benefits and likely economic costs of prepositioning strategies. It describes a general approach that can be taken by local communities to estimate these factors and explains how the results could be used to support informed decision making. In particular, this section presents a modeling approach that is recommended for use in evaluating potential health benefits and the likely economic costs of alternative prepositioning strategies. Thus instead of recommending any particular strategy, the committee recommends that each community use this approach to identify and evaluate strategies appropriate to its own needs, objectives, value trade-offs, and constraints. This section also provides a synthesis of the existing evidence regarding the potential health benefits and likely costs of the various strategies. Note that, referring to the decision-aiding framework presented earlier in Box 5-1, two of the elements of evaluation of potential MCM prepositioning strategies for anthrax—evaluation of potential health risks and consideration of practicality—were discussed in detail in Chapter 4, and that discussion is not repeated here (although health risks are touched on briefly in the context of evaluating potential health benefits).

Evaluation of Potential Health Benefits

Prepositioning has two potential health benefits. First, prepositioning can directly reduce time to prophylaxis, defined here as the time from when an individual is exposed to anthrax (which is assumed for purposes of this discussion to be the same as the time of the release) until the time he or she receives antibiotics for anthrax. Because the intent of prepositioning is to place the MCM close to the point of dispensing, the MCM are expected to be available for dispensing sooner. Second, prepositioning can potentially reduce the overall time to prophylaxis for the community indirectly by reducing demand on some PODs, thus allowing those individuals seeking prophylaxis from these PODs to receive antibiotics sooner. Ultimately, both of these benefits, if achieved, could translate into reductions in mortality (as well as morbidity), compared with a base case of no prepositioning, if an attack occurred. Conversely, if a prepositioning strategy delayed time to prophylaxis (e.g., by creating additional traffic jams, queuing delays, and travel time requirements), it could result in increased mortality.

Health benefits are defined here, then, as reduced mortality compared with the base case of no prepositioning. The value of any health benefit, of course, depends strongly on both the size and the type of the affected community and the attack scenario. For example, in the case of a small anthrax attack with known exposure (e.g., a known attack in a specific building), predispensing in homes might provide little benefit, whereas in the case of a large and diffuse attack (e.g., aerosol dispersal of anthrax spores over a large metropolitan region), predispensing might have the potential to provide significant health benefits. Similarly, health benefits will depend on the intensity of spore dispersal and inhalation. For example, individuals who have inhaled few spores may become sick later than individuals who have inhaled many spores, or not at all (Baccam and Boechler, 2007; Brookmeyer et al., 2003; Coleman et al., 2008). As discussed below, health benefits also will depend on the time between the release and when the decision is made to order mass dispensing and use of MCM. For example, if an alarm were declared relatively early (e.g., within a couple of days after the attack occurred) compared with a typical 4- to 8-day incubation period for anthrax (Chapter 2), reductions in time to prophylaxis due to prepositioning might have little effect on mortality.

As indicated by the decision-aiding framework presented earlier in Box 5-1, prepositioning also entails potential health risks that must be weighed against the above benefits. These risks were discussed in detail in Chapter 4. In sum, forward-deployed MCM would not be associated with additional health risks relative to more centralized MCM storage strategies. Cached MCM also would not be associated with additional health risks if appropriate secure storage were used. Predispensed MCM, however, would

pose potential health risks. The most extensive body of relevant evidence (statistics on the misuse of antibiotics prescribed for routine medical care) suggests that inappropriate use would be high if predispensing were implemented broadly for the general public. Inappropriate use could result in adverse reactions, increased community and individual antibiotic resistance, and other concerns related to storage conditions and medication disposal. For groups and individuals lacking timely access to MCM through other dispensing mechanisms, however, the risk of not receiving postexposure prophylaxis following an anthrax attack may outweigh the potential health risks associated with inappropriate use. In addition, with a more focused strategy targeting vulnerable subpopulations, it might be easier to develop systems to decrease inappropriate use.

Evaluation of Likely Economic Costs

A range of costs are associated with prepositioning, including not only the quantifiable economic costs of creating and maintaining antibiotic stockpiles but also potentially nonquantifiable social costs that might result from prepositioning (over and above those that might exist without prepositioning). The latter might include costs due to possible inequities among different groups of people in the population at risk created by the existence of prepositioning; medical consequences of misuse of prepositioned MCM; social costs due to possible civil unrest, black market activities, and the like that might be engendered by the existence of prepositioned MCM; or costs arising from false confidence, moral hazard effects, or other distortions of incentives to manage risks created by prepositioning. Without downplaying the importance of such nonfinancial costs to society, the present discussion focuses on quantifiable economic costs.

The economic costs of prepositioning include the costs of purchasing the antibiotics; transporting them to their storage locations; maintaining the stockpiles, including the costs of labor, storage facilities, inventory tracking and replacement, and security; and dispensing, which may vary according to the type and amount of prepositioning.

Many of the economic costs associated with prepositioning are fixed: they are incurred regardless of whether an attack occurs. These include, for example, the costs to purchase, store, and maintain stockpiles of prepositioned antibiotics. Other economic costs may be incurred only in the event of an attack. These include, for example, the cost of lost time for people who must wait in line for antibiotics and wages for those who will manage and dispense the MCM. A well-designed approach for determining an appropriate prepositioning strategy (if any) must take into account all of these different economic costs within the context of different types and sizes of communities and alternative attack scenarios.

A Recommended Modeling Approach

As noted above, benefits and costs will depend on the prepositioning strategy, the size and type of community, and the attack scenario. Because of the great variability in communities across the United States (e.g., in size, population density, geographic area, transportation network, and risk of an attack), different communities may benefit most from different prepositioning strategies, including the possibility of no prepositioning. Thus, "one size does *not* fit all," and the decision to use (and design) a prepositioning strategy must be based in the context of the particular community. This section describes a modeling approach that can—and the committee believes should—be used by individual communities to inform their decisions regarding prepositioning of antibiotics for anthrax. The committee recommends that each community seek to populate a table with the following conceptual scheme:

Attack Scenario (and Modeling Assumptions)	Prepositioning Strategy	Expected Deaths Averted*	Costs*		
			Initial	Annual	Only in event of an attack

*Compared with the base case of no incremental prepositioning.

A range of potential attack scenarios should be considered in evaluating any potential prepositioning strategy. For example, the first column of the above table should list community-relevant attack scenarios. These might include such scenarios as the following:

- Scenario A—small attack with known exposure (e.g., anthrax enclosed in a letter to a member of Congress);
- Scenario B—medium attack with known exposure (e.g., release at a known subway station);
- Scenario C—large attack with unknown exposure (e.g., a crop duster flying over a large metropolitan area); and
- Scenario D—a "reload" multicity attack scenario (three cities attacked, and two additional cities attacked 2 weeks later) (Danzig, 2003; HHS, 2011).

The above are only examples; other scenarios could be envisioned. As discussed above, if information about the likelihood of different attack scenarios is available, it should be used. If not, the model can be used to explore the likely benefits and costs of different prepositioning strategies given different assumptions about the likelihood of these scenarios.

The second column of the table could include the following general categories:

- no prepositioning—no prepositioning of antibiotics for members of the public (referred to here as the *base case*);
- prepositioning in local warehouses—prepositioning in local warehouses for shipment to PODs (not stockpiled for closed PODs);
- prepositioning in health care settings—prepositioning in local hospital/pharmacy/health provider stockpiles or institutional facilities for older adults;
- prepositioning in workplace caches—prepositioning in government and private workplaces (e.g., state and local government infrastructure, Fortune 500 companies, small businesses); and
- predispensing in homes, of two types (either of which could be done with home MedKits or personal stockpiles dispensed via normal prescribing routes):
  — mass predispensing to the general public, or
  — targeted predispensing to specific individuals or groups.

The following sections first present models for estimating the information in the third column of the above table: the health benefits (expected deaths averted) associated with various prepositioning strategies under different attack scenarios and in different types of communities. Two possible models are described: a simple analytical model that can be used to estimate the distribution of time to prophylaxis and the resulting fraction of exposed individuals saved in a community, and a more detailed simulation-based model that estimates these quantities. Next, methods for estimating economic costs associated with prepositioning strategies are discussed. The final section describes how these estimates of benefits and costs can be used to inform decisions about prepositioning strategies.

Modeling to Evaluate Health Benefits

A first-order model This section presents a simplified first-order mathematical model that can be used to estimate health benefits for a given anthrax attack scenario in a given community. The committee does not argue for the accuracy (or even the general form) of this particular model. Rather, given the magnitude of the uncertainties in the various components

of the model—such as delays between release and the decision to dispense, the nature and shape of the anthrax incubation curve, and the ability of a community to achieve its planned POD dispensing time goals—any model that is more detailed than this first-order model will have enough uncertainty in its outputs to make claims of greater accuracy irrelevant.

The underlying approach is straightforward. To determine the health benefits that might accrue from a particular prepositioning strategy, the committee posits some likely parameters describing release/exposure scenarios and then develops a model for computing and comparing estimates of health outcomes for that strategy. The model is described briefly here; full details are provided in Appendix C.

Let δ denote the time between anthrax release (and, by assumption, exposure) and the decision to dispense. Assume that all individuals are exposed at the moment of release. For any community, estimates of δ should ideally be informed by submodels that incorporate the capabilities of currently used (or planned) monitoring and surveillance systems—as well as data from past BioWatch Actionable Results, accidental releases, and exercises—to estimate the various times contributing to the value of δ. These include the time required to determine clinically that at least one individual has been infected and the time between positive diagnosis and the decision by the responsible public health authority to issue an order to dispense MCM to the population at risk.

Define g as the required time to deliver prophylaxis, from the decision to dispense to completion of prophylaxis for all exposed individuals. Assume that, once dispensing begins, PODs work at full capacity with no idle dispensing staff and that prepositioning of MCM can reduce g: stockpiles located in the community can be available for dispensing sooner than inventories from the SNS, thus enabling prophylaxis to begin—and end—sooner than if there are no local stockpiles.

Define a function $f(t)$ that represents, for any particular release scenario, "the fraction of potential victims that can, in principle, be saved as a function of the time at which medical intervention begins" (Wilkening, 2006, p. 7593), where t is the time since exposure. The curve $f(t)$ is based on data and values for the incubation period, as discussed in Chapter 2. As pointed out in Chapter 2, data with which to compute this survival function are either suspect or limited, and the function will depend on many unknown scenario variables. Nevertheless, to obtain insights into the potential health benefits of prepositioning, the committee has taken the liberty of fitting $f(t)$ to the survival data (based on the Sverdlovsk release) presented by Wilkening (2006, 2008) and Brookmeyer et al. (2001, 2005). Using these data, the curve $f(t)$ can be well fit, for values of t up to about 200 hours, by $f(t) = e^{-(.004t)^2}$. (Note that although this curve does not have a fixed "minimum incubation period," for t = 24 hours the fraction surviving

is higher than .99.) This function can in turn be approximated (for t up to around 150 hours) by $f(t)=1-(.004t)^2$.

Finally, define S as the expected fraction of the population that will be saved for any prepositioning strategy and any assumed time δ after release at which the decision to dispense is made. Given the above assumptions, the quantity S can be calculated (for $\delta + g < 150$ hours) using the formula below (details are given in Appendix C):

$$S = 1 - \frac{(.004)^2\left((\delta+g)^3-\delta^3\right)}{3g}$$

This equation is valid for $g > 0$; since the practical realities of even the most ideal strategy for predispensing to individuals will involve some finite delay, for all practical purposes g will never be exactly equal to 0. In this first-order model, the estimated fraction of individuals who survive a release is a simple function of the time between anthrax release and the decision to dispense (δ) and the time from the start of dispensing MCM to completion (g).

Insights from the first-order model A great deal of insight can be obtained from using the above first-order model, although this simple model is not meant to be the sole basis for quantitative decision making; much more detailed models would need to be used by any jurisdiction to determine precise prepositioning strategies. Given different values of δ—the time until the decision to dispense—one can evaluate the fraction of exposed individuals who will be saved, S, for different times until completion of dispensing, g. This latter quantity can be reduced by prepositioning.

Table 5-1 shows results of an illustrative example. In this example, three prepositioning strategies are considered: no prepositioning, prepositioned caches, and predispensed antibiotics. For the case of no prepositioning, it is assumed that prophylaxis is completed within 48 hours of the decision to dispense (g = 48 hours); this is the current goal of PODs (CDC, 2010). For the case of caches, it is assumed that prophylaxis is completed within 12 hours of the decision to dispense (g = 12). For the case of predispensed MCM, it is assumed that prophylaxis occurs immediately when the decision to dispense is made (g = 0).

In this example, it is also assumed that a BioWatch Actionable Result occurs 24 hours after the anthrax event, an additional 24 hours is required until the first positive anthrax diagnosis is made, and an additional 12 hours is required to confirm that diagnosis (IOM, 2011). Four scenarios are considered. In the first, prophylaxis begins as soon as the BioWatch Actionable Result occurs (24 hours after the anthrax event). In the second, prophylaxis begins as soon as the first positive clinical anthrax diagnosis is

TABLE 5-1
Example Results Using the First-Order Model: Fraction of Exposed Individuals Saved (S) for Different Times Until the Decision to Dispense Is Made (δ) and Different Times for Completion of Prophylaxis After the Decision to Dispense (g)

		Fraction of Exposed Individuals Saved (S)			
Prepositioning Strategy	**Time Between Decision to Dispense and Completion of Prophylaxis (g, hours)**	SCENARIO 1 Prophylaxis Starts at BioWatch Actionable Result (δ = 24 hours)	SCENARIO 2 Prophylaxis Starts at Time of First Clinical Positive Diagnosis (δ = 48 hours)	SCENARIO 3 Prophylaxis Starts After Laboratory Confirmation of First Positive Diagnosis (δ = 60 hours)	SCENARIO 4 Prophylaxis Starts Ater Delayed Detection and Diagnosis* (δ = 120 hours)
No Prepositioning	48	0.96	0.91	0.88	0.67
Prepositioned Caches	12	0.99	0.95	0.93	0.75
Predispensed MCM	0	0.99	0.96	0.94	0.77

*This corresponds to a scenario in which, for example, there is no warning of an attack (e.g., no terrorist announcement), no environmental detection of the attack, and a delay in clinical diagnosis.

made (48 hours after the anthrax event).[1] In the third, prophylaxis begins as soon as the first positive diagnosis is confirmed through laboratory testing (60 hours after the anthrax event). In the fourth scenario, the initiation of prophylaxis occurs after delayed detection and diagnosis (120 hours after the anthrax event). For each of these scenarios, the first-order model was used to calculate the expected fraction of exposed individuals who will be saved (the quantity *S* in the first-order model) for each of the three prepositioning strategies.

Table 5-1 quantifies the increase in the fraction of individuals who will be saved as the time to complete dispensing decreases. In the first scenario (prophylaxis begins 24 hours after attack detection), for example, an expected 96 percent of individuals will be saved if prophylaxis is completed within 48 hours. If local stockpiles enable completion of prophylaxis within 12 hours, or if prophylaxis is completed immediately, the expected fraction of lives saved increases to 99 percent. As another example, in the third scenario (prophylaxis begins 60 hours after attack detection), if prophylaxis is completed within 48 hours of the decision to dispense, the result is an 88 percent expected fraction saved. This can be compared with the 93 percent fraction saved for those who take an average of 12 hours to receive prophylaxis, or the 94 percent fraction saved for those who can receive prophylaxis immediately. In the fourth scenario, where the decision to dispense is not made until 120 hours after the event, if prophylaxis is completed in 48 hours, only 67 percent of the exposed population will be saved, whereas 75 percent of exposed individuals who can receive prophylaxis within 12 hours and 77 percent of individuals with home stockpiles will be saved.

One critical assumption of this analysis is that the MCM is essentially 100 percent effective when dispensed before an exposed individual becomes symptomatic. If data are available that allow calculating the percent effectiveness for a particular MCM and target population, the numbers in Table 5-1 can simply be multiplied by that percentage. This provides the opportunity to introduce into the assessment of the value of a prepositioning strategy the possibility that the prepositioned MCM might have a lower percent efficacy due to such factors as improper storage, wrong dosage, or lower patient adherence.

[1]As described in Chapter 2, symptoms of inhalational anthrax do not appear until 4-8 days postexposure or longer. However, symptoms of cutaneous anthrax may appear as quickly as 1-3 days following exposure and could result in detection of the attack following a clinical anthrax diagnosis.

Another insight from this simple model is of interest. If:

- the decision to dispense is approximately the time at which the first case can be clinically and positively diagnosed;
- the survival function is 1.0 for t less than some time period t_m, and $f(t - t_m)$ for $t > t_m$ (t_m can be interpreted to be a "minimum incubation period"); and
- the shape of the exponential "drop-off" of $f(t)$ is the same as that given in the example above;

then the health benefits of any prepositioning strategy will essentially be those shown in Table 5-1. In other words, the health benefits depend more on the shape of the survival function than on the minimum incubation period.

Whether the increase in the fraction saved among the exposed population who have access to prepositioned MCM is outweighed by the costs and inequities of the policy providing that access is, of course, the major question that must be answered. The model, however, provides a basis for framing this question in specific terms.

These illustrative analyses show how the simple first-order model could be used to estimate the fraction of exposed individuals saved for different times to decision to dispense, different times until all exposed individuals can be dispensed an initial supply of prophylactic antibiotics, and different assumptions about the anthrax survival curve. As has been emphasized, communities should derive their own estimates of these quantities using data and assumptions specific to their own locale. A copy of the Excel spreadsheet containing the first-order model can be downloaded from www.iom.edu/anthraxreadiness.

More detailed modeling of health benefits Bravata and colleagues (Brandeau et al., 2008; Bravata et al., 2006; Zaric et al., 2008) developed a more detailed logistics model combined with a population-level model of anthrax disease to evaluate the likely impact, in terms of the distribution of time to prophylaxis and thus the fraction of lives saved, for different prepositioning strategies. This spreadsheet-based model numerically projects relevant logistical and disease factors in a population at risk after an anthrax attack. The logistics model captures the flow of antibiotics to PODs and to people, local dispensing capacity, local hospital capacity, and queues for prophylaxis and treatment. The disease model captures the progression of anthrax in the population at risk given the logistical constraints.

For different attack scenarios and different levels and types of prepositioning, the combined model estimates the distribution of time to prophy-

laxis for the population. The time to prophylaxis calculated by the model can be used to estimate mortality in the population and thus deaths averted compared with the base case of no prepositioning. This calculation is made by combining the curve describing the distribution of time to prophylaxis in the population with a curve describing the probability of anthrax survival as a function of how long after exposure the antibiotics are received. Several such curves have been estimated from data for both human and animal populations (Brookmeyer et al., 2001, 2005; Wilkening, 2008), as described in Chapter 2.

Behavior of the public is an important factor affecting the effectiveness of response to an anthrax attack in general and prepositioning strategies in particular (see Chapter 4 for a detailed discussion). Relevant behavioral factors include the rate at which unexposed and exposed people seek prophylaxis, adherence to prophylaxis, and load balancing at the PODs (which may affect the distribution of time to prophylaxis). The model can be used to evaluate changes in these factors and, thus, to evaluate the potential health benefits of prepositioning strategies in light of different assumptions about the behavior of the public, as well as strategies of public health and other officials for communicating with the public. (See Brandeau et al., 2008.)

The analyses of Bravata and colleagues (Brandeau et al., 2008; Bravata et al., 2006; Zaric et al., 2008) were intended to provide general insights into the logistics of anthrax preparation and response, but they were not tailored to specific communities. Communities must perform their own analyses to evaluate the likely benefits and costs of prepositioning strategies in their locale.

Determining Likely Economic Costs

The committee commissioned a paper from PRTM Management Consultants (Appendix D) to evaluate likely costs and time to response for the following prepositioning strategies:

- no incremental prepositioning (e.g., public PODs supplied by the SNS);
- workplace caches, along with workplace PODs, that could serve 20 percent of the population, used to augment inventories supplied by the SNS and public PODs;
- hospital and pharmacy caches, along with associated PODs, that could serve 20 percent of the population, used to augment inventories supplied by the SNS and public PODs; and
- predispensed MCM using home MedKits.

The paper estimates the likely costs of each prepositioning strategy, using as a case study data for Minneapolis-St. Paul. The specific results of the authors' cost estimates are summarized and discussed below in the section on the committee's findings and recommendations. The authors estimated costs of three types:

- *initial costs* of purchasing and stockpiling antibiotics,
- *annual costs* associated with managing and replacing the antibiotics and with ongoing training of dispensing personnel, and
- *costs incurred only in the event of an attack* (the costs of dispensing the antibiotics from PODs).

The commissioned paper provides a detailed description of the many different factors and assumptions that would go into estimating likely costs associated with prepositioning strategies. Specific estimates for likely costs would have to be determined by each community using data specific to that community and appropriate assumptions about prepositioning (e.g., the proportion of the population that workplace caches would be expected to cover), but the cost analysis presented in the paper could serve as a practical model for jurisdictions to use in developing their own cost estimates.

Using Estimates of Health Benefits and Economic Costs to Inform Decisions

The above sections have described ways in which the health benefits and economic costs of various prepositioning strategies can be estimated for given attack scenarios and in given communities. This section describes how these estimated quantities can be used to inform decision making.

Evaluating prepositioning strategies for given attack scenarios Given estimates of the health benefits and economic costs of alternative prepositioning strategies, one can consider several measures of cost-benefit. In general, the cost-benefit ratio of an intervention strategy is defined as follows:

$$\text{Cost-benefit ratio} = \frac{\text{Incremental cost of a strategy}}{\text{Incremental benefit of a strategy}}$$

Similarly, if both costs and benefits of strategies are monetized, their difference provides a monetary estimate of the net benefit (positive or negative) of implementing the strategy:

$$\text{Net benefit} = \text{Incremental benefit of a strategy} - \text{Incremental cost of a strategy}$$

(If cost and benefit estimates are uncertain, and especially if the uncertainties are correlated, their ratio or difference will have an associated probability distribution. If the cumulative distribution of net benefits for one strategy lies to the right of the cumulative distribution of net benefits for another, the first may be said to have greater net benefits even though the actual quantity of those benefits may be quite uncertain.) The measure of net benefits should be determined by the user (examples are given below). Whatever measure is used, the committee does not recommend its monetization.

To evaluate prepositioning strategies, one can compare the costs and benefits of any of the prepositioning strategies incremental to the base case of no prepositioning:

$$\text{Cost-benefit ratio} = C_0/C_p$$

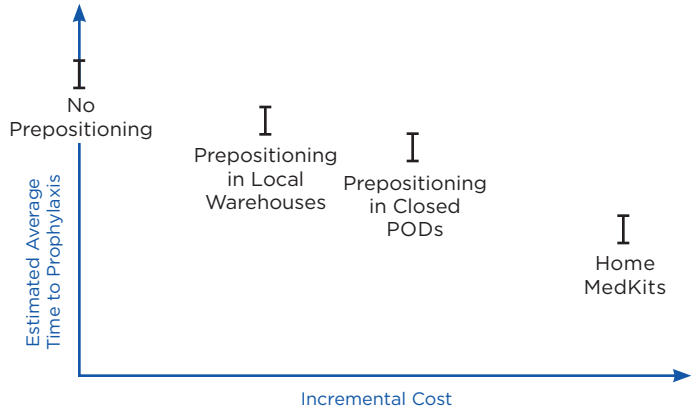
where:

C_0 = incremental cost of prepositioning compared with the base case of no prepositioning, and
C_p = incremental benefits of prepositioning compared with the base case of no prepositioning.

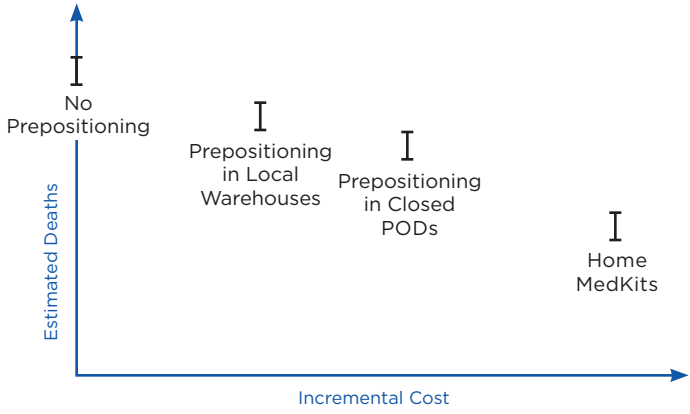
To evaluate the cost-effectiveness of strategies aimed at improving health, benefit typically is measured in terms of the incremental health benefits generated by a strategy (Gold et al., 1996). For the case of response to an anthrax attack, an intuitive measure of health benefits is deaths averted. However, one could also use average time to prophylaxis, a benefit measure that is not explicitly a health measure. Considering average time to prophylaxis as a measure of benefit could be useful because of the uncertainty surrounding the time to respond to an anthrax attack and resulting survival. Thus, two cost-benefit measures are considered here: incremental cost per death averted and incremental cost per reduction in average time to prophylaxis. Note that average time to prophylaxis may not be very relevant for predicting health outcomes, which may depend more on the tails of the time-to-prophylaxis distribution than on its mean; that is, if some members of the population do not receive medication for an especially long time, they are far more likely to fall ill. Also, the relationship between average time to prophylaxis and health consequences may be unknown or ambiguous, depending on the rest of the time-to-prophylaxis distribution. The evaluation of alternative strategies will differ with different measures of benefit. In particular, *deaths averted* and *average time to prophylaxis* may yield different results.

For each attack scenario, the estimated costs and benefits can be used

to create a figure showing cost on the x-axis; average time to prophylaxis on the y-axis; and a vertical bar for each of the prepositioning strategies, including the base case of no prepositioning. The vertical bar for each strategy reflects the variability in estimated deaths. (If costs are variable as well,



(a) Incremental costs and estimated average time to prophylaxis



(b) Incremental costs and estimated deaths

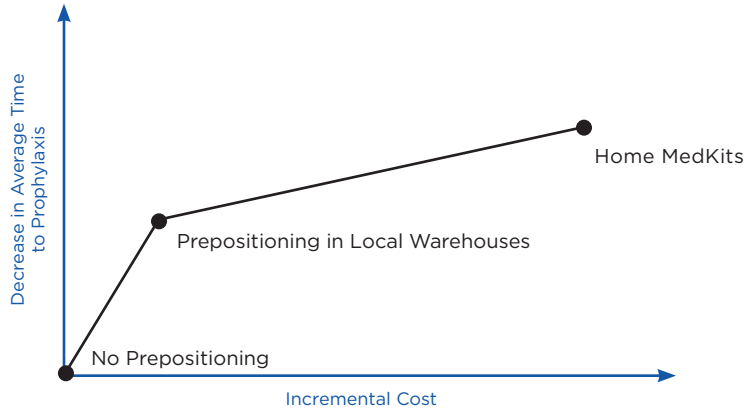
FIGURE 5-1
Envisioned model output: incremental costs and absolute benefits, assuming the occurrence of a given attack scenario.

NOTES: These figures are designed to illustrate an example of the envisioned model output; actual results will vary for each jurisdiction.

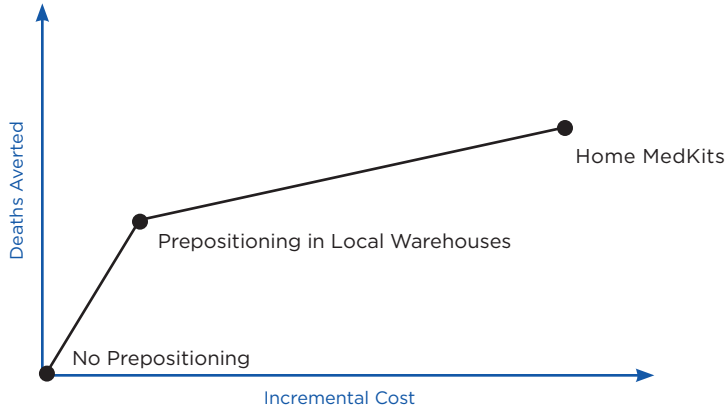
POD = point of dispensing.

the vertical bar will become a rectangle.) A similar figure can be created showing deaths on the y-axis. Examples are shown in Figure 5-1.

Similarly, it is useful to create figures showing costs and benefits incremental to the base case of no prepositioning (Figure 5-2). From such a



(a) Incremental costs and changes in average time to prophylaxis



(b) Incremental costs and deaths averted

FIGURE 5-2
Envisioned model output: incremental costs and incremental benefits, assuming the occurrence of a given attack scenario.

NOTE: These figures are designed to illustrate an example of the envisioned model output; actual results will vary for each jurisdiction.

figure, one can determine the cost-benefit frontier: these are strategies for which no other strategy or linear combination of strategies achieves greater benefits for less cost. (Note that in this example, it is assumed that the costs and benefits of strategies scale linearly, making it possible to draw straight lines between strategies in creating the cost-benefit frontier.) Strategies on the cost-benefit frontier are said to be *undominated*. The approach suggested here presents both costs and benefits for each prepositioning strategy and attack scenario so that decision makers can make their own value judgments about how to trade off these opposing attributes.

Evaluating expected costs and benefits of prepositioning strategies The expected cost-benefit ratio for any prepositioning strategy (measured either as cost per death averted or cost per hour of decrease in average time to prophylaxis) depends not only on the attack scenario (e.g., size, diffusion, time to detect) but also on the probability that an attack will occur. For example, the expected cost-effectiveness of prepositioning strategies that yield significant benefits primarily in the case of a relatively unlikely attack scenario may be lower than the expected cost-effectiveness of strategies that yield significant benefits for more likely attack scenarios. For a given probability of an attack of a given type (or assumptions about a given probability of a specific type of attack), one can calculate the cost-effectiveness of each prepositioning strategy relative to the base case strategy of no prepositioning (see Bravata et al., 2006; Zaric et al., 2008).

It should be emphasized that "point estimates" of benefits from prepositioning can be misleading. Prepositioning strategies must be evaluated in the context of the many potential attack scenarios that could occur, ranging from no attack to a large, diffuse attack that potentially would affect many people.

FINDINGS AND RECOMMENDATIONS ON THE BENEFITS, COSTS, AND SUITABILITY OF ALTERNATIVE PREPOSITIONING STRATEGIES

This section presents the committee's findings and recommendations regarding the benefits, costs, and suitability of alternative prepositioning strategies. The goal is to help inform decision making in communities as part of a comprehensive evaluation of the benefits and costs of alternative prepositioning strategies.

Findings

Importance of Adequate Dispensing Capability and Timely Decision to Dispense

The committee reviewed evidence regarding the effect on population survival of dispensing capability and the time until the decision to dispense is made. These factors are important in determining the effectiveness of any response to an anthrax attack, regardless of whether MCM are prepositioned. The committee's findings establish the importance of these factors in influencing the effectiveness of potential MCM prepositioning strategies.

Bravata and colleagues (Bravata et al., 2006; Zaric et al., 2008) developed a model, described above, that can be used to evaluate the likely impact, in terms of the distribution of time to prophylaxis, of different prepositioning strategies for anthrax MCM, assuming that all locally prepositioned MCM would be used in public PODs. The authors analyzed time to prophylaxis as well as the number of deaths that might occur for a variety of attack scenarios (e.g., large and small attacks with different numbers of individuals exposed and potentially exposed, and different times until attack detection) and a variety of logistical scenarios (e.g., different times to receive MCM from the SNS, different levels of local inventories of MCM, different levels of local dispensing capacity). They implemented their model using data for a representative metropolitan area with 5 million people.

The analyses of Bravata and colleagues showed that local dispensing capability, not local anthrax antibiotic inventories, is likely to be the rate-limiting factor in response to an anthrax attack: "because of the reportedly rapid availability of regional inventories, the critical determinant of mortality following anthrax bioterrorism is local dispensing capacity. Bioterrorism preparedness efforts directed at improving local dispensing capacity are required before benefits can be reaped from enhancing local inventories" (Bravata et al., 2006, p. 244). The analyses also showed the importance of timely attack detection in preventing deaths from anthrax. Zaric and colleagues (2008, p. 332) conclude that "improved surveillance systems can significantly reduce deaths from such an attack, but only if the local community has sufficient antibiotic dispensing capacity." In the model presented above, both dispensing capacity and population requiring prophylaxis are reflected in the parameter g, defined as the time from decision to dispense to completion of prophylaxis.

A community's dispensing capability does not impact the effectiveness of predispensing strategies because predispensed MCM are already dispensed to anticipated users. Some might see this as an argument in favor of widely implementing predispensing strategies in communities in which dispensing capability is low. In fact, the committee instead recommends

that resources be dedicated to enhancing dispensing capability in those communities. The findings that led to this conclusion are discussed in more detail later in this chapter.

Finding 5-2: *In the event of an attack, forward-deployed stockpiles and caches will have the potential to decrease morbidity and mortality only if there is adequate dispensing capability, and the time from release to the decision to dispense is short compared with the minimum incubation time. Analytical models of existing distribution strategies show that in the event of a large-scale attack, dispensing capability—not antibiotic inventories—is likely to be the rate-limiting step in getting antibiotics to the potentially exposed population.*

In another analysis using the same model, Brandeau and colleagues (2008) show that the behavior of the public is an important factor that can affect the ability of local public health officials to dispense antibiotics in a timely fashion. Depending on the type and amount of communication regarding an anthrax attack that has occurred, members of the public may have different levels of trust in—and understanding of—the messages issued by public health authorities. The level of trust may affect the rate at which exposed individuals seek and receive prophylaxis, the number of unexposed people seeking prophylaxis, and the number of individuals who report to different PODs requesting prophylaxis (thus potentially creating workload imbalances across PODs). The analyses of Brandeau and colleagues (2008) show that each of these factors can have a significant impact on effective dispensing capacity and consequently on mortality. Behavior of the public was also mentioned numerous times in expert testimony to the committee as an important factor affecting dispensing capacity and effectiveness (e.g., Bernier, 2011).

Finding 5-3: *Behavior of the public is an important factor affecting dispensing capacity and must be considered in evaluating a community's likely dispensing capability and thus in evaluating the potential benefits of prepositioned MCM for anthrax.*

Potential Effectiveness of Prepositioning Strategies

As mentioned above, the committee commissioned a paper from PRTM Management Consultants (Appendix D) to evaluate likely costs and time to response for the following prepositioning strategies:

- no incremental prepositioning (e.g., public PODs supplied by the SNS);

- workplace caches, along with workplace PODs, that could serve 20 percent of the population, used to augment inventories supplied by the SNS and public PODs;
- hospital and pharmacy caches, along with associated PODs, that could serve 20 percent of the population, used to augment inventories supplied by the SNS and public PODs; and
- predispensed MCM using home MedKits.

The authors developed estimates of cost and time to response for the Minneapolis-St. Paul metropolitan statistical area.

As expected, and consistent with other analyses (e.g., Bravata et al., 2006; Herrmann and Houck, 2011; Zaric et al., 2008), the analysis by PRTM showed that time to prophylaxis decreases as more inventory is forward-deployed, assuming sufficient local capacity for dispensing that inventory. Using specific assumptions about the population (e.g., 1.7 million people needing prophylaxis, 745,000 households), local dispensing capacity (e.g., 20 public PODs that could each provide prophylaxis for 1,000 people per hour), and local dispensing strategy (e.g., one household member could obtain antibiotics for all members of his/her household at a public POD), the authors derived the following estimates:

- If there were no prepositioning, dispensing could be completed in just over 48 hours from the decision to dispense (assuming 745,000 households needing prophylaxis and 20 PODs with dispensing capacity of 1,000 people per hour).
- Dispensing from public PODs, along with hospital/pharmacy caches and associated PODs that could serve 20 percent of the population, could be completed in approximately 43 hours (assuming 20 PODs with dispensing capacity of 1,000 people per hour; 19 hospitals with caches, each having a dispensing capacity of 100 people per hour and serving approximately 29,000 individuals; and 310 pharmacies with caches, each having a dispensing capacity of 100 people per hour and serving 120,000 individuals).
- Dispensing from public PODs, along with workplace caches and associated PODs that could serve 20 percent of the population, could be completed in approximately 43 hours (assuming 20 PODs with dispensing capacity of 1,000 people per hour; 17 workplaces serving approximately 170,000 individuals and each having a dispensing capacity of 1,000 people per hour; and 566 small workplaces serving a total of 170,000 individuals and each having a dispensing capacity of 100 people per hour).
- Dispensing from home MedKits could be accomplished almost instantaneously.

Although these numbers are based on specific assumptions for a specific community, they show the potential decreases in time to prophylaxis associated with different levels and types of prepositioning.

It should be noted that the PRTM analysis assumes that dispensing from home MedKits could be accomplished almost instantaneously. In practice, such dispensing might not be completed for several hours or more because people might not learn immediately of the need to take the antibiotics, and when they did learn, might not be at home. Delays in the time required to complete home dispensing would reduce the time benefit accruing from home prepositioning relative to other prepositioning strategies.

It should also be noted that the PRTM analysis assumes that the hospital/pharmacy and workplace caches and PODs could each serve 20 percent of the population. If these new PODs served a larger fraction of the population, the overall time to complete prophylaxis in the population would be less than that estimated above; conversely, if the new PODs served a smaller fraction of the population, the time to complete prophylaxis would be longer than that estimated.

Using a model derived from that of Bravata and colleagues (Bravata et al., 2006; Zaric et al., 2008), Herrmann and Houck (2011) show that predispensing (e.g., using home MedKits) would reduce time to prophylaxis not only for individuals who had the MedKits but also for other exposed individuals in the population by reducing demand on public PODs, assuming that the capacity of public PODs would not be reduced in light of the availability of MedKits. Because individuals with home MedKits would not have to obtain MCM from public PODs, demand at those PODs would be reduced, and thereby the time needed for the PODs to serve those who did have to use them. Similarly (although not explicitly considered in the analysis of Herrmann and Houck [2011]), the introduction of any incremental closed PODs could reduce demand at public PODs and thereby reduce time to prophylaxis for individuals who used the public PODs to receive MCM.

If the capacity of public PODs were reduced when prepositioning was introduced, these latter benefits would be attenuated, or perhaps even eliminated. Moreover, for the case of home predispensing, people might seek antibiotics from public PODs even if they had a 10-day supply at home. Additionally, if individuals with home stockpiles had used the medication inappropriately before the attack, or if the medication stockpiled in homes were not effective against the strain of anthrax used in the attack, these individuals would need to go to a public POD to receive prophylactic antibiotics. In these cases, the benefits of prepositioning accruing from reduced demand at public PODs would be reduced.

Finding 5-4: *Prepositioned MCM have the potential to reduce the expected time until exposed individuals in the population receive prophylaxis. If associated with closed PODs, prepositioned MCM could directly benefit*

those receiving MCM from the closed PODs, reducing their time to prophylaxis; by reducing demand at public PODs, they could also benefit those receiving MCM from public PODs, reducing their time to prophylaxis.

The example results estimated in Table 5-1 suggest that prepositioning provides greater benefits when the time from attack until the decision to dispense increases, and conversely, provides lesser benefits for shorter times until the decision to dispense. For example, if the time to the decision to dispense is 48 hours, then with no prepositioning, 91 percent of the exposed population will be saved; with local caches that take an average of 12 hours to complete dispensing of initial doses, 95 percent will be saved; and if dispensing can be accomplished instantaneously from home stockpiles, 96 percent will be saved. In comparison, if the time to the decision to dispense is 120 hours after the event, then with no prepositioning, only 67 percent of the exposed population will be saved; with local caches that take an average of 12 hours to complete dispensing of initial doses, 75 percent will be saved; and if dispensing can be accomplished instantaneously from home stockpiles, 77 percent will be saved. In the first case (48 hours until decision to dispense), if prepositioning can reduce time to prophylaxis to 12 hours, then the fraction saved increases by 4 percent above the baseline fraction of 91 percent. In the second case (120 hours until decision to dispense), the increase in fraction saved for the same prepositioning strategy is 8 percent (calculated as 75-67 percent).

These results occur because of the distribution of the incubation period of anthrax across exposed individuals: reducing time to prophylaxis from 48 to 24 hours after exposure, for example, will likely have little impact on the fraction saved because few individuals will develop prodromal anthrax within that period. On the other hand, reducing time to prophylaxis from, for example, 120 to 96 hours after exposure can significantly improve the fraction saved because many individuals are likely to develop prodromal anthrax between 96 and 120 hours after exposure, as can be seen from the estimated incubation period curves published by various authors (e.g., Brookmeyer et al., 2001, 2003; Wilkening, 2006, 2008).

Finding 5-5: *The benefits of prepositioning, measured in terms of time to prophylaxis and resulting fraction of the exposed population saved, increase as the time from attack until decision to dispense increases.*

Resources Needed for Prepositioning Strategies

The paper commissioned for this study also estimates the likely costs of each prepositioning strategy, again using data for Minneapolis-St. Paul. The authors' cost estimates are summarized in Table 5-2. The table summarizes the authors' estimates for the *initial costs* of purchasing and stockpiling

TABLE 5-2
Estimated Costs of Alternative Prepositioning Strategies for the Minneapolis-St. Paul Metropolitan Statistical Area

	Initial Costs	Annual Costs				Costs Incurred in the Event of an Attack	
Strategy	Inventory Purchase/ Stockpiling Cost ($)[a]	Inventory Replacement Cost ($)[b]	Inventory Management Cost for Prepositioned MCM ($)[c]	Costs of Training Dispensing Personnel for SNS-Supplied PODs	Costs of Training Dispensing Personnel for Incremental PODs	Dispensing Costs at SNS-Supplied PODs	Dispensing Costs Associated with Locations Supplied by Prepositioned MCM
No prepositioning (SNS-RSS-PODs)	—	—	—	895,000	—	1,630,000	—
Prepositioning in hospital/pharmacy caches that would serve 20 percent of the population	718,000	0	6,000	895,000	0	1,298,000	77,000
Prepositioning in workplace caches that would serve 20 percent of the population	723,000	726,000	6,000	895,000	3,683,000	1,298,000	307,000
Prepositioning in all homes	16,542,000	14,154,000	0	0	0	0	0

NOTES: A population of 1.7 million individuals in 745,000 households is assumed. All estimates are rounded to the nearest $1,000; MCM = medical countermeasures; POD = point of dispensing; RSS = receiving, staging, and storing; SNS = Strategic National Stockpile.

[a] For hospital, pharmacy or workplace caches, this includes the cost of purchasing antibiotics and delivering them to the caches. For home prepositioning, this additionally includes the cost of predispensing the medications. The analysis assumes that a 10-day dose stored in a hospital, pharmacy, or workplace cache would cost $2.10, and that a 10-day dose in a home MedKit would cost $5.12. Shipping costs were estimated assuming that a combination of U.S. Postal Service and FedEx shipping would be used.

[b] Includes costs to purchase replacement antibiotics and deliver them to the caches (or homes), but does not include costs of disposing of expired inventory.

[c] For hospital, pharmacy and workplace caches, a storage/management cost of $14 per 10,000 antibiotic bottles per month is assumed.

SOURCE: PRTM, 2011.

antibiotics; *annual costs* associated with managing and replacing the antibiotics and with ongoing training of dispensing personnel; and *costs that would be incurred only in the event of an attack* (the costs of dispensing the antibiotics from PODs). With regard to predispensing strategies, the discussion presented here first focuses on predispensing if implemented as a public health strategy. Individual purchase of personal stockpiles is discussed briefly below.

Initial costs As shown in Table 5-2, the estimated initial purchasing and stockpiling costs for the hospital/pharmacy and workplace prepositioning strategies are quite similar, at approximately $720,000 for this example (based on an estimated cost of $2.10 for a 10-day course of antibiotics, multiplied by 340,000 10-day doses, and a total shipment cost of $3,664 for 340,000 10-day doses), corresponding to an average cost per 10-day dose purchased and delivered of $2.13. The home MedKit strategy would incur estimated initial costs of $16.5 million, an amount that is more than 20 times higher. This amount comprises an estimated $8.7 million to purchase the MedKits (1.7 million at $5.12 per MedKit), plus $5.4 million to ship them (1.7 million shipped at an average cost of $3.18 per kit), plus $2.4 million to dispense them, leading to a total initial cost of $16.5 million—approximately $10 per MedKit.

Annual costs Estimated annual costs of the strategies also vary significantly. Notably, annual inventory replacement costs for the hospital/pharmacy prepositioning strategy are estimated to be negligible (inventories can be rotated into stock when they near their expiration date); annual inventory replacement costs for the workplace prepositioning strategy are estimated to be approximately $726,000; and annual inventory replacement costs for the home prepositioning strategy are estimated to be approximately $14.1 million (comprising $8.7 million to purchase new MedKits plus $5.4 million to ship them to homes). The estimated annual replacement cost of home MedKits is more than 20 times higher than the annual replacement cost for workplace caches for this example (which assumes 100 percent MedKit coverage but 20 percent workplace cache coverage); on a per capita basis, the estimated replacement cost for MedKits is more than four times higher than that for workplace caches.

Note that these estimated annual replacement costs do not include the cost of returning and disposing of expired antibiotics—costs that may be particularly relevant for the case of home MedKits. The vast majority of the MedKits dispensed will reach their expiration date unused. Because of concerns related to improper disposal of antibiotics, it will likely be necessary to include in this strategy a means of enabling people to dispose of their unused MedKits safely. This could involve, for example, includ-

ing a drug disposal mailer (such as the Sharps TakeAway envelope) in the MedKit packaging, with the cost for disposal (estimated at $3 per MedKit[2]) being incorporated in the product price (Sharps Compliance, Inc., 2011).

The PRTM analysis estimates that annual inventory management costs would be zero for the case of home MedKits and that hospital, pharmacy, and workplace caches would incur very small annual storage/management costs of approximately $6,000 (based on the assumption that storing/managing a pallet of 10,000 bottles of antibiotics would cost $14/month). The committee believes that annual inventory management costs for prepositioned MCM could be higher than this estimate, particularly for workplace caches managed by private-sector entities that lack occupational health programs and infrastructure, because staff time would be needed to monitor storage conditions, oversee disposal and replacement, and ensure compliance with all laws and regulations.

The PRTM estimate of annual costs associated with training dispensing personnel is $895,000 for the case of no prepositioning and for the case of hospital/pharmacy prepositioning (based on the assumption that no incremental dispensing training would be needed for hospital/pharmacy personnel); $4,578,000 for workplace prepositioning ($895,000 for training dispensing personnel for SNS-supplied PODs plus $3,683,000 for training dispensing personnel for workplace PODs); and zero for home MedKit prepositioning. This latter value stems from the assumption made in the analysis that, if MedKits are available in all homes, SNS-supplied public PODs will not be needed. To the extent that public PODs are needed, this annual training cost will increase above zero. The analysis assumes that all dispensing staff associated with workplace PODs will have to be trained annually. However, annual costs of training personnel for workplace PODs could vary greatly depending on the workplace. For example, many large corporations have occupational health programs and health personnel on staff who would not need much training, so annual training costs for these workplaces would be lower than those for workplaces without this infrastructure.

Costs incurred in the event of an attack Finally, the PRTM analysis estimates the dispensing costs that would be incurred in the event of an attack for each of the prepositioning strategies. For the case of no prepositioning, the cost of dispensing from public PODs is estimated to be approximately

[2]Personal communication to committee member Erin Mullen from Claude Dance, Senior Vice President of Sales and Marketing, Sharps Compliance, Inc. The amount of $3 represents a "ballpark estimate" for the cost of including a self-mailer in the package for a Food and Drug Administration (FDA)-approved MedKit.

$1.6 million. For the case of hospital/pharmacy prepositioning, the cost of dispensing from public PODs is reduced to $1.3 million (as the hospital/pharmacy PODs are assumed to serve 20 percent of the population), and the cost of dispensing from hospital/pharmacy PODs is $77,000 (less than the cost of dispensing an equivalent amount of MCM from public PODs because hospital pharmacists and other health care providers at the hospitals could dispense the MCM, whereas some contract staff would likely have to be hired for PODs), leading to a total dispensing cost of approximately $1.4 million. For the case of workplace prepositioning, the cost of dispensing from public PODs is estimated to be $1.3 million (the workplace caches are assumed to serve 20 percent of the population), and the cost of dispensing from workplace PODs is estimated to be $307,000 (slightly less than the cost of dispensing an equivalent amount of MCM from public PODs), leading to a total dispensing cost of approximately $1.6 million. The analysis assumes that the cost of home dispensing in the event of an attack would be zero and that if home MedKits were prepositioned in all homes, public PODs would not be required and thus would incur no dispensing cost. To the extent that public PODs would be needed if home MedKits were available, the cost of dispensing from public PODs would increase above zero.

Relative costs The above cost estimates, although preliminary and specific to the Minneapolis-St. Paul case, highlight some of the cost differentials among the prepositioning strategies. The hospital/pharmacy prepositioning strategy would incur modest incremental initial and ongoing annual costs compared with the strategy of no prepositioning. The workplace prepositioning strategy would incur incremental initial costs similar to those of the hospital/pharmacy prepositioning strategy, but it would likely incur higher annual costs because of the need to replace inventory and train dispensing personnel. Home prepositioning is by far the most costly strategy, with both initial and ongoing annual costs being many times higher than those for the hospital/pharmacy and workplace prepositioning strategies.

Additional costs associated with a Food and Drug Administration (FDA)–approved home MedKit The above estimates of costs associated with home stockpiling do not take into account the costs that would be associated with the development of an FDA-approved home MedKit. The PRTM paper uses the cost per unit of the Emergency Use Authorization (EUA) MedKit provided to postal workers who volunteered in the Minneapolis-St. Paul postal pilot program. Of note, an EUA-approved MedKit does not necessarily require the safety studies and the additional costs associated with standard FDA approval. As noted previously, however, EUA MedKits have been used only for specific targeted groups under carefully limited

conditions, and they have never been used for large groups of the population outside of a research context. The committee observes that the costs of past EUA-approved MedKits do not serve as a good estimate of the cost of an FDA-approved MedKit for sale to the general public, which is likely to be a significantly higher. Use of an FDA-approved MedKit would increase costs over those for either an EUA MedKit or personal stockpiling because of the following additional expenses.

Development cost: Doxycycline is approved for the treatment and prevention of anthrax infection. However, because MedKits would have different packaging and instructions and be dispensed pre-exposure for long-term storage by the ultimate user, FDA approval would be needed for the indication of a prepositioned MCM (NBSB, 2008). While the path forward for FDA approval of a MedKit for anthrax postexposure prophylaxis is not clear, it may be reasonable to assume that the required studies would be similar to those for an antiviral MedKit intended for treatment or postexposure prophylaxis of pandemic influenza. The manufacturers of the antivirals oseltamivir (Roche's Tamiflu®) and zanamivir (GlaxoSmithKline's Relenza®) submitted proposals for pandemic influenza MedKits that each proposed four studies to examine labeling comprehension; compliance; and other issues, such as mixing and dosing for pediatric populations (FDA, 2008). Average costs for such studies can range from $610,000 each for nonclinical studies to $5.3 million each for clinical studies (Tufts Center for the Study of Drug Development, 2007). Additionally, as a condition for approval, there may be requirements for continued postmarketing studies and risk evaluation and mitigation strategies (REMS), which, depending on how comprehensive the REMS requirements are, can cost up to $1 million for start-up costs and $100,000/month for ongoing operational maintenance (Morel and Murphy, 2009; Shelley, 2009). If predispensing strategies targeted specific individuals or groups, and not the general public, development costs per capita would be higher.

Packaging costs: Because of different labeling requirements and unit-of-use packaging, MedKits would have higher costs for packaging relative to personal stockpiling.

Insurance coverage: Given their commitment to keep health care costs down, insurers may not cover the increased cost of a MedKit given that a low-cost generic form of doxycycline already is available in the marketplace. Thus, the full cost of a MedKit is likely to be borne by individuals.

Market considerations: It is unclear what the business case would be for industry to develop a product that already is available as a low-cost generic unless a committed market were identified ahead of time. In the current marketplace, once patent protection is lost, conversion to lower-cost generic alternatives reaches 84-94 percent within the first month (Medco, 2009). Given that the costs associated with development of a MedKit and

other related costs would be expected to be recouped through product sales, reduced demand due to generic competition would also require a higher per-MedKit cost.

In sum, FDA-approved MedKits are likely to be substantially more expensive than either EUA-approved MedKits or personal stockpiles attained through the currently available means of prescription given the additional costs of safety studies and packaging. While the costs of disposal of expired drugs may be similar, moreover, costs of replacing the more expensive MedKits would reflect their higher price.

Finding 5-6: *Although potentially effective for ensuring that large numbers of people have rapid access to antibiotics, prepositioning strategies will require more resources than strategies that rely on distribution from central locations after an attack. Therefore, prepositioning strategies will provide the greatest value in responding to a large-scale attack in high-risk areas with limited dispensing through the POD system and/or other specific characteristics that would be addressed effectively using prepositioning. Prepositioning strategies may have little added value in areas in which the risk of an attack is low and/or dispensing capacity is sufficient. For these reasons, each jurisdiction should perform its own evaluation of the cost-effectiveness of alternative prepositioning strategies.*

As highlighted in the above discussion, predispensing strategies are likely to be much more expensive than other potential prepositioning strategies, probably by at least an order of magnitude (particularly if FDA-approved MedKits are developed and used). Moreover, as highlighted in Chapter 4, they are likely to pose significant safety risks not associated with forms of prepositioning that do not involve home stockpiling. Based on expert testimony provided to the committee, however, there may be cases in which predispensing is appropriate—for example, for individuals who cannot leave their residence or for first responders who do not muster at a workplace.

Based on the available evidence and expert judgment, the committee finds that it is important to consider how to provide antibiotics for those who will be expected to report to work and stay at work during an attack in order to respond and maintain critical functions within the community. These include such individuals as critical infrastructure personnel (e.g., health care workers and power company employees) and first responders. Because these workers would be unable to leave their positions to stand in line at a POD, they would be disadvantaged by a strategy that relied solely on open PODs. Alternative strategies are needed to ensure coverage for such subpopulations. Many jurisdictions also include the families of these workers in their targeted dispensing programs.

The concerns and risks described above for MedKits and personal stockpiles apply equally to the general population and to critical infrastructure personnel, first responders, and their families. Therefore, the committee finds that, where feasible, workplace caches are likely to be a more effective strategy with fewer risks than personal stockpiles in homes. There may be some cases, however, in which workplace caches are not feasible or are not an effective strategy—for example, critical infrastructure personnel and first responders who do not muster at a workplace, and critical infrastructure personnel and first responders for whom it would be infeasible to bring antibiotics from workplace caches back to their families. For this reason, the committee recognizes that communities should retain the flexibility to select various prepositioning strategies, with the suggestion that they select workplace caches over personal stockpiling where possible.

With regard to vulnerable individuals for whom predispensing might be appropriate because of their medical condition and/or social situation, this would likely involve predispensing of a personal stockpile, done through standard prescribing practices and depending on the usual relationship between physician and patient. In this situation, public health would not bear the cost of the predispensed MCM, but similar concerns about risks would exist.

The discussion of ethical principles earlier in this chapter notes that there is no *ethical* argument against individuals pursuing purchase of personal stockpiles (because these medications are not in short supply, so that purchase by some people does not impose a shortage on others or exacerbate existing inequities in society), and doing so is allowed under current prescribing practices. However, that discussion adds that a final decision on whether individuals *should* maintain home stockpiles requires a full assessment of the other factors discussed in this report, such as the local risk of attack, the well-documented risks associated with taking antibiotics in inappropriate doses or for the wrong indication, cost, effectiveness, and flexibility. Given this ethical analysis and the findings presented above, the committee does not recommend that individuals pursue personal stockpiles (with the potential exception of those lacking other timely access to MCM). At the same time, with reference to the existing prescription practices, physician-patient relationships, and respect for individual liberties, the committee does not find it advisable to explicitly prohibit this practice either.

Finding 5-7: *The use of predispensing as a broad public health strategy for the general population is unlikely to be cost-effective and carries significant risks. Based on a community's comprehensive risk assessment, however, targeted predispensing may sometimes prove to be an appropriate strategy, particularly for individuals or groups that would lack timely access to anti-*

biotics through the existing dispensing system. These might include, for example:

- *vulnerable individuals, such as homebound or medically vulnerable individuals for whom physicians and patients agree that predispensing is an appropriate strategy;*
- *critical infrastructure personnel and first responders who do not muster at a workplace; and*
- *critical infrastructure personnel and first responders for whom it would be infeasible to bring antibiotics from workplace caches back to their families.*

Finding 5-8: *The added safety features that might be provided by an FDA-approved MedKit relative to a personal stockpile obtained through regular prescribing practice are unlikely to justify the significant additional cost of developing and purchasing the MedKits. Personal stockpiling currently is allowed under normal prescribing practices, and it could be used to predispense to those targeted groups and individuals for whom predispensing is an appropriate option.*

Factors Affecting the Appropriateness of Alternative Prepositioning Strategies

The committee heard testimony from numerous individuals on factors that may affect the appropriateness of different prepositioning strategies, as well as potential health, economic, and other consequences of the strategies. Key aspects of this information are synthesized in Table 5-3, which presents, for a range of prepositioning strategies, qualitative characteristics that describe when each strategy would be most likely to be appropriate, along with a qualitative description of the consequences of each strategy.

The first two columns of the table describe, for a continuum of MCM storage locations (first column), associated strategies to consider (second column). The prepositioning strategies are listed in the rows of the table according to increasing levels of forward deployment. The first row, no prepositioning, corresponds to the current situation of inventories held primarily in centralized SNS stockpiles, with no incremental prepositioning. The next row, forward-deployed MCM, corresponds to stockpiles held locally in warehouses, either as part of the SNS or other federal deployment (e.g., Department of Defense [DOD] or Department of Veterans Affairs [VA]) or in commercial warehouses. The next row, cached MCM, corresponds to stockpiles held in specific local caches, such as hospitals, pharmacies, or workplaces. Finally, the last row, predispensed MCM, corresponds to personal stockpiles or home MedKits—the maximum level of prepositioning.

TABLE 5-3
Appropriateness and Consequences of Alternative Prepositioning Strategies: Qualitative Summary

Continuum of MCM Storage Locations	Strategies to Consider[a]	Factors Affecting Appropriateness of Strategies			Consequences of Strategies			
		Risk Status[b]	Public Health Dispensing Capability[c]	Gaps in Sub-populations Covered[d]	Cost to Public Health[e]	Time to Prophylaxis[f]	Inventory Flexibility[g]	Potential for Misuse[h]
No Pre-positioning	– Centralized stockpiles (SNS, other)	Low	Adequate	None	Limited	Baseline	Greatest	None
Forward-Deployed MCM	– SNS forward-deployed – Other federal forward-deployed (e.g., DOD, VA) – Private forward-deployed	High	Adequate	n/a	Moderate	Shorter	Medium	None
Cached MCM	– Hospital/ pharmacy caches – Workplace caches	High	Limited	Some	Moderate	Shorter	Less	Some/little
Predispensed MCM	– Personal stockpiles – MedKits	Extremely High	Inadequate	Many	Limited High	Shortest	Least	Moderate/ high

NOTE: DOD = Department of Defense; MCM = medical countermeasures; n/a = not applicable; SNS = Strategic National Stockpile; VA = Department of Veterans Affairs.

[a] Combinations of strategies may be appropriate.

[b] Likelihood of an attack and likelihood of an attack of a given type or size.

[c] MCM dispensing capability in the event of a large attack.

[d] Subpopulations that may not be covered by MCM dispensing capacity in the event of an attack.

[e] The cost incurred by public health authorities to store and maintain inventories of MCM. Other costs may be borne by other entities, such as private-sector workplaces (e.g., storage, training, and maintenance of workplace caches) and individuals or private insurers (e.g., personal stockpiles). Research and development costs for MedKits may be borne by the federal government, by a private-sector company, or by some combination of these.

[f] The time from the decision to dispense until MCM can be delivered to all exposed and potentially exposed individuals.

[g] Inventory flexibility includes the potential for use of multiple drugs, the potential for redeployment of inventories based on need, and the ease with which stockpiles can be rotated.

[h] Potential for misuse of the prepositioned MCM (e.g., individuals taking the antibiotics for other conditions or not in the event of an anthrax attack).

Factors related to the appropriateness of strategies (the middle columns of Table 5-3) include threat status (the likelihood of an attack and the likelihood of an attack of a given type or size), public health dispensing capacity (capacity to dispense MCM after an anthrax attack), and gaps in coverage of subpopulations (subpopulations that may not be covered by public health MCM dispensing in the event of an attack). These factors would be determined through a local community's assessment of its anthrax risk and its response capabilities in accordance with the decision-aiding framework presented in this chapter. In Table 5-3, these factors are expressed qualitatively by level (e.g., low versus high versus extremely high threat status).

Consequences of strategies (the rightmost columns of Table 5-3) include the cost to public health (the cost to store and maintain the inventories of MCM), time to prophylaxis (the time from the decision to dispense until MCM can be delivered to all exposed and potentially exposed individuals), inventory flexibility (potential for redeployment of inventories based on need), and potential for misuse (of the prepositioned MCM). Again, these consequences are expressed in Table 5-3 qualitatively (e.g., limited versus moderate versus high cost to public health).

The table consists of a set of suggested "if-then" rules, stored in its rows: if a situation is well described by the entries in a row under "Factors Affecting Appropriateness of Strategies," then the prepositioning strategy or strategies in the corresponding row might be appropriate to consider. For example, in a community with "some" gaps in covered populations, prepositioning in hospital, pharmacy, or workplace caches might be appropriate. On the other hand, in a community with "low" threat status, "adequate" dispensing capacity, and "no gaps" in covered subpopulations, no prepositioning may be most appropriate.

Similar reasoning can be applied with respect to the consequences of implementing a strategy. As an example, the bottom row (for the MedKits strategy) will lead to the shortest time to prophylaxis, but with a high cost and the least flexibility and the greatest potential for misuse. This strategy is recommended for consideration only if the threat status is "extremely high" (which the committee leaves undefined) and public health dispensing capacity is "inadequate" (also left undefined, but meant to be suggestive). Other strategies in the table represent different trade-offs among cost, flexibility, time to prophylaxis, and potential for misuse, and they are recommended for consideration for different levels of threat status, public health dispensing capacity, and gaps in covered subpopulations.

The rows in Table 5-3 are not meant to be exhaustive—for example, there is no row showing what strategies to consider if threat status is "low" but public health dispensing capacity is "inadequate"—but rather to summarize and synthesize the types of qualitative considerations and trade-offs suggested during discussions for this study of when each strategy most

likely would be appropriate. Although such qualitative summaries can be misleading, as terms such as *high* and *moderate* have no precise definitions, and there may be exceptions to the general rules suggested, these summaries do illustrate the types of trade-offs that communities will probably face.

The committee draws several key observations from Table 5-3. First, prepositioning becomes potentially more useful in communities with relatively high threat status, limitations on public health dispensing capacity, and/or gaps in covered subpopulations. Second, prepositioning of MCM is likely to decrease time to prophylaxis but will decrease flexibility, increase costs, and increase the potential for misuse of MCM.

Finding 5-9: *Table 5-3 summarizes qualitatively factors related to the appropriateness of various MCM prepositioning strategies and the consequences of implementing these strategies. Prepositioning is potentially useful in communities with relatively high risk status, limitations on public health dispensing capacity, and/or gaps in covered subpopulations. Prepositioning is likely to decrease time to prophylaxis but will decrease flexibility, increase costs, and increase the potential for misuse of MCM.*

Recommendations

The above sections have presented an approach for evaluating the benefits and costs of alternative MCM prepositioning strategies, as well as the committee's findings regarding the benefits, costs, and suitability of these strategies. These findings lead to the following recommendations.

Recommendation 5-3: Consider the risk of attack, assess detection and dispensing capability, and evaluate the use of prepositioning strategies to complement points of dispensing.
State, local, and tribal governments should, in partnership with each other and with the federal government, the private sector, and community organizations:

- **Consider their risk of a potential anthrax attack.**
- **Assess their current detection and surveillance capability.**
- **Assess the current capability of and gaps in their medical countermeasures dispensing system.**
- **Based on their risk and capability assessment, evaluate whether specific prepositioning strategies will fill identified gaps and/or improve effectiveness and efficiency. The decision-making framework should include, for a range of anthrax attack scenarios:**
  - **— evaluation of the potential health benefits and health risks of alternative prepositioning strategies;**

- **evaluation of the relative economic costs of alternative prepositioning strategies;**
- **comparison of the strategies with respect to health benefits, health risks, and costs, taking into account available resources; and**
- **consideration of ethical principles and incorporation of community values (see Recommendation 5-2).**

Recommendation 5-4: Give priority to improving dispensing capability and developing prepositioning strategies such as forward-deployed or cached medical countermeasures.

In public health planning efforts, state, local, and tribal jurisdictions should give priority to improving the dispensing capability of points of dispensing and push strategies and to developing forward-deployed or cached prepositioning strategies.

The committee does not recommend the development of public health strategies that involve *broad* use of predispensed medical countermeasures for the general population. In some cases, however, *targeted* predispensed medical countermeasures might be used to address specific gaps in jurisdictions' dispensing plans for certain subpopulations that lack access to antibiotics via other timely dispensing mechanisms. These might include, for example, some first responders, health care providers, and other workers who support critical infrastructure, as well as their families.

Personal stockpiling might also be used for certain individuals who lack access to antibiotics via other timely dispensing mechanisms (for example, because of their medical condition and/or social situation) and who decide—in conjunction with their physicians—that this is an appropriate personal strategy. This is allowed under current prescribing practice and would usually be done independently of a jurisdiction's public health strategy for dispensing medical countermeasures.

The following recommendation addresses the development of an FDA-approved MedKit. The committee found that among predispensing strategies, FDA-approved MedKits are likely to be more costly than personal antibiotic stockpiles and EUA-approved MedKits because of the additional costs associated with the rigorous process of FDA approval. Depending on how the MedKit was developed, these costs could be shared between the federal government and the private sector, but consumers and cash-strapped state and local public health agencies might also bear the brunt of these additional costs. There is limited evidence to suggest that FDA-approved MedKits would be less prone to inappropriate use than other forms of

predispensing and, similar to other forms of predispensing, they cannot respond flexibly to different anthrax attack scenarios. The following recommendation does not preclude the use of an EUA MedKit, which would be less costly than an FDA-approved MedKit, but would be appropriate only for targeted use in specific contexts.

Recommendation 5-5: Do not pursue development of a Food and Drug Administration-approved MedKit unless this is supported by additional safety and cost research.

The committee does not recommend the development of a Food and Drug Administration-approved MedKit designed for prepositioning for an anthrax attack until and unless research demonstrates that MedKits are significantly less likely to be used inappropriately than a standard prescription and can be produced at costs comparable to those of standard prescription antibiotics.

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6

Recommended Actions for Moving Forward

The committee concludes this report by offering a summary of its recommendations for moving forward, which include actions recommended for state, local, and tribal public health officials and those recommended at the federal/national level, as well as research needed to provide a stronger evidence base for decision making on prepositioning. Although these actions are proposed in the context of the selection, development, and implementation of prepositioning strategies, many would also help enhance the nation's overall ability to distribute and dispense antibiotics rapidly following an anthrax attack, regardless of the specific decisions made about prepositioning.

ACTIONS FOR STATE, LOCAL, AND TRIBAL PUBLIC HEALTH OFFICIALS

The following recommendations are intended to assist state, local, and tribal public health officials in evaluating the potential benefits, health risks, and costs of developing prepositioning strategies in their community.

Recommendation 5-2: Integrate ethical principles and public engagement into the development of prepositioning strategies within the overall context of public health planning for bioterrorism response. **State, local, and tribal governments should use the following principles as an ethical framework for public health planning of prepositioning strategies:**

- **Promotion of public health—Strive for the most favorable balance of public health benefits and harms based on the best available research and data.**
- **Stewardship—Demonstrate stewardship of public health resources.**
- **Distributive justice—Distribute benefits and harms fairly, without unduly imposing burdens on any one population group.**
- **Reciprocal obligations—Recognize the professional's duty to serve and the reciprocal obligation to protect those who serve.**
- **Transparency and accountability—Maintain public accountability and transparency so that community members grasp relevant policies and know from whom they may request explanation, information, or revision.**
- **Proportionality—Use burdensome measures, such as those that restrict liberty, only when they offer a commensurate gain in public health and when no less onerous alternatives are both available and feasible.**
- **Community engagement—Engage the public in the development of ethically sound dispensing plans for medical countermeasures, including plans to preposition antibiotics, so as to ensure the incorporation of community values.**

Recommendation 5-3: Consider the risk of attack, assess detection and dispensing capability, and evaluate the use of prepositioning strategies to complement points of dispensing.

State, local, and tribal governments should, in partnership with each other and with the federal government, the private sector, and community organizations:

- **Consider their risk of a potential anthrax attack.**
- **Assess their current detection and surveillance capability.**
- **Assess the current capability of and gaps in their medical countermeasures dispensing system.**
- **Based on their risk and capability assessment, evaluate whether specific prepositioning strategies will fill identified gaps and/or improve effectiveness and efficiency. The decision-making framework should include, for a range of anthrax attack scenarios:**
  - **— evaluation of the potential health benefits and health risks of alternative prepositioning strategies;**
  - **— evaluation of the relative economic costs of alternative prepositioning strategies;**
  - **— comparison of the strategies with respect to health benefits, health risks, and costs, taking into account available resources; and**

— consideration of ethical principles and incorporation of community values (see Recommendation 5-2).

Recommendation 5-4: Give priority to improving dispensing capability and developing prepositioning strategies such as forward-deployed or cached medical countermeasures.

In public health planning efforts, state, local, and tribal jurisdictions should give priority to improving the dispensing capability of points of dispensing and push strategies and to developing forward-deployed or cached prepositioning strategies.

The committee does not recommend the development of public health strategies that involve *broad* use of predispensed medical countermeasures for the general population. In some cases, however, *targeted* predispensed medical countermeasures might be used to address specific gaps in jurisdictions' dispensing plans for certain subpopulations that lack access to antibiotics via other timely dispensing mechanisms. These might include, for example, some first responders, health care providers, and other workers who support critical infrastructure, as well as their families.

Personal stockpiling might also be used for certain individuals who lack access to antibiotics via other timely dispensing mechanisms (for example, because of their medical condition and/or social situation) and who decide—in conjunction with their physicians—that this is an appropriate personal strategy. This is allowed under current prescribing practice and would usually be done independently of a jurisdiction's public health strategy for dispensing medical countermeasures.

FEDERAL/NATIONAL-LEVEL ACTIONS

The following are federal/national-level actions that would facilitate the evaluation and development of prepositioning strategies.

Recommendation 4-1: Develop national guidance for public-private coordination in the prepositioning, distribution, and dispensing of medical countermeasures.

The Department of Health and Human Services should convene state, local, and tribal governments and private-sector organizations to develop national guidance that will facilitate and ensure consistency for public-private cooperation in the prepositioning, distribution, and dispensing of medical countermeasures and help leverage existing private-sector systems and networks.

Recommendation 5-1: Enhance assessment of performance in implementing distribution and dispensing plans for medical countermeasures. **The Centers for Disease Control and Prevention should continue to facilitate assessment of state, local, and tribal jurisdictions' performance in implementing dispensing plans for medical countermeasures, in addition to assessing planning efforts. More specifically, the Centers for Disease Control and Prevention, in collaboration with state, local, and tribal jurisdictions, should facilitate assessment of the entire distribution and dispensing system by:**

- **demonstrating Strategic National Stockpile distribution capabilities to high-risk jurisdictions;**
- **facilitating large-scale, realistic exercises in high-risk jurisdictions to test dispensing capability; and**
- **continuing efforts to identify objective criteria and metrics for evaluating the performance of jurisdictions in implementing mass dispensing.**

Recommendation 5-5: Do not pursue development of a Food and Drug Administration-approved MedKit unless this is supported by additional safety and cost research.
The committee does not recommend the development of a Food and Drug Administration–approved MedKit designed for prepositioning for an anthrax attack until and unless research demonstrates that MedKits are significantly less likely to be used inappropriately than a standard prescription and can be produced at costs comparable to those of standard prescription antibiotics.

RESEARCH NEEDS

The significant costs of establishing and maintaining a distribution and dispensing system warrant a thorough understanding of the most efficient and effective mass prophylaxis strategies for a community. Throughout this report, the committee has highlighted areas in which additional research is needed to better characterize the risk of an anthrax attack, the distribution and dispensing capability needed to provide prophylaxis for a population within an appropriate time period, what that time period is, and the role of prepositioning in an overall bioterrorism preparedness and response system. The remaining evidence gaps in each of these areas, as well as others identified below (see Table 6-1), need to be filled in a systematic and rigorous manner by quantitative and qualitative research. Any and all data from real-world events should be used to guide the formulation of research questions. The committee does not intend that decision making should

TABLE 6-1
Evidence to Inform Prepositioning Decision Making: Research Needs

General Category	Specific Research Areas
Epidemiological and Medical Issues Regarding Anthrax and Postexposure Prophylaxis (PEP) for Anthrax	– Further understanding of the distribution of incubation periods across a range of plausible exposures, and to what degree exposure influences the incubation period – Efficacy of prophylaxis by host factors and timing of initiation – Alternative agents for drug-resistant anthrax – Development of appropriate pediatric formulation for PEP and impact on home stockpiling – Improvement of early detection through environmental sensors, clinical diagnostics, and other means
Operations and Logistics	– Evaluation of an operational target (time window) for dispensing initial doses of prophylaxis to the entire at-risk population – Exploration of a logistics model to assess the effectiveness of current distribution strategies for different jurisdictions and the cost-effectiveness of various alternative distribution strategies for filling gaps in capability – Demonstration of the current time to receive medical countermeasures (MCM) from the Strategic National Stockpile (SNS) in a target community – Assessment of costs and effectiveness of alternative means to improve SNS distribution time – Accurate assessment of local dispensing capacity, including existing closed points of dispensing (PODs) – Assessment of populations not adequately served by PODs – Further assessment of existing prepositioning models, including the MedKit component of the postal model – Potential impact of behavior of the public on a dispensing system (e.g., if individuals with home stockpiles also attempt to receive MCM from a public POD) – Potential impact of antibiotic prepositioning strategies on time to initiation of anthrax vaccine – Logistics and costs of replacement and appropriate disposal of prepositioned antibiotics

continued

TABLE 6-1 *Continued*

General Category	Specific Research Areas
Behavior and Communications	*Attitudes and behavior related to different prepositioning strategies* – Acceptability of a given strategy in the absence of a perceived acute threat – Trust and perceived inequities regarding availability of antibiotic prophylaxis, use of different antibiotics, and potential need to change public health recommendations after an attack – Prescriber behavior around personal stockpiling *Effectiveness of communications* – Compliance with public health messaging – Directions for storage, preparation for pediatric dosage, saving drug for attack, direction for use during attack *Adherence* – Assessment of the risk for inappropriate use among varied populations: willingness to take drugs only upon notification – Behavior of the public in response to other disasters (e.g., U.S. use of potassium iodide after Japanese nuclear disaster)
Safety	– Adverse events and impact on adherence – Impact on general community antimicrobial resistance patterns – Influence of packaging of predispensed antibiotics on inappropriate use
Cost-Effectiveness	– Further assessment of the likely total costs of alternative prepositioning strategies in different communities – Further assessment of health benefits of alternative prepositioning strategies in different communities – Further assessment of cost-effectiveness of alternative prepositioning strategies in different communities

await the research results, but those results should be used to refine plans in the future.

Recommendation 6-1: Perform additional research to better inform decision making about prepositioning strategies. **Results of such research would strengthen the decision-aiding framework proposed in this report for determining whether prepositioning strategies would be beneficial within a community. The Department of**

BOX 6-1
Priority Research Needs

- Further understanding of the anthrax incubation period, i.e., the minimum time before symptom onset and the distribution of the incubation period for a set of exposed individuals (e.g., what subpopulation factors affect anthrax incubation periods);
- Evaluation of a standard goal for the time within which jurisdictions must administer an initial dose of prophylaxis to the entire at-risk population;
- Assessment of costs and effectiveness of alternative means of improving Strategic National Stockpile (SNS) distribution time;
- Assessment of factors related to behavior and communication, including acceptability of, trust in, and adherence to recommended medical countermeasures (MCM);
- Estimate of rate of misuse of antibiotics in a home stockpiling context; and
- Assessment of the likely efficacy, costs, cost-effectiveness, and safety of a Food and Drug Administration (FDA)–approved home MedKit.

Health and Human Services should conduct additional research in the following broad areas: epidemiological and medical issues regarding anthrax and postexposure prophylaxis for anthrax, operations and logistics, behavior and communications, safety, and cost-effectiveness.

In recognition of limited public health resources, Box 6-1 summarizes the research needs that are most critical.

CONCLUDING REMARKS

Prepositioning is just one potential component of a larger endeavor to enhance the nation's capability to prevent illness and death from an anthrax attack. Other components include national security efforts to prevent an attack or mitigate its effects; efforts to enhance detection and surveillance capability; further development of strategies for anthrax prevention (e.g., anthrax vaccine) and treatment (e.g., anthrax antitoxin); continuous refinement of the current medical countermeasures (MCM) distribution and dispensing system; and efforts to engage the private sector in both the development and the delivery of MCM. To best protect the public's health and to make optimal use of resources, decision making about prepositioning must take place within the context of the entire system.

Appendix A

Acronyms

ADE	adverse drug event
APUA	Alliance for Prudent Use of Antibiotics
ASPR	Assistant Secretary for Preparedness and Response (Department of Health and Human Services)
AVA	anthrax vaccine adsorbed (a licensed anthrax vaccine)
BAR	BioWatch Actionable Result
BARDA	Biomedical Advanced Research and Development Authority
BENS	Business Executives for National Security
BERM	Bioterrorism and Epidemic Outbreak Response Model
CDC	Centers for Disease Control and Prevention
CERT	Community Emergency Response Team
cGMP	current good manufacturing practice
CHC	community health center
CI	confidence interval
CRI	Cities Readiness Initiative
DHS	Department of Homeland Security
DOD	Department of Defense
DTD	decision to dispense
EPA	Environmental Protection Agency
EUA	Emergency Use Authorization

FDA	Food and Drug Administration
FFDCA	Federal Food, Drug, and Cosmetic Act
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HoH	head of household
HPP	Hospital Preparedness Program
HRSA	Health Resources and Services Administration
IND	Investigational New Drug
IOM	Institute of Medicine
IV	intravenous
KI	potassium iodide
MCM	medical countermeasures
MCMDD	Medical Countermeasures Distribution and Dispensing
MDR	multi-drug-resistant
MERC	Medical Emergency Response Cache (New York State)
MOA	memorandum of agreement
MOU	memorandum of understanding
MSA	metropolitan statistical area
MTD	Material Threat Determination
NBSB	National Biodefense Science Board
NRC	U.S. Nuclear Regulatory Commission
OMB	Office of Management and Budget
PCR	polymerase chain reaction
PEP	postexposure prophylaxis
PHEP	Public Health Emergency Preparedness
PhRMA	Pharmaceutical Research and Manufacturers of America
POD	point of dispensing
PREP Act	Public Readiness and Emergency Preparedness Act
QA/QC	quality assurance/quality control
REMS	risk evaluation and mitigation strategies
RSS	receiving, staging, and storage
SHSP	State Homeland Security Program
SLEP	Shelf Life Extension Program

SNS	Strategic National Stockpile
TAR	Technical Assistance Review
THIRA	Threat and Hazard Identification and Risk Assessment
UASI	Urban Area Security Initiative
USPS	U.S. Postal Service
VA	Department of Veterans Affairs
VMI	vendor-managed inventory

Appendix B

Public Meeting Agendas

PUBLIC WORKSHOP

Day 1: Monday, February 28, 2011

Washington Plaza Hotel
10 Thomas Circle
Washington, DC

Workshop Goals

1. Identify gaps and challenges in the existing infrastructure and strategies for dispensing antibiotics to protect the public against a terrorist attack using *Bacillus anthracis* or a similar pathogen.
2. Assess current prepositioning efforts and identify challenges.
3. Discuss appropriate target population groups, advantages, issues, and challenges associated with a range of prepositioning strategies, including workplace caches, hospital caches, caches in schools/universities/daycares, caches in institutional facilities for older adults, and household stockpiles.
4. Examine ethical, legal, regulatory, and safety issues relevant to the development of prepositioning strategies.
5. Discuss methods, metrics, and available data for evaluating the cost and effectiveness of prepositioning strategies.

8:00 a.m. Welcome and Introductions

ROBERT BASS, *Committee Chair*
Executive Director
Maryland Institute for Emergency Medical Services Systems

TIA POWELL, *Committee Vice-Chair*
Director
Montefiore-Einstein Center for Bioethics

SESSION 1: FEDERAL STAKEHOLDER PERSPECTIVES

Session Objectives:

- Describe relevant federal efforts associated with prepositioning antibiotics for anthrax.
  - — Examine the gaps, challenges, and emerging issues that federal agencies are facing.
- Discuss which prepositioning strategies are likely to be successful under which circumstances and for which segments of the population, and the potential role of these strategies within an overall strategy for dispensing antibiotics.

8:15 a.m. ROBERT BASS, *Session Chair*
Executive Director
Maryland Institute for Emergency Medical Services Systems

ELIN GURSKY
Senior Advisor
Office of the Assistant Secretary for Preparedness and Response
Department of Health and Human Services

GREG BUREL
Director, Division of Strategic National Stockpile
Office of Public Health Preparedness and Response
Centers for Disease Control and Prevention

KATHRYN BRINSFIELD
Director, Workforce Health and Medical Support Division
Office of Health Affairs
Department of Homeland Security

9:10 a.m. Discussion with Committee

9:45 a.m. BREAK

SESSION 2: STATE AND LOCAL PERSPECTIVES

Session Objectives:

- Identify gaps, challenges, and emerging issues associated with current state and local strategies for dispensing antibiotics to the public: What evidence supports the need for further refinement of medical countermeasures dispensing plans?
- Describe relevant state and local efforts associated with prepositioning antibiotics for anthrax.
  — Where available, examine data assessing current prepositioning strategies.
- Discuss which prepositioning efforts are likely to be successful under which circumstances and for which segments of the population, and the potential role of these strategies within an overall strategy for dispensing antibiotics.
- Discuss state and local needs associated with developing prepositioning strategies.

10:00 a.m. HERMINIA PALACIO, *Session Chair*
Executive Director
Harris County Public Health and Environmental Services, Texas

SUSAN COOPER
Commissioner
Tennessee Department of Health

DAVID STARR
Director, Countermeasures Response
Office of Emergency Preparedness and Response
New York City Department of Health and Mental Hygiene

ANDREA MATHIAS
Deputy Health Officer
Worcester County, Maryland

10:50 a.m. Discussion with Committee

SESSION 3: PUBLIC ENGAGEMENT ON PREPOSITIONING

Session Objective: Discuss concurrent public engagement project on prepositioning, also sponsored by ASPR, and general considerations for engaging the public on prepositioning strategies.

11:30 a.m. KEVIN MASSEY, *Session Chair*
Director, Lutheran Disaster Response
Evangelical Lutheran Church of America

ROGER BERNIER
Member
Medical Countermeasure Public Engagement Initiative
Steering Committee

11:45 a.m. Discussion with Committee

12:00 p.m. LUNCH
Note: The committee met in closed session from 12:00-1:00 p.m.

SESSION 4: PREPOSITIONING EFFORTS IN OTHER DOMAINS

Session Objective: Examine successes and lessons learned through the implementation of prepositioning strategies in other domains, including prepositioning of atropine in Israel, potassium iodide provided to people living near nuclear facilities, and household antibiotic kits provided to postal workers and their families in Minneapolis-St. Paul.

1:00 p.m. DANIEL LUCEY, *Session Chair*
Adjunct Professor of Microbiology and Immunology
Georgetown University Medical Center

DANIEL LAOR *(by teleconference)*
Director
Emergency and Disaster Management Division
Ministry of Health, Israel

JAMES BLANDO
Assistant Professor
School of Community and Environmental Health
Old Dominion University

JAYNE GRIFFITH
State Bioterrorism Epidemiologist
Minnesota Department of Health

1:30 p.m. Discussion with Committee

SESSION 5: MODELING ANTHRAX

Session Objective: Examine data and models of inhalational anthrax: dose response, incubation period distribution, disease progression and clinical outcomes, and medical consequences of the timing of providing antibiotics. In particular, assess the evidence supporting the commonly used 48-hour goal for dispensing antibiotics to the affected population.

2:00 p.m. TONY COX, *Session Chair*
President
Cox Associates

SID BACCAM
Senior Scientist
Innovative Emergency Management (IEM)

DEAN WILKENING *(by teleconference)*
Senior Research Scientist
Center for International Security and Cooperation
Stanford University

KENNETH RAPUANO
Director of Advanced Systems and Policy
Homeland Security Systems Engineering and Development Institute
The MITRE Corporation

3:00 p.m. BREAK

SESSION 6: LEGAL AND REGULATORY ISSUES

Session Objective: Discuss federal and state legal and regulatory issues associated with prepositioning antibiotics using strategies such as workplace caches, hospital caches, and household stockpiles.

3:15 p.m. ERIN MULLEN, *Session Chair*
Assistant Vice President, Rx Response
Pharmaceutical Research and Manufacturers of America

ELIZABETH SADOVE
Regulatory Counsel
Office of Counterterrorism and Emerging Threats
Food and Drug Administration

DANIEL O'BRIEN
General Counsel, Dimensions Healthcare
(Formerly) Principal Counsel, Assistant Attorney General
Department of Health & Mental Hygiene, Office of the Attorney General, Maryland

MITCHEL ROTHHOLZ
Chief of Staff
American Pharmacists Association

3:45 p.m. Discussion with Committee

SESSION 7: SAFETY ISSUES

Session Objective: Discuss safety concerns associated with prepositioning strategies, including workplace caches and household stockpiles. This may include both issues such as adverse effects of antibiotics as well as, for example, concerns related to health literacy.

4:15 p.m. ROBERT HOFFMAN, *Panel Chair*
Director
New York City Poison Control Center

NADINE SHEHAB
Senior Service Fellow
Division of Healthcare Quality Promotion
National Center for Emerging and Infectious Zoonotic Disease
Centers for Disease Control and Prevention

KENT SEPKOWITZ
Vice Chairman of Clinical Affairs
Director, Hospital Infection Control
Memorial Sloan-Kettering Cancer Center

DANIEL FAGBUYI
Medical Director, Disaster Preparedness and Emergency Management
Assistant Professor of Pediatrics and Emergency Medicine
The George Washington University School of Medicine
Children's National Medical Center

4:45 p.m. Discussion with Committee

5:15 p.m. Closing Remarks

ROBERT BASS, *Committee Chair*
Executive Director
Maryland Institute for Emergency Medical Services Systems

TIA POWELL, *Committee Vice-Chair*
Director
Montefiore-Einstein Center for Bioethics

5:30 p.m. ADJOURN DAY 1

Day 2: Tuesday, March 1, 2011

Washington Plaza Hotel
10 Thomas Circle
Washington, DC

8:00 a.m. Welcome and Summary of Day 1

ROBERT BASS, *Committee Chair*
Executive Director
Maryland Institute for Emergency Medical Services Systems

TIA POWELL, *Committee Vice-Chair*
Director
Montefiore-Einstein Center for Bioethics

SESSION 8: VULNERABLE POPULATIONS AND ETHICAL ISSUES

Session Objectives:

- Identify the specific needs of vulnerable populations with regard to prepositioning antibiotics (e.g., children, pregnant women, people with disabilities, people with chronic illnesses, older adults).
  - Discuss mechanisms for prepositioning antibiotics in environments where these populations will most likely be during an event (e.g., school, child care, at home, care facility).
- Discuss ethical issues relevant to developing prepositioning strategies, including those related to equity and health literacy.

8:15 a.m. TIA POWELL, *Session Chair*
Director
Montefiore-Einstein Center for Bioethics

MICHAEL ANDERSON
Vice President and Associate Chief Medical Officer
University Hospitals *and*
Associate Professor of Pediatric Critical Care
Rainbow Babies & Children's Hospital, Cleveland, Ohio

ALEXIS SILVER
Vice President of Policy and Clinical Affairs
Home Care Association of New York State

KEVIN SMITH
Emergency Disaster Services Director
Florida Division of The Salvation Army

9:05 a.m. Discussion with Committee

9:45 a.m. BREAK

SESSION 9: PRIVATE-SECTOR PERSPECTIVES AND WORKPLACE CACHES

Session Objectives:

- Review current private-sector efforts to preposition antibiotics within the organization.

- Discuss development and implementation of workplace caches:
  - What kind of companies would be appropriate for the strategy?
  - What are the advantages associated with the strategy?
  - How could challenges and issues associated with the strategy be addressed?
  - Would private sector organizations be interested in additional involvement in prepositioning? What barriers would need to be addressed?
- Consider lessons learned from private-sector initiatives to stockpile antivirals that may apply to stockpiling antibiotics.

10:00 a.m. BRAD BREKKE, *Panel Chair*
Vice President of Assets Protection
Target Corporation

ANDREW SHULMAN
Chief Operating Officer
Affiliated Physicians

JOCELYN STARGEL
Business Assurance Principal
Southern Company Services, Inc.

PENNY TURNBULL *(by teleconference)*
Senior Director, Business Continuity
Marriott Hotels International, Ltd.

10:30 a.m. Discussion with Committee

SESSION 10: HOSPITAL AND COMMUNITY HEALTH CENTER CACHES

Session Objectives:

- Review current efforts to preposition antibiotics within hospitals, community health centers, or other health care institutions.
- Discuss development and implementation of caches within health care institutions:
  - What kind of health care settings would be appropriate for the strategy?
  - What are the advantages associated with the strategy?
  - How could challenges and issues associated with the strategy be addressed?

  - Would health care institutions be interested in additional involvement in prepositioning? What barriers would need to be addressed?
- Consider lessons learned from initiatives to stockpile antivirals that may apply to stockpiling antibiotics.

11:00 a.m. JEFFREY UPPERMAN, *Panel Chair*
Director of Trauma, Children's Hospital of Los Angeles
Associate Professor of Surgery, Keck School of Medicine
University of Southern California

MICHAEL ROBBINS
Strategic National Stockpile Director
Chicago Department of Public Health

THOMAS TIGHE
President and Chief Executive Officer
Disaster Relief International

AMELIA MUCCIO
Director of Disaster Planning
New Jersey Primary Care Association

11:30 a.m. Discussion with Committee

12:00 p.m. LUNCH
Note: The committee met in closed session from 12:00-1:00 p.m.

SESSION 11: OTHER PREPOSITIONING STRATEGIES

Session Objective: Discuss development and implementation of additional strategies for prepositioning antibiotics. For each strategy, discuss:

- Who would be appropriate targets for the strategy (e.g., population groups, geographic factors, threat status)?
- What are the advantages associated with the strategy?
- How could challenges and issues associated with the strategy be addressed?

1:00 p.m. Panel A: Household MedKits

ANDREW PAVIA, *Session Chair*
George and Esther Gross Presidential Professor
University of Utah School of Medicine
Division of Pediatric Infectious Diseases

DEBRA YESKEY
Director, Regulatory and Quality Affairs Division
Biomedical Advanced Research and Development Agency
Office of the Assistant Secretary for Preparedness and Response
Department of Health and Human Services

MICHAEL ROBBINS
Strategic National Stockpile Director
Chicago Department of Public Health

ELAINE VAUGHAN *(by teleconference)*
Research Professor and Professor Emerita of Psychology and Social Behavior
School of Social Ecology
University of California, Irvine

1:30 p.m. Discussion with Committee

2:00 p.m. Panel B: Other Prepositioning Strategies

ROBERT BURHANS, *Panel Chair*
(Retired) Director of Health Emergency Preparedness
New York State Department of Health

JAMES TURNER
Immediate Past President
American College Health Association

TIM STEPHENS
Public Health Advisor
National Sheriff's Association

2:30 p.m. Discussion with Committee

3:00 p.m. BREAK

SESSION 12: MODELS, COST, AND EFFECTIVENESS

Session Objectives: Identify currently available economic evidence regarding prepositioning strategies. What potential models exist that may be helpful? Discuss appropriate measures and metrics (e.g., cost, efficacy, effectiveness).

3:15 p.m. Panel A: Modeling Prepositioning Strategies

STEPHEN POLLOCK, *Panel Chair*
Herrick Emeritus Professor of Manufacturing
University of Michigan

JEFFREY HERRMANN
Associate Professor
Department of Mechanical Engineering and Institute for Systems Research
University of Maryland

NATHANIEL HUPERT
Director, Preparedness Modeling Unit
Centers for Disease Control and Prevention *and*
Associate Professor of Public Health and Medicine
Weill Medical College, Cornell University

SID BACCAM
Senior Scientist
Innovative Emergency Management (IEM)

3:45 p.m. Discussion with Committee

4:15 p.m. Panel B: Evaluating Cost and Effectiveness of Prepositioning Strategies

MARGARET BRANDEAU, *Panel Chair*
Coleman F. Fung Professor of Engineering
Stanford University

FADIA T. SHAYA
Associate Professor
University of Maryland School of Pharmacy

FRED SELCK
Doctoral Student in Health Economics
Department of Health Policy and Management
Johns Hopkins Bloomberg School of Public Health

NIKHIL NATARAJAN
Associate Director
Office of Health Emergency Preparedness
New York State Department of Health

4:45 p.m. Discussion with Committee

5:15 p.m. Closing Remarks

ROBERT BASS, *Committee Chair*
TIA POWELL, *Committee Vice-Chair*

5:30 p.m. ADJOURN DAY 2

Open Session at Committee Meeting #3

Day 1: Wednesday, April 20, 2011

The Beckman Center, Board Room
100 Academy Drive
Irvine, CA 92617

Open Session Goals

1. Examine ethical issues and considerations for at-risk populations relevant for the development of prepositioning strategies such as (1) hospital and pharmacy caches; (2) caches in locations such as workplaces, educational institutions, and care facilities; and (3) household MedKits.
2. Receive updated briefing on ASPR's public engagement project and discuss how ASPR anticipates using the results of that project in conjunction with the IOM report.

8:00 a.m. Welcome and Introductions

ROBERT BASS, *Committee Chair*
Executive Director
Maryland Institute for Emergency Medical Services Systems

TIA POWELL, *Committee Vice-Chair*
Director
Montefiore-Einstein Center for Bioethics

SESSION 1: ETHICAL ISSUES AROUND PREPOSITIONING

Session Objective: Discuss ethical issues associated with the development of prepositioning strategies, including caches in workplaces, educational institutions, care facilities, and household MedKits.

8:15 a.m. TIA POWELL, *Panel Chair*
Director
Montefiore-Einstein Center for Bioethics

DRUE BARRETT
CAPT, U.S. Public Health Service
Lead, Public Health Ethics Unit
Office of Science Integrity
Office of the Associate Director for Science
Centers for Disease Control and Prevention

NANCY KASS *(by videoconference)*
Phoebe R. Berman Professor of Bioethics and Public Health
Johns Hopkins Bloomberg School of Public Health

SESSION 2: PREPOSITIONING FOR AT-RISK POPULATIONS

Session Objectives: Discuss how effective the prepositioning strategies under consideration would be for reaching at-risk populations. Highlight any equity issues that may arise, and discuss how members of these groups may view the development and implementation of these strategies.

Note: This session will focus specifically on populations who, by virtue of socioeconomic status and/or demographic characteristics, may be at systemically increased risk for lower access to disaster mitigation response—for example, people with low incomes/limited transportation outcomes, people with no or limited English proficiency, historically underserved ethnic/racial groups, people with disabilities (especially vision impaired,

hearing impaired, mobility impaired), people who are homeless, and people who are homebound.

9:15 a.m. HERMINIA PALACIO, *Panel Chair*
Executive Director
Harris County Public Health and Environmental Services, Texas

MANDI JANIS *(by videoconference)*
Program Director
Catholic Charities USA

ROBERTA CARLIN *(by videoconference)*
Executive Director
American Association on Health and Disability

BOB SPEARS
Director of Emergency Services
Los Angeles Unified School District

10:15 a.m. BREAK

SESSION 3: PUBLIC ENGAGEMENT ON PREPOSITIONING

Session Objective: Receive updated briefing on ASPR public engagement project and discuss how ASPR anticipates using the results of that project in conjunction with the recommendations in the IOM report.

10:30 a.m. ELIN GURSKY
Senior Advisor
Office of the Assistant Secretary for Preparedness and Response
Department of Health and Human Services

11:00 a.m. ADJOURN OPEN SESSION

Appendix C

First-Order Model

In this appendix, the committee develops a first-order model that estimates health outcomes (measured as fraction of exposed individuals who survive) for any prepositioning strategy. For convenience of presentation, the term *survival* is used instead of *saved* to refer to those exposed individuals who have been protected from becoming symptomatic by timely prophylaxis with effective medical countermeasures (MCM). The model development is as follows.

1. **δ = time between release (and, by assumption, exposure) and decision to dispense (DTD).** For any community, estimates of δ should ideally be informed by existing submodels that incorporate the capabilities of currently used (or planned) monitoring and surveillance systems, as well as data from past BioWatch Actionable Results, accidental releases, and drills, to estimate the various times contributing to the value of δ. These include the time:

- needed to deliver MCM from the nearest Strategic National Stockpile (SNS) location,
- required to determine clinically that at least one individual has been infected, and
- between positive diagnosis and the decision by the responsible public health authority to issue an order to dispense.

Note that in what follows, the assumption is made that all individuals will be exposed at the moment of release. This is an "optimistic" assumption,

in the sense that individuals exposed later will not require prophylaxis as soon as those exposed immediately and thus will fare better as a result of any dispensing campaign.

2. **X = for *any particular individual*, the time from DTD to that person's prophylaxis.** The value of X is not just clearly different for each individual, but is an *uncertain quantity* for any individual. In other words, for any individual, X is a random variable.

3. **The probability distribution $\Phi(x)$ for X** can be interpreted to be either:

- $\Phi(x)$ = probability that a randomly selected individual will experience a time X less than or equal to x, or, equivalently,
- $\Phi(x)$ = the fraction of randomly selected individuals who will experience a time X less than or equal to x.

4. **g = goal for the points of dispensing (PODs) for the time from start of dispensing MCM to completion.** Using the simplifying assumptions that the size of the dispensing staff is constant, that staff are never idle, and that the service time is constant at the PODs, it can readily be shown that, given the goal g for the time from starting to completing dispensing, the distribution function for X is uniform:

$$\Phi(x) = \frac{x}{g},\ 0 \le x \le g$$

with associated density function:

$$\phi(x) = \frac{1}{g},\ 0 \le x \le g$$

5. **T = time from exposure to prophylaxis (TTP) = $\delta + X$.** It follows from the definition of X that T is a random variable with probability density function $p(t)$, where

$$p(t) = \frac{1}{g},\ \delta \le t \le \delta + g \qquad (1)$$

6. **The survival function $f(t)$ represents, for any particular release scenario, one of the various incubation period curves or values discussed at length in Chapter 2, where t is the time since exposure.** As pointed out in Chapter 2,

data with which to compute this survival function are either uncertain or limited, and the function will depend on many unknown scenario variables. Nevertheless, to obtain insight into the potential health advantages of prepositioning, the committee has taken the liberty of fitting $f(t)$ to the survival data (based on the Sverdlosk release) presented by Wilkening (2006, 2008) and Brookmeyer et al. (2001, 2005). Using these data, $f(t)$ can be well fit, for values of t up to about 200 hours, by

$$f(t) = e^{-(.004t)^2}$$

This function can in turn be approximated (for t up to around 150 hours) by

$$f(t) = 1 - (.004t)^2 \tag{2}$$

7. **S = the expected fraction of the population that will survive a release, described by a particular scenario, using a particular prepositioning strategy.** From the definition of $f(t)$ and $p(t)$, S can be computed from

$$S = \int f(t)p(t)\,dt$$

In particular, using the uniform distribution for $p(t)$ given by equation (1) yields:

$$S = \int_{\delta}^{\delta+g} f(t)\frac{1}{g}\,dt \tag{3}$$

Using the approximation for $f(t)$ given by equation (2), S can then be obtained analytically (for $\delta + g < 150$ hours) from equation (3), yielding:

$$S = \frac{1}{g}\int_{\delta}^{\delta+g}\left(1-(.004t)^2\right)dt = 1 - \frac{(.004)^2\left((\delta+g)^3 - \delta^3\right)}{3g} \tag{4}$$

This equation is valid for $g > 0$; since the practical realities of even the most ideal strategy for predispensing to individuals will involve some finite delay, for all practical purposes, g will never be exactly equal to 0.

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Brookmeyer, R., E. Johnson, and S. Barry. 2005. *Statistics in Medicine* 24(4):531-542.

Wilkening, D. A. 2006. Sverdlovsk revisited: Modeling human inhalation anthrax. *Proceedings of the National Academy of Sciences* 103(20):7589-7594.

Wilkening, D. A. 2008. Modeling the incubation period of inhalational anthrax. *Medical Decision Making* 28(4):593-605.

Appendix D

Commissioned Paper: A Cost and Speed Analysis of Strategies for Prepositioning Antibiotics for Anthrax[1]

James Guyton, Principal, PRTM, lead author

Robert Kadlec, Chandresh Harjivan, Shabana Farooqi, Sheana Cavitt, and Joseph Buccina, PRTM, co-writers and contributors

This paper was prepared by PRTM Management Consultants, LLC (PRTM) under a contract with the Institute of Medicine (IOM) and submitted in April 2011. This publication is limited to the approach and analysis described herein and on information available as of April 15, 2011. No representation or warranty (express or implied) is given as to the accuracy or completeness of the information contained in this publication, and to the extent permitted by law, PRTM and its members, employees, and agents do not accept any liability, responsibility, or duty of care for any consequences of the Committee or anyone else acting, or refraining to act, in reliance on the information contained in this publication or for any decision based on it.

INTRODUCTION

Currently, the United States Government (USG) stores the vast majority of its contingency medical countermeasures (MCM) in 12 centralized locations as part of the Centers for Disease Control and Prevention's (CDC's) Strategic National Stockpile (SNS); adopting the concept of prepositioning could alter this *modus operandi*. Prepositioning for public health preparedness is the placement and storage of MCM in caches that are geographically closer to the metropolitan areas and the corresponding populations at

[1]This paper was commissioned by the Institute of Medicine (IOM) to provide background for the deliberations of the Committee on Prepositioned Medical Countermeasures for the Public. The responsibility for the content of this paper rests with the authors, and the paper does not necessarily represent the views of the IOM or its committees and convening bodies.

risk. The primary goal of prepositioning is to increase the speed of MCM distribution and dispensing during a high-consequence biological incident.

In the event of an attack with aerosolized *Bacillus anthracis* (anthrax), administering oral antibiotics immediately following exposure has demonstrated the potential to save lives (Friedlander et al., 1993). Anthrax exists in vegetative and spore forms. The spore is an extremely hardy, dormant form of the bacterium; it can persist for decades in the environment. When a spore enters a live host, it transforms into its vegetative, disease-causing state. Once active, anthrax produces toxins that are lethal. Given its high lethality and potential ease of acquisition, production, and dissemination, the release of aerosolized anthrax is the type of high-consequence biological attack that is of most concern.

The Center for Biosecurity at the University of Pittsburgh Medical Center notes that anthrax is considered one of the most serious bioterrorism threats for the following reasons (UPMC Center for Biosecurity, 2007):

- widespread availability of starter cultures in culture collection banks around the world;
- widespread natural availability in endemic areas;
- wide commercial availability of equipment and techniques for mass production and aerosol dissemination;
- robustness of anthrax spores, making anthrax easier to weaponize for aerosol dissemination than other biological agents of concern;
- high fatality rate in untreated inhalational cases;
- relatively low infectious dose, based on nonhuman primate animal data;
- risk of antibiotic-resistant strains that exist in nature or that may be easily cultivated for use in an intentional release; and
- recent use of anthrax during the 2001 Amerithrax attacks.

During the 2001 Amerithrax attacks, the median incubation time for inhalational anthrax was 4 days (Jernigan et al., 2001). It is estimated that if oral antibiotics are not administered before the onset of clinical symptoms, the mortality rate, even in intensively treated cases, could potentially exceed 90 percent (UPMC Center for Biosecurity, 2007). In the few inhalational anthrax cases treated in 2001, intensive clinical treatment resulted in a mortality rate of 45 percent (Jernigan et al., 2001). Depending on the initial infective dose and when the exposure is detected, the effective window for antibiotic administration may be considerably less than 96 hours. As a matter of USG policy, current requirements have set the objective of delivery of oral antibiotics to potentially exposed individuals within 48 hours of the decision to do so (CDC, 2010a). Prepositioning can enable more rapid dispensing of oral antibiotics following an anthrax attack, thus increasing

the likelihood that a larger proportion of infected individuals will receive antibiotics during the asymptomatic incubation period.

The Institute of Medicine's (IOM's) Committee on Prepositioned Medical Countermeasures for the Public commissioned this paper to provide background for its deliberations on prepositioning strategies for anthrax antibiotics. PRTM analyzed three prepositioning strategies:

- caches in hospitals and pharmacies;
- caches in workplaces of different types (e.g., state and local government, private infrastructure, Fortune 50 companies, small businesses), schools, universities, daycare centers, and institutional facilities for older adults (for simplification, the PRTM team categorized these into large and small places of work); and
- approved MedKits (or similar dose packs) stored in individual households and intended for use by occupants.

This paper focuses largely on two variables: the cost of each prepositioning strategy, and the time to antibiotic distribution and dispensing. The paper also examines the implications of these strategies in three different settings: urban, suburban, and rural. PRTM chose the Minneapolis-St. Paul metropolitan statistical area (MSA) as a case study because of the availability of relevant cost and delivery time data and its confluence of urban, suburban, and rural environments. The prepositioning strategies are compared with two scenarios:

- The current approach of SNS to receiving, storage, and staging (RSS) sites to points of dispensing (PODs)—This approach serves as the baseline model.
- The postal distribution model—In 2008, federal health officials announced the beginning of a postal distribution pilot project in the cities of Minneapolis and St. Paul (Roos, 2008). In this model, postal workers deliver antibiotics directly to individuals' homes in the event of an anthrax attack.

Other approaches also are considered in the section below on alternative dispensing strategies, including a forward-deployed SNS model and vendor-managed inventory. In addition, in the course of this effort, PRTM uncovered several areas for additional consideration, which are highlighted in a later section. Note that detailed data on which the discussion of the various dispensing strategies is based are presented in Appendix D.1.

In conducting research for this paper, PRTM performed an extensive review of open-source literature and interviewed more than 40 subject matter experts. Appendix D.2 provides a list of interviewees.

STRATEGIES FOR PREPOSITIONING

This section provides a brief background on CDC's current strategy for distribution and dispensing of antibiotics and a description of each prepositioning strategy. The current approach, based on PODs, is the standard, practiced model for delivering MCM, such as oral antibiotics and vaccines, to an impacted locale following a biological attack. This model is the backbone of several MCM dispensing strategies that were reviewed. Whereas the prepositioning strategies are intended to increase the speed with which a 10-day supply of oral antibiotics is delivered, they are intended only as an adjunct to the POD dispensing approach. The SNS-RSS-POD approach serves as the principal means to distribute and dispense the remainder of the full 60-day course of antibiotics, and vaccination as necessary, to all those affected.

Current Approach for Distribution and Dispensing: Points of Dispensing

The current distribution and dispensing model (Figure D-1) is managed by CDC in conjunction with state, local, and tribal health departments. Antibiotics and other MCM are stored in 12 undisclosed locations across the United States in the SNS. The exact amount of antibiotics stored in these caches is not made public, for security reasons. In the event of an attack, CDC guarantees the delivery of a "Push Package" of medical material, including oral antibiotics, to the affected location within 12 hours of a request (CDC, 2010b). A Push Package is a large package of medications and other medical supplies that can be transported quickly from one of the SNS locations. The oral antibiotics (approximately 500,000 doses in the Push Package) are intended to be an initial supply. Additional quantities of oral antibiotics are transported to the area from a larger reserve contained in a vendor-managed inventory, or inventory controlled by the manufacturer that is guaranteed to be available to the federal government upon request.

Once the Push Package has been transported from the SNS, state authorities receive it at a predesignated RSS site. At this point, the MCM are transitioned from federal to state control. The RSS staff unpacks the

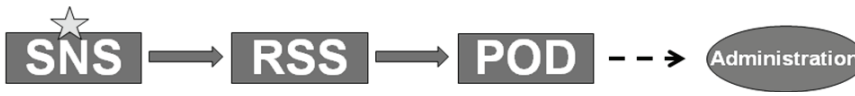


FIGURE D-1
Strategic National Stockpile (SNS) to receiving, storage, and staging (RSS) sites to points of dispensing (POD) model.
NOTE: The star denotes where the antibiotics are stored.

medications and transfers them to trucks, which are bound for individual PODs. The amount of antibiotics delivered to each POD is predetermined by the estimated number of people to be served by each.

Once the antibiotics reach the PODs, they may remain under state control or be turned over to local (county or city) control, depending on the jurisdiction. Although the conceptual approach was developed by CDC, the PODs' actual operation and staffing are determined by the state or local jurisdiction. At the PODs, public health practitioners screen the public for contraindications to the antibiotics, educate them on the use of the antibiotics, and then dispense a 10-day supply to each person. Different jurisdictions employ a variety of approaches to increase throughput, such as having the head of the household retrieve drugs for everyone in that household, as one interviewee from Tennessee indicated, or having the necessary paperwork completed before a potential event to avoid time spent filling out forms during an emergency, as an interviewee from New York noted.

Caching in Hospitals and Pharmacies

Prepositioning contingency antibiotics in hospitals and pharmacies (Figure D-2) would effectively result in increasing the on-hand antibiotic supply beyond current inventories for routine use in such facilities. Generally, hospitals and pharmacies stock enough antibiotics to meet their immediate daily needs. They rely on distributors to continuously provide "just in time" supplies of antibiotics so they have enough stock to fill their needs, but not so much that they have extra stock on hand. Notable exceptions to this practice are Department of Veterans Affairs (VA) hospitals, Department of Defense (DOD) medical treatment facilities, and some private hospitals that maintain a limited stockpile to provide to their staff and patients in the event of a biological attack.

Expanding this practice to all hospitals, and possibly clinics, would require significant increases in their stock on hand and the costs associated with excess inventory. While they would likely still use the first-in/first-out

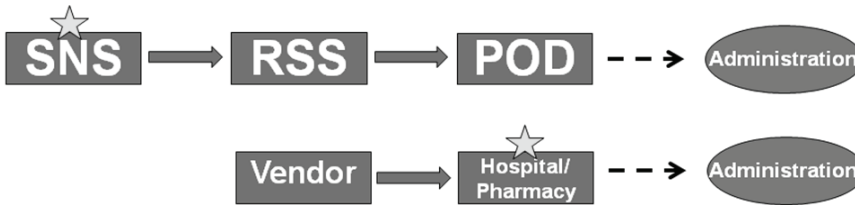


FIGURE D-2
Hospital/pharmacy prepositioning model.
NOTE: The stars denote where the antibiotics are stored.

approach to lessen the impact of expiry, actual costs associated with expiry would depend on the ratio of the size of the cache to the turnover volume of routine use of the antibiotics.

While hospitals, clinics, and pharmacies could maintain contingency antibiotic stockpiles, the manner in which those institutions could dispense such products would be significantly different. Hospitals would serve only as closed PODs. A closed POD is a location that is not open to the general public, but is set up to serve a predefined population. Hospitals would provide prophylactic antibiotics only to patients, staff, and families of staff. This practice would increase the likelihood that essential hospital workers would report for duty. Limiting dispensing to hospital personnel would be intended to maintain operations for treating current patients and those who needed treatment during the emergency. This dispensing strategy would not accommodate the general public, who, if they sought such treatment, would likely inundate the facility and possibly render it incapable of performing its essential functions.

In contrast, pharmacies and some clinics could serve as open PODs. They would be able to dispense antibiotics to the general public during an emergency. One advantage of this model is that pharmacies and clinics are numerous and have high prevalence in the United States, and people have a general familiarity with the location of their local pharmacy or neighborhood clinic. This approach, however, would require that pharmacies rapidly package antibiotics for swift dispensing, as opposed to routine operations whereby prescriptions are filled on an ad hoc basis.

Hospitals, pharmacies, and some clinics already have some security measures in place for safeguarding medications, so during nonemergencies they likely would not incur an incremental security cost. However, in the event of a biological attack, additional security would likely be necessary to augment existing security activities during dispensing operations. Hospitals, clinics, and pharmacies also would have medical staff on hand who would be licensed to dispense antibiotics and could conduct the necessary prescreening of patients.

Caching in the Workplace

Prepositioning in workplaces (Figure D-3) would effectively create additional closed PODs. In this approach, private companies would stock enough antibiotics to dispense to their employees during an emergency. It would be the company's decision whether to also provide antibiotics to employee families. The manner by which private companies could participate is two-fold. They could purchase and store antibiotics on site themselves, or they could identify themselves to local public health authorities to serve as a closed POD. In the latter case, the local authorities would provide the

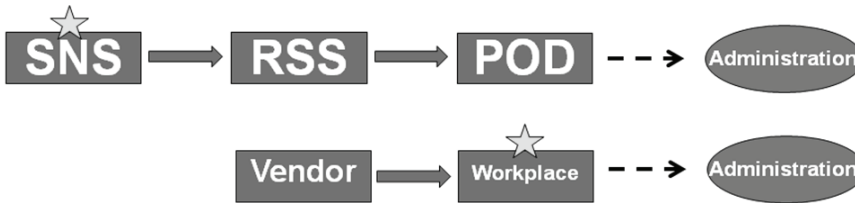


FIGURE D-3
Workplace prepositioning model.
NOTE: The stars denote where the antibiotics are stored.

antibiotics to the workplace by way of the SNS. The former approach, prepositioning on site, would offer the advantage of decreasing the time to dispensing. Serving as a closed POD would not necessarily increase speed over the baseline because no prepositioning would be taking place, and the delivery of antibiotics to the workplace would be contingent on the speed of delivery of the SNS assets.

Caching in workplaces would effectively decrease the percentage of the population that would have to be serviced by public PODs. Employees would benefit from being able to access antibiotics from a familiar place. However, workplaces would likely need to bring in medical personnel for screening and dispensing if they did not already have medically trained personnel on site. Alternatively, the workplace could conduct prescreening of personnel before the event, a practice that was performed in one interviewee's workplace. This approach might allow the antibiotics to be dispensed by nonmedical personnel following an anthrax incident.

Caching in the Home (MedKits)

Prepositioning antibiotics in the home would entail providing MedKits to a predefined segment of the population within a certain area (Figure D-4). In lieu of a Food and Drug Administration (FDA)–approved MedKit or an over-the-counter product, a prescription would be required for each recipient's doctor, or recipients would have to be subject to some screening by a health care worker before the MedKits could be issued. This approach would involve screening every person prior to dispensing to determine contraindications, such as allergies, and dosing changes. The appropriate type and numbers of bottles of antibiotics would then be shipped to every household. These bottles would be encased in plastic bags with instructions on storage and use of the antibiotics. Each bag would contain enough antibiotics to cover each person in the household for 10 days. Figure D-5 shows a depiction of a home MedKit.

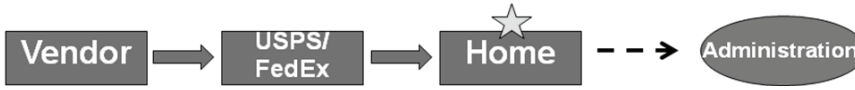


FIGURE D-4
Home MedKit prepositioning model.
NOTE: The star denotes where the antibiotics are stored. USPS = U.S. Postal Service.

FIGURE D-5
Depiction of a home MedKit.
SOURCE: CDC, 2008.

CDC conducted a study in which it dispensed MedKits to a predefined population in St. Louis to determine how MedKits would be handled and whether people would appropriately follow the instructions provided (CDC, 2008). It was found that the large majority of the population (97 percent) did not use the antibiotics inappropriately and returned the MedKits intact. The study also showed that people had a generally positive response to the MedKits and felt more prepared having one in the home.

The advantage of this model is speed of dispensing in response to an event. The public could be alerted and begin taking the antibiotics immediately without needing to leave their homes. However, many variables could impede the effectiveness of this model. These include little or no medical oversight of prescription medications, loss of the medication, incorrect storage, compliance and tampering, product expiry and returns, and inappropriate usage during other periods of illness. Because of the risk of antibiotic-resistant strains of anthrax, moreover, it could be necessary to have multiple types of antibiotics in the MedKit, which would further complicate the use of this approach.

Postal Distribution Model

One additional model used in this study for comparison is the postal distribution model (Figure D-6). This model is a variation on the standard SNS-RSS-POD model. Rather than the pull approach of that model, the postal distribution model serves to push MCM out to the population. The pilot for this model was sponsored by the Cities Readiness Initiative (CRI) and was employed in the Minneapolis-St. Paul MSA.

In this model, the medications are shipped from the SNS to the RSS, as in the standard model. From there, the medications are delivered to the postal service rather than to PODs. The medications are then delivered to residences in the affected area by postal workers, who agree to deliver the antibiotics on a volunteer basis. In exchange, they are given one MedKit for their home and one for work to cover them and their families. During an emergency, the postal workers would report to the postal service and receive enough MCM to cover approximately two normal routes, as well as a security escort. They would then deliver one bottle of antibiotics to each household on the predetermined routes (Plessas, 2010). As the postal workers cover these routes every day, they are trained to make these deliveries and have done so with efficiency in limited-scope trials in Seattle, Boston, and Philadelphia.

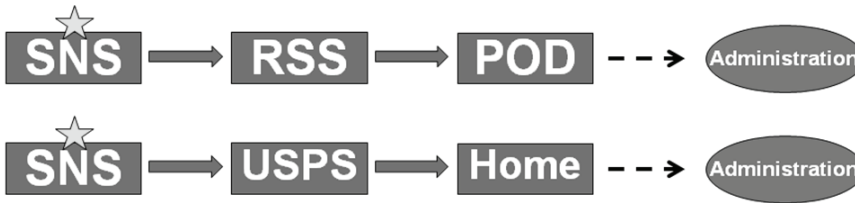


FIGURE D-6
Postal distribution model.
NOTE: The stars denote where the antibiotics are stored. USPS = U.S. Postal Service.

ANALYTICAL FRAMEWORK

PRTM used the analytical framework shown in Figure D-7 to compare the above dispensing models. In conducting the analysis, the PRTM team sought to compare the different prepositioning strategies included within the scope of this paper with the current SNS-RSS-POD baseline. To accomplish this, the team estimated total costs associated with:

- product,
- transport,
- inventory management, and
- dispensing.

For each dispensing strategy, the team examined the time required to dispense antibiotics from the cache to the subset of the population served, as well as the total time required to dispense antibiotics to the general public using a combined SNS-RSS-POD and prepositioned cache strategy. By measuring the SNS-RSS-POD baseline, the team was able to estimate time savings over the baseline, as well as time savings per dollar spent for each prepositioning strategy.

It is important to note that the time savings referenced above apply to the subset of the population served by the various prepositioning strategies. According to a Georgia Institute of Technology study, 20 percent participation by the private sector is a reasonable goal, taking into consideration anticipated reluctance to participate (Lee, 2011). As a result, the team estimated that 20 percent of the population would receive an

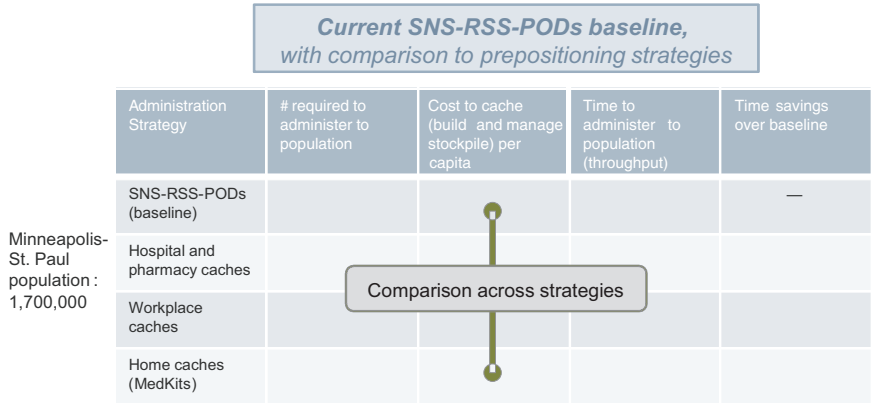


FIGURE D-7
Analytical framework.

initial dose of MCM through prepositioned caches at workplaces or hospitals/pharmacies, while the remaining 80 percent would still need to receive MCM through PODs. For those scenarios, referenced time savings are therefore applicable only to the 20 percent of the population that would receive MCM through the prepositioned caches. In addition to enabling initial time savings, prepositioned caches would help alleviate the burden on PODs by decreasing the total number of individuals that would visit PODs to receive their initial dose of MCM.

To allow for additional analysis and comparison, the team reviewed cost and speed implications associated with employing the postal model in the Minneapolis-St. Paul MSA. To facilitate an accurate comparison, the team assumed the same treatment and dosage as planned for the postal model (consisting of an initial treatment course of 10 days, with two pills per dose), as well as the same target population (the Minneapolis-St. Paul postal plan is intended to serve residents in 20 zip codes, with a combined population of 1.7 million individuals), according to estimates provided by interviewees.

COMPONENTS OF COST AND SPEED FOR DISPENSING STRATEGIES

PRTM assessed each strategy by taking into consideration three key variables: (1) total population served, (2) total cost, and (3) total speed of dispensing. The following sections decompose the general methodology employed by the team, including major assumptions, to derive the estimated population, cost, and speed for each strategy assessed. Additional detail on these calculations can be found in Appendix D.1.

Total Population Served

Both total cost and speed will vary greatly depending on the expectation of the total population to be served by each dispensing location. Table D-1 lists the PRTM team's assumptions related to estimating the population served.

TABLE D-1
Assumptions Related to Estimating the Population Served Under Each Dispensing Strategy

Dispensing Strategy[a]	Total Population Assumed Served by Referenced Dispensing Strategy
Workplace Cache	The team assumed that a representative large workplace consists of 10,000 employees and a small workplace 300 employees, referencing data from the U.S. Bureau of Labor Statistics.[b] The team further assumed that each prepositioning cache would include treatment for dependents, estimating an average household size of 2.28 individuals (Minnesota Department of Administration, 2000).
Hospital Cache	To arrive at total hospital cache requirements, the team determined the total number of hospital employees, dependents, and patients, assuming that a hospital would act as a closed POD. Dependents were determined assuming 2.28 individuals per household, and patients by determining the total number of hospital beds in the Minneapolis-St. Paul area and assuming a 67 percent average patient occupancy rate.
Pharmacy Cache	To determine pharmacy cache requirements, the team assumed that pharmacies would operate as open PODs and would store enough product to cover the remaining population that is assumed to be served by prepositioned caches but that hospitals lack the capacity to handle. The team then divided the total population assumed to obtain MCM through pharmacies by the total number of pharmacies in the Minneapolis-St. Paul area to determine the average number of individuals each pharmacy could expect to serve.
MedKit	The team assumed that 100 percent of the population would receive the initial dose of MCM through MedKits.

[a]The team assumed that 20 percent of the total population (1.7 million in this study), would receive the initial 10-day dose of antibiotics through workplace or hospital/pharmacy caches, with the remainder served by PODs.

[b]See www.bls.gov.

Total Cost

Total cost can be decomposed into the components listed earlier:

- product,
- transport,
- inventory management, and
- dispensing.

Where possible, the team used empirical data to derive the various cost estimates; where data were not readily available or could not be shared, the team estimated the total cost by using information obtained during its interviews and literature review to develop assumptions and model different dispensing strategies. Note that there are additional costs and considerations that could not be quantified for each strategy, such as security, POD or equivalent worker reliability, or public acceptance of the MCM, although these may be significant issues during a potential biological attack.

Product

Product costs are incurred when prepositioned caches or MedKits in homes are established or replenished. Cost components and key assumptions related to product costs are shown in Table D-2.

Transport

Transport costs are incurred when products are shipped to a hospital, pharmacy, workplace, or household to establish or replenish prepositioned caches or MedKits. Cost components and key assumptions related to transport are shown in Table D-3.

TABLE D-2
Product-Related Cost Components and Key Assumptions

Product-Related Cost Component	Key Assumptions
Product Type	The project team chose to focus its analysis on the dispensing of doxycycline because a 2008 Biomedical Advanced Research and Development Authority (BARDA) Emergency Use Authorization (EUA) application requested that the FDA issue an EUA for the pre-event provision and potential use of doxycycline hyclate tablet emergency kits for inhalational anthrax (Hamburg, 2010). Interviewee feedback supported the idea that doxycycline is the method of treatment preferred by the federal government.
Product Cost	The team assumed a total product cost of $0.10 per pill, or $0.20 per daily dose of doxycycline, which is a member of the tetracycline antibiotics family (Medscape Reference, 2010).
Product Dose	The team assumed that prepositioned caches, in combination with the baseline POD capability, would carry enough MCM to supply the total population served, including dependents, with a 10day prophylactic course of doxycycline.

TABLE D-3
Transport-Related Cost Components and Key Assumptions

Transport-Related Cost Component	Key Assumptions
Shipping Mode	Total shipping costs were determined by averaging the rates of commercial shippers, assuming ground shipping and varied shipment weights and distances traveled.
Shipping Weight	For each prepositioning scenario, the team estimated total weight by referencing shipping weight data from online sources[a] for one bottle of 100 mg, 20-count doxycycline tablets, and multiplying by the total number of bottles required by each hospital, pharmacy, workplace, or household.
Shipment Origin/ Destination	To determine transport costs associated with hospital/ pharmacy or workplace caches, the team assumed that MCM would be shipped directly from pharmaceutical distributors. The team determined the location of a representative, authorized Pfizer[b] distributor located within Minnesota for use as an origin zip code. The representative urban and suburban zip codes identified served as the destination zip codes.

NOTE: The team assumed no additional transportation costs would be incurred post-event, since MCM would already be positioned at PODs. In some cases, additional transport could be required to move product held in a central facility to decentralized PODs. However, these costs generally represent opportunity costs, as organizations would typically use their own assets to move product and would not pay out of pocket for services provided by commercial carriers.

[a]http://www.amazon.com/Source-Naturals-Shii-lem100mgTablets/dp/B000K9CFWC/ref=sr_1_6?s=hpc&ie=UTF8&qid=1302287454&sr=1-6.

[b]Pfizer is a major manufacturer of Vibramycin.

Inventory Management

Once MCM had been purchased and had arrived at storage facilities, hospitals, pharmacies, and workplaces would incur additional costs related to maintaining inventory, including labor, storage, and inventory replenishment costs. While costs related to labor and storage do not apply to the MedKit dispensing strategy, inventory replenishment costs do. Cost components and key assumptions related to inventory management are shown in Table D-4.

Dispensing

Dispensing costs are incurred post-event and include salaries for administrative staff, supplemental nurses, and security personnel, as well as costs

TABLE D-4
Inventory Management-Related Cost Components and Key Assumptions

Inventory Management-Related Cost Component	Key Assumptions
Labor and Storage Cost/Pallet	To determine labor and storage costs, the team assumed a cost per pallet derived from an average of two estimates provided by interviewees. In the absence of additional data to differentiate further among prepositioning locations, the team held this cost/pallet estimate constant for hospitals/pharmacies and workplaces.
Total Pallets Requiring Storage	To estimate total pallet requirements, the team referenced a report on the Cities Readiness Initiative (CRI) in Philadelphia, which indicated that a pallet can hold 10,000 bottles (Baccam, 2007). Assuming total population estimates for each scenario, as described above, the team was able to determine the total pallet requirement associated with holding inventory on site.
Product Expiry	For purposes of this analysis, the team assumed a product expiry of 1 year. Since hospitals and pharmacies manage their own supply and distribute doxycycline for other purposes, the team assumed that they could manage their inventory on a first-in/first-out basis, thereby eliminating the need to replenish inventory every year. In the workplace and MedKit scenarios, products would require full replenishment each year. Replenishment includes costs associated with replacing product in full, as well as shipping new product to prepositioning locations.

associated with training and operations. Note that dispensing costs are applicable to all strategies considered, with the exception of MedKits. Cost components and key assumptions related to dispensing are shown in Table D-5.

Dispensing Speed

Dispensing speed is a factor in the throughput at each dispensing location. To determine the total speed associated with dispensing, the team assumed varying throughput estimates per dispensing strategy employed. Key assumptions are shown in Table D-6.

TABLE D-5
Dispensing-Related Cost Components and Key Assumptions

Dispensing-Related Cost Component	Key Assumptions
Salaries for Administrative Staff	To estimate salaries for administrative staff on the day of dispensing, the team assumed that the number of staff required to implement each dispensing strategy should reflect the same staff-to-patient ratio as that expected for PODs. According to one interviewee, an average POD operates with 300 administrative staff per 24-hour period. Assuming that 20 PODs would serve a total population of 1.7 million and that only one representative from each household would collect MCM, the team derived the total number of patients each POD would be expected to serve. Assuming a constant staff-to-patient ratio, the team estimated total salary costs by determining the staffing requirements for each dispensing strategy, assuming an average hourly wage of $18.64 (Zaric et al., 2008).
Supplemental Nurses	The team assumed that workplaces would incur additional costs associated with employing supplemental nurses to aid in dispensing. One study assumes two supplemental nurses on the day of dispensing for a closed POD (Lee, 2011). The team maintained this assumption for large workplaces, but assumed that small workplaces and hospitals/pharmacies would require only one supplemental nurse/shift worked.
Additional Security Measures	In assessing costs associated with employing additional security measures, the team assumed that hospitals have sufficient such measures in place and would not incur additional security costs, but that pharmacies might employ a security guard at $29.01 per hour, representing the average hourly wage for a police officer in the Minneapolis-St. Paul area as indicated by the U.S. Bureau of Labor Statistics (BLS, 2010). To determine security requirements for workplaces, the team assumed the same security guard-to-patient ratio as that for PODs, as recommended by Bioterrorism and Epidemic Outbreak Response Model (BERM) (AHRQ, 2011).
Nonlabor Costs	As with the Georgia Institute of Technology study, the team assumed additional administrative costs for pharmacies and workplaces of $5,000 per day to cover all other nonlabor costs associated with dispensing MCM (Lee, 2011). The team also referenced study estimates for training of $5,000-$50,000 per site, assuming annual training. The team estimated training at the lower end of this spectrum for small workplaces and on the higher end for large workplaces. No additional training costs were included for hospitals and pharmacies, as the team assumed that their staff already possess requisite skills for dispensing.

TABLE D-6
Key Assumptions About Throughput for Dispensing Locations

Dispensing Location	Key Assumptions
Large Workplaces and PODs	For large workplaces and PODs, the team estimated a throughput of 1,000 people per hour. This estimate is the gold standard for throughput time, as indicated by interviewees and as identified during the team's literature review.
Small Workplaces, Hospitals, and Pharmacies	For smaller workplaces, hospitals, and pharmacies that are less well equipped to dispense MCM, the team assumed a throughput rate of 100 people per hour, as was determined feasible over the course of the interviews.

OBSERVATIONS FROM STRATEGY COMPARISONS

By leveraging its literature review and interviews, the team constructed a model for estimating the overall cost and dispensing time for each of the antibiotic dispensing strategies. These estimates were calculated for the dispensing of a 10-day prophylactic course to each of the 1.7 million individuals in the Minneapolis-St. Paul MSA. This section presents the data on costs, dispensing times, and the trade-offs between these two variables for all five dispensing options. Figures D-8, D-9, and D-10 illustrate these estimates. Each of the antibiotic dispensing strategies is analyzed in greater depth to determine the sources of variability in cost and dispensing time and provide a brief overview of the strategic implications of these data.

Figure D-8 shows the dispensing time for each of the strategies. While the SNS-RSS-POD baseline is estimated to exceed the CRI target time of 48 hours, all other dispensing strategies fall below the 48-hour ceiling. For the prepositioning strategies, the public POD component has a considerably longer dispensing time than that of hospitals, pharmacies, or workplaces; the same dynamic occurs for the postal model.

Figure D-9 depicts the overall cost for each of the dispensing strategies. The home MedKit strategy costs substantially more than any other option. The hospital/pharmacy model has a slightly lower overall cost than the SNS-RSS-POD option, and these two strategies are easily the two lowest-cost.

Figure D-10 illustrates the trade-offs between cost and dispensing time for each of the strategies. The home MedKit option is the clear outlier, with a very high cost and a negligible dispensing time. The hospital/pharmacy and postal models fare best in terms of balancing cost-efficiency with speed of dispensing.

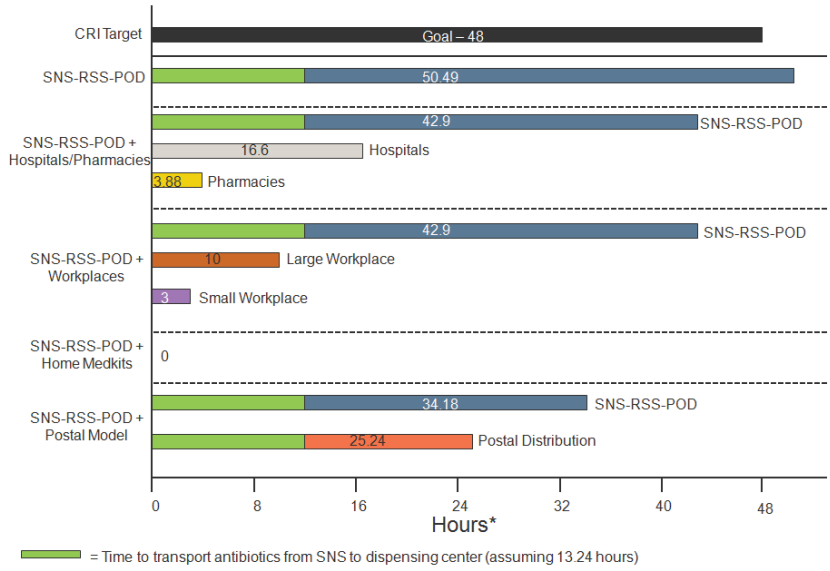


FIGURE D-8
Comparison of times to dispensing of first 10-day supply for prepositioning strategies. *Distribution speed should include margin of error to accommodate varying throughput estimates.

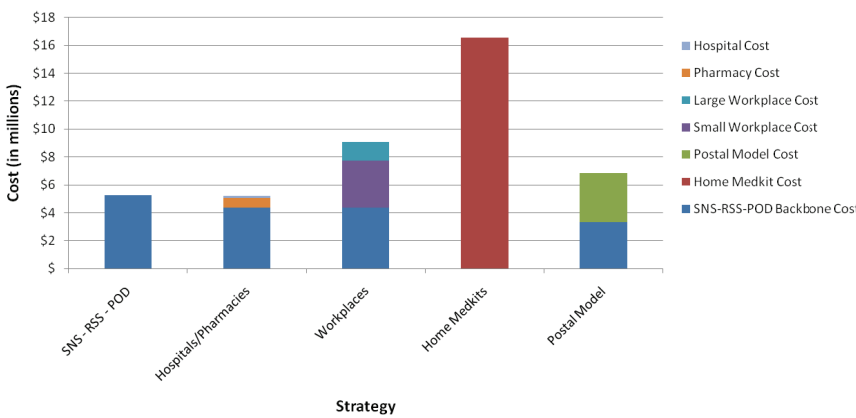


FIGURE D-9
Comparison of overall strategy costs.

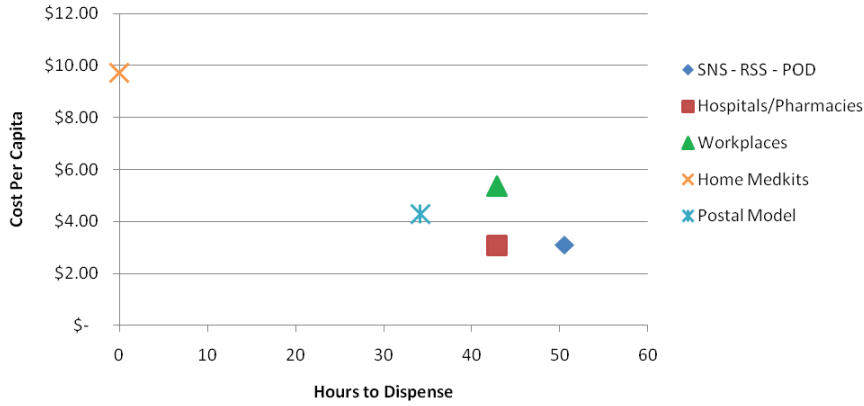


FIGURE D-10
Comparison of per capita costs and dispensing times.

Observations on the SNS-RSS-POD Baseline Scenario

The primary baseline scenario is the traditional SNS to RSS to POD model. In the pre-event stage, antibiotics are stored centrally at the SNS. When an event has been detected and the decision is made to mobilize SNS antibiotics, they are shipped to state-managed RSS sites and then distributed to locally administered PODs. This is the current *modus operandi* for the majority of U.S. localities in the event of an anthrax attack. Moreover, with the exception of the home MedKits model, each of the other prepositioning strategies includes a component that is served by the SNS-RSS-POD model; these options utilize more than one complementary strategy.

The SNS-RSS-POD model is the second-least costly of the five scenarios. The low cost and low speed of dispensing stem from the same central feature: this strategy utilizes a small number of dispensing sites that can leverage economies of scale to serve large population groups. Interviews indicated that the case study MSA has 20 PODs and a population of 1.7 million; each POD effectively serves 85,000 individuals. Given that a head of household can obtain MCM for his/her immediate family, the average POD will have to process only 37,281 individuals. Interviews and the literature review indicated that the throughput for a POD is 1,000 individuals per hour; only large workplaces, with similar economies of scale,

are assumed to achieve a similarly high throughput. The PODs' economies of scale also yield benefits in terms of lower overall dispensing, security, and training costs as compared with the smaller-scale hospital/pharmacy and workplace models.

On the other hand, the SNS-RSS-POD model features the longest overall dispensing time. Moreover, the data analysis indicates that the SNS-RSS-POD model's estimated antibiotic dispensing time of 50.49 hours would exceed the CRI goal of 48 hours by roughly 2.5 hours. Given the throughput, there are simply too many individuals per POD to dispense all of the antibiotics within the 48-hour goal. There are other inherent challenges to the POD-only approach. Because of the potential pressure of time and uncertain psychosocial responses of a population subject to a biological attack, security becomes an essential adjunct to maintain the desired throughput. PODs also are highly dependent on volunteers to staff the process, and there is no guarantee that workers will report for duty in the event of an attack.

To meet the CRI requirements using this strategy, the throughput or number of PODs would have to be increased. Alternatively, complementary strategies could be leveraged to offload a portion of the public from the SNS-RSS-POD model; this option is examined with the hospital/pharmacy cache, workplace cache, and postal distribution models.

Observations on Caching in Hospitals and Pharmacies

The hospital/pharmacy strategy is by far the least expensive prepositioning option, and it is even slightly less costly than the SNS-RSS-POD baseline strategy. Several factors account for the relatively low cost of this option. First, hospitals and pharmacies are staffed by trained medical professionals; unlike the workplace option, this strategy requires no training or supplemental nurses. Second, the security costs of this strategy have the potential to be inherently lower or minimal; hospitals already have a security presence, while one officer can likely provide sufficient security for a pharmacy. In contrast, workplace and POD dispensing options entail moderate security costs, and the postal option entails a large security cost ($1.03 million for the postal component alone). In the event of a biological attack, it is likely that all dispensing approaches and sites would require additional security; for this study, the team estimated the level of security that would be needed.

It is important to note that hospitals and pharmacies can make use of managed inventory, an approach that lowers potential replenishment costs. Under this approach, hospitals and pharmacies rotate antibiotic stock on a first-in/first-out basis that minimizes the costs of replacing the medication. An additional benefit is the ability to routinely track and manage manufacturer recalls for defective batches of antibiotics. Hospitals and

pharmacies could expand the size of their pre-existing antibiotic stocks, which could provide a sufficient quantity of antibiotics in the event of an anthrax attack. The routine hospital or pharmacy utilization of antibiotics, particularly doxycycline, would determine what percentage of the contingency supply would be used in a given year and what amount would need to be replenished.

The hospital and pharmacy dispensing time of 42.9 hours is roughly midway between the postal model (34.18 hours) and the SNS-RSS-POD option (50.49 hours). Under the assumption that 20 percent of the MSA population would receive antibiotics from hospitals and pharmacies, the rate-limiting component of this strategy is the 80 percent of the population that would go to public PODs.

Figures D-11 and D-12 are notional representations of the number of hospitals and pharmacies in the Minneapolis-St. Paul MSA. The MSA has 19 hospitals[2] and an estimated 310 pharmacies.[3] By utilizing these locations as prepositioning and dispensing sites, this approach would greatly increase the number of antibiotic dispensing sites in the MSA. With a 20 percent population burden, the hospital/pharmacy sites would complete dispensing well before the public PODs. Moreover, offloading 20 percent of the population from the public PODs would decrease their dispensing time by nearly 8 hours. This reduction in dispensing time would place the SNS-RSS-POD strategy 5.1 hours below the CRI recommendation of 48 hours.

Observations on Caching in the Workplace

The workplace prepositioning option entails considerably higher costs than the SNS-RSS-POD model (73 percent higher) or the postal distribution model (25 percent higher). Conceptually, the workplace model is most similar to the hospital/pharmacy model; it is worthwhile to analyze the component costs to uncover why the workplace option is roughly 75 percent more expensive than the hospital/pharmacy option. First, workplaces would require considerable training (the working assumptions are $50,000 per large workplace and $5,000 per small workplace [Lee, 2011]) in properly storing and dispensing antibiotics; hospitals and pharmacies already are properly staffed and equipped for these functions. Second, since the vast majority of workplaces lack trained medical staff, their dispensing labor would have to be augmented by supplemental nurses, whose training to predict or manage associated adverse events would be highly varied. Third, workplace caches would not benefit from routine utilization of the stored antibiotics, which would have to be replaced and replenished at least

[2]See Ucomparehealthcare.com.

[3]Derived from National Association of Chain Drug Stores estimate of 56,000 pharmacies throughout the United States.

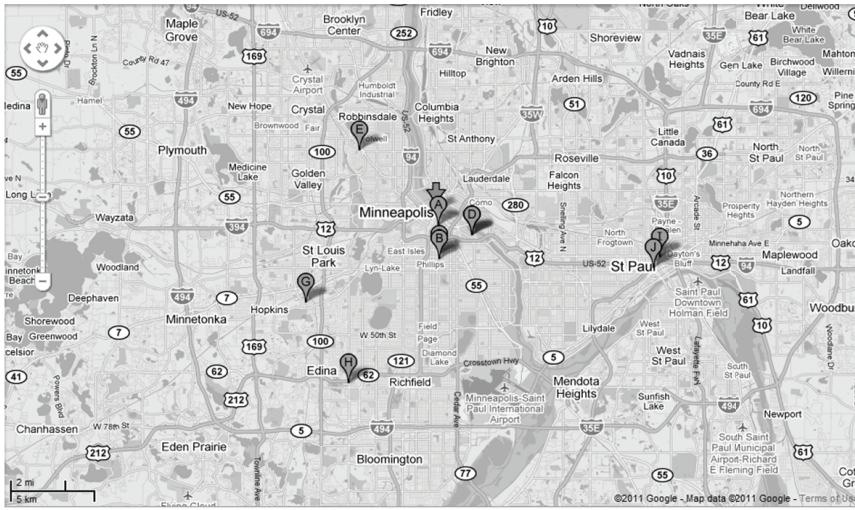


FIGURE D-11
Google map depiction of hospitals in the Minneapolis-St. Paul metropolitan statistical area (MSA).

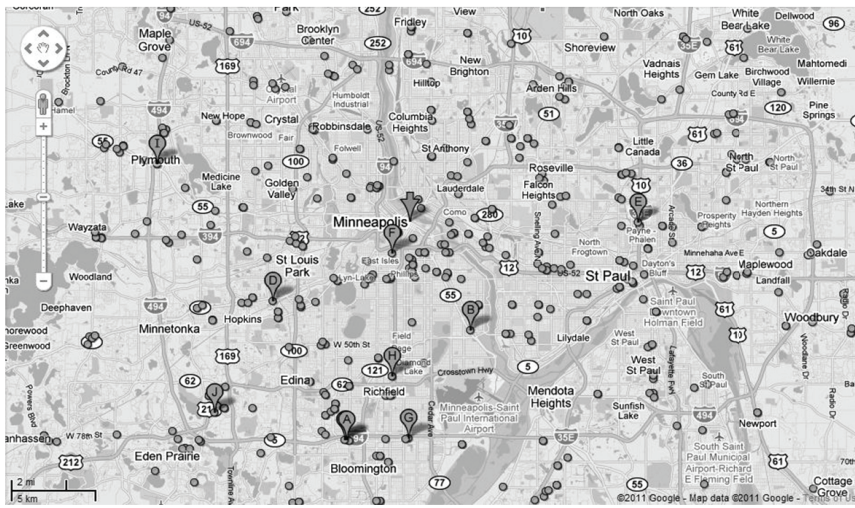


FIGURE D-12
Google map depiction of pharmacies in the Minneapolis-St. Paul metropolitan statistical area (MSA).

yearly under current FDA requirements. Finally, while large workplaces offer significant economies of scale, small workplaces yield a distinct disadvantage in this regard. Assuming 567 small workplaces of 300 individuals each, considerable fixed costs are associated with training, augmenting with supplemental nurses, and shipping MCM for each workplace. Large workplaces offer greater economies of scale than small workplaces; on a per capita basis, small workplaces are roughly 251 percent more costly. This differential suggests that a workplace prepositioning strategy focused more heavily on large workplaces would be more cost-effective.

The dispensing time for the workplace option is 42.9 hours, which is equivalent to that for the pharmacy and hospital prepositioning strategy. The same dynamic comes into play: the public POD component of this strategy is the rate-limiting factor.

The literature review (Lee, 2011) and interviews indicated that 20 percent is a reasonable assumption for the proportion of the population that could be served by prepositioned workplace caches; the team chose the same assumption for the hospital/pharmacy option to allow for an equivalent comparison. An analysis of these two strategies suggests that overall dispensing time for both could be lowered further if a higher proportion of the population could be served by workplaces or hospitals/pharmacies, as opposed to public PODs.

Observations on Caching in the Home (MedKits)

The home MedKit strategy features the highest cost and shortest dispensing time. This strategy yields a dispensing time of essentially zero; the MedKits would be stored pre-event in individual homes, and the team assumed they would not need to be distributed in the event of an anthrax attack. However, home prepositioning carries a significant financial cost. At $16.54 million, this approach is 215 percent more costly than the SNS-RSS-POD baseline scenario and 127 percent more costly than the postal model. It should be noted that the team used an extreme case of this strategy for illustrative purposes, assuming no use of PODs for distributing the initial 10-day prophylactic course of antibiotics.

The high cost of the home MedKit option is due primarily to two factors. First, the cost of the MedKit includes much more expensive packaging than that entailed in any other option. Home MedKits would cost $5.12 per person for a 10-day course of doxycycline, while the equivalent cost for all other options is considerably less. Second, there is a high distribution cost ($5.45 million) for shipping the medication to each individual's home. With the exception of the postal model, all other options entail antibiotics being shipped in larger quantities to fewer locations. The cost of telephone prescreening for home MedKits is comparable to the labor cost of screen-

ing at public PODs; thus this cost does not represent an additional burden relative to the baseline scenario.[4]

It is important to note that this option also features the highest replenishment costs ($14.51 million annually). Under current FDA Emergency Use Authorization (EUA) regulations, each home MedKit would have to be replaced annually. Thus, annual replenishment costs would include the full cost of the MedKit itself and the transportation cost; this model assumes that telephone screening would not be necessary on an annual basis, but that some degree of rescreening would be necessary on a semiannual basis.

Observations on the Postal Distribution Model

The prepositioning strategies were also compared with the postal distribution model. This model has been adopted much less widely than the SNS-RSS-POD model. However, there is a standing executive order for the United States to establish a postal MCM dispensing capability, and the Minneapolis-St. Paul MSA is carrying out an ongoing postal distribution pilot project. Thus, it is worthwhile to compare the prepositioning strategies with this postal distribution model.

The postal distribution model ranks third out of five strategies for overall cost. Its cost falls roughly halfway between the SNS-RSS-POD model and the workplace cache option, and is less than half that of the home MedKit model. The postal model does not place a heavy emphasis on screening recipients, and it delivers one 10-day course of doxycycline to each household, regardless of the number of residents. Thus, compared with other models, its dispensing costs are relatively low. On the other hand, the requirement for one police officer paired up with each postal worker yields a higher security cost ($1.03 million) for only a 12-hour operational period.

This model also is notable for its relatively rapid dispensing. The postal model is second only to home MedKits in terms of overall distribution speed. Through the postal model, each household would receive one 10-day course of antibiotics in 25.24 hours: 13.24 hours for transporting the medication from SNS to RSS to post office and 12 hours for postal workers to deliver it. Under the current concept of operations, the remaining doses to complete 10-day courses for the MSA would be provided through the

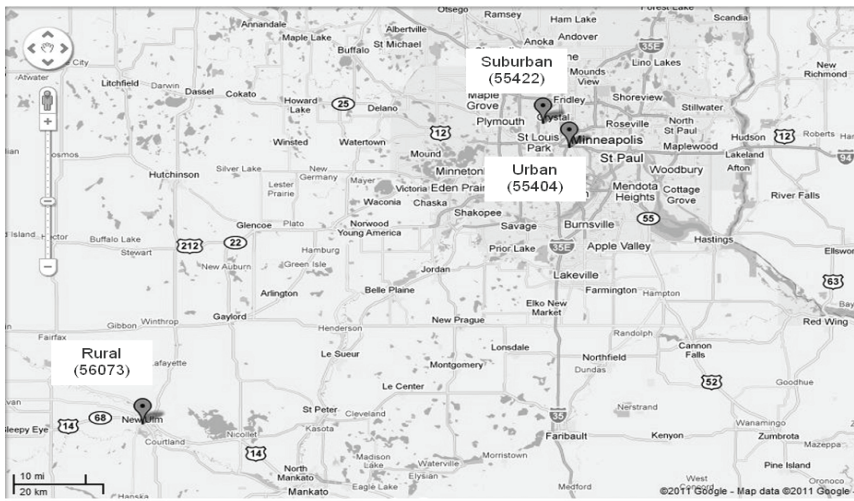
[4]Prescreening for MedKits is not an additional cost relative to public PODs. People at public PODs are screened as well, but that screening takes place the day of the event, rather than beforehand. The team reasons that the screening time, and hence the costs, are fairly similar. In fact, the team based its estimate of prescreening labor and cost for MedKits on the time it would take to screen individuals at a public (or for that matter, closed) POD.

traditional SNS-RSS-POD model. The rate-limiting step in this strategy is the SNS-RSS-POD component, which is estimated to take 34.18 hours.

CASE METROPOLITAN STATISTICAL AREA FOR COMPARISON: MINNEAPOLIS-ST. PAUL

The team assessed the differences associated with employing each dispensing strategy in geographic areas with varying degrees of population density. To conduct this analysis, the team selected representative zip codes that closely reflect the population density of an urban, suburban, and rural setting (see Figure D-13) (Zipskinny, 2000). Representative zip codes provide population and distance assumptions that were used to estimate the cost and speed of distribution to these areas.

The team selected the most densely populated zip code to represent an urban environment and one relatively less dense to reflect a suburban population. Note that among other factors, the U.S. Census Bureau classifies urban areas as densely settled territory consisting of "core census block groups or blocks that have a population density of at least 1,000 people per square mile and surrounding census blocks that have an overall density of at least 500 people per square mile" (U.S. Census Bureau, 2011). Areas



Urban population – 27,282
Suburban population – 27,810
Rural population – 17,199

FIGURE D-13
Google map depiction of selected representative urban, suburban, and rural zip codes in Minnesota.

that do not meet this criterion are classified as rural. No specific definition is provided for suburban areas. Since the postal model serves only urban and suburban areas, the team selected an alternative zip code within the vicinity of Minneapolis-St. Paul as representative of a rural area.

When performing the calculations for the populations in each zip code, the team noted no significant quantitative differences among strategies across the different areas. Costs and speed of distribution are virtually the same for the representative zip codes using the data that were collected. It is likely that such variables as number of pharmacies and hospitals or ratio of large to small businesses would differ across zip codes. However, these data were unavailable. In lieu of a quantitative analysis, this section provides a qualitative discussion of how the various strategies would differ across geographic settings.

Urban Area Profile

The high density of urban areas can carry many advantages and disadvantages in terms of antibiotic dispensing. First, a greater number of people would be vying for access to PODs, which could create much longer lines relative to less densely populated areas. However, people would not have to travel as far to get to a POD since there would likely be a greater number of PODs per square mile in an urban area.

Urban areas also are likely to have more hospitals, pharmacies, and workplaces per square mile than suburban and rural areas. This feature of urban areas could provide more POD options to the general public and thus could relieve the pressure on any one POD or strategy. Urban health departments also tend to be larger, with more personnel, than those in suburban and rural areas. They would have more specialized personnel as well (e.g., an urban health department could have an emergency planner, whereas a rural area could not support such a position). Therefore, urban environments would have a greater workforce available to staff PODs.

In addition, many urban areas have a large commuter workforce. It is safe to assume that the population of an urban area is higher during the day than at night, when commuters return to suburban or rural areas. Planning for dispensing would need to account not only for population density, but also for the population that did not necessarily reside in the area but was located there during the workday. Tourism is another factor that could increase the population of an urban area at any given time.

Suburban Area Profile

Suburban areas are the most difficult areas to define. As noted, the U.S. Census Bureau does not even provide a definition for a suburban area.

These areas can have many characteristics of both urban and rural areas, as their population density can vary widely between the two.

One unique characteristic of a suburban area is that most residents have cars. Some locales have run exercises showing that drive-through PODs are a highly effective model for suburban areas. These PODs would function like a drive-through restaurant in that people would not have to leave their cars to receive MCM.

As mentioned above, one also must account for the commuter population. Many suburban residents will have workplaces in the city, so the population of a suburban area will be greater at night and on weekends than during the day on weekdays.

Rural Area Profile

The smaller population density of a rural area means that the population is much more spread out than in urban and suburban areas. If planning accounts for a POD to serve a standard number of people, the number of PODs will be much lower in a rural area. With PODs being more spread out, it is safe to assume that travel times to reach them will be much longer. This could be a disadvantage if it takes a long time to get to a POD; however, it could also be an advantage if arrival times are staggered, which could reduce POD queues. Another factor to consider is the length of time it would take for a POD to receive MCM from the RSS. Rural areas are locations where prepositioning could particularly save time. However, they are likely to have fewer pharmacies, hospitals, and businesses in which prepositioning could occur.

In addition, health departments in rural areas have fewer employees. The employees also are less specialized, so there is likely less manpower devoted to emergency planning. Moreover, fewer public health employees would be available to man PODs.

One interesting model for dispensing MCM in rural areas is what one interviewee referred to as the "school bus" model. This model would involve loading a school bus or equivalent with MCM, basically serving as a mobile POD that would travel to predetermined locations in rural areas to deliver the MCM to the public.

ALTERNATIVE DISPENSING STRATEGIES

For this study, the team identified the alternative MCM dispensing strategies depicted in Figure D-14.

The current strategy for distributing antibiotics relies on the SNS-RSS-POD model, which is a centralized to decentralized model. As noted earlier, the SNS is contained in a set of central storage sites, which is funded by

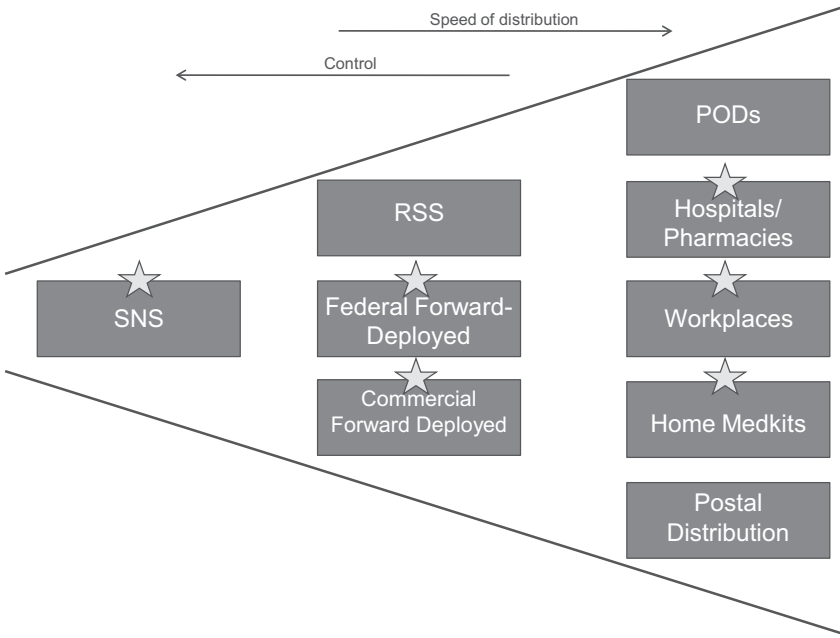


FIGURE D-14
Comparison of alternative dispensing strategies.
NOTE: The stars indicate possible storage locations.

the federal government; these sites also are set up and staffed by the federal government. The RSS sites reside under either state or local control, depending on the locale. These are simply throughput sites used for receiving MCM from the SNS and distributing them to PODs. The PODs themselves are the most decentralized. The number of PODs and their locations are determined by local authorities.

One advantage of the medications being controlled by the federal government is the Shelf Life Extension Program (SLEP). If not controlled by the federal government, MCM must be replaced annually in accordance with prescription laws. The number of years for which MCM can be extended under SLEP is determined by the FDA; in general, however, SLEP could double or triple the shelf life of these medications, which would lead to lower replenishment costs. However, this advantage must be weighed against the fact that tetracyclines can show significant decreases in efficacy and increases in adverse events over short periods of time.

In addition to avoidance of yearly replenishment costs and/or expiry issues, a federally controlled forward-deployed stock would be geographi-

cally closer to areas that might need it than would be the case if those areas had to rely on the central SNS warehouses. Alternatively, CDC has investigated the possibility of decreasing the distribution time from the SNS to PODs by having more regional storage sites. This would, in theory, remove the RSS stage of the process while retaining federal control so SLEP could be applied. CDC expects that this model could decrease the distribution time from the SNS to PODs from around 12 hours to around 6 hours.

Other examples of facilities that could be used for federal forward-deployed stocks are VA or DOD medical storage facilities. The VA is experienced with caching as it currently stores many medications and medical supplies on VA property. Storing MCM in existing warehouses on federal property could greatly reduce storage costs over the use of contracted warehouses. The VA has many central hospitals and other facilities located in major metropolitan areas, as well as clinics and other facilities spread throughout cities. In Minneapolis, the VA hospital is centrally located (see Figure D-15), and the many clinics located around the city could serve as

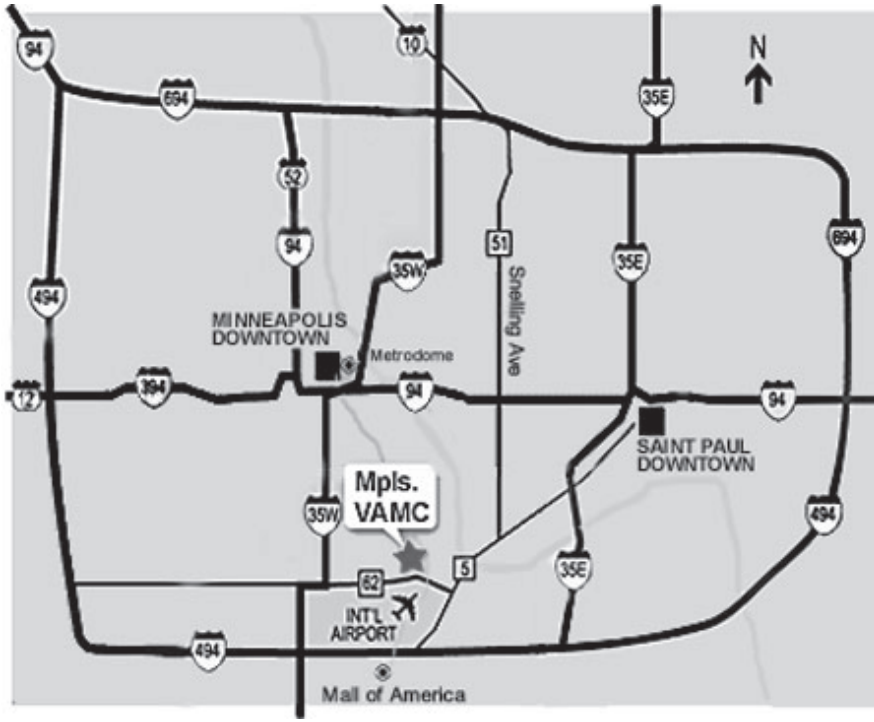


FIGURE D-15
Location of the Department of Veterans Affairs (VA) hospital in Minneapolis.

PODs. The VA also has medical staff on site who could assist with dispensing. Similarly, DOD medical treatment facilities could be used, although they are fewer in number and restricted to areas where they are collocated with military installations.

Another option is a commercially controlled forward-deployed stock. One example is a pharmaceutical distributor, where MCM could serve as vendor-managed inventory. For example, New York City has been working with pharmaceutical distributors to hold extra inventory in their supply chains. Pharmaceutical distributors have agreed to keep extra stock of antibiotics on hand, and the department of health has agreed to pay the cost difference for storing the extra medication. The cost is pennies on the dollar. This strategy brings the MCM closer to the population because pharmaceutical distributors are usually regionally located. These distributors also are selling these drugs daily for normal medical use, and by using the first in/first out approach could avoid the expiry issue that most caching strategies entail. Also, pharmaceutical distributors store and deliver medications every day and can quickly alter their destination sites over a wide area based on demand. Therefore, they may be better equipped to handle these tasks during an emergency than an entity that does not perform these tasks daily. However, as these resources would be outside of immediate federal control, there may be trade-offs as far as resource prioritization and decision-to-action cycle time.

Through these upstream changes, downstream distribution and dispensing could occur much more rapidly. Any of these forward-deployed stocks could be distributed to traditional public PODs, closed PODs, or alternative dispensing sites. Moving stocks farther downstream pre-event could dramatically reduce overall dispensing time. Many of these mechanisms also could serve to decrease overall costs.

ADDITIONAL CONSIDERATIONS

This section addresses some additional considerations that were highlighted during the course of the team's research. These considerations fall into six categories: variability, liability, amount of medication required, efficiency, packaging, and ongoing prophylaxis. These considerations are challenges to the implementation of any prepositioning strategy.

Variability

- **State/Local Capability:** It is difficult to speak of any of the costs or benefits of alternative dispensing strategies in absolute terms since many variables depend on the state or local capability. For example, many states have a health department run by the state itself,

whereas others have a conglomeration of local or regional health departments. States vary as well in size of population, population density, budget, and storage space. Thus it is difficult to make assumptions that will apply to all locations, although there are issues that apply to all states.

Liability

- **Product Approval:** Since the medications are being prescribed for use outside of their normal purview, each strategy requires an EUA for an investigational new drug (IND). This is much easier to achieve when the drugs remain under federal control until they are ready for dispensing, but is far more difficult for home MedKits. Doxycycline, like any other prescription medication, carries a high risk of adverse reactions if proper patient assessment by a clinician does not occur. The team's analysis does not address the time and cost of acquiring an EUA for placing antibiotics in the home, which can be a time-consuming and costly process.
- **Return and Disposal of Expired Antibiotics:** What will be done with expired home MedKits needs to be considered. If MedKits are to be returned to an official location after expiry, the cost of return shipping must be accounted for. Simply asking the public to throw away their MedKits after expiry poses a substantial risk since doxycycline becomes toxic and can cause kidney damage once it has expired (Drugs.com, 2009).

Amount of Medication Required

- **Uncertainty of Household Needs:** An additional consideration for the postal distribution model is the number of pills to be handed out. In the home MedKit model, each person receives enough pills to last for 10 days. In the postal model, each household receives 20 pills, regardless of the number of residents. The result could be increased pressure on PODs for those households with large numbers of people.
- **Need for More Medication Overall with Prepositioning:** Any prepositioning strategy will require medications farther downstream relative to more centralized strategies. Therefore, more antibiotics will have to be purchased overall to acquire enough to fill each cache in each location. If each location requires enough antibiotics to cover its population, those drugs will have to be purchased in addition to what is currently held in the SNS. The cost of all these additional antibiotics must be considered.

- **"Double Dippers":** The more prepositioning strategies are employed, the more "double dippers" must be accounted for. If people have access to MCM at a workplace, a POD, and a local pharmacy, what is to prevent them from taking advantage of all three? This possibility must be considered when one is looking at the number of antibiotics provided overall in an affected area, as must tracking mechanisms for those who have received medications and those who have not.

Efficiency

- **Reliance on Push Packages:** Each prepositioning strategy will require the use of a Push Package to get the medications to a POD or to the postal service as soon as possible. An issue with the Push Package is that it does not contain just antibiotics. The Push Package consists of 130 cargo containers with a combined weight of 50 tons (Baccam, 2007). This means that in addition to the antibiotics needed for an anthrax attack, an RSS would receive material that might not be necessary initially for that emergency. The result would be extra cost for weight and transport, as well as extra time needed to sort through the pack to get to what is really needed. And what is to be done with the remaining materials that are not needed?
- **Throughput:** The team found that the rate-limiting factor is not speed of transportation but speed of dispensing. Prepositioning closer to the impacted locale can greatly increase speed, but without the manpower to dispense the MCM, that gain in speed becomes moot. Most state and local health authorities speak about throughput goals; however, they all wish for higher throughput. Most mention a goal of 1,000 people per hour, but in large cities with populations in the millions, even this goal could overwhelm the POD system. More effort should be expended on finding ways to increase the rate of dispensing.

Packaging

- **Packaging Efficiency:** Antibiotics in the Push Package are stored in unit-of-use bottles (20 pills to a bottle). The bottles are spacious for the number of pills they contain. This leads to the need for increased storage space for the antibiotics, which in turn leads to increased storage costs. Also, the pill bottles can be too large for some mail slots in the postal model. A more efficient practice could be the production of smaller unit-of-use pill bottles.

- **Scalability of Labor for Breakdown and Packaging:** Many strategies involve receiving the MCM in bulk. In fact, all medications coming from the SNS-managed inventory (not the Push Package) are delivered in bulk. Extra costs are entailed for materials and labor to portion out the medications in the appropriate dose. For example, the Minnesota Department of Health portions out antibiotics for the MedKits for postal volunteers. This is no small undertaking. It requires many hours of labor for two trained medical professionals to place the pills into bottles, label the bottles, and ensure that the correct medications are going to each home. Scaling this amount of labor and materials to meet the demand for a larger population would be unwieldy. Also, taking time to portion out medications while PODs are running during an event would increase dispensing time and labor costs.

Ongoing Prophylaxis

- **Dispensing Strategy for a 60-Day Courses to Cover the Population:** Each prepositioning strategy covers only the initial immediate need for antibiotics. A concrete strategy is needed for providing the rest of the 60-day course to those who are impacted. There will be additional pressure on PODs to provide the rest of the course, as well as adherence issues for the public with respect to finishing the course (see below). In addition, more clinical studies are needed to better determine the long-term safety impact of 60-day therapy with doxycycline in large populations.
- **Antibiotic Resistance:** One negative effect of failure to complete an antibiotic course is antibiotic resistance. Adherence is a major issue for any dispensing strategy. The development of an antibiotic resistant strain of anthrax following an anthrax attack would be a very unfortunate outcome.

CONCLUSIONS

This study has attempted to estimate the costs and time savings associated with each of the three identified prepositioning strategies, as well as other possible approaches. It is not intended as an exhaustive cost/benefit analysis for use in determining whether any of these prepositioning strategies should be deployed. As events and circumstances frequently do not occur as expected, there may be material differences between the estimates in this paper and actual outcomes.

The analysis does suggest that the strategy of caching in hospitals and pharmacies and the delivery of antibiotics through the U.S. postal system

both could yield significant time savings without a commensurate increase in cost. These approaches could be further enhanced through the use of regional warehousing that would position the antibiotics closer to the impacted population than the current SNS model. Home MedKits, although comparatively expensive, could be appropriate for certain segments of the population for whom immediate availability of antibiotics would be worth the cost, such as essential first responders. In any city or region that chooses to preposition antibiotics, it is likely that a combination of these strategies should be considered.

While PRTM has attempted to add some quantitative dimension to the cost and time of prepositioning strategies through this paper, many uncertainties remain. Access to additional data will clarify some unknowns, as will the continued evolution of federal and state prepositioning policies. Further study of the relative benefits and trade-offs of each of these strategies would be required to provide more concrete recommendations for prepositioning MCM based on quantitative analysis.

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Appendix D.1

Detailed Data

This appendix provides the calculations that form the basis of the Observations from Strategy Calculations, incorporating the assumptions described in Components of Cost and Speed for Dispensing Strategies. Note that some cells in the following tables have been redacted to protect sensitive information.

TABLE D.1-1
High-Level Overview Data

	Prepositioning Strategy		
	20% Hospitals and Pharmacies; 80% SNS-RSS-POD	**20% Large and Small Workplaces; 80% SNS-RSS-POD**	**Home MedKits**
Overall Cost	$5,212,761	$9,096,388	$16,542,288
Per Capita Cost	$3.07	$5.35	$9.73
% Difference in Overall Cost vs. SNS-RSS-POD Baseline	–0.82	73.08	214.75
% Difference in Overall Cost vs. Postal Model	–28.47	24.82	127.00
Overall Dispensing Time (hours)	42.9	42.9	0
% Difference in Dispensing Time vs. SNS-RSS-POD Baseline	–15.03	–15.03	N/A
% Difference in Dispensing Time vs. Postal Model	25.51	25.51	N/A
Cost Per Hour Reduction vs. SNS-RSS-POD	–$5,655	$506,022	$223,541
Per Capita Cost Per Hour Reduction vs. SNS-RSS-POD	$0.00	$0.30	$0.13
Cost Per Hour Reduction vs. Postal Model	N/A	N/A	$270,767
Per Capita Cost Per Hour Reduction vs. Postal Model	N/A	N/A	$0.16
Replenishment Costs (annual)	If vendor-managed inventory is utilized, then replenishment costs are negligible.	[redacted]	$14,154,000

Replenishment Costs (SLEP)	[redacted]	0
Replenishment Costs (annual + SLEP)		$14,154,000

	Alternative Strategies	
	SNS-RSS-POD	**44% Postal Model; 56% SNS-RSS-POD**
Overall Cost	$5,255,680	$7,287,466
Per Capital Cost	$3.09	$4.29
Overall Dispensing Time (hours)	50.49	34.18
Replenishment Costs (annual)	0	$42,656
Replenishment Costs (SLEP)	[redacted]	
Replenishment Costs (annual + SLEP)		

NOTE: Due to insufficient information, the SNS-RSS-POD transportation costs have been excluded from our cost calculations.

TABLE D.1-2
SNS-RSS-POD Data

Costs Description	Data	Calculations
Individuals	1,700,000	
Households	745,000	
Product Purchase Price		
Product Purchase Price - Costs per daily dosage- Propylaxis, Doxycycline	[redacted]	
Product Purchase Price - Additional Medication Costs Per Daily Dosage (packaging, etc.)		
Product Purchase Price - Total Costs for Medication Per Daily Dosage		
Product Purchase Price - Total Costs for Medication (per household)		
Product Purchase Price - Total Costs for Medication (overall)		
Transportation		
Transportation - SNS to RSS to Postal Office	N/A	not available
Transportation Costs (overall)	**$0.00**	not available
Dispensing		
Dispensing - Labor - Salaries (per POD, per day)	$44,736.00	300 staff per POD/day (source: interview with state public health official) × 8 hours/day × $18.64/hr (source: Zaric et al.)
Dispensing - Labor - Salaries (20 PODs, per day)	$894,720.00	Labor per day per POD × 20 PODs

Costs Description	Data	Calculations
Individuals	1,700,000	
Dispensing - Labor - Salaries (total)	**$1,388,680.00**	37.25 hours × 1 day/24 hours × $894,720/day
Dispensing - Labor - Training (annual)	**$894,720.00**	300 staff per POD × 8 hours of training/yr × $18.64/hr
Dispensing - Administrative Fees/ Operational Costs (daily, per POD)	$5,000.00	
Dispensing - Administrative Fees/ Operational Costs (daily, 20 PODs)	$100,000.00	$5,000 × 20 PODs
Dispensing - Administrative Fees/ Operational Costs (total)	**$155,208.33**	37.25 hours × 1 day/24 hours × $100,000/day
Dispensing - Security (daily, per POD)	$2,784.96	
Dispensing - Security (daily, 20 PODs)	$55,699.20	
Dispensing - Security (total)	**$86,449.80**	37.25 hours × 1 day/24hours × $2,784.96/POD per day × 20 PODs
Dispensing - Total Costs	**$2,525,058.13**	Labor-salaries (total) + labor-training (total) + security (total)
Inventory Management		
Inventory Management - Labor	[redacted]	
Inventory Management - Cost of Storage/Pallet (yearly)		
Inventory Management - # of Bottles/Pallet		
Inventory Management - # of Pallets Required		

continued

TABLE D.1-2
Continued

Costs Description	Data	Calculations
Individuals	1,700,000	
Inventory Management - Storage (total)	[redacted]	
Inventory Management - Total Costs (excluding replenishment costs)		
Inventory Management - Replenishment - Product Purchase (overall)		
Inventory Management - Replenishment - Transportation (overall)	**$0**	
Inventory Management - Replenishment - Dispensing (overall)	**$0.00**	
Inventory Management - Replenishment Costs (total, SLEP)	[redacted]	**Total costs for product purchase + total costs for dispensing**
Total Costs		
Product Purchase Price	[redacted]	
Transportation	**$0.00**	
Dispensing	**$2,525,058.13**	
Inventory Management (without replenishment)	[redacted]	
Total Cost (without replenishment)	**$5,255,679.73**	
Replenishment Costs (SLEP)	[redacted]	
Total Dispensing Time for Strategy		

Costs Description	Data	Calculations
Individuals	1,700,000	
Dispensing Time - SNS to RSS to POD Transportation (hours)	**13.24**	(source: calculations derived from presentation - Burel, G. An SNS Perspective on Pre-positioning Medical Countermeasures. Centers for Disease Control and Prevention, February 28, 2011. Presented to IOM Committee on Prepositioned Medical Countermeasures for the Public)
Dispensing Time - POD Operating Time (hours)	**37.25**	(745,000 households / 20 pods × 1 hr/1,000 households)
Dispensing Time for Strategy - Total (hours)	50.49	SNS to RSS to POD + POD Operating Time

TABLE D.1-3
Hospital/Pharmacy Data

Hospital/Pharmacy Component	Hospital		Pharmacy	
Costs Description	**Data**	**Calculations**	**Data**	**Calculations**
Individuals	65,758.05	Population served by hospital derived from calculating patient population and hospital employees from ucomparehealthcare.com	274,242.95	(1,700,000 × .20) - (population served by pharmacy)
Households	28,841.25	65,758.05 individuals × 1 household/2.28 individuals	120,282.00	274,242.95 individuals × 1 household/2.28 individuals
Hospitals/Pharmacies	19	Source - ucomparehealthcare.com	310.1	56,000 pharmacies/ US (source - National Association of Chain Drug Stores) × US population /307,006,550 individuals (source - U.S. Census Bureau) × 1.7 million in MSA
Costs				
Product Purchase Price				
Product Purchase Price - Costs per daily dosage - Prophylaxis, Doxycycline	$0.20	$0.10/pill × 2 pills per day	$0.20	$0.10/pill × 2 pills per day
Product Purchase Price - Additional Medication Costs Per Daily Dosage (packaging, etc.)	$0.01		$0.01	

Hospital/Pharmacy Component	Hospital		Pharmacy	
Costs				
Description	**Data**	**Calculations**	**Data**	**Calculations**
Product Purchase Price - Total Costs for Medication Per Daily Dosage	$0.21	$0.20 per daily dosage + $0.01 additional medication costs per dosage	$0.21	$0.20 per daily dosage + $0.01 additional medication costs per dosage
Product Purchase Price - Total Costs for Medication (per household)	$2.10	$0.21/day × 10 days	$2.10	$0.21/day × 10 days
Product Purchase Price - Total Costs for Medication (overall)	**$138,092**	**(65,758.05 individuals × one 10-day course per individual × $2.10 per 10-day course)**	**$575,910**	**(274,242.95 individuals × one 10-day course per individual × $2.10 per 10-day course)**
Transportation				
Transportation - Shipping Medications to Hospitals/ Pharmacies	$353.02	Source - average estimated shipping cost of USPS and FedEx	$3,310.80	Source - average estimated shipping cost of USPS and FedEx
Transportation (overall)	**$353.02**		**$3,310.80**	
Dispensing				
Dispensing - Labor - Salaries (per hospital/pharmacy, per day)	$2,684.16	6 staff × 18.64/hr × 8 hr/shift × 3 shifts	$894.72	2 staff × $18.64/hr × 8 hr/day × 3 shifts
Dispensing - Labor - Salaries (19 pharmacies/310.1 pharmacies, per day)	$50,999.04	$2,684.16 × 19 hospitals	$277,453	$894.72 × 566.67 small workplaces
Dispensing - Labor - Salaries (total)	**$32,256.89**	15.18 hours × 1 day/24 hours × $266,179.20/day	**$44,855**	3.88 hours × 1 day/24 hours × $507,011/day

continued

TABLE D.1-3
Continued

Hospital/Pharmacy Component	Hospital		Pharmacy	
Costs Description	**Data**	**Calculations**	**Data**	**Calculations**
Dispensing - Labor - Training (annual)	**$0.00**	Since hospitals and pharmacies have trained medical staff, assume that no training is necessary (source: Georgia Tech paper)	**$0**	Since hospitals and pharmacies have trained medical staff, assume that no training is necessary (source: Georgia Tech paper)
Dispensing - Labor - Supplemental Nurses (per hospital/pharmacy, per day)	$0.00	Since hospitals and pharmacies have trained medical staff, assume that no supplemental nurses are necessary (source: Georgia Tech paper)	$0	Since hospitals and pharmacies have trained medical staff, assume that no training is necessary (source: Georgia Tech paper)
Dispensing - Labor - Supplemental Nurses (19 pharmacies/310.1 pharmacies, per day)	$0.00	Since hospitals and pharmacies have trained medical staff, assume that no supplemental nurses are necessary (source: Georgia Tech paper)	$0	Since hospitals and pharmacies have trained medical staff, assume that no training is necessary (source: Georgia Tech paper)
Dispensing - Labor - Supplemental Nurses (19 pharmacies/310.1 pharmacies)	**$0.00**	Since hospitals and pharmacies have trained medical staff, assume that no supplemental nurses are necessary (source: Georgia Tech paper)	**$0**	Since hospitals and pharmacies have trained medical staff, assume that no training is necessary (source: Georgia Tech paper)
Dispensing - Administrative Fees/ Operational Costs (total)	**$0.00**	Opportunity cost absorbed by hospital	**$0.00**	Opportunity cost absorbed by pharmacy

Hospital/Pharmacy Component	Hospital		Pharmacy	
Costs Description	**Data**	**Calculations**	**Data**	**Calculations**
Dispensing - Security (per workplace, per day)	$0.00	Hospitals already have a security presence	$696.24	1 officer × 3 shifts × $29.01/hr × 8 hrs/shift
Dispensing - Security (19 pharmacies/310.1 pharmacies, per day)	$0.00	Hospitals already have a security presence	$215,904.02	($696.24 × 310.1 pharmacies)
Dispensing - Security (total for 19 pharmacies/310.1 pharmacies)	**$0.00**	Hospitals already have a security presence	**$34,904.48**	$394,538.32 × 3.88 hours operating time × 1 day/24 hours
Dispensing - Total Costs	**$32,256.89**	Labor-salaries (total) + labor-training (total) + security (total)	**$79,759.33**	Labor-salaries (total) + labor-training (total) + security (total)
Inventory Management				
Inventory Management - Labor	0	not available	0	not available
Inventory Management - Cost of Storage/Pallet per month	$14	Average of interview data	$14	Average of interview data
Inventory Management - # of Bottles/Pallet	10,000	Interview	10,000	Interview
Inventory Management - # of Pallets Required	6.58	65758.05 bottles × 10,000 bottles/pallet	27.42	274241.95 bottles × 10,000 bottles/pallet
Inventory Management - Storage (total/annual)	$1,105	6.58 pallets × $14/month x 12 months/1 year	$4,607	27.42 pallets × $14/ month × 12 months/ 1 year
Inventory Management - Total Costs (annual, excluding replenishment costs)	**$1,105**		**$4,607**	

continued

TABLE D.1-3
Continued

Hospital/Pharmacy Component	Hospital		Pharmacy	
Costs Description	**Data**	**Calculations**	**Data**	**Calculations**
Inventory Management - Replenishment - Product Purchase (overall)	**$0**	Hospitals and pharmacies can use first-in, first-out managed inventory, which makes replenishment costs negligible.	**$0**	Hospitals and pharmacies can use first-in, first-out managed inventory, which makes replenishment costs negligible.
Inventory Management - Replenishment - Transportation (overall)	**$0**		**$0.00**	
Inventory Management - Replenishment - Dispensing (overall)	**$0.00**		**0**	
Inventory Management - Replenishment Costs (total, annual)	**$0.00**	**Total costs for product purchase + total costs for transportation**	**$0.00**	**Total costs for product purchase + total costs for transportation**
Total Costs	**Hospital Component (3.87%, 6,5758.05 individuals)**		**Pharmacy Component (16.13%, 2,74241.95 individuals)**	
Product Purchase Price	**$138,091.91**		**$575,910.20**	
Transportation	**$353.02**		**$3,310.80**	
Dispensing	**$32,256.89**		**$79,759.33**	
Inventory Management (without replenishment)	**$1,105**		**$4,607**	

Hospital/Pharmacy Component	Hospital		Pharmacy	
Costs Description	Data	Calculations	Data	Calculations
Total Cost (without replenishment)	**$171,806.55**		**$663,587.61**	
Replenishment Costs (annual)	$0.00		$0.00	
Total Costs	**Hospitals and Pharmacies Combined (20%, 340,000 individuals)**			
Product Purchase Price	$714,002.10			
Transportation	$3,663.82			
Dispensing	$112,016.23			
Inventory Management (without replenishment)	$5,712.02			
Total Cost (without replenishment)	**$835,394.16**			
Replenishment Costs (annual)	$0.00			
Dispensing Time	**Hospitals**		**Pharmacies**	
Dispensing Time - Transportation (hours)	**0**	Caches are prepositioned	**0**	Caches are prepositioned
Dispensing Time - Closed POD/ Hospital and Pharmacy Dispensing Time (hours)	**15.18**	28,841.25 individuals/19 hospitals × 1 hr/100 individuals (throughput)	**3.88**	120,282 individuals/310.1 pharmacies × 1 hr/100 individuals (throughput)
Dispensing Time - Total (hours)	**15.18**		**3.88**	

continued

TABLE D.1-3
Continued

POD Component		
Costs **Description**	**Data**	**Calculations**
Individuals	1,360,000	1,700,000 - population served by pharmacy/ hospital)
Households	596,491	1,360,000 individuals × 1 household/2.28 individuals
Product Purchase Price		
Product Purchase Price - Costs per daily dosage-Propylaxis, Doxycycline	[redacted]	
Product Purchase Price - Additional Medication Costs Per Daily Dosage (packaging, etc.)		
Product Purchase Price - Total Costs for Medication Per Daily Dosage		
Product Purchase Price - Total Costs for Medication (per household)		
Product Purchase Price - Total Costs for Medication (overall)		
Transportation		
Transportation - SNS to RSS to Postal Office	N/A	not available

POD Component		
Costs **Description**	**Data**	**Calculations**
Transportation Costs (overall)	**$0.00**	not available
Dispensing		
Dispensing - Labor - Salaries (per POD, per day)	$44,736.00	300 staff per POD/day (source: interview with state public health official) × 8 hours/day × $18.64/hr (source: Zaric et. al.)
Dispensing - Labor - Salaries (20 PODs, per day)	$894,720.00	Labor per day per POD × 20 PODs
Dispensing - Labor - Salaries (total)	**$1,105,724.80**	29.66 hours × 1 day/24 hours × $894,720/day
Dispensing - Labor - Training (annual)	**$894,720.00**	300 staff per POD × 8 hours of training/yr × $18.64/hr
Dispensing - Administrative Fees/Operational Costs (daily, per POD)	$5,000.00	
Dispensing - Administrative Fees/Operational Costs (daily, 20 PODs)	$100,000.00	$5,000 × 20 PODs
Dispensing - Administrative Fees/Operational Costs (total)	**$123,583.33**	29.66 hours × 1 day/24 hours × $100,000/day
Dispensing - Security (daily, per POD)	$2,784.96	
Dispensing - Security (daily, 20 PODs)	$55,699.20	

continued

TABLE D.1-3
Continued

POD Component		
Costs **Description**	**Data**	**Calculations**
Dispensing - Security (total)	**$68,834.93**	29.66 hours × 1 day/24 hours x $2,784.96/ POD per day × 20 PODs
Dispensing - Total Costs	**$2,192,863.06**	Labor-salaries (total) + labor-training (total) + security (total)
Inventory Management		
Inventory Management - Labor	[redacted]	
Inventory Management - Cost of Storage/Pallet		
Inventory Management - # of Bottles/Pallet		
Inventory Management - # of Pallets Required		
Inventory Management - Storage (total)		
Inventory Management - Total Costs (excluding replenishment costs)		
Inventory Management - Replenishment - Product Purchase (overall)		
Inventory Management - Replenishment - Transportation (overall)		

POD Component		
Costs Description	**Data**	**Calculations**
Inventory Management - Replenishment - Dispensing (overall)	[redacted]	
Inventory Management - Replenishment Costs (total, SLEP)		
Dispensing Time		
Dispensing Time - SNS to RSS to Postal Office Transportation (hours)	**13.24**	(source: calculations derived from presentation - G. Burel. An SNS Perspective on Pre-positioning Medical Countermeasures. Centers for Disease Control and Prevention, February 28, 2011. Presented to IOM Committee on Prepositioned Medical Countermeasures for the Public)
Dispensing Time - POD Operating Time (hours)	**29.66**	(596,491.23 households / 20 pods × 1 hr/1,000 households)
Dispensing Time - Total (hours)	**42.9**	SNS to RSS to POD transportation time + POD Operating Time
Total Costs - POD (80%, 955,000 doses/individuals, 418,859.65 heads of household)		

continued

TABLE D.1-3
Continued

POD Component		
Costs **Description**	**Data**	**Calculations**
Product Purchase Price	[redacted]	
Transportation	**$0.00**	
Dispensing	**$2,192,863.06**	
Inventory Management (without replenishment)	[redacted]	
Total Cost (without replenishment)	**$4,377,366.46**	
Replenishment Costs (SLEP)	[redacted]	
Total Costs - Hospital/Pharmacy Component + POD Component		
Product Purchase Price	[redacted]	
Transportation	$3,664	
Dispensing	$2,304,879	
Inventory Management	[redacted]	
Total Cost (without replenishment)	**$5,212,761**	
Replenishment Costs (annual)	$0.00	
Replenishment Costs (SLEP)	[redacted]	
Replenishment Costs (annual + SLEP)		
Total Dispensing Time for Strategy		

POD Component		
Costs **Description**	**Data**	**Calculations**
Dispensing Time for Hospital Component (hours)	15.18	
Dispensing Time for Pharmacy Component (hours)	3.88	
Dispensing Time for POD Component (hours)	42.9	
Rate-Limiting Step (hours)	42.9	
Total Dispensing Time for Strategy (hours)	**42.9**	

TABLE D.1-4
Workplace Data

Workplace Component	Large Workplace		Small Workplace	
Description	**Data**	**Calculations**	**Data**	**Calculations**
Individuals	170,000	1,700,000 × .10	170,000	1,700,000 × .10
Households	74,561.40	170,000 individuals × 2.28 individuals/household	74,561.40	170,000 individuals × 2.28 individuals/household
Workplaces	17	170,000 individuals × 1 large workplace/10,000 individuals	566.67	170,000 individuals × 1 small workplace/300 individuals
Costs				
Product Purchase Price				
Product Purchase Price - Costs per daily dosage - Prophylaxis, Doxycycline	$0.20	$0.10/pill × 2 pills per day	$0.20	$0.10/pill × 2 pills per day
Product Purchase Price - Additional Medication Costs Per Daily Dosage (packaging, etc.)	$0.01		$0.01	
Product Purchase Price - Total Costs for Medication Per Daily Dosage	$0.21	$0.20 per daily dosage + $0.01 additional medication costs per dosage	$0.21	$0.20 per daily dosage + $0.01 additional medication costs per dosage
Product Purchase Price - Total Costs for Medication (per household)	$2.10	$0.21/day × 10 days	$2.10	$0.21/day × 10 days
Product Purchase Price - Total Costs for Medication (overall)	**$357,000**	**(170,000 individuals × one 10-day course per individual × $2.10 per 10-day course)**	**$357,000**	**(170,000 individuals × one 10-day course per individual × $2.10 per 10-day course)**

Workplace Component	Large Workplace		Small Workplace	
Description	**Data**	**Calculations**	**Data**	**Calculations**
Transportation				
Transportation - Shipping Medications to Workplaces	$3,392.18	Source - average estimated shipping cost of USPS and FedEx	$5,519.37	Source: average estimated shipping cost of USPS and FedEx
Transportation (overall)	**$3,392.18**		**$5,519.37**	
Dispensing				
Dispensing - Labor - Salaries (per workplace, per day)	$15,657.60	35 staff (source: derivation from public POD labor requirement based on population served per workplace) × 18.64/hr (source: Zaric et al.) × 8 hr/shift × 3 shifts	$894.72	2 staff (source: derivation from public POD labor requirement based on population served per workplace) × 18.64/hr (source: Zaric et al.) × 8hr/shift × 3 shifts
Dispensing - Labor - Salaries (17 large/566.67 small workplaces, per day)	$266,179.20	$15,657.60 × 17 large workplaces	$507,011	$894.72 × 566.67 small workplaces
Dispensing - Labor - Salaries (total)	**$110,908.00**	10 hours × 1 day/24 hours × $266,179.20/day	**$63,376**	3 hours × 1 day/24 hours × $507,011/day
Dispensing - Labor - Training (annual total for 17 large/566.67 small workplaces)	**$850,000.00**	$50,000 training cost per workplace (source: Georgia Tech paper) × 17 large workplaces	**$2,833,350**	$5,000 training cost per workplace (source: Georgia Tech paper) × 566.67 small workplaces
Dispensing - Labor - Supplemental Nurses (per workplace, per day)	$1,731.36	2 nurses × 2 shifts × 12 hours/shift × 36.07/hr	$866	1 nurses × 2 shifts × 12 hours/shift × 36.07/hr
Dispensing - Labor - Supplemental Nurses (17 large/566.67 small workplaces, per day)	$29,433.12	$1,731.36 × 17 large workplaces	$490,555	$1,731.36 × 566.67 small workplaces
Dispensing - Labor - Supplemental Nurses (total for 17 large/ 566.67 small workplaces)	**$12,263.80**	$29,433.12 cost/day × 10 hours operating time × 1 day/24 hours	**$61,319**	$490,555 × 3 hours operating time × 1 day/24 hours

continued

TABLE D.1-4
Continued

Workplace Component	Large Workplace		Small Workplace	
Description	**Data**	**Calculations**	**Data**	**Calculations**
Dispensing - Administrative Fees/ Operational Costs (total)	**$0.00**	Opportunity cost absorbed by company	**$0.00**	Opportunity cost absorbed by company
Dispensing - Security (per workplace, per day)	$1,392.48	2 officers/shift × 3 shifts × $29.01/hr × 8 hrs/shift	$696.24	1 officer × 3 shifts × $29.01/hr × 8 hrs/shift
Dispensing - Security (17 large/566.67 small workplaces, per day)	$23,672.16	$1,392.48 ×17	$394,538.32	696.24 × 566.67
Dispensing - Security (total for 17 large/566.67 small workplaces)	**$9,863.40**	$23,672.16 cost/day × 10 hours operating time × 1 day/24 hours	**$49,317.29**	$394,538.32 × 3 hours operating time × 1 day/24 hours
Dispensing - Total Costs	**$983,035.20**	Labor-salaries (total) + labor-training (total) + security (total)	**$3,007,363.02**	Labor-salaries (total) + labor-training (total) + security (total)
Inventory Management				
Inventory Management - Labor	0	not available	0	not available
Inventory Management - Cost of Storage/ Pallet per month	$14	Average of interview data	$14	Average of interview data
Inventory Management - # of Bottles/Pallet	10,000	Interview	10,000	Interview
Inventory Management - # of Pallets Required	17	170,000 bottles × 10,000 bottles/pallet	17	170,000 bottles × 10,000 bottles/pallet
Inventory Management - Storage (total/ annual)	$2,856	17 pallets × $14/month × 12 months/1 year	$2,856	17 pallets × $14/month × 12 months/1 year
Inventory Management - Total Costs (excluding replenishment costs)	**$2,856**		**$2,856**	

Workplace Component	Large Workplace		Small Workplace	
Description	**Data**	**Calculations**	**Data**	**Calculations**
Inventory Management - Replenishment - Product Purchase (overall)	**$357,000**	170,000 individuals × one 10-day course per household × $2.10 per 10-day course	**$357,000**	170,000 individuals × one 10-day course per household × $2.10 per 10-day course
Inventory Management - Replenishment - Transportation (overall)	**$3,392**		**$5,519.37**	
Inventory Management - Replenishment - Dispensing (overall)	**$0.00**		**0**	
Inventory Management - Replenishment Costs (total, annual)	**$360,392.18**	**Total costs for product purchase + total costs for transportation**	**$365,375.37**	**Total costs for product purchase + total costs for transportation**
Total Costs	**Large Workplace Component (10%, 170,000 individuals)**		**Small Workplace Component (10%, 170,000 individuals)**	
Product Purchase Price	**$357,000.00**		**$357,000.00**	
Transportation	**$3,392.18**		**$5,519.37**	
Dispensing	**$983,035.20**		**$3,007,363.02**	
Inventory Management (without replenishment)	**$2,856**		**$2,856**	
Total Cost (without replenishment)	**$1,346,283.38**		**$3,372,738.39**	
Replenishment Costs (annual)	$360,392.18		$365,375.37	
Total Costs	**Large and Small Workplaces Combined (20%, 340,000 individuals)**			

continued

TABLE D.1-4
Continued

Workplace Component	Large Workplace		Small Workplace	
Description	**Data**	**Calculations**	**Data**	**Calculations**
Product Purchase Price	$714,000.00			
Transportation	$8,911.55			
Dispensing	$3,990,398.22			
Inventory Management (without replenishment)	$5,712.00			
Total Cost (without replenishment)	$4,719,021.77			
Replenishment Costs (annual)	$725,767.55			
Dispensing Time	**Large Workplaces**		**Small Workplaces**	
Dispensing Time - Transportation (hours)	**0**	Caches are prepositioned	**0**	Caches are prepositioned
Dispensing Time - Closed POD/Workplace Dispensing Time (hours)	**10**	170,000 individuals/ component × 10,000 individuals/ large workplace × 17 workplaces × 1,000 individuals/hour	3	170,000 individuals/ component × 300 individuals/large workplace × 566.67 workplaces × 100 individuals/hour
Dispensing Time - Total (hours)	**10**		**3**	

POD Component		
Description	**Data**	**Calculations**
Costs		
Individuals	1,360,000	
Households	596,491	
Product Purchase Price		
Product Purchase Price - Costs per daily dosage - Propylaxis, Doxycycline	[redacted]	
Product Purchase Price - Additional Medication Costs Per Daily Dosage (packaging, etc.)		
Product Purchase Price - Total Costs for Medication Per Daily Dosage		
Product Purchase Price - Total Costs for Medication (per household)		
Product Purchase Price - Total Costs for Medication (overall)		
Transportation		
Transportation - SNS to RSS to Postal Office	N/A	not available
Transportation Costs (overall)	**$0.00**	not available
Dispensing		
Dispensing - Labor - Salaries (per POD, per day)	$44,736.00	300 staff per POD/day (source: interview with state public health official) × 8 hours/day × $18.64/hr (source: Zaric et al.)
Dispensing - Labor - Salaries (20 PODs, per day)	$894,720.00	Labor per day per POD × 20 PODs
Dispensing - Labor - Salaries (total)	**$1,105,724.80**	29.66 hours × 1 day/24 hours × $894,720/day

continued

TABLE D.1-4
Continued

POD Component		
Description	**Data**	**Calculations**
Costs		
Dispensing - Labor - Training (annual)	**$894,720.00**	300 staff per POD × 8 hours of training/yr × $18.64/hr
Dispensing - Administrative Fees/Operational Costs (daily, per POD)	$5,000.00	
Dispensing - Administrative Fees/Operational Costs (daily, 20 PODs)	$100,000.00	$5,000 × 20 PODs
Dispensing - Administrative Fees/Operational Costs (total)	**$123,583.33**	29.66 hours × 1 day/24 hours × $100,000/day
Dispensing - Security (daily, per POD)	$2,784.96	
Dispensing - Security (daily, 20 PODs)	$55,699.20	
Dispensing - Security (total)	**$68,834.93**	29.66 hours × 1 day/24hours × $2,784.96/POD per day × 20 PODs
Dispensing - Total Costs	**$2,192,863.06**	Labor-salaries (total) + labor-training (total) + security (total)
Inventory Management	[redacted]	
Inventory Management - Labor		
Inventory Management - Cost of Storage/Pallet		
Inventory Management - # of Bottles/Pallet		
Inventory Management - # of Pallets Required		
Inventory Management - Storage (total)		
Inventory Management - Total Costs (excluding replenishment costs)		

POD Component		
Description	**Data**	**Calculations**
Costs		
Inventory Management - Replenishment - Product Purchase (overall)	[redacted]	
Inventory Management - Replenishment - Transportation (overall)	**$0**	
Inventory Management - Replenishment - Dispensing (overall)	**$0.00**	
Inventory Management - Replenishment Costs (total, SLEP)	[redacted]	
Dispensing Time		
Dispensing Time - SNS to RSS to Postal Office Transportation (hours)	**13.24**	(source: calculations derived from presentation - Burel, G. An SNS Perspective on Prepositioning Medical Countermeasures. Centers for Disease Control and Prevention, February 28, 2011. Presented to IOM Committee on Prepositioned Medical Countermeasures for the Public)
Dispensing Time - POD Operating Time (hours)	**29.66**	(596491.23 households/20 pods × 1 hr/1,000 households)
Dispensing Time - Total (hours)	**42.9**	SNS to RSS + POD Operating Time
Total Costs - POD (80%, 955,000 doses/individuals, 418,859.65 heads of household)		
Product Purchase Price	[redacted]	
Transportation	**$0.00**	
Dispensing	**$2,192,863.06**	
Inventory Management (without replenishment)	[redacted]	
Total Cost (without replenishment)	**$4,377,366.46**	
Replenishment Costs (SLEP)	[redacted]	

continued

TABLE D.1-4
Continued

POD Component		
Description	**Data**	**Calculations**
Costs		
Total Costs - Workplace Component + POD Component		
Product Purchase Price	[redacted]	
Transportation	$8,912	
Dispensing	$6,183,261	
Inventory Management	[redacted]	
Total Cost (without replenishment)	**$9,096,388**	
Replenishment Costs (annual)	$725,767.55	
Replenishment Costs (SLEP)	[redacted]	
Replenishment Costs (annual + SLEP)		
Total Dispensing Time for Strategy		
Dispensing Time for Large Workplace Component (hours)	10	170,000 individuals/component × 10,000 individuals/large workplace × 10 workplaces × 1,000 individuals/hour
Dispensing Time for Small Workplace Component (hours)	3	170,000 individuals/component × 300 individuals/small workplace × 566.67 workplaces × 100 individuals/hour
Dispensing Time for POD Component (hours)	42.9	
Rate-Limiting Step (hours)	42.9	
Total Dispensing Time for Strategy (hours)	**42.9**	

TABLE D.1-5
MedKit Data

Costs Description	Data	Calculations
Individuals	1,700,000	
Product Purchase Price		
Product Purchase Price - Medication Costs Per MedKit- Prophylaxis, Doxycycline	$4	Source: interview with state public health official - cost for MedKits for postal workers
Product Purchase Price - Additional Costs Per MedKit (packaging, etc,)	$1.12	Cost derived by comparing cost of packaging for non-doxycycline, commercially available MedKits
Product Purchase Price - Total Costs for Medication Per Daily Dosage	$5.12	Medication costs + Additional Costs
Product Purchase Price - Total Costs for Medication (overall)	**$8,704,000**	**(1,700,000 individuals × $5.12 per MedKit)**
Transportation		
Transportation - Shipping MedKits - Vendor to Households	$5,450,000.00	Average of sending 1.7 million MedKits via FedEx and USPS = ($7,300,000 + $3,600,000)/2
Transportation Costs (overall)	**$5,450,000**	
Dispensing		
Dispensing - Labor - Screening	**$2,370,000**	Calculuation derived from POD screening time and labor (according to BERM model)
Dispensing - Labor - Hotline	**$18,288**	10 days labor for a hotline
Dispensing Costs (overall)	**$2,388,288**	
Inventory Management		
Inventory Management - Total Costs (excluding replenishment costs)	**0**	Excluding replenishment costs, no inventory management costs for MedKits

continued

TABLE D.1-5
Continued

Costs Description	Data	Calculations
Inventory Management - Replenishment - Product Purchase (overall)	**$8,704,000**	1,700,000 individuals × one 10-day course per individual × $5.12 per 10-day course
Inventory Management - Replenishment - Transportation (overall)	**$5,450,000**	
Inventory Management - Replenishment - Dispensing (overall)	**$0.00**	
Inventory Management - Replenishment Costs (total, annual)	**$14,154,000**	**Total costs for product purchase + total costs for transportation + total costs for dispensing**
Total Costs per Dispensing for 10-day course to population		
Product Purchase Price	**$8,704,000**	
Transportation	**$5,450,000**	
Dispensing	**$2,388,288**	
Inventory Management (without replenishment)	**$0**	
Total Cost (without replenishment)	**$16,542,288**	
Replenishment Costs (annual)	$14,154,000	
Total Dispensing Time for Strategy		
Total Dispensing Time for Strategy (hours)	**0**	**No dispensing time for MedKits**

TABLE D.1-6
Postal Data

Postal Component		
Description	**Data**	**Calculations**
Individuals	745,000	
Households	745,000	
Costs		
Product Purchase Price		
Product Purchase Price - Costs per daily dosage-Propylaxis, Doxycycline	[redacted]	
Product Purchase Price - Additional Medication Costs Per Daily Dosage (packaging, etc.)		
Product Purchase Price - Total Costs for Medication Per Daily Dosage		
Product Purchase Price - Total Costs for Medication (per household)		
Product Purchase Price - Total Costs for Medication (total postal dispensing)		
Product Purchase Price - Total Costs for Postal Workers' MedKits	$42,655.74	[2,540 workers × 2.28 MedKits (for household) × $5.12 per MedKit] + [2,540 workers × 1 MedKit (for work) × 5.12 per MedKit]
Product Purchase Price - Total Costs for Medication (overall)	[redacted]	
Transportation		
Transportation - SNS to RSS to Postal Office	N/A	not available
Transportation Costs (overall)	**$0.00**	not available

continued

TABLE D.1-6
Continued

Postal Component		
Description	**Data**	**Calculations**
Dispensing		
Dispensing - Labor - Postal workers	**$843,483.20**	[(2,540 workers × 8 hours × 23.72/hr) + (2,540 workers × 4 hours OT wage [1.5 regular])] - 332.08 per worker
Dispensing - Administrative Fees/Operational Costs	**$460,000**	$23,000 per zip × 20 zip codes (source: Interview with federal official)
Dispensing - Security (per officer)	$406.16	12 hour shift, 8 regular/4OT, for MnSP using BLS rate of $29.01/hr
Dispensing - Security needs (# of officers)	2,540	2/3 (volunteer rate) × 3,810 (total USPS carriers in MnSP) - (source: interview with federal official)
Dispensing - Security (total)	**$1,031,646.40**	2,540 × $406.16
Dispensing - Total Costs	**$2,335,129.60**	(Labor - postal workers) + (Dispensing - Administrative Fees/Operational Costs) + (Dispensing - Security)
Inventory Management		
Inventory Management - Labor	[redacted]	
Inventory Management - Cost of Storage/Pallet		
Inventory Management - # of Bottles/Pallet		
Inventory Management - # of Pallets Required		
Inventory Management - Storage (total)		
Inventory Management - Total Costs (excluding replenishment costs)		

Postal Component		
Description	**Data**	**Calculations**
Inventory Management - Replenishment - Total Costs for Medication (total postal dispensing)	[redacted]	
Inventory Management - Replenishment - Total Costs for Postal Workers' MedKits	$42,655.74	[2,540 workers × 2.28 MedKits (for household) × $5.12 per MedKit] + [2,540 workers × 1 MedKit (for work) × 5.12 per MedKit]
Inventory Management - Replenishment - Total Costs for Product Purchase (overall)	[redacted]	
Inventory Management - Replenishment - Labor - Postal workers	$0.00	
Inventory Management - Replenishment - Security (total)	$0.00	
Inventory Management - Replenishment - Total Costs for Dispensing	$0.00	
Inventory Management - Replenishment Costs (total)	[redacted]	
Dispensing Time		
Dispensing Time - Postal Dispensing (hours)	**12**	(source: interview with federal employee and Georgia Tech paper)
Dispensing Time - SNS to RSS to Postal Office Transportation (hours)	**13.24**	(source: calculations derived from presentation - G. Burel. An SNS Perspective on Pre-positioning Medical Countermeasures. Centers for Disease Control and Prevention, February 28, 2011. Presented to IOM Committee on Prepositioned Medical Countermeasures for the Public)

continued

TABLE D.1-6
Continued

Postal Component		
Description	**Data**	**Calculations**
Dispensing Time - Total (hours)	**25.24**	Postal Dispensing (hours) + SNS to RSS to Postal Office Transportation (hours)
Total Costs - Postal (43.82%, 745,000 doses/ households)		
Product Purchase Price	[redacted]	
Transportation	$0.00	
Dispensing	$2,335,129.60	
Inventory Management	[redacted]	
Total Cost (without replenishment)	**$3,495,285.34**	
Replenishment Costs (annual)	[redacted]	

POD Component	Data	Calculations
Costs		
Individuals	955,000	
Households	418,859.65	
Product Purchase Price		
Product Purchase Price - Costs per daily dosage - Propylaxis, Doxycycline	[redacted]	
Product Purchase Price - Additional Medication Costs Per Daily Dosage (packaging, etc.)		
Product Purchase Price - Total Costs for Medication Per Daily Dosage		

POD Component	Data	Calculations
Costs		
Product Purchase Price - Total Costs for Medication (per household)	[redacted]	
Product Purchase Price - Total Costs for Medication (overall)		
Transportation		
Transportation - SNS to RSS to Postal Office	N/A	not available
Transportation Costs (overall)	**$0.00**	not available
Dispensing		
Dispensing - Labor - Salaries (per POD, per day)	$44,736.00	300 staff per POD/day (source: interview with state department of health official) × 8 hours/day × $18.64/hr (source: Zaric et al.)
Dispensing - Labor - Salaries (20 PODs, per day)	$894,720.00	Labor per day per POD × 20 PODs
Dispensing - Labor - Salaries (total)	**$780,643.20**	20.94 hours × 1 day/24 hours × $894,720/day
Dispensing - Labor - Training (annual)	**$894,720.00**	300 staff per POD × 8 hours of training/yr × $18.64/hr
Dispensing - Administrative Fees/Operational Costs (daily, per POD)	$5,000.00	
Dispensing - Administrative Fees/Operational Costs (daily, 20 PODs)	$100,000.00	$5,000 × 20 PODs
Dispensing - Administrative Fees/Operational Costs (total)	**$87,250.00**	20.94 hours × 1 day/24 hours × $100,000/day
Dispensing - Security (daily, per POD)	$2,784.96	
Dispensing - Security (daily, 20 PODs)	$55,699.20	

continued

TABLE D.1-6
Continued

POD Component	Data	Calculations
Costs		
Dispensing - Security (total)	**$48,597.55**	20.94 hours × 1 day/24 hours × $2,784.96/POD per day × 20 PODs
Dispensing - Total Costs	**$1,811,210.75**	Labor-salaries (total) + labor-training (total) + security (total)
Inventory Management		
Inventory Management - Labor	[redacted]	
Inventory Management - Cost of Storage/Pallet		
Inventory Management - # of Bottles/Pallet		
Inventory Management - # of Pallets Required		
Inventory Management - Storage (total)		
Inventory Management - Total Costs (excluding replenishment costs)		
Inventory Management - Replenishment - Product Purchase (overall)		
Inventory Management - Replenishment - Transportation (overall)		
Inventory Management - Replenishment - Dispensing (overall)		
Inventory Management - Replenishment Costs (total, SLEP)		
Dispensing Time		
Dispensing Time - SNS to RSS to Postal Office Transportation (hours)	**13.24**	(source: CDC presentation)

POD Component	Data	Calculations
Costs		
Dispensing Time - POD Operating Time (hours)	**20.94**	418,859.65 households/20 pods × 1 hr/1,000 households
Dispensing Time - Total (hours)	**34.18**	SNS to RSS to Postal Office Transportation + POD Operating Time
Total Costs - POD (56.18%, 955,000 doses/ individuals, 418,859.65 heads of household)		
Product Purchase Price	[redacted]	
Transportation	**$0.00**	
Dispensing	**$1,811,210.75**	
Inventory Management (without replenishment)	[redacted]	
Total Cost (without replenishment)	**$3,345,180.35**	
Replenishment Costs (SLEP)	[redacted]	
Total Costs - Postal Component + POD Component		
Product Purchase Price	[redacted]	
Transportation	$0.00	
Dispensing	$4,146,340.35	
Inventory Management	[redacted]	
Total Cost (without replenishment)	**$6,919,617.69**	
Replenishment Costs (annual)	$42,655.74	
Replenishment Costs (SLEP)	[redacted]	
Replenishment Costs (annual + SLEP)		
Total Dispensing Time for Strategy		

continued

TABLE D.1-6
Continued

POD Component	Data	Calculations
Costs		
Dispensing Time for Postal Component (hours)	25.24	
Dispensing Time for POD Component (hours)	34.18	
Rate-Limiting Step (hours)	34.18	
Total Dispensing Time for Strategy (hours)	**34.18**	

Appendix D.2

Authors, Acknowledgments, and Interviewees

AUTHORS AND ACKNOWLEDGMENTS

James Guyton is the lead author of this paper. The following PRTM employees served as co-writers or contributors to this effort:

- Dr. Robert Kadlec
- Dr. Chandresh Harjivan
- Shabana Farooqi
- Sheana Cavitt
- Joseph Buccina

PRTM enjoyed the privilege of working with the Institute of Medicine (IOM). PRTM would like to thank Clare Stroud, who served as an immensely helpful point of contact. PRTM expresses its gratitude to the Committee on Prepositioned Medical Countermeasures for the Public for the opportunity to contribute to its mission. PRTM would also like to thank Kristin Viswanathan for her assistance with the document review and all IOM employees that contributed to this effort.

PRTM interviewed more than 40 subject matter experts on this topic. The team would like to thank each of them for their time and their keen insights.

INTERVIEWEES

The following is a list of individuals who were interviewed by PRTM for the purposes of this paper. Affiliations listed reflect the individual's primary association as of the date of the interview.

Sid Baccam, *Innovate Emergency Management, Inc.*
Mike Berzig, *Department of Veterans Affairs*
Tara Blackley, *Virginia Department of Health*
Joseph Canzolino, *Department of Veterans Affairs*
Norm Coleman, *Department of Health and Human Services (HHS), Assistant Secretary for Preparedness and Response (ASPR), Office of Policy and Planning (OPP)*
Susan Cooper, *Tennessee Department of Health*
Victoria Davey, *Department of Veterans Affairs*
Adele Etheridge, *Office of Public Health Preparedness and Response, Centers for Disease Control and Prevention (CDC)*
Matthew Feltman, *Kroger/Giant*
Sue Gorman, *Office of Public Health Preparedness and Response, CDC*
Jayne Griffith, *Minnesota Department of Health*
Roy Herman, *Office of Public Health Preparedness and Response, CDC*
Laura Herrera, *Department of Veterans Affairs*
Jack Herrmann, *National Association of County and City Health Officials (NACCHO)*
Mary Beth Hill-Harmon, *HHS/ASPR/Biomedical Advanced Research and Development Authority (BARDA)*
Jeffrey Holmes, *PRTM*
Nathaniel Hupert, *CDC and Weill Medical College, Cornell University*
Terrie Kolodziej, *HHS/ASPR/BARDA*
Lisa Koonin, *CDC*
George Korch, *HHS/ASPR*
Joe Larsen, *HHS/ASPR/BARDA*
Eva Lee, *Georgia Tech University*
Aggie Leitheiser, *Minnesota Department of Health*
Rebecca Lipsitz, *HHS/ASPR*
Rich McNally, *HHS/ASPR*
Carter Mecher, *National Security Staff*
Matthew Minson, *Texas A&M University*
Amanda Fuller Moore, *North Carolina Department of Health and Human Services*
Stephen Morris, *HHS/ASPR/BARDA*
Chris Motsek, *Office of Public Health Preparedness and Response, CDC*
Paul Peterson, *Tennessee Department of Health*

Jude Plessas, *U.S. Postal Service*
Ken Rapuano, *The MITRE Corporation*
Marjorie Sidebottom, *University of Virginia*
David Starr, *Office of Emergency Preparedness and Response, New York City Department of Health and Mental Hygiene*
Jason Stear, *Office of Public Health Preparedness and Response, CDC*
Thomas Tighe, *Direct Relief International*
Penny Turnbull, *Marriott Hotels International*
James Turner, *American College Health Association Representative, Utility Services Provider*
Michael Valentino, *Department of Veterans Affairs*

Appendix E

Committee Biosketches

Robert R. Bass, M.D. (*Chair*), is executive director of the Maryland Institute for Emergency Medical Services Systems (MIEMSS). Dr. Bass received his undergraduate and medical degrees with honors from the University of North Carolina at Chapel Hill in 1972 and 1975, respectively. Prior to completing his undergraduate education, he was employed as a police officer in Chapel Hill, North Carolina, and served as a volunteer member of the South Orange Rescue Squad. Dr. Bass completed an internship and residency in the U.S. Navy. He is board certified in emergency medicine and is a life fellow of the American College of Emergency Physicians. He has served as a medical director for emergency medical services (EMS) systems in Charleston, South Carolina; Houston, Texas; Norfolk, Virginia; and Washington, DC. He has been executive director of MIEMSS, the state agency responsible for oversight of Maryland's EMS and trauma system, since 1994. He is a clinical associate professor of emergency medicine at the University of Maryland in Baltimore. Dr. Bass is past president of the National Association of State EMS Officials and the National Association of EMS Physicians, and past chair of the EMS Committee of the American College of Emergency Physicians. He was a member of the Institute of Medicine (IOM) Committee on the Future of Emergency Care in the United States Health System. He currently serves as chair of the Atlantic EMS Council and is a member of the board of directors of the American Trauma Society.

Tia Powell, M.D. (*Vice Chair*), is director of the Montefiore-Einstein Center for Bioethics and professor of clinical epidemiology and clinical psychiatry

at Albert Einstein College of Medicine and the Montefiore Medical Center. She served from 2004 to 2008 as executive director of the New York State Task Force on Life and the Law and from 1992 to 1998 as director of clinical ethics at Columbia-Presbyterian Hospital in New York City. Dr. Powell is a graduate of Harvard-Radcliffe College and Yale Medical School. She performed her psychiatric internship, her residency, and a fellowship in consultation-liaison psychiatry at Columbia University, College of Physicians and Surgeons, and the New York State Psychiatric Institute. She is a fellow of the American Psychiatric Association and of the New York Academy of Medicine and a member of the American Society of Bioethics and Humanities. In 2007 she co-chaired the New York State Department of Health's work group to develop guidelines for allocating ventilators during an influenza pandemic.

Margaret L. Brandeau, Ph.D., is Coleman F. Fung professor of engineering and professor of medicine (by courtesy) at Stanford University. She holds a B.S. in mathematics and an M.S. in operations research from the Massachusetts Institute of Technology (MIT), and a Ph.D. in engineering-economic systems from Stanford. She is an operations researcher and policy analyst with extensive background in the development of applied mathematical and economic models, and a distinguished investigator in HIV. Among other awards, Professor Brandeau has received the President's Award from the Institute for Operations Research and Management Science (INFORMS) for contributions to the welfare of society, the Pierskalla Prize from INFORMS for research excellence in health care management science, a Presidential Young Investigator Award from the National Science Foundation, the Department of Management Science and Engineering Graduate Teaching Award, and the Eugene L. Grant Faculty Teaching Award. She is a Fellow of INFORMS. Professor Brandeau has published numerous articles in areas of applied operations research and policy analysis; co-edited the books *Modeling the AIDS Epidemic: Planning, Policy, and Prediction* and *Operations Research in Health: A Handbook of Methods and Applications*; and has served as principal investigator on a broad range of funded research projects. She has served on the board of several journals, including *Operations Research*, *Management Science*, and *Health Care Management Science*. Her HIV research focuses on using mathematical and economic models to assess the value of different HIV and drug abuse interventions, both in the United States and abroad. Recently, she has studied policies for control of hepatitis B both in the United States and abroad, as well as preparedness planning for potential bioterror attacks.

Brad Brekke, J.D., M.A.T.S., has been vice president of Assets Protection for Target Corporation since 2001, leading a diverse team of executives in

a comprehensive effort to mitigate risk, minimize loss and business disruption, and provide a safe and secure environment for Target and the communities it serves. Under Mr. Brekke's leadership, Target Assets Protection has developed strategic partnerships with law enforcement, emergency management, and public health organizations to continue to enhance the company's strong commitment to public safety and preparedness. Specifically, through the premiere, innovative public-private partnership Target & BLUE, Target shares expertise and resources with local, state, and federal law enforcement, building critical relationships that help make Target and its surrounding communities safer places to live and work. This includes partnering with organizations such as the International Association of Chiefs of Police, the U.S. Department of Justice Community Oriented Policing Services, and the Police Executive Research Forum to develop innovative solutions to public safety challenges. Mr. Brekke serves on a number of boards and foundations, including the International Association of Chiefs of Police Foundation, the Overseas Security Advisory Council for the State Department, the International Security Management Association, the National Cyber-Forensics and Training Alliance, the Security Executive Council, and the Conference Board Council of Corporate Security Executives. A licensed attorney, Mr. Brekke formerly practiced in a Minneapolis law firm. Previously, he served as a special agent with the FBI, investigating complex cases involving financial fraud and public corruption. He received his B.A. from the University of Minnesota, his M.A.T.S. from Bethel Seminary, and his J.D. from the University of Minnesota Law School.

Robert L. Burhans recently retired as director of health emergency preparedness for the New York State Department of Health (DOH). With 32 years of public health experience, Mr. Burhans was director of the state's Office of Health Emergency Preparedness, which coordinated DOH's comprehensive all-hazards preparedness and response activities, including integrating local health departments and the health care system in readiness activities. He was DOH's primary preparedness liaison with other federal, state, and local agencies and key community partners. He also served on the state Office of Homeland Security's Executive Committee and was DOH's representative to the state's Disaster Preparedness Commission. In addition, he served as chair of the Association of State and Territorial Health Officials' Directors of Public Health Preparedness Executive Committee. Mr. Burhans earned a B.A. in biological science from the State University of New York, New Paltz, and completed graduate-level coursework at the Nelson A. Rockefeller School of Public Administration and the State University of New York at Albany School of Public Health. He is a graduate of the School of Public Health's Northeast Public Health Leadership Institute and has completed the National Preparedness Leadership Initiative at

Harvard University's John F. Kennedy School of Government and School of Public Health. He currently is a consultant in health emergency preparedness, management, and response.

Louis Anthony (Tony) Cox, Jr., Ph.D., is president of Cox Associates, a Denver-based applied research company specializing in health risk analysis, statistics, and operations research. From 1987 to 1996, Dr. Cox led business and engineering modeling for US WEST Advanced Technologies in Boulder, Colorado. Dr. Cox holds a Ph.D. in risk analysis (1986) and an S.M. in operations research (1985), both from MIT's Department of Electrical Engineering and Computer Science. He holds an A.B. from Harvard University (economics) and is a graduate of the Stanford Executive Program (1993). Dr. Cox is honorary full professor of mathematics at the University of Colorado at Denver, where he has lectured on biomathematics and health risk modeling, computational statistics, and machine learning. He is also clinical professor of preventive medicine and biometrics at the University of Colorado Health Sciences Center. He is a member of INFORMS and the American Statistical Association and a fellow of the Society for Risk Analysis. His current research interests center on computational statistical methods for causal inference and modeling problems arising in risk analysis and data mining of customer and epidemiological databases.

Robert S. Hoffman, M.D., is associate professor of emergency medicine and medicine (clinical pharmacology) for the New York University School of Medicine and director, New York City Poison Control Center, as well as attending physician in the Department of Emergency Medicine at Bellevue Hospital Center. Dr. Hoffman received a B.A. in chemistry from Brandeis University in 1980 and immediately entered New York University School of Medicine, where he received his medical degree. He completed a 3-year internship and residency in internal medicine, also at the New York University School of Medicine, followed by a fellowship in medical toxicology at the New York City Poison Control Center/Bellevue Hospital Center. He subsequently achieved board certification in internal medicine, medical toxicology, and emergency medicine. In 1989 Dr. Hoffman became director of the Fellowship in Medical Toxicology at the New York City Poison Control Center, and in 1994 he became director of the center. He has authored more than 200 peer-reviewed publications in various aspects of toxicology that include basic science, animal, and clinical investigations. He has also authored numerous textbook chapters for major references in medicine and emergency medicine. He lectures around the world on various aspects of toxicology and has helped establish poison control centers in both Europe and Asia. Dr. Hoffman has held office in all three American toxicology societies, including being a member of the board of trustees of

the American Academy of Clinical Toxicology and current president elect; a member of the board of directors of the American Association of Poison Control Centers; and secretary/treasurer, vice president, and president of the American College of Medical Toxicology.

Daniel Lucey, M.D., M.P.H., is adjunct professor of microbiology and immunology at the Georgetown University Medical Center, where he has taught graduate students in the Biohazardous Threat Agents and Emerging Infectious Diseases program since its founding in 2004. During this time, he has also worked on biopreparedness for the Department of Emergency Medicine EROne Institute of the Washington Hospital Center in Washington, DC (www.BePast.org). He has written on inhalation anthrax issues in particular, devising a new clinical staging system and advocating stockpiling of assets in anticipation of the need for mandatory pleural drainage. Dr. Lucey earned his B.A. at Dartmouth College; an M.D. at Dartmouth Medical School, where he was in the Alpha Omega Alpha Honor Medical Society; and his master of public health (M.P.H.) at the Harvard School of Public Health. In 2004 he coordinated the start of the Cities Readiness Initiative (CRI) in Washington, DC, while serving as interim chief health officer at the DC Department of Health. His awards include the Walter Reed Medal for his role in Washington's preparedness and response to anthrax bioterrorism (2001); the Commander's Award for Public Service (2002) from the Department of the Army for hospital care of persons injured at the Pentagon on September 11, 2001; and a Distinguished Service Award from the District of Columbia Hospital Association for Bioterrorism Preparedness (2003). From 1998 to 2002, Dr. Lucey served as director, Infectious Disease Service, at the Washington Hospital Center. Earlier he served in the U.S. Public Health Service at the Food and Drug Administration (FDA), where he was a medical reviewer for biodefense vaccines, and at the National Institutes of Health (NIH), where he served as attending physician on the Infectious Disease consult service for 3 years.

Kevin Massey, M.Div., is director of Lutheran Disaster Response, a collaborative program of the Evangelical Lutheran Church in America and the Lutheran Church Missouri Synod. He received a bachelor of arts degree with distinction in linguistics from the University of Wisconsin and completed his master of divinity degree at Luther Seminary in St. Paul, Minnesota. Rev. Massey is an ordained pastor of the Evangelical Lutheran Church in America and a board-certified chaplain with the Association of Professional Chaplains. He was a chaplain and spiritual care trainer and coordinator with Advocate Health Care in Chicago from 1999 to 2005. He has also worked extensively in the field of disaster spiritual care administration and training with the American Red Cross and Church World Service,

including service at Ground Zero in the fall of 2001 and in response to Hurricane Katrina in 2005. Rev. Massey was assistant director of domestic disaster response for the Evangelical Lutheran Church in America from 2005 to 2007 and has been director of Lutheran Disaster Response since 2007. In 2009 he served as a member of the Community Core Committee, supporting the development of the National Health Security Strategy. Rev. Massey currently serves as vice president of the board of directors for National Voluntary Organizations Active in Disaster and has written extensively on such diverse topics as spiritual care, clinical ethics, pandemic influenza preparedness, disaster response, linguistics, archaeology, and interreligious dialogue.

Erin Mullen, R.Ph., Ph.D., CEM, is assistant vice president, Rx Response, for the Pharmaceutical Researchers and Manufacturers of America (PhRMA). She is responsible for overseeing and managing the Rx Response program, an information-sharing forum comprising pharmaceutical manufacturers, distributors, pharmacies, hospitals, disaster relief agencies, and state/federal government agencies that helps support the continuing provision of medicines to patients whose health is threatened by a severe public health emergency. Rx Response engages during a severe natural disaster, large-scale terrorist attack, or pandemic that disrupts the normal supply of medicines. Dr. Mullen is co-chair of the Healthcare Sector Coordinating Council, the private-sector body representing health care in matters related to critical infrastructure protection and emergency response. Prior to leading Rx Response, she was the first public health preparedness pharmacist for the Florida Department of Health and practiced pharmacy in a variety of settings: as a community pharmacist, clinical adjunct faculty with the Colleges of Pharmacy at the University of Florida and Florida A&M University, and disaster responder. Dr. Mullen graduated from the Massachusetts College of Pharmacy with a B.S. in pharmacy. She earned her Ph.D. in microbiology and immunology from the University of Miami.

Joanne M. Nigg, Ph.D., is professor of sociology and former director of the Disaster Research Center at the University of Delaware. She is currently coordinator of the emergency and environmental management concentration for sociology majors, a core faculty member of the graduate program in disaster science and management, and a core faculty member of the Disaster Research Center. Dr. Nigg earned her Ph.D. in sociology from the University of California, Los Angeles, in 1979. Her areas of expertise include societal response to natural, technological, and environmental hazards and disasters. She headed a multidisciplinary team that conducted a congressionally required public risk assessment for the proposed high-level nuclear waste repository at Yucca Mountain in Nevada. She was also a member of the

Research Committee (which set the cross-disciplinary research agendas) for the National Science Foundation (NSF)–funded Multidisciplinary Center for Earthquake Engineering Research. Dr. Nigg has been involved in several federal reviews of the National Earthquake Hazards Reduction Program and has twice given testimony before Congress on the reauthorization of that program. She has served on a variety of federal commissions and task forces on disaster policies and has been a member of the National Research Council's (NRC's) Board on Natural Disasters, as well as the NRC's Committee on Earthquake Engineering. Dr. Nigg was the first woman and social scientist to serve as president of the Earthquake Engineering Research Institute. She also served on the Division Review Committee for the Environment and Energy Division of Los Alamos National Laboratory, where she held a Q clearance. Dr. Nigg is the author, co-author, or editor of 7 books and more than 100 articles, book chapters, reports, and papers on individual, organizational, and governmental response to, preparation for, mitigation of, and recovery from natural and technological threats and disasters. She is currently coordinating a team of researchers looking at policy and health issues associated with the BP oil blowout in the Gulf of Mexico.

Herminia Palacio, M.D., M.P.H., is executive director of Harris County [Texas] Public Health and Environmental Services (HCPHES), the local health department for approximately 1.8 million people. Dr. Palacio received her medical degree from the Mount Sinai School of Medicine in New York City, where she was also inducted into the Alpha Omega Alpha Honor Medical Society. She completed her residency training at the University of California, San Francisco (UCSF) Primary Care Internal Medicine Program at San Francisco General Hospital. After becoming a board-certified internist, she obtained an M.P.H., with an emphasis in epidemiology, from the University of California, Berkeley School of Public Health. Dr. Palacio spent several years on the faculty of UCSF, where she served as principal investigator or co-investigator for several federally funded and private foundation HIV epidemiology and health services research studies. She is the author of numerous articles in peer-reviewed scientific journals and was featured in a permanent exhibit entitled *AIDS: The War Within* established by the Chicago Museum of Science and Industry in 1994. She currently holds faculty appointments at the Baylor College of Medicine and the University of Texas School of Public Health. In 2009 she was appointed to the National Advisory Committee of The Robert Wood Johnson Foundation Clinical Scholars Program. Dr. Palacio provides oversight for a wide variety of public health emergency responses. For example, she served as medical branch director for the Astrodome/Reliant Park mega-shelter operation for more than 27,000 evacuees during Hurricane Katrina and as incident

commander for the public health response to many infectious disease and environmental incidents, and she is currently tasked with playing a lead role in local pandemic influenza preparedness planning. She was also a member of the steering committee for the Medical Countermeasure Public Engagement Initiative, sponsored by the U.S. Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response.

Andrew Pavia, M.D., is George and Esther Gross presidential professor at the University of Utah School of Medicine. Dr. Pavia is chief of pediatric infectious diseases and professor of pediatrics and medicine at the University of Utah. His research focuses on the epidemiology and management of respiratory infections, including seasonal and pandemic influenza, pneumococcal disease, antibiotic-resistant organisms, and respiratory viral infections. He has served on the National Vaccine Advisory Committee and the National Biodefense Science Board and is also a member of the board of directors of the Infectious Diseases Society of America. Dr. Pavia received his M.D. at Brown University, then completed a residency in internal medicine and served as chief resident at Dartmouth-Hitchcock Medical Center. He was an officer in the Epidemic Intelligence Service at the Centers for Disease Control and Prevention (CDC) in Atlanta, and completed a residency in preventive medicine, also at CDC. He completed his training in infectious diseases at the University of Utah.

Stephen M. Pollock, Ph.D., is Herrick emeritus professor of manufacturing and professor emeritus of industrial and operations engineering at the University of Michigan. He has been involved in applying operations research and decision analysis methods to understand and influence a variety of operational phenomena, including military search and detection, criminal recidivism, manufacturing process monitoring, sequential allocation of resources, predictive and proactive maintenance, networks of queues, the stochastic behavior of infectious disease epidemics, and the optimization of radiation oncology plans. He has authored more than 60 technical papers; co-edited two books; and served as a consultant to more than 30 industrial, governmental, and service organizations. Professor Pollock was associate editor and area editor of *Operations Research*, senior editor of *IIE Transactions*, and associate editor of *Management Science*, and he served on the editorial boards of other journals. He has served on various advisory boards for NSF and on the Army Science Board. He was president of the Operations Research Society of America in 1986 and was awarded the 2001 INFORMS Kimball Medal for contributions to operations research and the management sciences. Professor Pollock is a fellow of INFORMS and the American Association for the Advancement of Science (AAAS) and is a member of the National Academy of Engineering. He was a member

of the NRC's Committee on Applied and Theoretical Statistics. Among other NRC activities, he chaired the Committee on National Statistics' panel on Operational Test Design and Evaluation of the Interim Armored Vehicle, and he served on the panel on Statistical Methods for Testing and Evaluating Defense Systems, the Committee on Technologies to Deter Currency Counterfeiting, and the Panel on Methodological Improvements to the DHS Biological Agent Risk Analysis. He recently served on the NRC/IOM committee on the Effectiveness of National Biosurveillance Systems: BioWatch and the Public Health System and is currently a member of the NRC/Board on Mathematical Sciences and Their Applications (BMSA) committee on Mathematical Foundations of Verification, Validation, and Uncertainty Quantification.

Reed V. Tuckson, M.D., FACP, is executive vice president and chief of medical affairs at UnitedHealth Group, a Fortune 25 diversified health and well-being company. He is responsible for working with all of the company's business units to improve the quality and efficiency of health services. Formerly, Dr. Tuckson served as senior vice president, professional standards, for the American Medical Association (AMA). He is former president of the Charles R. Drew University of Medicine and Science in Los Angeles, has served as senior vice president for programs of the March of Dimes Birth Defects Foundation, and is a former commissioner of public health for the District of Columbia. Dr. Tuckson is an active member of the IOM and served as chairperson of its Quality Chasm Summit Committee and as a member of its Committee on the Consequences of the Uninsured. He is immediate past chair of the Secretary of Health and Human Services' Advisory Committee on Genetics, Health and Society. Additionally, he recently served as commissioner, Certification Commission on Health Information Technology, and is currently a member of the Performance Measurement Workgroup, Ambulatory Care Quality Alliance, and the Quality Workgroup, American Health Information Community. Dr. Tuckson has also held other federal appointments, including serving on cabinet-level advisory committees on health reform, infant mortality, children's health, violence, and radiation testing. He was featured on the cover of the February 2009 issue of *Black Enterprise* magazine and named one of the 100 Most Powerful Executives in Corporate America. He was also selected as one of the 2009 *Modern Healthcare/Modern Physician* 50 Most Powerful Physician Executives in Healthcare. Last year, Dr. Tuckson was named one of *Modern Healthcare's* Top 25 Minority Executives in Healthcare for 2008 and was on *Ebony* magazine's 2008 Power 150: The Most Influential Blacks in America list. He is a graduate of Howard University, Georgetown University School of Medicine, and the Hospital of the University of Pennsylvania's General Internal Medicine Residency and Fellowship programs.

Jeffrey S. Upperman, M.D., is director of trauma at Childrens Hospital Los Angeles and associate professor of surgery at the Keck School of Medicine of the University of Southern California's Division of Pediatric Surgery. Dr. Upperman graduated from Stanford University in 1987 with a bachelor's degree in human biology and a master's degree in sociology. He earned his medical degree from New Jersey Medical School in 1991 and completed his surgical residency at the same institution. He completed his fellowship training in pediatric surgery at Children's Hospital of Pittsburgh and served on the faculty at the University of Pittsburgh School of Medicine at Children's Hospital of Pittsburgh until 2006, where he was interim director of the Benedum Pediatric Trauma Program in 2005. He was recruited to Childrens Hospital Los Angeles in January 2006 and assumed directorship of trauma in 2007. Dr. Upperman's disaster and trauma research focuses on the organizational-level preparedness of health care workers, intestinal inflammation, sepsis, and pediatric trauma. His work has been funded by the Department of Health and Human Services, the National Institutes of Health, and The Robert Wood Johnson Foundation. He publishes clinical work in the area of pediatric disaster preparedness, pediatric trauma, and computerized physician order entry. He is currently director of the Pediatric Disaster Resource and Training Center. Dr. Upperman has extensive experience in community involvement, serving on committees in national academic societies. He is a permanent member of the Pediatric Study Section at the National Institute of Child Health and Development. He serves his country as a U.S. Army reservist and saw combat duty during Operation Iraqi Freedom 2 in a region outside of Baghdad, Iraq.

Index

[Page numbers followed by *b, f, n,* or *t* refer to boxed text, figures, footnotes, or tables, respectively.]

A

D

G

H

Q

R

S

T

U

V

W