
# Protecting the Frontline in Biodefense Research: The Special Immunizations Program

ISBN
978-0-309-20924-3

194 pages
6 x 9
PAPERBACK (2011)

Committee on Special Immunizations Program for Laboratory Personnel Engaged in Research on Countermeasures for Select Agents; National Research Council

# PROTECTING THE FRONTLINE IN BIODEFENSE RESEARCH

## The Special Immunizations Program

Committee on Special Immunizations Program for Laboratory Personnel
Engaged in Research on Countermeasures for Select Agents

Board on Life Sciences
Division on Earth and Life Studies

NATIONAL RESEARCH COUNCIL
*OF THE NATIONAL ACADEMIES*

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
**www.nap.edu**

**THE NATIONAL ACADEMIES PRESS 500 Fifth Street NW Washington, DC 20001**

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This project was supported by Contract HHSP23320042509XI (Task Order HHSP23337007T) between the National Academy of Sciences and the Department of Health and Human Services. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. government.

International Standard Book Number-13: 978-0-309-20924-3
International Standard Book Number-10: 0-309-20924-2

Additional copies of this report are available from the National Academies Press, 500 Fifth Street NW, Lockbox 285, Washington, DC 20055; (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area); Internet, http://www.nap.edu.



Printed in the United States of America.

# THE NATIONAL ACADEMIES

*Advisers to the Nation on Science, Engineering, and Medicine*

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Charles M. Vest is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

**www.national-academies.org**

## COMMITTEE ON SPECIAL IMMUNIZATIONS PROGRAM FOR LABORATORY PERSONNEL ENGAGED IN RESEARCH ON COUNTERMEASURES FOR SELECT AGENTS

**DONALD S. BURKE** (*Chair*), Dean, Graduate School of Public Health; UPMC-Jonas Salk Chair in Global Health; Associate Vice Chancellor for Global Health; and Director, Center for Vaccine Research, University of Pittsburgh, Pittsburgh, Pennsylvania

**W. EMMETT BARKLEY**, President, Proven Practices, Bethesda, Maryland

**GERARDO CHOWELL**, Assistant Professor, School of Human Evolution and Social Change, Arizona State University; Research Associate, Fogarty International Center, U.S. National Institutes of Health, Tempe, Arizona

**ALAN S. CROSS**, Professor of Medicine, Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland

**STEPHEN W. DREW**, President, Drew Solutions LLC, Summit, New Jersey

**KATHRYN M. EDWARDS**, Sarah Sell Professor of Pediatrics; Director, Vanderbilt Vaccine Research Program, Vanderbilt University, Nashville, Tennessee

**ROBERT J. HAWLEY**, Independent Consultant, Biological Safety, Biosecurity and Biosurety Issues, Frederick, Maryland[1]

**THOMAS G. KSIAZEK**, Professor, Department of Pathology and Department of Microbiology and Immunology; Director, National Biodefense Training Center; Senior Staff Scientist and Director, High Containment Operations Core, Galveston National Laboratory, University of Texas Medical Branch at Galveston, Galveston, Texas

**THOMAS P. MONATH**, Partner, Pandemic and Biodefense Fund, Kleiner Perkins Caufield and Byers; Adjunct Professor, Harvard School of Public Health, Cambridge, Massachusetts

**PETER A. PATRIARCA**, Senior Clinical Consultant, Biologics Consulting Group, Inc., Bethesda, Maryland

**HOLLY A. TAYLOR**, Assistant Professor, Department of Health Policy and Management, Bloomberg School of Public Health; Core Faculty, Berman Institute of Bioethics, Johns Hopkins University, Baltimore, Maryland

**THOMAS E. WALTON**, Former Associate and Acting Deputy Administrator for Veterinary Services, Animal and Plant Health Inspection Service, U.S. Department of Agriculture (retired), Eloy, Arizona

[1]Senior Advisor, Science, Midwest Research Institute, Frederick, Maryland, until April 2011

**Staff**

**KATHERINE BOWMAN**, Study Director and Senior Program Officer
**ADAM FAGEN**, Study Director and Senior Program Officer (until June 2010)
**CARL-GUSTAV ANDERSON**, Program Associate
**NORMAN GROSSBLATT**, Senior Editor

# Acknowledgments

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 the 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 of 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 thank the following individuals for their review of this report:

**R. Mark Buller**, *Saint Louis University School of Medicine*
**Arturo Casadevall**, *Albert Einstein College of Medicine of Yeshiva University*
**Janet Garber**, *Garber Consulting, LLC*
**Adolfo García-Sastre**, *Mount Sinai School of Medicine*
**John Grabenstein**, *Merck & Co., Inc.*
**Barbara Johnson**, *Johnson & Associates, LLC*
**Gigi Kwik Gronvall**, *University of Pittsburgh Medical Center*
**Steven Projan**, *MedImmune*
**Pierre Rollin**, *Centers for Disease Control and Prevention*

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 **Adel Mahmoud**, *Princeton University*. Appointed by the National Research Council, he was 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.

# Contents

# Summary

This report focuses on the role of immunization for the protection of laboratory workers engaged in research on hazardous pathogens (including viruses, bacteria, and toxins) and specifically on the Special Immunizations Program (SIP), which is located at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, MD, as part of the U.S. Army Medical Research and Materiel Command (USAMRMC). The SIP provides immunizations to laboratory personnel who are at risk of exposure to hazardous pathogens and is the only such program in the United States. Its mission is to provide additional protection through vaccines to at-risk personnel, to ensure the safety and well-being of program participants through continuous medical evaluation, to provide evaluation and treatment of occupational exposures, and to collect safety and immunogenicity data to further medical research on these vaccines.

The SIP is designed to augment the protection provided by other components of laboratory biosafety, including best practices, engineering controls, and personal protective equipment for working with hazardous pathogens. The vaccines offered within the SIP include both products licensed by the Food and Drug Administration and vaccines that have not been licensed and remain under Investigational New Drug (IND) status. The administration of these IND vaccines is, therefore, considered to be part of the ongoing clinical trials necessary to meet regulatory requirements. The SIP IND vaccines are available in limited amounts and are currently administered only at Fort Detrick, MD.

Currently, the SIP includes *IND vaccines* against botulinum toxins, the equine encephalitides (eastern, western, and Venezuelan), Rift Valley fever, Q fever, and tularemia, and *licensed vaccines* for protection against anthrax, hepatitis B, Japanese encephalitis, rabies, smallpox, and yellow fever.

In 2004, when biodefense research was undergoing a rapid expansion, a U.S. Homeland Security Council Policy Coordinating Committee (HSC PCC) approved an expansion of the SIP in an effort to provide access to the program for government and civilian academic researchers. The SIP was to be funded by fully burdened contributions by the departments and agencies making use of the program according to percentage use. After 5 years of experience with the new arrangement, the Biomedical Advanced Research and Development Authority (BARDA), in the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services (HHS), asked the National Research Council to examine technical issues related to the HSC PCC recommendations regarding the expansion of the SIP, and to consider the larger context of vaccination for researchers who work with potentially hazardous biological agents (i.e., bacteria, viruses, and biological toxins) (see Box 1.1 for the full Statement of Task).

The committee formed by the National Research Council examined the history and current operation of the SIP as well as the principles of biosafety and historical data on exposures and laboratory-acquired infections (LAI) when working with hazardous pathogens and toxins. Those data demonstrate that although incidents of laboratory-acquired infections have decreased markedly over time as biosafety procedures, primary biocontainment systems, personal protective equipment, and facilities engineering have improved, the risk has not been reduced to zero, and infections do continue to occur sporadically. Researchers working with pathogens having a very low infectious dose (that is, those pathogens for which exposure to a very small quantity of the microbe can cause a disease) such as Venezuelan equine encephalitis virus, *Brucella melitensis*, *Brucella abortus*, *Francisella tularensis*, and *Coxiella burnetii*, may be particularly at risk. The committee also considered the regulatory frameworks under which SIP vaccines are administered and how additional vaccines now available in the United States or other countries might be considered for inclusion in the SIP. Finally, the committee considered other factors that might influence the development and manufacturing of new vaccines for the SIP.

As a result of its deliberations, the committee arrived at a series of findings and corresponding recommendations about the SIP and the general role of immunization in the context of hazardous pathogen research in the United States.

## HISTORICAL VALUE OF THE SPECIAL IMMUNIZATIONS PROGRAM

The SIP has played a significant historical role in offering additional protection to laboratory workers involved in U.S. biodefense research. The lessons that have been learned through the program have advanced the practice of biosafety. Despite advances in other components of biosafety, immunization remains an integral component of an occupational safety program for people

who work with highly hazardous pathogens. Immunizations with certain IND vaccines, such as those currently offered in the SIP, remain an important component of an overall biosafety program for laboratory workers at risk of exposure to hazardous pathogens.

**Recommendation 1: Special Immunizations Program IND vaccines should be offered to laboratory workers on a voluntary basis, subject to risk assessments and informed consent. The use of immunizations should never be a substitute for careful adherence to all biosafety best practices,[1] but should be considered a component of an overall biosafety program.**

## EXPANSION OF THE SPECIAL IMMUNIZATIONS PROGRAM TO MEET CIVILIAN NEEDS AS WELL AS MILITARY NEEDS

The SIP is the only formal program in the United States, and probably in the world, that exists to provide vaccines (both licensed and investigational) to at-risk laboratory workers and other occupationally exposed personnel working with hazardous pathogens. USAMRMC has the history, personnel, clinic facilities, protocols, standard operating procedures, and regulatory infrastructure needed to successfully administer, monitor, and document immunizations provided through the SIP. While the SIP generally functions well for the USAMRIID military users, it has not met the anticipated needs of customers beyond USAMRIID, particularly personnel involved in civilian biodefense countermeasures and public health research.

**Recommendation 2: Federal agency stakeholders should modify the SIP to ensure that immunizations are readily available and accessible to all at-risk research workers, including those working on civilian as well as military projects.**

**Recommendation 3: In order to generate a specific list of pathogens for priority attention for inclusion in the SIP, a strategic review and systematic assessment on a pathogen-by-pathogen basis should be undertaken by the government stakeholders. The assessment should consider the characteristics of each pathogen and toxin and the characteristics of the threat posed by it, incorporating both military and civilian stakeholder perspectives. The SIP should not be a static program but instead should be enabled to evolve with respect to the vaccines that it offers.**

[1]Biosafety best practices include laboratory practices, use of personal protective equipment, and engineering controls.

## STATUS OF VACCINES CURRENTLY ADMINISTERED IN THE SPECIAL IMMUNIZATIONS PROGRAM

The IND vaccines currently used in the SIP were developed and manufactured largely in the 1970s and 1980s under standards that would likely be different from those required today. From the individual laboratory worker's perspective, a vaccine with a good safety profile and strong immunogenicity might well be expected to provide protection despite as-yet unproven efficacy in humans. From a societal perspective, use of IND vaccines in laboratory workers permits the ongoing collection of safety and immunogenicity data on new vaccines, and these data could someday be of substantial value in a future national biodefense emergency. Although meritorious in concept, the use of IND vaccines in the SIP is not ideal for several reasons: the vaccines are older products that have not been produced for many years, the safety and immunogenicity profiles of some of the vaccines are less than optimal, and immunization under the required Phase II clinical trial protocols places substantial cost and regulatory burdens on the program. The committee found that these vaccines could still nonetheless be beneficial for at-risk personnel and where options for immunization with newer or superior vaccines do not yet exist. The committee observed that it is important to evaluate the use of these SIP IND vaccines carefully case by case so that they are made available for researchers for whom the benefits of immunization outweigh the risks (as judged by appropriately conducted risk assessments).

**Recommendation 4: The SIP should offer the safest and most effective vaccines available, which would include use of licensed vaccines, where available, and/or replacing older vaccines in the SIP with newer IND vaccines that have substantially improved manufacturing, quality control, safety, and immunogenicity profiles. The safety and immunogenicity of all vaccines used in the SIP should be studied carefully, as these data may have substantial value in a potential future national biodefense emergency.**

## SOURCES OF NEW VACCINES FOR THE SPECIAL IMMUNIZATIONS PROGRAM

Numerous vaccine candidates of potential value to the SIP either are under development in the United States or abroad or are already licensed for use in other countries. Investigational vaccines developed in the United States that have proven valuable in other countries where the diseases are endemic may also be available.

**Recommendation 5: As research on medical countermeasures continues, new vaccine products should be systematically incorporated into the SIP**

**and older or outdated products for similar applications should be considered for removal. Products currently licensed for use in other countries, but not yet in the United States, could also be used to fill gaps in the SIP armamentarium. Such newly developed and/or imported products could replace the older IND products currently administered. These additional products could also expand the SIP to include vaccines against additional pathogens and toxins that reflect evolving national military and civilian medical countermeasures (MCM) priorities.**

## REGULATORY CHALLENGES CONCERNING THE SPECIAL IMMUNIZATIONS PROGRAM

The committee found that vaccines in the SIP typically have no or extremely limited commercial value, and therefore do not attract the interest of the biopharmaceutical industry. As a result, there is a need to explore regulatory and manufacturing options for these vaccines. There is also a need to consider regulatory options for vaccines already in use or in development outside the United States that could be considered for inclusion in an expanded SIP.

**Recommendation 6: The Food and Drug Administration and other relevant regulatory authorities should explore new administrative and regulatory pathways to facilitate the development and licensure of SIP vaccines. Options might include a form of "restricted" or "conditional" licensure or an "exceptional circumstances" pathway (similar to that available in Europe). U.S. government (HHS, DOD) vaccine production and procurement plans should be designed to take full advantage of the SIP program and to consider SIP vaccine needs.**

## GOVERNANCE OF THE SPECIAL IMMUNIZATIONS PROGRAM

The SIP appears to lack a governance structure that enables regular strategic review of the investigational and licensed vaccines included in the program and to lack mechanisms to address identified gaps in vaccines.

**Recommendation 7: If the SIP is to serve effectively as an immunization program for all at-risk researchers working with hazardous pathogens, the committee recommends that the governance of the SIP be revised to develop processes for shared priority-setting and operational oversight by key stakeholders from civilian (HHS, USDA) as well as military (DOD) and other agencies. The revised system should build upon the wealth of SIP expertise available at USAMRMC.**

## MANAGEMENT OF THE SPECIAL IMMUNIZATIONS PROGRAM

The committee identified several obstacles faced by civilian biodefense research workers that prevented ready access to SIP vaccines. Paramount among these are cost and travel.

**Recommendation 8: All biodefense contracting and granting agencies should consider covering the cost of immunizing at-risk research workers, so that this cost is not borne solely by the institutions working on government-supported programs. The committee supports the idea of central SIP administration but recommends that the SIP explore options for having a small number of satellite clinic locations around the country to reduce travel and inconvenience for other participating institutions (provided that they are able to adhere to the IND protocols).**

# 1

# Introduction

This report focuses on the role of immunization in the protection of laboratory workers who are engaged in research on hazardous pathogens (viruses, bacteria) and toxins; specifically, it focuses on the Special Immunizations Program (SIP), which is housed at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID, Fort Detrick, MD, as part of the U.S. Army Medical Research and Materiel Command (USAMRMC). The SIP provides immunizations to staff that are at risk of exposure to hazardous pathogens and toxins and is the only such program in the United States. Its missions are (Boudreau, 2010)

- To provide additional protection with vaccines to at-risk personnel.
- To ensure the safety and well-being of participants through continuous medical evaluation.
- To provide evaluation of and treatment for occupational exposures.
- To collect vaccine safety and immunogenicity data to further medical research.

The SIP vaccines augment the protection provided by laboratory best practices, engineering controls, and personal protective equipment for working with hazardous pathogens and toxins. Most of the vaccines used in the SIP are not licensed by the Food and Drug Administration but have Investigational New Drug (IND) status. The administration of the vaccines is therefore considered to be part of a set of continuing clinical trials that involve intensive regulatory requirements.[1] The SIP vaccines are available only in limited amounts and are

[1]As discussed in more detail in Chapters 3 and 4, the IND immunizations administered through the SIP are part of Phase II clinical trials that provide safety and immunogenicity data.

currently administered only at USAMRIID, and they must be stored, maintained, and tested periodically for potency (Boudreau 2010). Those factors and the regulatory requirements associated with the clinical protocols that guide the SIP make the special immunizations expensive. In the early 2000s, the high costs and limited availability of SIP vaccines led the Department of Defense (DOD) to restrict enrollment in the SIP of personnel working for or funded by non-DOD agencies unless the costs of participation for these personnel were covered by the non-DOD users. The result was that fewer non-DOD government and civilian academic researchers had access to SIP immunizations at the same time that the population of such researchers was undergoing a rapid expansion.

To address the cost and location issues in the program, a U.S. Homeland Security Council (HSC) policy coordinating committee (PCC) approved an expansion of the SIP in 2004. The U.S. Army Medical Research and Materiel Command (USAMRMC) and USAMRIID were directed to continue conducting an expanded program at Fort Detrick and at one or two new satellite locations. The HSC PCC directed that the program expansion be funded by cost sharing with fully burdened contributions from the using departments and agencies according to their percentage use of the program. However, the non-DOD user agencies did not set aside funds to pay for an expanded SIP accessible to all potential users, and at-risk researchers in non-DOD government and academic settings continued to work without immunization while potentially protective vaccines were available from DOD. In addition, some of the SIP vaccines are nearing the end of their lifespan and may need to be replaced.

In late 2008, the Biomedical Advanced Research and Development Authority (BARDA), in the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services (HHS), asked the National Research Council to examine technical issues related to the HSC PCC recommendation for the expansion of the SIP in the larger context of immunization of researchers working with potentially hazardous pathogens and toxins. The present report is the result of that examination.

This chapter sets the SIP and the U.S. biological defense (biodefense) program into context and provides a background for later chapters on specific elements of the program and committee findings and conclusions. The U.S. medical countermeasures enterprise, including military and civilian biodefense priorities and the state of potentially relevant vaccine research, development, and manufacturing, are continually changing. To the best of the committee's knowledge, the information provided in this report is accurate at the time of publication. After briefing the sponsor, the committee made a limited number of factual corrections and clarifications, none of which affected the conclusions or recommendations.

## 1.1 THE CURRENT CONTEXT OF PATHOGEN RESEARCH

For more than 200 years, from the earliest discoveries of such luminaries as Edward Jenner, Robert Koch, and Louis Pasteur to the present day, scientists have conducted research on microorganisms and other pathogens that cause infectious diseases.[2,3] Their research has produced vaccines and therapies that have greatly decreased the risks posed by infectious diseases. As a National Research Council committee noted in 2009, "it is not an exaggeration to attribute increased human lifespan and better human health to the research of legions of microbiologists and other biomedical researchers on the biology of bacteria and viruses and the toxins they produce" (NRC 2009: 21). Research on microorganisms improves our ability to prevent infectious disease outbreaks, to treat them more effectively when they occur, and to detect the pathogens and toxins more rapidly both in patients and in the environment.

Shortly after the September 11, 2001, attacks, the United States received a new impetus to support and conduct pathogen research when a second set of attacks occurred, this time involving the bacterium *Bacillus anthracis*, the etiologic agent of the disease anthrax. Since then, the nation's capacity to conduct pathogen research has expanded substantially. According to a recent analysis of the biodefense budget, U.S. government civilian biodefense funding increased from $633.4 million in FY 2001 to a requested $6.5 billion in FY 2011, which brought the U.S. government investment during FY 2001–2011 to a total of $61.9 billion. In FY 2011, $4.7 billion of the requested $6.5 billion (over 70%) is for HHS, and 37% of this amount ($1.75 billion) is for the National Institutes of Health (NIH) to support research related to biodefense (Franco and Sell 2010).

An important outcome of the funding amplification has been an expansion of the research infrastructure. The number of biological safety level (BSL) 4 laboratories—which are used for research on the most dangerous pathogens, those that pose the highest risk of disease and for which no vaccine or therapy is available—increased from two before 1990 to at least seven in 2009, with a projected expansion to at least 13[4] (GAO 2009). Such laboratories are no

[2]Edward Jenner is well known for his investigations on the use of cowpox vaccination to protect against smallpox, and Robert Koch formulated the criteria in "Koch's postulates" to establish whether a specific microorganism causes a specific disease and isolated *Bacillus anthracis*, among other discoveries. Louis Pasteur discovered that the growth of microorganisms causes fermentation and investigated microbial theories of disease; he did early work on the development of rabies and anthrax vaccines.

[3]For the purposes of this report, the committee generally uses *pathogen* to refer to a microorganism while its use of the term *agent* encompasses both microorganisms and microbial toxins. A fuller definition of *pathogen* may be found in Appendix B as well as in Casadevall and Pirofski (1999).

[4]In 2009, six entities reportedly were operating seven BSL-4 laboratories (four federal, two academic, and one private nonprofit) that were registered with the CDC-USDA Select Agent program, and six BSL-4 laboratories were in various stages of planning and construction (GAO 2009).

longer limited to the federal government but now include facilities in academic institutions, state and local public health departments, and the private sector (GAO 2007). The number of the much more numerous BSL-3 laboratories is unknown, but they also underwent rapid expansion during that period (GAO 2009).[5] Those increases in pathogen research laboratory capacity were made possible largely by the substantial influx of federal support already noted. For example, since 2003, the National Institute of Allergy and Infectious Diseases (NIAID) has supported the development of 11 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs) and 12 Regional Biocontainment Laboratories (RBLs). Each RCE comprises a consortium of universities and research institutions that serve a specific geographic region.[6] In the RCE program alone, there are nearly 500 principal investigators, mostly new to biodefense, in almost 300 participating institutions.

## 1.2 CATEGORIZATION OF PATHOGENS AND MANAGEMENT OF PATHOGEN RESEARCH

The conduct and management of pathogen research have evolved in response to concerns about safety and, more recently, security. This evolution has produced a number of practice and procedure frameworks that incorporate consideration of the relative risks of research on hazardous infectious microorganisms due to their biological properties and their potential as biological weapons (bioweapons).

Over the last 25 years, best practices have been designed, articulated, and accepted to reduce the likelihood that research with hazardous pathogens will cause harm either to laboratory workers or to the public or the environment because of accidents or accidental releases. HHS published the first edition of its *Biosafety in Microbiological and Biomedical Laboratories* (*BMBL*) in 1984, and the fifth edition was issued in 2007 and revised in December 2009 (CDC/NIH 2009). Although not codified in formal regulations, the *BMBL* guidelines are widely used performance-based criteria for how modern pathogen research laboratories are expected to operate. *BMBL* from it inception has constituted a set of guidelines for laboratory safety in the academic, government, and public

[5]Under the oversight system implemented for Select Agents (discussed in Section 1.2), the Centers for Disease Control and Prevention and the U.S. Department of Agriculture (USDA) have shared authorities and responsibilities for Select Agents and biocontainment laboratories, and USDA is responsible for authorizing and inspecting laboratories that work with animal and livestock pathogens, some of which are zoonotic Select Agents. Although the number of Select Agent BSL-3 facilities is known, other BSL-3 laboratories that do not work with Select Agents and are not required to register as such have been established in the public and private sectors.

[6]Further information on the RCEs is available from NIAID (2010). Information on the RBLs is available from NIAID (2011). An additional RBL, the Pacific Regional Biocontainment Laboratory at the University of Hawaii at Manoa, remains in planning.

health communities. *BMBL* categorizes infectious pathogens and laboratory activities into four biosafety levels (BSL-1 through BSL-4) and establishes safety guidelines for each level on the basis of risk:

- BSL-1 laboratories are designed for work with pathogens and toxins that do not consistently cause disease in healthy human adults.
- BSL-2 laboratories are designed for work with pathogens and toxins that can be spread by puncture, absorption through mucus membranes, or ingestion.
- BSL-3 laboratories are designed for work with pathogens and toxins that are capable of aerosol transmission and that may cause serious or lethal infection.
- BSL-4 laboratories are designed for work with pathogens and toxins that pose a high risk of life-threatening disease, that are capable of aerosol transmission, and for which there is generally no available therapy or vaccine.

BSL-3 and BSL-4 laboratories are considered to afford "high" and "maximum" biological containment (biocontainment), respectively, for research on the most dangerous pathogens. They require specialized expertise to design, construct, commission, operate, and maintain, and workers in these laboratories must follow stringent safety procedures and use specialized safety equipment. High- and maximum-containment laboratories may also be necessary for some diagnostic and analytic services.

The *BMBL* guidelines are not regulations, but research on many pathogens is subject to regulatory oversight via other programs, such as the HHS-USDA Select Agent program.[7] The program was created in 1996 by the Antiterrorism and Effective Death Penalty Act (Public Law 104-132), which was passed amid rising concerns about terrorism after a number of terrorist acts, including the Oklahoma City bombing. Before 2001, the statute governed primarily the transfer of biological pathogens and toxins between research laboratories. The act directed the secretary of HHS and the secretary of USDA to regulate the transport of biological agents that have the potential to pose severe threats to public, animal, or plant health and safety through their use in bioterrorism. The HHS secretary delegated that authority to the Centers for Disease Control and Prevention (CDC) and the USDA secretary to the Animal and Plant Health Inspection Service (APHIS). To ensure that the pathogens and toxins were transferred only between responsible parties, CDC and APHIS required that laboratories that transfer Select Agents be registered and that transfers be

[7]Select Agents are defined in Title 42, *Code of Federal Regulations* (CFR) Part 73 for CDC and 9 CFR Part 121 for USDA.

reported to CDC and APHIS and conducted under a permitting system (42 CFR § 72.6; NRC 2009).

After the anthrax attacks of 2001, the regulations governing Select Agents were greatly expanded under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (Public Law 107-188, 116 Stat. 594 [2002]) into a rigorous and formal oversight system to ensure that persons seeking to possess, use, or transfer Select Agents or Toxins have a lawful purpose. Among its requirements, the law

- Requires all facilities possessing Select Agents to register with the secretary of HHS or USDA, not just facilities sending or receiving Select Agents. Registration is for 3 years, and facilities must demonstrate that they meet the requirements delineated in *BMBL* for working with particular Select Agents. Such requirements include having proper laboratory and personal protective equipment, precautionary signs, monodirectional and high-efficiency particulate air (HEPA) filtered ventilation, controlled access, and biosafety operations manuals. Facilities must describe the laboratory procedures that will be used, provide a floor plan of the laboratory where Select Agents will be handled and stored, and describe how access will be limited to authorized personnel. And facilities must describe the objectives of the work that requires use of Select Agents. Each facility must identify a responsible facility official who is authorized to transfer and receive Select Agents on behalf of the facility.
- Restricts access to pathogens and toxins by persons who do not have a legitimate need and who are considered by federal law-enforcement and intelligence officials to pose a risk.
- Requires transfer registrations to include information regarding the characterization of pathogens and toxins to facilitate their identification, including their source.
- Requires the creation of a national database with information on all facilities and persons that possess, use, or transfer Select Agents.
- Directs the secretaries of HHS and USDA to review and publish the Select Agents list biennially, making revisions as appropriate to protect the public.
- Requires the secretaries of HHS and USDA to impose more detailed and different levels of security for different Select Agents on the basis of their assessed level of threat to the public.

The regulations are applicable to all federal, public, and private research institutions and individuals associated with the institutions that possess, handle, store, and conduct research activities and programs that use Select Agents and Toxins (42 CFR Part 732, 7 CFR Part 331, and 9 CFR Part 121). The Select

Agents list is maintained by CDC for human pathogens and toxins and by APHIS for plant and animal pathogens.[8] The list (see Table 1.1), first introduced in 1997, has grown from 42 pathogens and toxins to the current 82, 40 pathogens are HHS-only agents, 32 are USDA-only agents (24 animal pathogens and eight plant pathogens), and 10 are zoonotic pathogens that overlap both HHS and USDA.

The criteria for including a particular pathogen or toxin on the Select Agents list address threats to public, animal, and plant health and safety but go further to include more security-oriented considerations. Historically, pathogens that had been previously weaponized by the United States or other countries have been considered to pose the greatest risks,[9] including the ability to incapacitate affected people or cause highly lethal infections in a short period, lack of availability of preventive or therapeutic measures, ease of production, stability as an aerosol, and capability of being dispersed as small particles. The following considerations have generally been used as the basis for conferring Select Agent status on particular microorganisms. Some of them deal with health risks, others with potency or effectiveness as potential biological weapon (bioweapons):

- Virulence, pathogenicity, or toxicity of the microorganism; its potential to cause death or serious disease.
- Availability of treatments, such as vaccines or drugs, to control the consequences of a release or epidemic.
- Transmissibility of the microorganism; its potential to cause an uncontrolled epidemic.
- Ease of preparing the microorganism in sufficient quantity and stability for use as a biological terrorism (bioterrorism) agent, for example, the ability to prepare large quantities of stable microbial spores.
- Ease of disseminating the microorganism in a bioterrorism event to cause mass casualties, for example, by aerosolization.
- Public perception of the microorganism; its potential to cause societal disruption by mass panic.
- Known research and development efforts on the microorganism by national bioweapons programs.

NIAID has also developed a classification of pathogens using a category A, B, and C system (Table 1.2). The system is used to set research priorities and

[8]A few Select Agents that affect both humans and animals are considered overlap agents and appear on both CDC and APHIS lists.

[9]Pathogens most often considered as posing the greatest human health threats include *Bacillus anthracis* (anthrax), *Clostridium botulinum* toxin, *Francisella tularensis* (tularemia), *Yersinia pestis* (plague), and variola virus (smallpox).

**TABLE 1.1** Select Agents and Toxins

| HHS SELECT AGENTS AND TOXINS | OVERLAP SELECT AGENTS AND TOXINS |
|---|---|
| Abrin | *Bacillus anthracis* |
| Botulinum neurotoxins | *Brucella abortus* |
| Botulinum neurotoxin–producing species of *Clostridium* | *Brucella melitensis* |
| *Cercopithecine herpesvirus* 1 (herpes B virus) | *Brucella suis* |
| *Clostridium perfringens* epsilon toxin | *Burkholderia mallei* (formerly *Pseudomonas mallei*) |
| *Coccidioides posadasii/Coccidioides immitis* | *Burkholderia pseudomallei* (formerly *Pseudomonas pseudomallei*) |
| Conotoxins | Hendra virus |
| *Coxiella burnetii* | Nipah virus |
| Crimean-Congo hemorrhagic fever virus | Rift Valley fever virus |
| Diacetoxyscirpenol | Venezuelan equine encephalitis virus |
| Eastern equine encephalitis virus | |
| Ebola virus | USDA SELECT AGENTS AND TOXINS |
| *Francisella tularensis* | |
| Lassa fever virus | African horsesickness virus |
| Marburg virus | African swine fever virus |
| Monkeypox virus | Akabane virus |
| Reconstructed replication-competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (reconstructed 1918 Influenza virus) | Avian influenza virus (highly pathogenic) |
| | Bluetongue virus (exotic) |
| | Bovine spongiform encephalopathy prion |
| | Camelpox virus |
| | Classical swine fever virus |
| Ricin | *Ehrlichia ruminantium* (heartwater) |
| *Rickettsia prowazekii* | Foot-and-mouth disease virus |
| *Rickettsia rickettsii* | Goat pox virus |
| Saxitoxin | Japanese encephalitis virus |
| Shiga-like ribosome inactivating proteins | Lumpy skin disease virus |
| Shigatoxin | Malignant catarrhal fever virus (*Alcelaphine herpesvirus* type 1) |
| South American hemorrhagic fever viruses | Menangle virus |
| Flexal | *Mycoplasma capricolum* subspecies *capripneumoniae* (contagious caprine pleuropneumonia) |
| Guanarito | *Mycoplasma mycoides* subspecies *mycoides* small colony (*Mmm*SC) (contagious bovine pleuropneumonia) |
| Junin | Peste des petits ruminants virus |
| Machupo | Rinderpest virus |
| Sabia | Sheep pox virus |
| Staphylococcal enterotoxins | Swine vesicular disease virus |
| T-2 toxin | Vesicular stomatitis virus (exotic): Indiana subtypes VSV-IN2, VSV-IN3 |
| Tetrodotoxin | Virulent Newcastle disease virus |
| Tick-borne encephalitis complex (flavi) viruses | |
| Central European tick-borne encephalitis | |
| Far Eastern tick-borne encephalitis (formerly known as Russian spring and summer encephalitis) | |
| Kyasanur Forest disease | |
| Omsk hemorrhagic fever | |
| Variola major virus (smallpox virus) | |
| Variola minor virus (alastrim) | |
| *Yersinia pestis* | |

**TABLE 1.1** Continued

| USDA PLANT PROTECTION AND QUARANTINE (PPQ) SELECT AGENTS AND TOXINS |
|---|
| *Peronosclerospora philippinensis* (*Peronosclerospora sacchari*) |
| *Phoma glycinicola* (formerly *Pyrenochaeta glycines*) |
| *Ralstonia solanacearum* race 3, biovar 2 |
| *Rathayibacter toxicus* |
| *Sclerophthora rayssiae* var *zeae* |
| *Synchytrium endobioticum* |
| *Xanthomonas oryzae* |
| *Xylella fastidiosa* (citrus variegated chlorosis strain) |

SOURCE: Adapted from NRC 2009.

uses different criteria for classification. The criteria stress ease of dissemination, associated mortality after infection, potential for public health impact and social disruption, and required special action for public health preparedness. A larger universe of pathogens is included in the NIH assessment, and some pathogens on the NIH list are not captured on the Select Agents list.

It should be clear from the foregoing discussion that research with hazardous pathogens and toxins is associated with a risk of accidental exposure. Many of the laboratory workers, technicians, and others who are exposed to these pathogens and toxins are part of the broad military and public health enterprise to develop medical countermeasures against potential biological threat (biothreat) agents and emerging infectious diseases. However, the current view in the United States is that these risks are part of a necessary investment to protect public health, agriculture, and national security. In addition, risks to laboratory workers are mitigated by laboratory best practices, equipment, facilities, and in some cases the availability of additional protections in the form of vaccines, antibiotics, antiviral drugs, and antibodies. The USAMRIID SIP, which provides access to a limited set of IND vaccines to at-risk laboratory workers, is one tool in this web of protection.

## 1.3 CHARGE TO THE COMMITTEE

Given both the substantial expansion in research with hazardous pathogens since 2001 and current efforts to review national biodefense and infectious disease countermeasures programs, the HHS BARDA asked the National Research Council's Board on Life Sciences to examine the SIP and its role in helping to protect researchers who work with highly hazardous pathogens. The SIP, administered by USAMRIID, provides access to licensed and investigational vaccines against selected highly hazardous pathogens and toxins for scientists, technicians, and other workers who may be exposed to these microorganisms as part of their employment.

**TABLE 1.2** NIAID Category A, B, and C Priority Pathogens

| **Category A** | **Category B** |
|---|---|
| *Bacillus anthracis* (anthrax) | *Burkholderia pseudomallei* (melioidosis) |
| *Clostridium botulinum* toxin (botulism) | *Coxiella burnetii* (Q fever) |
| *Yersinia pestis* (plague) | *Brucella* spp. (brucellosis) |
| Variola major (smallpox) and other related pox viruses | *Burkholderia mallei* (glanders) |
| *Francisella tularensis* (tularemia) | *Chlamydia psittaci* (Psittacosis) |
| Viral hemorrhagic fevers | Ricin toxin (from *Ricinus communis*) |
| Arenaviruses | Epsilon toxin of *Clostridium perfringens* |
| —lymphocytic choriomeningitis (LCM) virus, Junin virus, Machupo virus, Guanarito virus | *Staphylococcus* enterotoxin B |
| —Lassa fever virus | *Rickettsia prowazekii* (typhus) |
| Bunyaviruses | Foodborne and waterborne pathogens |
| —Hantaviruses | —Bacteria |
| —Rift Valley fever virus | ○ Diarrheagenic *Escherichia coli* |
| Flaviviruses | ○ Pathogenic *Vibrio* spp. (e.g., *cholerae*) |
| —Dengue viruses | ○ *Shigella* spp. |
| Filoviruses | ○ *Salmonella* spp. |
| —Ebola virus | ○ *Listeria monocytogenes* |
| —Marburg virus | ○ *Campylobacter jejuni* |
| | ○ *Yersinia enterocolitica* |
| | —Viruses (Caliciviruses, hepatitis A) |
| | —Protozoa |
| | ○ *Cryptosporidium parvum* |
| | ○ *Cyclospora cayatanensis* |
| | ○ *Giardia lamblia* |
| | ○ *Entamoeba histolytica* |
| | ○ *Toxoplasma* spp. |
| | —Fungi |
| | ○ *Microsporidium* spp. |
| | Additional viral encephalitides |
| | —West Nile |
| | —LaCrosse |
| | —California encephalitis |
| | —Venezuelan equine encephalitis |
| | —Eastern equine encephalitis |
| | —Western equine encephalitis |
| | —Japanese encephalitis |
| | —Kyasanur Forest disease |

**TABLE 1.2** Continued

| **Category C** |
|---|
| Emerging infectious disease threats, such as Nipah virus and additional hantaviruses |
| NIAID priority areas: |
| Tickborne hemorrhagic fever viruses |
| —Crimean–Congo hemorrhagic fever viruses |
| Tickborne encephalitis viruses |
| Yellow fever virus |
| Tuberculosis (TB), including drug-resistant TB |
| Influenza viruses |
| Other *Rickettsia* species |
| Rabies virus |
| Prions |
| Chikungunya virus |
| Severe acute respiratory syndrome–associated coronavirus (SARS-CoV) |
| Antimicrobial resistance, excluding research on sexually transmitted organisms[a] |
| —Research on mechanisms of antimicrobial resistance |
| —Studies of the emergence and/or spread of antimicrobial resistance genes within pathogen populations |
| —Studies of the emergence and/or spread of antimicrobial-resistant pathogens in human populations |
| —Research on therapeutic approaches that target resistance mechanisms |
| —Modification of existing antimicrobials to overcome emergent resistance |
| Antimicrobial research, as related to engineered threats and naturally occurring drug-resistant pathogens, focused on development of broad-spectrum antimicrobials |
| Innate immunity, defined as the study of nonadaptive immune mechanisms that recognize and respond to microorganisms, microbial products, and antigens |
| *Coccidioides immitis* (added February 2008) |
| *Coccidioides posadasii* (added February 2008) |

[a]**NIAID Category C Antimicrobial Resistance—Sexually Transmitted Excluded Organisms**
Bacterial vaginosis, *Chlamydia trachomatis*, cytomegalovirus, *Granuloma inguinale*, *Hemophilus ducreyi*, hepatitis B virus, hepatitis C virus, Herpes simplex virus, human immunodeficiency virus, human papillomavirus, *Neisseria gonorrhoeae*, *Treponema pallidum*, *Trichomonas vaginalis*
SOURCE: NIAID 2009.

A committee of experts in such fields as pathogen research, infectious diseases, vaccine effectiveness and safety, vaccine manufacturing, regulatory affairs, biosafety and laboratory operations, and biological ethics (bioethics) was convened to address the charge given in Box 1.1. The committee met four times over 10 months to review information on the SIP, the broader context of research with highly hazardous human and animal pathogens, and stakeholder perspectives.

**BOX 1.1**
**Committee on Special Immunizations Program for Laboratory Personnel Engaged in Research on Countermeasures for Select Agents**

**Statement of Task**

A National Research Council (NRC) committee will examine technical issues related to a decision made by the U.S. Homeland Security Council (HSC) Policy Coordinating Committee (PCC) in 2004 to expand the United States Army Medical Research Institute of Infectious Diseases' (USAMRIID's) Special Immunizations Program (SIP) and the larger context of vaccination for researchers working with potentially dangerous pathogens. The purpose of an expanded immunizations program would be to provide additional protection for researchers engaged in developing next generation countermeasures against agents of bioterrorism, most of which are now identified as Select Agents (42 CFR Parts 72 and 73; 7 CFR Part 331; 9 CFR Part 121). People eligible for vaccination may be expanded beyond personnel in government laboratories belonging to the Department of Defense (DOD) to include personnel of other federal agencies (e.g., National Institutes of Health) as well as in academic laboratories conducting such research with federal funding and other settings in which exposure to Select Agents and other high-hazard pathogens may occur including some diagnostic, public health, or emergency response laboratories. The NRC committee will consider the needs outlined in 2004 for the HSC PCC along with information on the current status of the SIP (vaccine supplies and viability), the value of immunization beyond the current implementation of the SIP, and the growth of research on high hazard organisms since 2004. Questions the committee may consider include:

- What should the general role of vaccines be in protecting laboratory workers from effects caused by the materials they work with?
- Are there specific pathogens that researchers are working with now for which it would be highly desirable to have a vaccine?
- Which pathogens should receive priority attention?
- In an expanded program, what would be the advantages and disadvantages of continuing to use investigational vaccines as they have been used in the DOD Special Immunizations Program?
- If expansion of an immunization program is recommended, the committee should also consider issues of vaccine development and supply within and beyond the existing SIP.

The committee will focus on the more general questions above to inform the U.S. government's high level policy discussion on the role of vaccines in the context of research with high-hazard pathogens. The committee will not conduct a detailed analysis on the risk of each pathogen or the relative safety and efficacy of particular vaccines but may consult available data on these issues to address elements of the statement of task.

## 1.4 ORGANIZATION OF THE REPORT

The committee took a broad view in its deliberations, choosing to consider not only the increase in demand for the vaccines currently administered by the SIP but likely advances in vaccines, manufacturing, and regulatory science. Its discussions led the committee to consider and evaluate whether an effective researcher-immunization program should include options for broadening the scope of and products included in the SIP.

Chapter 2 discusses the history of the SIP and the role of vaccination as one component of safe laboratory practice in work with highly hazardous pathogens. The SIP arose as part of the U.S. Army's historical bioweapons program at Fort Detrick, MD, but it now serves both civilian and military personnel and scientists conducting biodefense research at facilities other than USAMRIID. Chapter 2 also presents information on the frequency of laboratory exposures and the lessons that have been learned from experience in providing vaccinations to workers engaged in hazardous-pathogen research. Chapter 3 provides additional detail on the U.S. medical countermeasures enterprise, including research priorities and recommendations from recent reports, to provide a framework for a discussion of the current SIP. Chapters 4 and 5 discuss potential options relevant to the SIP in regulatory guidance and in vaccine development and manufacturing, respectively. Chapter 6 presents several options discussed by the committee for how the SIP might meet its goals. Chapter 7 presents the committee's conclusions regarding the role of vaccines in protecting laboratory workers, the value of maintaining a program like the SIP to make the vaccines available, and how additional vaccines might be selected for inclusion. The committee suggests a framework for actions that could be considered over short, medium, and long terms to address some of the issues identified.

# 2

# History of the Special Immunizations Program and Lessons Learned from Occupational Immunization Against Hazardous Pathogens

## 2.1 HISTORICAL PATHOGEN AND COUNTERMEASURES RESEARCH AND THE ORIGINS OF THE SPECIAL IMMUNIZATIONS PROGRAM

Research involving hazardous pathogens has been a component of the U.S. military scientific enterprise for many years. In 1941, Secretary of War Henry L. Stimson suggested that a program be initiated to investigate "the present situation and future possibilities" of both offensive and defensive biological warfare (biowarfare) (Covert 2000). In 1942, President Roosevelt authorized Secretary Stimson to establish a civilian agency to take the lead on all aspects of the biowarfare effort. The War Research Service (WRS), under George W. Merck, in the civilian Federal Security Agency was tasked to begin development of the U.S. biowarfare program with both offensive and defensive objectives. WRS organized a research and development (R&D) program in the Department of War and requested that the Army assume responsibility for the large-scale R&D program in November 1942. Construction and operation of laboratories and pilot plants at Camp Detrick (now Fort Detrick), in Frederick, MD, began in April 1943 (Covert 2000).[1]

The risk to scientists, laboratory technicians, and other staff from exposure to high-risk pathogens was recognized during the planning of the R&D program, as discussed in greater detail in Section 2.4. Arnold G. Wedum joined the U.S. biowarfare program in 1946 and served as the director of industrial health

[1]In addition to *Cutting Edge: A History of Fort Detrick, Maryland*, 4th Edition (Covert 2000), information on the history of Fort Detrick and on the historical offensive and defensive U.S. biological weapons programs may be found in *Medical Aspects of Chemical and Biological Warfare* (U.S. Department of the Army 1997) and *Medical Aspects of Biological Warfare* (U.S. Department of the Army 2007).

and safety at Fort Detrick until 1972. Pathogen research conducted at Fort Detrick during the period of the offensive biowarfare program often involved high concentrations of microorganisms, aerosol challenge experiments involving laboratory animals, and pilot production of high-risk pathogens and toxins. Those operations placed laboratory workers at substantial risk for exposure and disease, particularly because the availability of treatments, including antibiotics and antiviral drugs, was severely limited at the time. Beginning in the 1950s, the United States operated a parallel program at Fort Detrick that conducted research on defensive measures against biological weapons (bioweapons) (Rusnak et al. 2004c). The United States maintained its offensive bioweapons program from 1943 to 1969, when it was discontinued under President Nixon; the defensive research program continued.

The Special Immunizations Program (SIP) at Fort Detrick began as an immunization program to provide an additional measure of protection of laboratory workers against occupational infections. A Special Procedures Section performed medical examinations on personnel assigned to work in the biowarfare sections, saved blood samples—which also allowed the detection of asymptomatic infections, and maintained records. In 1962, the Special Procedures Section became the SIP. Both licensed and investigational vaccines were used as part of the overall safety program to protect Fort Detrick personnel. Immunization of laboratory workers was mandatory,[2] and the use of investigational vaccines was considered essential for occupational safety when licensed vaccines were not available.

The occupational health and safety of laboratory workers had the highest priority in the Fort Detrick industrial health and safety program, and procedures were implemented to support the biological safety (biosafety) goals. Annual medical examinations were provided for all Fort Detrick employees, and immunizations were provided for all laboratory personnel. The serum storage and collection program conducted annual serologic testing to detect seroconversion. Every infection was treated as laboratory-acquired until proved otherwise. All medical treatment and hospitalization were provided at no expense to infected workers. Reporting of exposures was encouraged and was not subject to disciplinary action. An active disease surveillance program provided a quick response to exposures that enabled both immediate medical care and the op-

[2]Use of investigational vaccines in the SIP was considered outside Army Regulation AR 70-25, *Use of Volunteers as Subjects of Research* (U.S. Department of the Army 1990). That regulation, initially formulated in 1962 and last revised in 1990, states that voluntary informed consent is necessary in administering an investigational product to a human subject in the conduct of a research study. Additional information on the use of human subjects in Army research can be found in Chapter 24 of *Medical Aspects of Biological Warfare*, "Ethical and Legal Dilemmas in Biodefense Research" (U.S. Department of the Army 2007).

portunity to assess the causes and effects of incidents, and it modeled corrective actions that were needed to prevent recurrence of incidents.[3]

Over time, the SIP extended the use of its investigational vaccines to laboratory workers involved in biological defense (biodefense) research projects throughout the United States and Canada at 117 external sites. In 1972, federal regulation of biologics was transferred to the Food and Drug Administration (FDA), and in 1987 a memorandum of understanding (MOU) between the Department of Defense (DOD) and FDA that allowed the exempt use of investigational biologics in the SIP or Force Health Protection Program ended.[4] Shortly thereafter, the SIP underwent marked change.

Beginning in 1997, the SIP was required to adhere to FDA current Good Clinical Practice guidelines (cGCP); this requirement led to compliance with FDA-mandated cGCP and current Good Manufacturing Practice (cGMP). The maintenance of multiple extramural vaccination locations was discontinued in 1999 when these sites could no longer meet the rigorous regulatory requirements necessary for monitoring investigational vaccines. In 2000, FDA placed the SIP tularemia and Q fever vaccination protocols on clinical hold until reports on their use in 1963–1998 were submitted and their safety and immunogenicity data analyzed. During that time, 11 tularemia and nine Q fever protocols were reviewed, and new protocols were written for seven of the SIP vaccines (Boudreau 2010).

## 2.2 THE HISTORY OF VACCINE PRODUCTION FOR THE SPECIAL IMMUNIZATIONS PROGRAM

### 2.2.1 Origin and Evolution of the Salk Institute's Government Services Division

The Salk Institute's Government Services Division (GSD) was the site of process development and manufacture of most of the vaccines now used in the SIP. In 1897, Richard M. Slee established Pocono Biological Laboratories in

[3]The data collected by the SIP have also been used to study the long-term health outcomes of participants receiving investigational vaccines (for example, Pittman et al. 2004, 2005a,b).

[4]An MOU was established in 1964 between DOD and the Department of Health, Education, and Welfare (now the Department of Health and Human Services, which houses the National Institutes of Health). The MOU was updated in 1974 and again in 1987 (52 Federal Register 33472-33474, September 3, 1987, "Memorandum of Understanding Between the Food and Drug Administration and the Department of Defense, Concerning Investigational Use of Drugs, Antibiotics, Biologics, and Medical Devices by the Department of Defense"). The MOU established in 1987 between FDA and DOD states that "DOD has been able to carry out effectively its responsibilities for national security without compromising the intent of the above-cited statutes and regulations; *and that certain exemptions, relieving the DOD from the need to meet the ordinary requirements of the Investigation New Drug (IND) and Investigational Device Exemption (IDE) regulations are no longer necessary*" (52 Fed. Reg. 33473 [1987], emphasis added).

Swiftwater, PA, to manufacture and distribute smallpox vaccine. That decision was influenced by his work with George Sternberg (surgeon general of the Army in 1893–1902 and a pioneer in infectious diseases) and his studies at the Pasteur Institute in France. In 1930, the National Drug Company, a Division of Richardson-Merrell Inc. of Philadelphia, purchased the Swiftwater facility; in 1950, the Vick Chemical Co. purchased the property. The Swiftwater facility was subsequently donated to the Salk Institute in California, and part of the facility was then purchased by the Canadian firm of Connaught Laboratories Ltd. on January 3, 1978. However, the GSD, which had been built and operated by the Merrell National Laboratories of the National Drug Company to that point, was retained by the Salk Institute. The buildings were later acquired by sanofi pasteur (and its predecessor companies), which acquired Connaught in 1989 and now owns and operates the Swiftwater facility (Widmer 2000, sanofi pasteur 2010). The Salk Institute continued to operate the GSD facility at Swiftwater, however, until the GSD's closure in 1998.

### *2.2.2* Relationship of the U.S. Army with the Salk Institute

A 1991 report from the General Accounting Office (GAO; now the Government Accountability Office) examined details of the Army's relationship with the Salk Institute (GAO 1991). The U.S. Army issued a request for proposal to Merrell National Laboratories in March 1977 for a 5-year contract to research techniques for making vaccines against biological agents and to conduct other vaccine production research. Because Merrell had the only facility capable of making vaccines that were not commercially available and had received similar Army contracts since 1960, the Army decided that the proposed contract should be a sole-source contract. However, before the request for proposal's closing date, Merrell informed the Army that it was donating its Swiftwater facility, where the work would be performed, to the Salk Institute. According to Army contract officials (GAO 1991), Merrell had given the Army the opportunity to purchase the Swiftwater facility, but the Army had declined. Salk sold the commercial biological manufacturing operations at the Swiftwater facility to Connaught Laboratories, but retained a laboratory building where Merrell's Army work had been conducted and established the GSD as a separate nonprofit entity to operate the facility. In October 1977, Salk submitted a proposal in response to the Army's solicitation. The proposal was accepted, and Salk was awarded a 5-year contract that was effective on January 1, 1978. Salk later received two additional 5-year contracts from the Army to operate the Swiftwater facility. The three multiyear contracts awarded to Salk as part of the Biological Defense Research Program (BDRP) by the U.S. Army Medical Research and Development Command (USAMRDC; now USAMRMC) were valued at $75.4 million. Under those contracts, Salk was "to develop, produce, and test biological vaccines and to produce other biological products such as

cell cultures and diagnostic reagents" (GAO 1991: 2). Salk's 15-year contract period with the Army for biologics production thus ran from January 1978 through September 1993. Vaccines in storage in 1991 at the Salk Institute are indicated in Table 2.1. Salk produced most of these vaccines; some were produced by Merrell.

According to the 1991 GAO report, the Army considered Salk's GSD vaccine production facility "a vital part" of the BDRP. Major General Philip K. Russell, the commander of the USAMRDC in 1989, stated that Salk was "a national resource" and "was vital to the defense of the United States and its allies against potential biowarfare weapons" (GAO 1991: 9).

At the time of the 1991 GAO report, the Army's in-house capabilities were not sufficient to meet its demand for vaccines to counter biowarfare agents (GAO 1991). The report stated, however, that some Army officials had told GAO that the Army could improve and expand its in-house capabilities to meet its needs, and GAO's analysis agreed with this. At that time, the Walter Reed Army Institute of Research (WRAIR) was remodeling a facility to meet FDA requirements for producing human vaccines. The facility, now called the Pilot Bioproduction Facility (PBF), was constructed to produce small cGMP-compliant lots of infectious disease vaccines for use in clinical trials. However, to develop and produce vaccines to protect against biowarfare threat agents, the WRAIR facility would have needed to be upgraded to the biosafety level 3 (BSL-3) containment level available at the Salk facility. WRAIR officials stated that after such improvements, their facility could produce sufficient quantities of attenuated virus vaccines to meet Army requirements (GAO 1991).

**TABLE 2.1** Dates of Manufacture of Vaccines in Storage at the Salk Institute in 1991

| Vaccine | Dates of Manufacture |
|---|---|
| Tularemia | 1962, 1964, and 1985 |
| Q fever, phase 1, inactivated | 1970 |
| Q fever, chloroform and methanol residue, inactivated | 1988 |
| Chikungunya, live, attenuated | 1985 |
| Junin candidate I, live, attenuated | 1988 and 1989 |
| Rift Valley fever, live, attenuated | 1988 |
| Smallpox (TSI vaccinia strain) | 1990 and 1991 |
| Rift Valley fever, inactivated | 1978, 1979, and 1989 |
| Hepatitis A | 1990 |
| Venezuelan equine encephalitis, TC83, live, attenuated | 1968, 1970, 1971, and 1972 |
| Eastern equine encephalitis, inactivated | 1969, 1970, and 1989 |
| Western equine encephalitis, inactivated | 1981 |
| Venezuelan equine encephalitis, C84, inactivated | 1980 and 1981 |

SOURCE: GAO 1991.

The PBF remains in operation but was not upgraded to BSL-3 and remains at BSL-2 capability (WRAIR 2010). In the 1990s, the Army did renovate two laboratory suites at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) to meet FDA's requirements for the production of bulk botulinum toxoids. This facility was operated by Salk under its Army contract. In addition, the Army had established an agreement with the National Institutes of Health (NIH) to reimburse it for the renovation and operation of a wing of an NIH-owned drug production facility that was contractor-operated. That facility would be used by NIH's contractor to produce bulk anthrax vaccine. The bulk botulinum toxoid and anthrax vaccine produced by USAMRIID and NIH facilities were then shipped to a commercial supplier (the Michigan Department of Public Health) to be tested, processed into individual doses, and packaged. Those actions were taken by the Army to increase botulinum toxoid and anthrax vaccine production capabilities for Operation Desert Shield and Operation Desert Storm (GAO 1991).

### 2.2.3 Closing of the Salk Institute Government Services Division

In the late 1990s, the Salk Institute GSD ceased operations at its Swiftwater, PA facility. Although the laboratory at its peak in the early 1990s had employed a staff of 110 to study and develop vaccines for the U.S. Army, it came under criticism for using $14 million of government money for research on vaccine production for pathogens that were not validated biowarfare threat agents. This research included work on Chikungunya, Junin, and Rift Valley fever viruses (GAO 1991). Following the 1991 GAO report, funding lines were separated for biodefense and infectious diseases. In 1996, Salk lost its sole-source contract to develop vaccines, and in 1998, the Army awarded its biodefense vaccine contract to DynPort Vaccine Company; in September 1998, it was announced that the Salk GSD facility would be closed. DynPort manages countermeasures R&D through contractual mechanisms, including advanced development of a recombinant plague vaccine and a recombinant botulinum toxin vaccine, both originally developed at USAMRIID, but it does not maintain laboratory facilities of its own (DVC LLC 2011). Stocks of the vaccines produced by Salk under Investigational New Drug (IND) authority were later transferred to the control of DOD's Chemical Biological Medical Systems, and these stocks remain the primary source of investigational vaccines used in the SIP. With the closure of the Salk facility, no new stocks of those vaccines have been produced, and options for the production of new IND vaccines that might be added to the SIP remain limited. These issues are explored in more detail in Chapter 5.

Table 2.2 presents key events in the history of the SIP through 2000. More recent developments and the current operation of the SIP are described in Chapter 3.

**TABLE 2.2** Milestones in the History of the SIP, 1940s–1990s

| Decade | Important Events |
|---|---|
| 1940s | Opening of biological warfare laboratories at Fort Detrick<br>Establishment of Fort Detrick industrial health and safety program<br>Operation of Special Procedures Section |
| 1950s | Continuation of offensive and defensive bioweapons research |
| 1960s | SIP vaccination expanded to multiple external sites<br>Merrell facility in Swiftwater produces vaccines under Army contract<br>U.S. offensive bioweapons research ends (1969), but defensive research continues |
| 1970s | Swiftwater facility donated to Salk Institute<br>Salk Institute GSD in Swiftwater produces vaccines under Army contract |
| 1980s | DOD–FDA MOU allowing exempt use of investigational vaccines ends |
| 1990s | SIP vaccination at external sites ends<br>Salk contract with Army ends<br>Salk GSD closes<br>Army vaccine contract established with DynPort |

## 2.3 THE ROLE OF IMMUNIZATION IN RESEARCH WITH HAZARDOUS PATHOGENS AND LESSONS LEARNED

### 2.3.1 Laboratory Risk of Infection by Select Agents, Emerging Disease-Causing Pathogens, and Other Hazardous Pathogens

History suggests that often the first case of a laboratory-associated infection (LAI) is associated with the discovery and isolation of the causative agent of an emerging infectious disease, and infections are also a risk during the period of follow-on research involving animal experimentation and larger volumes of the pathogen. Exposure to materials that may contain infectious pathogens is the principal laboratory risk posed to workers who handle the materials or who work in laboratories where research with infectious pathogens is conducted. Even when containment procedures and appropriate microbiological practices are followed, occasional breaches can raise the risk of LAIs to a high level in research involving hazardous pathogens such as Select Agents.

The transmission of potentially high-risk agents in a biocontainment laboratory will most likely occur through direct routes, such as accidental percutaneous inoculation. Research involving animals and sharp instruments (such as syringes and needles) creates some of the most hazardous conditions. Exposure through respiratory, mucosal, and oral routes, such as in accidents or in the conduct of procedures that generate aerosols, also poses significant risks for laboratory workers. The potential for aerosol formation may be particularly

important to consider, and may be less obvious to detect that incidents such as needlesticks or animal scratches. *BMBL* notes, "procedures and equipment used routinely for handling infectious agents in laboratories, such as pipetting, blenders, non-self contained centrifuges, sonicators and vortex mixers are proven sources of aerosols" (CDC/NIH 2009: 14).

The first recorded LAIs with a number of pathogens that are classified today as Select Agents include, for example,

- *Burkholderia mallei* (glanders) in 1898—syringe or needle exposure (Riesman 1898).
- *Vibrio cholerae* (cholera) in 1894—pipette exposure (Kisskalt 1915).
- *Brucella* spp. (brucellosis) in 1897—syringe or needle exposure (Birt and Lamb 1899; Meyer and Eddie 1941).

Tables 2.3 and 2.4 provide information on the sources of exposure and types of accidents associated with laboratory infections from the 19th century to 1974.

### 2.3.2 Biosafety and the Role of Vaccines in Protecting Laboratory Workers

Biosafety is the laboratory discipline that seeks to ensure the safe handling and containment of infectious pathogens and other hazardous biological materials. The objective of biosafety is to reduce or eliminate exposure of laboratory workers, other persons, and the outside environment to potentially hazardous pathogens and toxins. A risk assessment of the hazardous characteristics of

**TABLE 2.3** Sources of Exposure for 3,921 Laboratory-Associated Infections from the End of the 19th Century Through 1974, Listed by Percentage of Total

| Source | No. | % |
|---|---|---|
| Worked with agent | 827 | 21.1 |
| Unknown or not indicated | 767 | 19.6 |
| Accidents | 703 | 17.9 |
| Animal and ectoparasite | 659 | 16.8 |
| Aerosol | 522 | 13.3 |
| Clinical specimen | 287 | 7.3 |
| Human autopsy | 75 | 1.9 |
| Discarded glassware | 46 | 1.2 |
| Intentional infection | 19 | 0.5 |
| Other | 16 | 0.4 |
| Total | 3,921 | 100 |

SOURCE: Adapted from Pike 1976.

**TABLE 2.4** Laboratory-Associated Infections Resulting from Various Types of Accidents from the End of the 19th Century Through 1974

| Type of Accident | No. | % |
|---|---|---|
| Needle or syringe exposure | 177 | 25.2 |
| Spill or spray exposure | 188 | 26.7 |
| Sharps injuries | 112 | 15.9 |
| Pipetting by mouth | 92 | 13.1 |
| Animal bite or scratch | 95 | 13.5 |
| Other | 3 | 0.4 |
| Not indicated | 36 | 5.1 |
| Total | 703 | 99.9 |

SOURCE: Pike 1976.

the infectious pathogens and toxins and the protocols that investigators carry out in the conduct of their research also determine the extent of laboratory containment that is used.

The basic concepts and principles that define biosafety as a laboratory discipline were developed at the U.S. Army Biological Research Laboratories at Fort Detrick during the period 1943–1969 under the leadership of Arnold G. Wedum, director of Industrial Health and Safety. Dr. Wedum developed a risk assessment paradigm for identifying exposure and infection risks associated with a proposed research protocol and for selecting control measures that would provide for the safe handling of high-risk pathogens and toxins in the Fort Detrick biodefense program (Wedum et al. 1972). The paradigm described the basic elements of a risk assessment, which included

- The number and severity of reported LAIs.
- Infective dose for humans.
- Potential for exposure to infectious pathogens and toxins in conducting protocols (for example, aerosols and contact with contaminated surfaces) or operating equipment (for example, needle stick exposure).
- Results of studies to determine the number of microorganisms released into the air during common laboratory techniques.
- Infection of cagemates by inoculated animals.
- Excretion of the infectious agent in urine, feces, or saliva of inoculated animals.
- Hazards peculiar to the animal species.
- Increased susceptibility by gender.
- Availability and use of specific therapy or effective vaccines.

The infective dose of a bacterial or viral pathogen that can cause disease by inhalation is typically small. For example, the inhalation of about 10 microorganisms of *Francisella tularensis* or *Coxiella burnetii* can cause disease in humans (Hornick et al. 1966).

The Fort Detrick industrial health and safety program developed the foundation on which the principles of biosafety that protect laboratory workers, the environment, and the public from exposure to infectious microorganisms that are handled and stored in the laboratory are based: risk assessment, standard microbiological practices, containment, and facility safeguards. The technical proficiency of laboratory workers in using safe microbiological practices and biocontainment equipment and good habits that sustain excellence in the performance of those practices have also become important elements of the risk assessment paradigm (CDC/NIH 2009).

### 2.3.3 Incidents of Laboratory-Associated Infections and the Utility of Prophylactic Immunizations for Researchers: Experience from Fort Detrick and the Centers for Disease Control and Prevention

Several analyses of laboratory exposures and infections have been undertaken that draw on the wealth of data available at USAMRIID and through the SIP. A review of the period 1943–1969 encompasses the Fort Detrick biowarfare program, during which workers handled concentrated samples of pathogens and conducted aerosol experiments, procedures that placed them at relatively higher risk of exposure. This period also overlaps with improvements in biosafety practices, such as the introduction of biosafety cabinets (BSCs) in 1950, and with the introduction of several investigational vaccines (Rusnak et al. 2004b). A decrease in anthrax cases was observed after 1946, attributed at least in part to the use of long-sleeved gowns and taped gloves. While 23 cases of cutaneous anthrax occurred in 1944 and 1945, two cases occurred during 1948–1952 after the change in biosafety practice. These biosafety measures were not fully protective, however, and a fatal case of inhalational anthrax occurred in 1951. Only three cases were observed during the 18 years from 1952 to 1969, following introduction of the anthrax vaccine. The authors also note that changes in biosafety practices and the introduction of BSCs contributed to a reduction in infections with *Burkholderia mallei*, for which a vaccine was not available. On the other hand, laboratory infections with *Francisella tularensis* continued after the introduction of BSCs and despite the use of the partially protective Foshay vaccine, with an average of 15 infections per year occurring during 1953–1959. Laboratory infections declined significantly, however, after the introduction of a live tularemia vaccine in 1959. Similarly, the introduction of BSCs reduced but was not sufficient to eliminate infections with *Coxiella burnetii* (Q fever) and with Venezuelan equine encephalitis (VEE) virus, which

continued at an average of 3.4 cases per year and 1.9 cases per year, respectively.[5] As with tularemia, the number of cases declined further after introduction of the Q fever vaccine in 1965 and the VEE TC-83 vaccine in 1963 (Rusnak et al. 2004b). As a result, the authors conclude, "most laboratory-acquired infections from agents with higher infective doses (e.g., anthrax, glanders, and plague) were prevented with personal protective measures and safety training alone. Safety measures (including BSCs) without vaccination failed to sufficiently prevent illness from agents with lower infective doses in this high-risk research setting" (Rusnak et al. 2004b).

Biosafety practices and engineering controls have continued to advance since 1969, and an analysis of USAMRIID laboratory exposures and infections was also undertaken for the period 1989–2002, during which biodefense research continued to be conducted (Rusnak et al. 2004a). During this period, 234 individuals were evaluated for potential exposures to 289 pathogens; five infections occurred—with *Burkholderia mallei*, *Coxiella burnetii*, vaccinia virus, VEE virus, and Chikungunya virus. Potential exposures largely occurred by aerosol or percutaneous routes, with 19% of the exposures occurring while working with animals; needlesticks continued to occur at a rate of approximately 1.7 per year. The 182 potential exposures to bacterial and rickettsial pathogens largely involved *Bacillus anthracis* (123 exposures), *Yersinia pestis* (23), and *Coxiella burnetii* (10), with smaller numbers of exposures to *Burkholderia* spp., *Brucella* spp., and *F. tularensis*. The 107 potential exposures to viral pathogens involved a larger number of viruses, with the most common potential exposures being to VEE virus (21), Rift Valley fever virus (20), and Hantavirus (11). Most of the individuals evaluated for potential exposure were vaccinated (where licensed or investigational vaccines were available), but vaccination breakthroughs did occasionally occur, for example, in the cases of *C. burnetii*, VEE, and vaccinia infections. In addition to biosafety practices and immunizations, USAMRIID also administered post-exposure prophylaxis where this was determined to be warranted based on risk assessments. Of note, the infection with *C. burnetii* reportedly occurred in a researcher working with high concentrations of pathogen in the context of a leaking BSC (Rusnak et al. 2004a).

The bioweapons and medical countermeasures research programs conducted at Fort Detrick have substantially advanced the community's knowledge about the safe conduct of research with highly hazardous pathogens and have documented the value of offering immunization to those working with such pathogens. As discussed above, significant decreases in cases of LAI were often observed following the introduction of immunization or the introduction of a

[5]Data on yearly rates of infection with *C. burnetii* and VEE viruses were not available for the period before BSCs were introduced in 1950.

more immunogenic vaccine, particularly in the cases of pathogens with low infective doses. For example (Rusnak et al. 2004c),

- *F. tularensis:* "The most notable decrease in infections was seen after vaccination was begun against tularemia. The rates of typhoidal tularemia decreased from 5.7 cases to 0.27 cases per 1000 at-risk employees with the introduction of NDBR 101 live, attenuated tularemia vaccine in the 1960s."
- *C. burnetii:* "From 1943 to 1965, Q fever was the third most frequent disease seen (55 cases diagnosed between 1950–1965). Only 1 confirmed case of Q fever has been diagnosed since use of the vaccine in 1965."
- VEE: "During the 13 years from 1950–1962, 39 cases of VEE were diagnosed, versus only 4 suspected or proven breakthrough infections in the 7 years after the use of the vaccine (1963–1969) and only 1 case from 1989 to 2002 (14 years)."

The role of vaccines in preventing laboratory infections is also vividly demonstrated by the case of yellow fever. Between the isolation of yellow fever virus in 1927 and availability of a vaccine against this highly lethal disease in 1931, there were 32 LAIs (5 fatal) among laboratory workers. The routine use of vaccines for protection of laboratory workers completely obviated this problem (Sawyer 1932).

The Fort Detrick experience in immunizing workers with investigational vaccines for high-risk pathogens and toxins is indicated in Table 2.5 (years 1943–1969).

Data of relevance to laboratory infections have also been compiled by the CDC for years 2003–2009 based on reporting of "loss" and "release" information. According to guidance issued by the CDC and the Animal and Plant Health Inspection Service, loss is defined as "failure to account for select agent or toxin" while release is defined as "a discharge of a select agent or toxin outside the primary containment barrier due to a failure in the containment system, an accidental spill, occupational exposure, or a theft. Any incident that results in the activation of a post-exposure medical surveillance/prophylaxis protocol should be reported as a release" (CDC/APHIS 2008). Dr. Richard Henkel of the CDC Division of Select Agents and Toxins (DSAT) told the committee that the DSAT received 395 reports of releases of Select Agents between 2003 and 2009. Seven reports informed the DSAT of the occurrence of LAIs: four with *B. melitensis*, two with *F. tularensis*, and one with an unspecified *Coccidioides* species. The CDC will publish an in-depth analysis of these events.

Table 2.6 provides information based on surveys from 1930 to 2009 on the number of reported LAIs that were caused by infectious pathogens that are now regulated as Select Agents. In addition to these reviews, the commit-

**TABLE 2.5** Fort Detrick Experience in Immunizing Workers with Investigational Vaccines Against High-Risk Pathogens and Toxins, 1943–1969

| Investigational Vaccine | Years Administered | Assessment[a] |
|---|---|---|
| Anthrax whole-cell vaccine | 1944–1951 | Limited to no protection; changes in practices provided protection |
| *Brucella* early vaccine candidates | 1943–1952 | No protection |
| Cell-free anthrax antigen vaccine | 1952–1969 | BSCs[b] were available in 1950; practices and BSCs provided protection; vaccination recommended for protocols with high potential for aerosolization |
| Phenolized tularemia vaccine (Foshay vaccine) | 1945–1959 | Ameliorated symptoms of disease; did not prevent infection after exposure; cases continued to occur after introduction of BSCs in 1950[c] |
| Live tularemia vaccine | 1959–1969 | Immediate decrease in infections; use of BSCs provided limited protection, perhaps related to work with lyophilized cultures[c] |
| Q fever vaccine | 1965–1969 | Vaccination prevented infections; BSCs provided limited protection from 1950 to 1965[c] |
| Early VEE vaccine candidates | 1950–1962 | No protective benefits |
| Live VEE TC-83 vaccine | 1963–1969 | Provided potential protection; BSCs provided limited protection[c] |
| Bivalent botulinum AB toxoid | 1944–1959 | Provided potential protection |
| Pentavalent botulinum ABCDE toxoid | 1959–1969 | Provided potential protection |

SOURCES: Wedum 1996; Rusnak et al. 2004b.

[a]Measures such as decreases in observed numbers of LAIs are taken as indicative of potential protection.

[b]BSCs were first introduced at USAMRIID under Dr. Wedum. The several classes of BSCs (I, II, III) offer various degrees of biological containment through directed airflow, filters, and other technologies and thus are suitable for safe laboratory work with different types of organisms.

[c]Probable cause of limited protection associated with BCSs was failure to maintain user technical proficiency.

tee examined the reports of several recent incidents of pathogen exposures in laboratory workers:

- As referenced above, a laboratory worker at USAMRIID became infected in 2000 with *Burkholderia mallei* and contracted glanders; a vaccine against *B. mallei* is not available. The case investigation noted

**TABLE 2.6** Laboratory-Associated Infections with Pathogens Now Classified as Select Agents

| | Period of LAI Report | | |
|---|---|---|---|
| Select Agents | 1930–1978[1,2,3] | 1979–2004[4] | 2005–2009[5] |
| **Viruses** | | | |
| Cercopithecine herpesvirus | 21 | 10 | |
| Crimean-Congo hemorrhagic fever | 8 | | |
| EEE | 4 | | |
| Ebola | 1 | 4 | |
| Lassa | 2 | 1 | |
| Marburg | 25 | 2 | |
| Monkeypox | | | |
| Hemorrhagic fever viruses | 368 | 9 | |
| Flexal | | | |
| Guanarito | | | |
| Junin | 21 | 1 | |
| Machupo | 1 | 1 | |
| Sabia | | 2 | |
| Central European encephalitis | | | |
| Far Eastern encephalitis | | | |
| Kyasanur Forest disease | 133 | | |
| Omsk hemorrhagic fever | 5 | 4 | |
| Russian spring and summer encephalitis | 8 | | |
| Hendra | | | |
| Nipah | | | |
| Rift Valley fever | 47 | 6[6] | |
| Venezuelan equine encephalitis | 146 | 1 | |
| **Bacteria** | | | |
| *Coccidioides* species[a] | 93 | 1 | 1(?) |
| *Coxiella burnetii* | 280 | 177 | |
| *Francisella tularensis* | 225 | 3 | 1 |
| *Rickettsia prowazekii* | 181 | 10 | |
| *Rickettsia rickettsii* | 72 | | |
| *Bacillus anthracis* | 40 | 1 | |
| *Brucella* spp. | 426 | 143 | 3 |
| *B. abortus* | | | |
| *B. melitensis* | | | 3 |
| *B. suis* | | | |
| *Burkholderia mallei* | | 3 | |
| *Burkholderia pseudomallei* | | | |

SOURCES: [1]Pike 1978; [2]Pike 1979; [3]Leifer et al. 1970; [4]Harding and Byers 2006; CDC, unpublished material, Nov. 2010; [6]Paweska et al. 2008.

[a]*Coccidioides immitis* and *Coccidioides posadasii* were only recently defined as separate species based on genomic analysis.

that the worker did not consistently follow appropriate biosafety and laboratory procedures and was likely exposed while handling laboratory equipment without gloves (CDC 2000).

- In 2002, an unvaccinated laboratory worker in Texas contracted cutaneous anthrax. The exposure likely occurred by handling a sample vial without gloves; the vial had not been cleaned with household bleach (sodium hypochlorite) and its lid contained *Bacillus anthracis* spores. Other personnel in the laboratory were also working with *B. anthracis* while unvaccinated (CDC 2002a,b).
- In 2005, three laboratory workers at Boston University contracted tularemia (one confirmed and two probable cases). The laboratory was working with the live, attenuated vaccine strain of *Francisella tularensis,* but the exposure may have occurred during routine lab procedures as a result of the stock being contaminated with a virulent wild-type strain. Inconsistent adherence to biosafety procedures may also have contributed to the exposure (Barry 2005).
- In 2006, a laboratory worker at Texas A&M University was infected with *Brucella*. The likely route of exposure was ocular during a procedure to clean an aerosol test chamber. That same year, three laboratory workers were also exposed to *Coxiella burnetii* as measured by serum antibodies, although they did not develop clinical illness (GAO 2007, Kaiser 2007).
- Two cases of infection with *Brucella melitensis* in 2006 were reported from clinical laboratories in Indiana and Minnesota. 146 workers at both labs were reportedly exposed due to a practice of handling unidentified isolates on open benchtops (CDC 2008a). The CDC reported the potential exposures of multiple clinical laboratory workers to attenuated *Brucella abortus* in 2007. Although no cases of infection were reported, the exposures again occurred due to laboratory handling practices. A vaccine against *Brucella* spp. is not available in the United Stats (CDC 2008c).
- Multiple cases of laboratory-associated exposures and infections to vaccinia virus have been reported. The CDC reviewed 5 cases of laboratory exposures to vaccinia (2005–2007, occurring in Connecticut, Iowa, Maryland, Pennsylvania, and New Hampshire), primarily associated with needlestick injuries. Three of the researchers were unvaccinated, one had received vaccination 10 years prior, and one had received an unsuccessful vaccination.[6] A case of vaccinia virus infection in an unvaccinated laboratory worker in Virginia was reported in 2008. The CDC's Advisory Committee on Immunization Practices recommends that workers handling non-highly-attenuated orthopox

[6]As judged by failure of a lesion to form at the vaccination site (CDC 2008b).

viruses, including vaccinia virus, receive immunization every 10 years with the licensed vaccine (CDC 2008b, 2009).

- In 2009, an unvaccinated laboratory worker at USAMRIID became infected with *Francisella tularensis*. In this case, the worker had contracted an unrelated case of tularemia in 1992 and positive serum titers had suggested that she retained a level of immunity (NRC 2010).
- Also in 2009, a fatal case of plague due to an attenuated strain of *Yersinia pestis* was reported in a laboratory worker, the first known fatal case of laboratory-acquired plague in the United States. Although the strain was attenuated, the researcher had potentially complicating health factors. The route of exposure to the pathogen was unclear, although inconsistent glove wearing while handling bacterial cultures may have contributed (CDC 2011b).

Summary information regarding the numbers of Select Agent loss and release reports is presented in Table 2.7. The types and numbers of Select Agents in the loss and release reports are presented in Table 2.8.

As observed in Table 2.7, reports of Select Agent releases increased from 2003 to 2009. The committee noted that that may be attributable, at least in

**TABLE 2.7** Select Agent and Toxin Potential Loss and Release Reports in the United States, 2003–2009

| Year of Report | No. Loss Reports | No. Release Reports |
|---|---|---|
| 2003 | 3 | 0 |
| 2004 | 8 | 8 |
| 2005 | 12 | 9 |
| 2006 | 6 | 21 |
| 2007 | 5 | 52 |
| 2008 | 15 | 113 |
| 2009 | 17 | 192 |
| Total | 66 | 395 |

SOURCE: CDC, unpublished material, Nov. 2010.

**TABLE 2.8** Type and Number of Pathogens and Toxins Noted in Reports of Potential Loss and Release, 2003–2009

| Type | No. Reports of Potential Loss | No. Reports of Potential Release |
|---|---|---|
| Toxins | 8 | 21 |
| Fungi | 2 | 30 |
| Bacteria | 50 | 303 |
| Rickettsia | 4 | 17 |
| Viruses | 10 | 51 |
| Total agents (reports) | 74 (66) | 422 (395) |

SOURCE: CDC, unpublished material, Nov. 2010.

part, to the broad definition of a release event and to the expansion in Select Agent research since 2001.

Tables 2.9 and 2.10, respectively, present the types of laboratory events that resulted in the reported loss or release of Select Agents. Even in regulated research environments where hazardous pathogens and toxins are handled, the tables demonstrate that errors still occur and such incidents as failure of the primary containment system, spills, and sharps injuries can potentially expose personnel to infectious agents.

Those data demonstrate that although incidents of LAI have decreased markedly as biosafety procedures have improved, risk has not been reduced to zero and some infections continue to occur. Other reviews have also noted that the risks of laboratory exposures and LAIs have been reduced but not eliminated (Kimman et al. 2008; Jahrling et al. 2009) and a recent analysis observed that the use of some forms of personal protective equipment and containment systems reduces worker dexterity (Sawyer et al. 2007). Despite training and precautions, accidents such as needlesticks, animal scratches, and broken equipment will occasionally happen, and may result in breaches of personal protective equipment or containment systems. As demonstrated

**TABLE 2.9** Activity Resulting in Potential Loss Events, 2003–2009

| Activity | No. Potential Loss Events |
|---|---|
| Inventory discrepancy | 35 |
| Sample lost or discarded | 12 |
| Shipment or transportation issue | 19 |
| Total loss events | 66 |

SOURCE: CDC, unpublished material, Nov. 2010.

**TABLE 2.10** Activity Resulting in Potential Release Events, 2003–2009

| Activity | No. Potential Release Events |
|---|---|
| Animal bite or scratch | 11 |
| Needlestick or sharps injury | 46 |
| Equipment mechanical failure | 23 |
| Personal protective equipment failure | 12 |
| Loss of containment | 196 |
| Procedural issue | 30 |
| Spill | 77 |
| Total release events | 395 |

SOURCE: CDC, unpublished material, Nov. 2010.

by several of the cases noted above, workers may also fail to rigorously follow biosafety procedures. The standard practices employed by a particular research or clinical laboratory may potentially expose workers as well. As a recent NRC committee noted, "human actions are probably the weakest link in biosafety" (NRC 2010: 34).

It has been noted that there is a level of risk associated with any high-containment laboratory. As the numbers of BSL-3 and -4 laboratories have expanded and the numbers of researchers working with hazardous pathogens such as Select Agents have increased, concerns have been raised that this expansion translates to an increased potential number of exposures and LAIs (GAO 2007). The same report also notes a disincentive to report exposure incidents due to scrutiny from funding agencies and concerns about public perception. The publicity surrounding the 2006 exposures of researchers at Texas A&M University to *Brucella* and to *C. burnetii* and subsequent CDC investigation provide some context for these discussions and again demonstrate that exposures to pathogens may occur even in settings with highly trained and experienced personnel.

A recent discussion of biosafety has noted the difficulty in trying to evaluate the effectiveness of various forms of biosafety practice, observing that "the regulations do not exactly specify the level of protection that they aim to afford, for example, in terms of diminishing exposure of the laboratory workers below a threshold level of infectivity. Furthermore, it is clear that the physical containment classes 1 to 4 afford increasing levels of containment, but it is not sufficiently clear and scientifically supported to what extent they provide effective protection with regard to prevention of infection of laboratory personnel, prevention of airborne escape, etc." (Kimman et al. 2008: 421). In this context, it is also difficult to clearly separate the role of immunization in preventing or reducing laboratory infections from the roles played by personal protective equipment or physical containment. However, the historical reviews of LAIs and recent examples of laboratory exposures to pathogens indicate to the committee that immunization has played a role in reducing LAIs, particularly for pathogens having low infective doses where BSCs alone are insufficient. Researchers working with pathogens such VEE virus, *Brucella melitensis*, *Brucella abortus*, *Francisella tularensis*, and *Coxiella burnetii* may be particularly vulnerable.

Additional experience demonstrating the utility of vaccination in reducing LAIs comes from the National Institute for Occupational Safety and Health, which operates the national hepatitis surveillance program that is used to estimate the number of hepatitis B virus (HBV) infections in health-care workers. The program estimated that 800 health-care workers became infected with HBV in 1995—a 95% decline from the 17,000 new infections estimated in 1983. That result was considered to be due to the federal requirement for the immunization of health-care workers with the hepatitis B vaccine and the use

of standard precautions and other measures required by the Occupational Safety and Health Administration bloodborne pathogens standard (29 CFR § 1910.1030) (NIOSH 1999).

In sum, the Fort Detrick experience, the data provided by DSAT, and reviews of recent laboratory incidents demonstrate that exposures to infectious pathogens, and LAIs, can occur even in the most highly regulated research environments where high-risk pathogens, such as Select Agents, are handled. Although the data indicate substantial progress in biosafety since the 19th century, the committee concluded that immunization remains a valuable and necessary additional safeguard in the practice of safe science.

## 2.4 LESSONS LEARNED FROM THE FORT DETRICK OCCUPATIONAL HEALTH AND SAFETY PROGRAMS

A variety of important lessons learned from these experiences have helped to shape the field of biosafety and safe laboratory practice:

- When a pathogen or toxin that may cause disease is studied in the laboratory, it is logical to expect that sooner or later some laboratory worker will become infected with it.
- Class III BSC systems can operate without LAIs in whole-body and head-only aerosol studies that use repetitive procedures with stable, well-trained, and well-disciplined workers.
- Research using repetitive procedures is less hazardous than research requiring frequent changes in technique and equipment.
- Pathogens with low infective doses (such as *F. tularensis*, VEE, *C. burnetii*, and *B. melitensis*) increase the risk of infection from aerosol exposures.
- In the absence of effective immunization, it is not possible to do basic research using Class I BSCs with a highly infective pathogen without LAIs. As a result of advances in biosafety equipment, research with highly infective pathogens is conducted with other types of BSCs (e.g., Class II and Class III BSCs).
- Analysis of disease surveillance data and lessons learned can provide guidance for making improvements in safe laboratory practices, research protocols, and the use of containment equipment.
- Current biodefense research to satisfy FDA requirements under the animal rule for product licensure (discussed further in Section 4.2.3) will require frequent animal inoculation and aerosol experiments to test the efficacy of biodefense vaccines and other medical countermeasures. That research will probably present an increased risk of exposure of laboratory workers.

**TABLE 2.11** *BMBL* Recommendations for the Use of Investigational Vaccines for the Immunization of Laboratory Workers Who Handle High-Risk Pathogens and Toxins

| Agent | Vaccine | Recommendation |
|---|---|---|
| Botulinum toxin | Pentavalent (ABCDE) botulinum toxoid IND (Investigational New Drug) vaccine | Vaccination is recommended for all personnel working in direct contact with cultures of neurotoxin-producing *Clostridium* species or stock solutions of botulinum neurotoxin; IND vaccine is available through CDC |
| Eastern equine encephalitis, Venezuelan equine encephalitis, and Western equine encephalitis viruses | IND vaccines may be available in limited quantities for each of these viruses | Use of these IND vaccines should be carefully considered and based on risk assessment; Reference is made to the possible availability from the SIP at USAMRIID |
| Rift Valley fever virus | Two vaccines under development | Not available at this time[a] |
| Central European tickborne encephalitis viruses[b] | Vaccine is available[c] | Use of this vaccine should be carefully considered if it is available and use is based on risk assessment; the efficacy of this vaccine against Russian spring–summer encephalitis virus[b] infections has not been established, but is probable based on published data |
| Q fever | Q fever vaccine | Use of the Q fever vaccine should be restricted to laboratory workers who are at high risk of exposure and who have no demonstrated sensitivity to Q fever antigen. Reference is made to the possible availability from the SIP at USAMRIID[d] |
| Other infectious agents | Licensed vaccines | Commercial vaccines should be made available to workers to provide protection against the risk posed by occupational exposure to an infectious agent they will handle[e] |

SOURCE: CDC/NIH 2009.

[a]One vaccine (live, attenuated) is available in the SIP IND program; the other is in clinical trial (National Institutes of Health Clinical Trials, ClinicalTrialsFeeds.org at http://clinicaltrialsfeeds.org/clinical-trials/show/NCT00869713).

[b]A group of closely related tickborne viruses reclassified from BSL-4 containment to BSL-3 containment, provided that workers are immunized. The reclassified viruses include Absettarov, Hanzalova, Hypr, and Kumlinge. Russian spring and summer encephalitis virus is now known as Far Eastern tick-borne encephalitis virus.

[c]Not currently available in the United States.

[d]A skin test is administered prior to Q fever vaccination to assess reaction to the Q fever antigen and to reduce adverse event. Use of Q fever vaccine is currently limited by skin test availability.

[e]Licensed vaccines against smallpox and yellow fever are available; the committee noted that research involving these pathogens should be performed only by vaccinated individuals.

CDC and NIH have incorporated concepts learned from the Fort Detrick experience and risk assessment paradigm in the writing of all five editions of *Biosafety in Microbiological and Biomedical Laboratories* (*BMBL*), which was first published in 1984. The *BMBL* 5th edition, published in December 2009, emphasizes evaluating the technical proficiency of laboratory workers in performing laboratory protocols as a major issue in conducting a risk assessment. Table 2.11 includes the specific recommendations found in the *BMBL* 5th edition for the use of investigational vaccines for the immunization of laboratory workers who handle high-risk pathogens and toxins (CDC/NIH 2009).

## 2.5 FINDINGS ON LABORATORY INFECTIONS

From its review of the early history of the SIP and data on experience with laboratory infections caused by hazardous pathogens, the committee found the following:

- *Finding 1:* The Special Immunizations Program has played an important role in offering additional protection to laboratory workers who are involved in U.S. biodefense research. The lessons that have been learned through the program have advanced the practice of biosafety.
- *Finding 2:* Despite advances in other components of biosafety, immunization remains an integral component of an occupational health and safety program for people who work with highly hazardous pathogens.

# 3

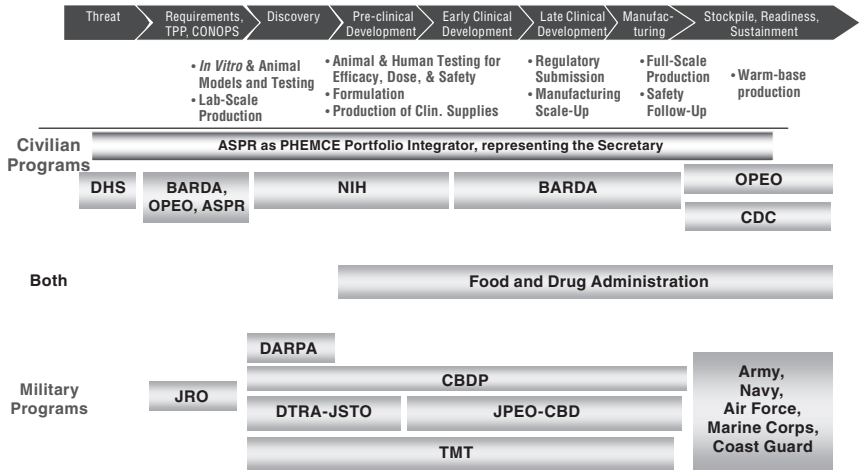
# The U.S. Medical Countermeasures Enterprise and Recent Reviews and Current Operation of the Special Immunizations Program

The Special Immunizations Program (SIP) remains a distinct but small component, but it is part of the overall U.S. military and civilian medical countermeasures (MCM) enterprise, so its effectiveness must be considered in this broader framework

## 3.1 THE U.S. MEDICAL COUNTERMEASURES ENTERPRISE

Overarching U.S. security goals and objectives relevant to MCM against biological threats and infectious diseases are derived from strategic documents, such as the U.S. *National Security Strategy* (White House 2010), the *National Strategy for Countering Biological Threats* (NSC 2009), the *National Health Security Strategy* (HHS 2009b), Homeland Security Presidential Directive 18 (White House 2007), and *Quadrennial Defense Reviews* (DOD 2010). Assessing which pathogens and toxins pose the most important risks to U.S. national security and establishing initiatives to develop and acquire MCM involve coordination among multiple agencies and offices of the federal government, as depicted in Figure 3.1. Assessments of risk and priority-setting guide the establishment of acquisition requirements, with the Department of Defense (DOD) assuming primary responsibility for the development and acquisition of MCM against military threats and the Department of Health and Human Services (HHS) focusing on threats to the civilian population. Those agencies also interact with extramural researchers and industry to develop the products needed for the MCM pipeline.

Within HHS, the Office of the Assistant Secretary for Preparedness and Response (ASPR) assumes a primary role for the oversight of programs to develop and acquire MCM for use in the civilian population. The office is re-




Key:

| | |
|---|---|
| ASPR | Assistant Secretary for Preparedness and Response |
| BARDA | Biomedical Advanced Research Development Authority |
| CDC | Centers for Disease Control and Prevention |
| CBDP | Chemical and Biological Defense Program |
| CONOPS | Concept of Operations |
| DARPA | Defense Advanced Research Projects Agency |
| DHS | U.S. Department of Homeland Security |
| DOD | U.S. Department of Defense |
| JPEO-CBD | Joint Program Executive Office for Chemical/Biological Defense |
| JRO | Joint Research Office |
| JSTO | Joint Science and Technology Office |
| NIAID | National Institute for Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| OPEO | Office of Preparedness and Emergency Operations |
| PHEMCE | Public Health Emergency Medical Countermeasures Enterprise |
| TMT | Transformational Medical Technologies Program |
| TPP | Target Product Profiles |

**FIGURE 3.1** Government agencies involved in the civilian and military MCM pathway. SOURCE: Adapted from NBSB 2010b.

sponsible for leading the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) and houses the Biomedical Advanced Research and Development Authority (BARDA), which provides an integrated, systematic approach to the development and purchase of vaccines, drugs, other therapies, nonpharmaceutical countermeasures, and diagnostic tools for public health medical emergencies, manages Project Bioshield, and participates in such initiatives as the Integrated Portfolio for CBRN Medical Countermeasures.[1] In addition to BARDA, created under the Pandemic and All-Hazard Preparedness Act of 2006, HHS supports MCM development and research through the

[1]Further information is available at the HHS Web site MedicalCountermeasures.gov at https://www.medicalcountermeasures.gov/default.aspx.

National Institutes of Health (NIH), particularly through the National Institute of Allergy and Infectious Diseases (NIAID 2007; HHS 2007, 2009b, 2010a). NIAID's research agenda includes construction and renovation of biosafety level 3 (BSL-3) and BSL-4 laboratories around the country, including an NIAID Integrated Research Facility at Fort Detrick, MD, an Integrated Research Facility at NIAID's Rocky Mountain Laboratories in Hamilton, MT, National Biocontainment Laboratories at Boston University and at the University of Texas Medical Branch at Galveston; and construction or renovation of numerous BSL-3 and BSL-2 biocontainment laboratory suites. The Centers for Disease Control and Prevention (CDC) also plays a role in the national enterprise by being the lead agency in the diagnostic and immediate public health response to emerging infections and maintaining the Strategic National Stockpile (SNS), which contains vaccines, therapeutics, and medical supplies that can be rapidly deployed in the event of a public health emergency.

The military MCM pipeline is complex, with important research and development roles played by the DOD Chemical and Biological Defense Program (CBDP), the Defense Advanced Research Projects Agency, the Joint Science and Technology Office for Chemical and Biological Defense (JSTO) which is part of the Defense Threat Reduction Agency (DTRA), and the DOD Transformational Medical Technologies (TMT, formerly TMTI) program. The military also maintains the Joint Program Office for Chemical and Biological Defense (JPEO-CBD), which includes the Joint Vaccine Acquisition Program (JVAP) as one of its activities. The JVAP plays an important role in the advanced development[2] of vaccines that have been identified as military needs and includes as its mission to "develop, produce, and stockpile U.S. Food and Drug Administration (FDA)–licensed vaccine systems to protect the Warfighter against biological warfare agents" (JPEO-CBD 2011). As a result, JVAP has a role that complements but is distinct from that of the SIP, which also serves researchers who are working at earlier stages in the scientific R&D pipeline and which offers Investigational New Drug (IND) vaccines that may not yet have been identified as direct warfighter needs or been transitioned into the advanced development pipeline. Although the individual armed services are depicted to the right of Figure 3.1 under the acquisition, stockpiling, and readiness of licensed products, research programs within the services, such as those at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), also make important contributions to R&D efforts. As discussed in Chapter 2, the U.S. Army and USAMRIID in particular have a long history of research on hazardous pathogens, and USAMRIID operates the only BSL-4 facility in

[2]In DOD terminology, the budget category that includes research, development, test, and evaluation (RDT&E) activities for the advanced development of vaccines with direct relevance to identified military need is often referred to as 6.3, Advanced Technology Development. Earlier-stage basic research and applied research are in categories 6.1 (basic research) and 6.2 (applied research).

DOD. As provided by DOD Directive 5160.05E (DOD 2008) and Chairman of the Joint Chiefs of Staff Instruction CJCSI 3112.01A (Joint Chiefs 2010), the Army also serves as the DOD executive agent for the CBDP, further highlighting its central role in U.S. biodefense efforts.

## 3.2 NATIONAL BIODEFENSE AND MEDICAL COUNTERMEASURES PRIORITIES

Through their assessment and requirements-setting processes, DOD, the Department of Homeland Security (DHS), and HHS establish lists of priority agents against which MCM are desired. They include historical pathogens of concern and, increasingly, more flexible strategies, such as broad-spectrum countermeasures, platform technologies, and products targeting new or emerging infectious agents.

Although the military (DOD-led) and civilian (HHS-led) MCM efforts have somewhat different missions and establish their own priorities, the agencies have also recognized their common interest in advancing the MCM pipeline and have attempted to coordinate and integrate their needs better. An understanding of pathogen priorities identified by the agencies can be discerned in recent program reports and reviews. For instance, the February 2010 report from the National Biodefense Science Board (NBSB), *Optimizing Industrial Involvement with Medical Countermeasure Development*, contains "Table 1: Top Priority Medical Countermeasures (MCMs) against Chemical, Biological, Radiological, and Nuclear Threats, Annotated by License and Stockpile Status, Reflecting HHS and DOD Programs, February 2010" (NBSB 2010a: 13), which includes the pathogens *Bacillus anthracis* (anthrax), *Clostridium botulinum* (botulism), filoviruses (Ebola and Marburg), Junin virus, variola major virus (smallpox), *Burkholderia mallei* (glanders) and *Burkholderia pseudomallei* (melioidosis), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia), and *Rickettsia prowazekii* (typhus). DOD and HHS have also established the Integrated Portfolio for CBRN Medical Countermeasures Portfolio (also commonly called "One Portfolio") (Newmark 2009). As presented in 2009 by the JPEO-CBD, priority biological countermeasures can be classified in three categories: DOD-unique, HHS-unique, and common (Newmark 2009):

- *DOD-unique:*
  - *Brucella* spp. (brucellosis) (prophylactic use).
  - Venezuelan equine encephalitis (VEE) virus, eastern equine encephalitis (EEE) virus, and western equine encephalitis (WEE) virus (prophylactic and therapeutic uses).
  - *Yersinia pestis* (plague) (prophylactic use).
  - *Clostridium botulinum* (botulism) (prophylactic use).
  - Staphylococcal enterotoxin B (prophylactic and therapeutic uses).

- *Francisella tularensis* (tularemia) (prophylactic use).
- Ricin (prophylactic and therapeutic uses).
- Other, unfunded.

- *HHS-unique*
  - *Burkholderia* spp. (therapeutic use).
  - Junin virus (therapeutic use).
  - *Yersinia pestis* (plague) (therapeutic use).
- *Common*
  - *Bacillus anthracis* (anthrax) (prophylactic and therapeutic uses).
  - Variola virus (smallpox) (prophylactic and therapeutic uses).
  - Ebola and Marburg viruses (prophylactic and therapeutic uses).
  - *Francisella tularensis* (tularemia) (therapeutic use).
  - *Clostridium botulinum* (botulism) (therapeutic use).

A recent presentation by DOD's TMT program, which seeks to exploit novel technologies for the development of next-generation countermeasures, similarly illustrates the universe of priority pathogen threats (Hough 2010), including additional infectious pathogens and toxins of interest to DOD that are not presented in the NBSB and One Portfolio documents and priorities for the development of countermeasures against broad-spectrum targets and emerging threats and is presented as Figure 3.2.

The creation of stockpiles of vaccines and other MCM for civilian use is supported through Project BioShield and added to the SNS as they are acquired. The acquisitions have focused largely on vaccines and therapeutics

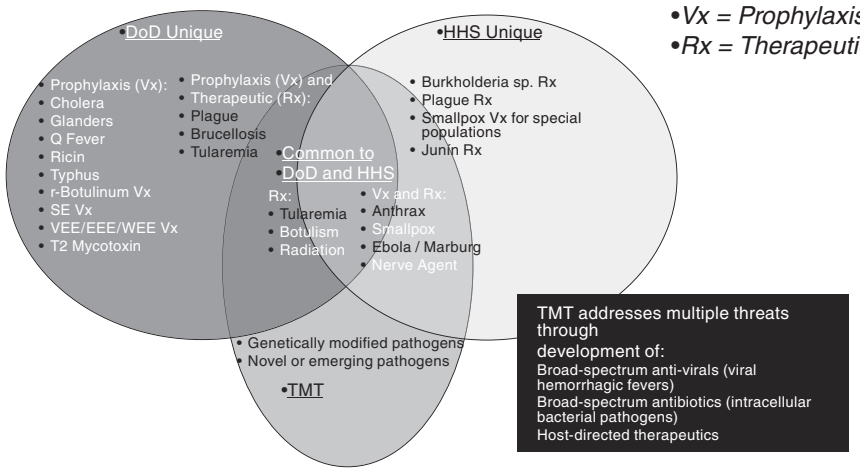



**FIGURE 3.2** U.S. MCM needs. SOURCE: Hough 2010.

against a narrow selection of pathogens—notably *Bacillus anthracis* (anthrax), the variola major virus (smallpox), and *Clostridium botulinum* (botulism)—with countermeasures against radiation exposure.

## 3.3 REVIEW OF PREVIOUS REPORTS RELEVANT TO BIODEFENSE MEDICAL COUNTERMEASURES

Numerous reports and reviews since 2001 have discussed the military and civilian U.S. MCM and biodefense vaccines pipeline.

### 3.3.1 The Military Medical Countermeasures Enterprise

Since the report to the deputy secretary of defense by an independent panel of experts (referred to as the Top Report) in 2001, there have been several external analyses of DOD's biodefense programs and strategies for MCM (Top et al. 2000 in DOD 2001; IOM 2002, 2004). The panel of experts that produced the Top Report noted the large number of DOD units involved in the development and acquisition of biodefense and infectious disease products at that time and the "fragmented" nature of the program, observed that DOD was not following best practices found in industry, and recommended creation of a dedicated DOD government-owned, contractor-operated (GOCO) vaccine production facility.[3] A 2002 Institute of Medicine (IOM) report likewise criticized DOD's administrative separation of the acquisition processes for vaccines intended to protect against naturally occurring infectious diseases and those for defense against biowarfare as scientifically and organizationally "unsound." The report recommended manufacturing arrangements to ensure "consistent vaccine availability" and suggested that DOD seek a "new paradigm" with FDA for regulation of special-use vaccines likely to remain in IND status.

The 2004 IOM report *Giving Full Measure to Countermeasures* recommended that funding for DOD countermeasures double in 5 years to $300–600 million and noted that new countermeasures require "substantial and sustained" effort, including having a strong scientifically knowledgeable leadership and adequate funding. It also recommended that the MCM program be given "genuine priority." To accomplish that, the report suggested that Congress authorize the creation of a new agency within DOD to provide the necessary infrastructure and creation of an external review committee of vaccinologists and other scientists to review and evaluate the DOD research program. Finally, the report called for more effective collaboration between academe, industry, and government and noted a need to address MCM regulatory challenges.

Those external reviews generally noted a complex and fragmented system

[3]The costs of this capacity were estimated to include $370 million for facility construction and $35–50 million per year per vaccine to be produced (Top et al. 2000 in DOD 2001).

of offices responsible for the DOD MCM development and acquisition pipeline and consistently recommended new approaches to achieving military vaccine development and acquisition goals, increased collaboration with the private sector, and development of a dedicated vaccine production facility. Although a new agency was not created within DOD to oversee all aspects of MCM, DOD restructured aspects of its CBDP in 2003. The current system of CBD responsibilities outlined in the CBDP annual report to Congress (CBDP 2010) includes overall coordination responsibilities through the Office of the Assistant to the Secretary of Defense for Nuclear and Chemical and Biological Defense Programs; the Army as executive agent for chemical, biological, radiological, and nuclear (CBRN) programs; and DTRA assuming substantial responsibilities for science and technology. The 2003 implementation plan was intended to streamline operations and resulted in the creation of the JPEO-CBD executed by the Army and JSTO-CBD responsibilities in DTRA.

### 3.3.2 The Civilian Medical Countermeasures Enterprise

Recent reports have also reviewed issues in the civilian MCM pipeline. The NBSB, which like BARDA was created under the authority of the 2006 Pandemic and All-Hazards Preparedness Act, provides the secretary of HHS expert advice on public health emergency preparedness, including biological threats and natural infectious diseases. In addition to voting members, the NBSB includes ex officio members who represent a variety of federal agencies. In 2010, the NBSB released two reports on medical countermeasures: *Optimizing Industrial Involvement with Medical Countermeasure Development* (Optimizing Report) and *Where Are the Countermeasures? Protecting America's Health from CBRN Events* (Countermeasures Report) (NBSB 2010a,b).

The Optimizing Report calls for "concerted action" among the various departments, agencies, and other entities of the U.S. government; expansion of MCM markets to include international partners, first responders, state and local governments, and laboratories; and innovative partnerships with industry, including long-term commitments and consistent funding. The report also identifies several barriers to government–industry collaborations to develop MCM, including difficulty in contracting, the need for clarity about MCM requirements, lack of coordination among federal agencies that have MCM development activities, inadequate understanding of the commercial biopharmaceutical enterprise in the federal government, an immature commercial market for MCM to create incentives for industry; and inadequate mechanisms to maintain industry involvement in MCM development by preserving manufacturing capacity after initial lots of MCM have been produced.

The Countermeasures Report points to a continued need to foster a shared vision and strong coordination among HHS-led efforts and across DOD and HHS countermeasures missions. The report emphasizes the need for a com-

prehensive national strategy and common purpose and the need to address regulatory concerns in MCM development, such as the application of FDA's "Animal Rule" (discussed in Section 4.2.3). The report highlights the progress made by the Integrated Portfolio approach being pursued by HHS and DOD and notes (NBSB 2010b: 9) that

> it is in the national interest to have distinct DOD and HHS programs in MCM development, and the Integrated Portfolio approach jointly adopted by these two Departments offers an impressive example of coordination and collaboration that other agencies could well use as a model. Collaboration between DOD and HHS, however, needs to continue to mature and broaden.

The report's executive summary (NBSB 2010b: 5) notes further that

> the federal MCM program to date can be characterized as a good effort conducted by talented people, but lacking in centralized leadership and with poor synchronization of the agencies within the Department of Health and Human Services (HHS). The effort has not fully tapped the talent of the Department of Defense (DOD) and the Department of Homeland Security (DHS). The combined effort is under-resourced and has largely failed to mobilize the productive skills and efforts of industry. There is no unified national strategy that prioritizes the array of threats and encompasses all aspects of responsiveness, from creating to stockpiling to distributing MCMs. Instead, development of MCMs has been too much a matter of selecting projects to fit within available budgets, instead of allocating the necessary funds to tackle a prioritized list of threats.

Recognizing those challenges, in December 2009 the secretary of HHS requested a review of the civilian countermeasures efforts. The IOM held a workshop on this topic in February 2010 and NBSB also published the two reports cited above. The review requested by the secretary and led by ASPR, *The Public Health Emergency Medical Countermeasure Enterprise Review: Transforming the Enterprise to Meet Long Range National Needs* was released by ASPR in August 2010 (HHS 2010b; IOM 2010).

The recommendations made in those military and civilian countermeasures reports highlight special challenges inherent in the development of vaccines and other countermeasures against biothreat agents and emerging infectious diseases, including limited commercial markets, the difficulty of conducting clinical trials and following a traditional path to FDA licensure, and a need to continue anticipating and addressing new and emerging threats. The reports conclude that U.S. countermeasures efforts are of value but that improvement can and should be made to enhance their effectiveness. Table 3.1 presents selected findings and recommendations from the studies, which broadly are in several categories:

**TABLE 3.1** Selected Findings and Recommendations from Extramural Reviews of Biodefense Vaccines and MCM

| Theme | Selected Findings and Recommendations |
|---|---|
| Leadership and priority-setting | "Establish a unified process for identifying and prioritizing threats and requirements" (Top et al. 2000 in DOD 2001).<br>"DOD needs to consolidate and integrate its vaccine research, development, and acquisition programs for BW defense and endemic disease protection" (Top et al. 2000 in DOD 2001).<br>"DOD must adopt industry practices, capture industry interest, and invest its own corporate resources in the management and execution of the AVP [Acquisition of Vaccine Production] program if it has any hope of solving its vaccine requirements" (Top et al. 2000 in DOD 2001).<br>"Combine all DOD vaccine acquisition responsibilities under a single DOD authority that includes the entire spectrum of responsibility—from potential threat definition through research and development, advanced product development, clinical trials, licensure, manufacture, procurement, and continued maintenance of manufacturing practice standards and regulatory compliance" (IOM 2002).<br>"Consolidate infrastructure, funding, and personnel for DOD acquisition programs for biodefense and naturally occurring infectious disease vaccines" (IOM 2002).<br>"Actively encourage the development, distribution, and use of a well-defined and validated research priority-setting mechanism, which could involve prioritized, weighted lists of infectious disease threats and formal scenario-planning exercises" (IOM 2002).<br>"The Secretary of Defense and Congress must make the DOD program for medical biodefense countermeasures a high priority" (IOM 2004).<br>"Congress should authorize the creation of the Medical Biodefense Agency, a new DOD agency responsible for the research and development program for medical countermeasures against biological warfare agents (IOM 2004)"<br>"Congress should establish an external review committee of experts in the development of vaccines and drugs to review and evaluate the program and performance of the DOD research and development program for medical biodefense countermeasures each year" (IOM 2004).<br>"The Secretary of HHS promptly tasks senior HHS leaders to develop a common set of prioritized research goals, prioritized product requirements, and prioritized dispensing goals for civilian populations; and coordinates these priorities with DOD" (NBSB 2010b).<br>"For FY2012 and beyond, the Secretary of HHS develops a coordinated budget request relevant to CBRN MCM budget lines within NIH, NIAID, BARDA, CDC, FDA, and ASPR (and in conjunction with DOD)" (NBSB 2010b).<br>"The Secretary of HHS develops a legislative plan to seek multi-year funding authority for CBRN MCM efforts" (NBSB 2010b).<br>Recommendations under Enhancements to the MCM Enterprise: 1. Strategic Leadership, Program, and Administrative Changes; 2. Updating the Requirements for Current and Future Products; 3. Multiyear Planning Process (HHS, 2010b) |

*continued*

**TABLE 3.1** Continued

| | |
|---|---|
| Partnerships | "Use an integrated strategy that includes: GOCO…, PSC, DOD biomedical laboratories, and DOD partnerships with commercial companies (including appropriate incentives), National Institutes of Health, Public Health Service, and academia" (Top et al. 2000 in DOD 2001).<br>"Leverage DOD research efforts by building greater interactions and an effective formalized coordinating structure that links DOD research to vaccine development activities carried out by the Department of Health and Human Services and other public and private groups" (IOM 2002).<br>"Ensure that there is an effective, ongoing senior advisory group—one providing perspectives from both within and outside of DOD—to assess program priorities and accomplishments, to act as a proponent for vaccines and other infectious disease countermeasures, and to maintain active relationships with current science and technology leaders in academic, government, and corporate sectors" (IOM 2002).<br>Several recommendations under "Establishing Effective Collaboration with Academia and the Private Sector" (IOM 2004).<br>"Various departments, agencies, and entities of the U.S. Government must act in concert to ensure success"(NBSB 2010a).<br>"The U.S. Government must create, sustain, and enhance innovative partnerships with private industry" (NBSB 2010a). |
| Manufacturing and regulatory barriers | "Work toward manufacturing arrangements that ensure consistent vaccine availability by addressing long-term commitment, predictable volumes and prices, indemnification, and intellectual property issues. These arrangements should include consideration of vaccine-specific, government partnerships with individual private manufacturers, a private manufacturer consortium, and government-owned, contractor-operated vaccine-production facilities" (IOM 2002).<br>"Vigorously seek a new paradigm for the regulation of special-use vaccines that remain in Investigational New Drug status with the Food and Drug Administration without reasonable prospects of licensure under current rules, ensuring demonstration of the safety and efficacy of these products commensurate with their anticipated use" (IOM 2002).<br>Meeting the Challenges of the Regulatory Process: several recommendations including, "the DOD agency should work with NIH and engage FDA to develop additional animal models that will be useful for specific agents or products of particular concern to DOD…. FDA should work with the scientific community to enrich the science base that the agency will have to draw on in order to apply the Animal Efficacy Rule…." (IOM 2004).<br>"[P]articipate in interdepartmental efforts to make a formal assessment of the need for facilities for animal testing and holding and for GMP-compliant manufacturing of material for clinical testing that will arise from research efforts to develop medical countermeasures to biowarfare or bioterrorism agents that are under way, planned, or likely" (IOM 2004).<br>"The ASPR promptly provides a plan to the Secretary of HHS to provide for centralized advanced development and manufacturing of selected biological MCMs, based on one or more public-private partnerships (PPPs) or federally funded research-and-development centers (FFRDCs)" (NBSB 2010b).<br>Several recommendations under New Infrastructure Initiatives, including: 1. 21st-Century Regulatory Science; 2. Flexible Manufacturing and Advanced Development Core Services Partnerships; 3. Expanding the Product Pipeline and Addressing Multiuse Potential (HHS 2010b). |

**TABLE 3.1** Continued

| | |
|---|---|
| Workforce and other needs | "The Medical Biodefense Agency should define the capabilities needed for its medical countermeasures workforce…." (IOM 2004).<br>"The U.S. Government should expand MCM markets to include international partners, State, local, and tribal governments, laboratorians, and first-responders in each of these sectors. These markets are relatively small, but including them would send industry an important message that the U.S. Government is not the only market. Adding MCMs to Standardized Equipment Lists (SELs) and Authorized Equipment Lists (AELs) would allow State and local first-responders to use federal grant funds to protect these personnel against occupational hazards" (NBSB 2010a). |

- *Strengthen leadership and priority-setting.* The reports suggest a need for additional mechanisms to coordinate and centralize authority throughout the life cycle of MCM development and acquisition, a need to establish and communicate MCM priorities with the development of a process of regular review and adjustment, and a need for consistent and multiyear funding.
- *Build partnerships.* The reports suggest a need to promote communication between military and civilian countermeasures programs to maximize the effectiveness of the enterprise and a need to strengthen partnerships with private industry.
- *Address manufacturing and regulatory barriers.* The reports suggest a variety of strategies to ensure MCM manufacturing capacity, such as creation of a GOCO vaccine facility, changes in the development and acquisition process to strengthen industry involvement in development and manufacturing, and new regulatory science in partnership with FDA.
- *Other needs.* The reports include calls to support a qualified and effective workforce and a suggestion to expand MCM market planning to consider international uses and uses in occupational health settings.

## 3.4 RECENT DEVELOPMENTS REGARDING THE SPECIAL IMMUNIZATIONS PROGRAM (2000–2010)

The committee examined both the recent history of the SIP (2000–2010) and the structure and operations of the current program in the context of efforts to review the overall MCM enterprise.

As noted in Chapter 2, immunizations provided through the SIP consist largely of legacy investigational vaccines produced by the Salk Institute Government Services Division (TSI GSD) facility, which is now closed. Using those supplies, the SIP continues to operate to provide IND and licensed vaccines to

at-risk military and civilian personnel, ensure the safety and occupational health of participants through continuous medical evaluation, provide evaluation of and treatment for occupational exposures, and collect safety and immunogenicity data (including long-term follow-up data) to further medical research.

The expansion of research in both emerging infectious diseases and biothreat agents created a larger scientific community potentially at risk, with the potential to require a corresponding increase in the immunization services provided by the SIP. From 2000 to 2002, the number of volunteers enrolled in the SIP grew from 600 to about 800 patients. The substantial cost of operating the program was borne solely by USAMRIID and its parent command, the U.S. Army Medical Research and Materiel Command (USAMRMC), in an unsustainable situation.

A report by an external biosafety assessment team issued in 2002 (*Findings and Recommendations on Alternative Strategies for Worker Protection*) noted that select agent vaccine support for "added" protection of laboratory workers provided by the SIP was essential not only for USAMRIID but for institutions throughout the United States in which work on special pathogens was being conducted. The report suggested that CDC's Advisory Committee on Immunization Practices (ACIP), not USAMRIID, should be responsible for deciding immunization practice with these experimental vaccines at the national level (Boudreau 2010).

In November 2002, at the American Society of Tropical Medicine and Hygiene meeting, a draft decision memo was developed by USAMRMC, NIAID, and CDC to explore possible solutions to the mounting costs and expertise required to ensure proper IND vaccine testing and volunteer safety and compliance with FDA requirements. In January 2003, an SIP interagency working group was formed to explore solutions to those problems, and an SIP subgroup of the Biodefense Vaccine and Immunologics Committee was convened on March 14, 2003. The subgroup comprised representatives of DOD, the U.S. Department of Agriculture (USDA), DHS, and HHS (CDC, NIAID, FDA, and NIH) and was chaired by a representative of HHS.

The SIP subgroup held five meetings to develop options, refine program costs, and validate enrollment projections; held executive briefings on its interim report for the commander of USAMRMC, the director of CDC, the director of NIAID, the commander of the U.S. Army Medical Command and the Army surgeon general, the deputy assistant secretary for defense for chemical and biological defense, the assistant secretary of defense for health affairs, DHS, the Office of Science and Technology Policy, and the associate administrator of the USDA Agricultural Research Service; held five interim meetings with the U.S. government interagency working group co-chair, Philip Russell; and gave an initial briefing to the full Weapons of Mass Destruction Medical Countermeasures (WMDMC) Subcommittee on June 20, 2003. The guidance

received at those executive briefings included the following: USAMRMC would be willing to accept the SIP mission with consistent supplemental funding from non-DOD users of the program; USAMRMC would maintain its own program to protect Army and DOD users. DHS would not designate funds to the program, nor could Project BioShield be used to support the program (Eitzen 2010). In 2003, the commander of USAMRIID also sent a memo to all agencies stating that a charge of $6,457 per person enrolled in the SIP (paid in advance) would be assessed to cover the continuing costs of the program. All enrolled participants would also be required to undergo annual medical evaluation (Henchal 2003).

At a briefing on May 27, 2004, Office of Management and Budget (OMB) representatives supported the developing SIP subgroup recommendations. The final report was given to the WMDMCS Senior Group (July 9, 2004), and on December 16, 2004, the chair of the SIP subgroup, Edward Eitzen, briefed the U.S. Homeland Security Council Policy Coordinating Committee (HSC PCC) on the proposed SIP recommendations (Eitzen 2004, 2010). The subgroup recommended that vaccines against the following be included in the SIP: pentavalent botulinum toxoid, tularemia, Rift Valley fever (RVF), VEE TC 83, VEE C 84, EEE, WEE, and Q fever. It also presented three options for the program structure:

1. An Army-sponsored SIP whereby the Army (USAMRMC) executes the SIP with funding provided by all participating federal agencies in a fully burdened cost-sharing arrangement according to use of the program (an option that also noted possible involvement of regional SIP sites).
2. An HHS- or DHS-sponsored SIP with regional immunization sites.
3. Two separate programs—an Army-sponsored SIP for military and DOD personnel and a civilian agency-sponsored SIP for civilian participants.

The subgroup concluded that a cost-sharing arrangement among agencies, according to program use, with one agency as sponsor of the program was the "only acceptable arrangement" (Eitzen 2004, 2010) and recommended option 1 because

- One program would maximize program management and avoid duplication of costs that would occur with two programs.
- The Army was willing to accept management of an expanded program with equitable cost-sharing agreements for the distribution of the fully burdened program costs among all participants.

- The approach would ensure that DOD contingency protocols are supported.
- The approach would provide experienced and trained staff (although this would require augmentation and facility site expansion to accommodate program growth and coverage of other agencies).
- A new program start with a separate IND holder would not be required (so there would be much less lag time to availability of vaccines to civilian researchers).
- Existing investments in an automated clinical database-management system would not require duplication.
- Proven efficiency in vaccine storage and shipment would be preserved.
- Having one sponsoring agency would conserve product availability.

Projected enrollment in the expanded SIP anticipated by the subgroup in its deliberations included 660 DOD users, about 800 HHS users (CDC, 550; NIH, 200; and FDA, 45), and additional users in USDA (60), DHS (100), other federal agencies (60), and private organizations (260). Cost estimates also were provided for the SIP at its current size (about 600 enrollees) and for an expanded program (of about 2,000 enrollees with the option of expansion to regional immunization sites—discussed in more detail in Section 3.5). The characteristics of the expanded SIP would include the following (Eitzen 2004, 2010):

- Overall cost sharing as a percentage of the total cost. Each agency's percentage would be calculated on the basis of estimates of the number of vaccines requested by it.
- Variable costs for program expenses related to different vaccines, which reflect the number of doses required for the primary series, the number of protocol-mandated follow-up visits, and the number of booster vaccinations anticipated per year (no charge is assessed for the investigational vaccines themselves).
- No individual invoicing by volunteer and no end-of-year refunds if total vaccines initially requested were not required.
- Overall program costs calculated on the basis of salaries of clinical and regulatory staff, equipment expense, inventory and storage of vaccines, vaccine-stability testing, medical supplies, diagnostic testing, overhead, training, travel, office supplies, and information technology support for clinical and electronic document databases and product testing and storage.

The total costs were to be divided by the total number of injections requested annually, and the appropriate share of program costs would be invoiced to individual agencies according to their stated requirements.

Those recommendations were in accord with the earlier (May 2003) memo by the deputy assistant secretary of the Army, which stated that the SIP was to be a fully reimbursable program that used both FDA-licensed and unlicensed vaccines, the latter administered under IND protocols, and that the U.S. Army Medical Materiel Development Activity (USAMMDA) was to be the proponent for the SIP. Although receipt of investigational vaccines was to be completely voluntary, mandatory risk assessments were required before receipt of investigational vaccines. Furthermore, there was to be an evaluation of all persons then enrolled in the SIP to ensure they met the newly issued requirements, and re-enrollment in the SIP was to be on a cost-reimbursable basis with a fee schedule established by USAMMDA (Fatz 2003).

The HSC PCC approved the expanded SIP program and ordered that it be implemented with fully burdened funding contributed by the participating departments and agencies according to their percentage of SIP use.[4] Under that arrangement, USAMRMC would continue to manage the program at Fort Detrick with a proposed expansion to three satellite locations. At this meeting, all participating agencies were in agreement that a cost-sharing program administered by DOD would be the model for a nationwide SIP, and the program was to be implemented in FY 2006 for a 5-year period. In its consideration of options and budget projections, the SIP subgroup included one-time costs of starting up regional sites and costs of testing and vialing new lots from bulk stocks of the existing SIP vaccines to meet the projected user base of 2,000 enrollees (Eitzen 2010). In his 2004 briefing paper, the subgroup chair noted that four additional IND vaccines might be of potential interest to the SIP (for Chikungunya virus, Hantavirus, Junin virus, and tickborne encephalitis virus) (Eitzen 2004). The subgroup did not, however, address the issue of existing vaccine supply for the SIP beyond considering the potential costs of vialing of new lots of existing Salk GSD vaccines from bulk stocks. The subgroup also did not consider in detail the addition of other existing vaccines or the development of new vaccines for inclusion in the SIP.

In February 2005, the Division of Medicine of USAMRIID and the Division of Regulatory Affairs of USAMMDA at Fort Detrick were asked to compile the number of vaccines requested by each government agency and to update budgetary projections for OMB. An initial estimate presented to OMB in January 2005 was $16.8 million, and the budget estimate for 2006 was $13.8 million. Those estimates allowed initiation of two new regional sites for vaccine administration in the southeastern and southwestern United States. Those regional sites were not established, however, because of budget constraints.

In a progress report written in May 2007, it was noted that in 3½ years since the HSC PCC ordered implementation of the expanded SIP, agencies had not set aside funding for an expanded SIP accessible to non-DOD as well

[4]The committee was unable to find formal documentation of this agreement.

as DOD researchers. Therefore, some potential users may have been working without access to potentially protective IND vaccines available in the SIP. The report suggested that an interagency implementation and oversight body be established to drive implementation of the HSC PCC order (Eitzen 2010). Table 3.2 summarizes some of these significant developments regarding the SIP.

In summary, both the 2002 and 2004 reviews of the SIP recommended that an expanded SIP be implemented to include workers in government agencies beyond the Army, both federal and state, and academe and industry.

## 3.5 THE CURRENT SPECIAL IMMUNIZATIONS PROGRAM

### 3.5.1 Scope and General Structure of the Program

The committee noted that the SIP is the only program in the United States that provides investigational vaccines for laboratory workers exposed to hazardous pathogens and toxins.[5] Although the SIP was conceived in support of laboratory personnel working at what is now USAMRIID, program reviews and agreements have expanded the array of participating organizations. As a result, the SIP currently offers selected investigational and licensed products to both military and civilian personnel working in a biohazardous environment who are at risk for pathogen and toxin exposure. The program also conducts medical monitoring of participants.

The SIP is housed in DOD under USAMRMC. It continues to operate within the Medical Division of USAMRIID, although a variety of offices in and outside USAMRIID support aspects of the overall program. The SIP facilities include the SIP clinic for administration of vaccines and medical follow-up and the SIP clinical laboratory. USAMRIID physicians from the Division of Medicine serve as principal investigators and subinvestigators for the protocols that govern the administration of investigational SIP vaccines.[6] Review of the IND protocols, enrollment of personnel receiving vaccines, and other regulatory compliance issues are also subject to oversight by the USAMRIID Institutional Review Board, the USAMRMC Office of Human Research Protection, and the Quality Assurance and Regulatory Compliance Office. In addition, the USAMRIID Medical Division houses the necessary medical monitoring services for SIP IND protocols and encompasses the medical surveillance function of the SIP. USAMRMC's USAMMDA serves as the IND sponsor representative on

[5]Several IND biologics (pentavalent botulinum toxoid and two antitoxins for therapeutic use [heptavalent botulism antitoxin and diphtheria antitoxin]) are available through the CDC Drug Service (CDC 2011a). Although the committee could not conduct a comprehensive search of international immunization programs, it is unaware of laboratory immunization programs in other countries equivalent to the SIP. An equivalent SIP does not exist in the United Kingdom (Simpson 2010) or in Sweden (Sjöstedt 2011).

[6]Except the IND for the SIP immunization against botulinum toxin, which is held by the CDC.

**TABLE 3.2** Important Events and Recent Reviews of the SIP (2000–2010)

| Decade | Important Events |
|---|---|
| 2000s | Increase in U.S. biodefense research<br>Army submits reports to FDA analyzing previous SIP immunization data and writes new investigational vaccination protocols<br>Report of external biosafety assessment team (2002)<br>Formation of SIP subgroup (2003)<br>HSC PCC SIP agreement on "expanded" SIP to be used by multiple agencies with cost sharing (2004)<br>Memo on status of implementation of 2004 agreement (2007) |
| **Panel** | **Conclusions and Recommendations** |
| Findings and Recommendations on Alternative Strategies for Worker Protection (2002) | Vaccines provide an essential extra measure of safety for laboratory workers. SIP is essential for internal and external customers conducting special pathogens work. CDC, via ACIP, not USAMRIID, should decide on use of IND vaccines at the national level. |
| WMDMC Subcommittee, SIP subgroup (2004) | Recommended SIP expansion with Army managing program on a pay-as-you-go, cost-sharing basis. |

behalf of the U.S. Army Medical Department Office of the Surgeon General, and USAMMDA also supports the SIP through product management and FDA regulatory support. That support includes oversight of regulatory compliance in such fields as vaccine-stability testing and product accountability. Finally, the stockpiles of IND vaccines used in the SIP are managed through the Joint Vaccine Acquisition Program (JVAP) of the Chemical Biological Medical Systems Joint Project Management Office (CBMS-JPMO), part of DOD's Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD). Those activities include vaccine storage and vial distribution. Figure 3.3 is a simplified representation of offices relevant to the SIP in DOD.

Personnel in USAMRIID are able to enroll directly in the program. Civilian personnel in federal agencies enroll under the establishment of an appropriate memorandum of agreement (MOA) between the relevant agency and USAMRMC, and civilian personnel in nonfederal institutions enroll after establishment of a cooperative research and development agreement (CRDA) with the relevant institution. An agreement takes about 3 months for approval by USAMRMC, USAMRIID, and USAMMDA.

Before participation in the SIP, an individual risk assessment is performed by a supervisor and safety officer at the referring agency or institution to establish the potential for exposure to pathogens and toxins, based on activities or tasks performed in the laboratory and by the SIP Physician for medical eligibility to enroll in the SIP. The SIP has established detailed protocols and standard

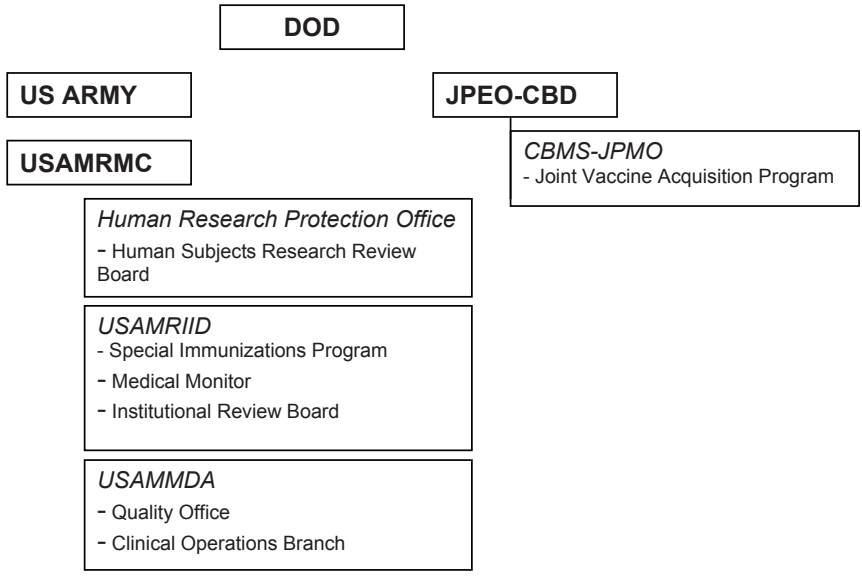



**FIGURE 3.3** DOD offices relevant to the SIP.

operating procedures for enrollment in the program based on relevant medical criteria along with informed-consent procedures (USAMRIID 2004; DOD 2009). The committee noted the importance of the risk assessment process and emphasized that SIP vaccines should be given only to at-risk persons.

### 3.5.2 Special Immunizations Program Customers

At the time of the 2004 agreement on the proposed SIP expansion and agency cost-sharing arrangements, about 600–800 participants were enrolled in the SIP. HHS, however, had substantially increased funding for research related to biodefense, largely through NIAID. HHS projected increases in SIP participants on the basis of potential request for proposal responses to new funding opportunities offered through NIH and BARDA. During the 2004 SIP review and discussions, NIAID alone anticipated that its needs would be about 1,000 vaccinees in 2005 and increase to over 1,800 in 2010. That would have represented 42% of SIP use by HHS. It also estimated that about 1,000–5,000 workers in BSL-3 suites would have sufficient potential exposure to warrant consideration of immunization (Crumrine 2010). As a result of agency estimates used by the 2004 SIP subgroup, use of the SIP program was projected

to increase from about 600 participants per year to 2,000 participants per year (Eitzen 2010).

The expected increases in SIP use did not occur. Although the SIP experienced an initial increase to over 900 participants (including both DOD and non-DOD users), participation has since declined to a steady number of about 600. In 2010, the number of participants in the SIP was 623—395 in USAMRIID and 228 in other government agencies and external organizations (Boudreau 2010). It is unclear whether the decline reflects a decrease in laboratory workers who require immunization or is due to the high cost and inconvenience of the SIP program, which discourages participation. The organizations that had SIP enrollees in 2010 now encompass multiple DOD customers, non-DOD federal agencies, state health departments, academic institutions, and industry. As discussed below, each participating organization pays a share of the SIP operating costs and covers regulatory costs associated with the specific vaccines received by the enrollees that it supports. These groups include (Boudreau 2010):

- *DOD*
  - Soldier Biological and Chemical Command
  - U.S. Army, Dugway Proving Ground
  - USAMRIID
  - U.S. Navy, Naval Medical Research Center
  - Defense Intelligence Agency
- *Non-DOD Government*
  - U.S. Department of State
  - CDC, Fort Collins
  - USDA, Ames, Iowa; University of Wyoming; Plum Island Animal Disease Center
  - DHS, National Bioforensic Analysis Center at the National Biodefense Analysis and Countermeasures Center
  - U.S. Department of Energy, Lovelace Respiratory Research Institute
  - HHS, NIAID
- *Nongovernment*
  - AlphaVax
  - Colorado State University
  - University of North Carolina
  - Johns Hopkins Applied Physics Laboratory
  - Boehringer Ingelheim
  - Southern Research Institute
  - New York State Department of Health
  - University of South Florida
  - University of Pittsburgh
  - University of Texas Medical Branch, Galveston

The current SIP customer base of about 20 organizations clearly fails to reflect program use by many of the researchers handling Select Agents. As of 2009, 388 "entities" were authorized to work with select agents: federal laboratories (65 entities), nonfederal government laboratories (121 entities), academic organizations (120 entities), and commercial and private entities (82 entities) (NRC 2009: 53). Overall, more than 13,000 individuals were cleared for involvement in Select Agent work in some fashion (NRC 2009: 8); this number far exceeds the number enrolled in the SIP.[7]

In the view of the SIP leadership, several factors may have influenced the observed magnitude of use. In some instances, participants enrolled in the SIP, received a single vaccine, and later left the program (Boudreau 2010); in these cases, SIP use was a discrete, one-time event. In other cases, laboratory personnel working with pathogens may not have been evaluated to be truly at risk and to benefit from SIP enrollment, because of the nature of the particular pathogens they were working with, the procedures they were conducting, or the type of biosafety environment in which they were working. The committee observed that use may have been lower than projected as agencies and organizations involved in medical countermeasures research and development focused on pathogens for which vaccines are not available from the SIP. In HHS, for example, an important component of BARDA's mission is preparedness for pandemic influenza, vaccines for which are not in the current SIP but may be available by other mechanisms. As noted in Chapter 1, BARDA's other significant mission focuses on the advanced development, and acquisition under Project Bioshield, of vaccines and therapeutics for civilian use against CBRN threats, particularly anthrax, smallpox, and botulinum toxin.[8] Although vaccines against those diseases are included in the current SIP, licensed products for anthrax and smallpox exist, and the IND for at least one product against botulinum toxin is held by CDC. As a result, those vaccines can be obtained for occupational immunization from sources other than the SIP. While NIAID researchers remain potential SIP customers, other potentially relevant agencies, such as contractors performing work sponsored by BARDA, appear to have been able to meet most of their occupational immunization needs through mechanisms outside of the SIP.

[7]The HHS-USDA Select Agents and Toxins list contains a larger number of pathogens and toxins than does the SIP. The committee does not have available to it the numbers of researchers working with the subset of pathogens and toxins that are currently included in the SIP, but presents these data on select agent research to illustrate the significant numbers of researchers working with the types of hazardous pathogens and toxins relevant to the SIP.

[8]BARDA's mission also includes advanced development and acquisition of countermeasures against acute radiation syndrome resulting from radiological or nuclear events.

### 3.5.3 Vaccines Offered in the Special Immunizations Program

The SIP provides access to 8 licensed vaccines against six diseases and to 10 investigational products (nine vaccines and the Q fever skin test) maintained under IND status. Tables 3.3 and 3.4 list current investigational and licensed

**TABLE 3.3** Current SIP Vaccines (IND)

| IND Vaccines | Year of Manufacture (FDA Submission) | Years of Supply Left[a] |
|---|---|---|
| Botulinum toxoid[b] (only nonlyophilized) | 1994 | 83 |
| Eastern equine encephalitis (TSI-GSD 104 Lot 2-1-89) (inactivated, dried) | 1989 (1967) | 73 |
| Rift Valley fever (TSI GSD 200 lot 7-2) (inactivated, dried) | 1978 (1969) | 11 |
| Rift Valley fever—MP12[c] (TSI-GSD 223 lot 7-2-88) (live, attenuated, lyophilized) | 1988 (1991) | 10 |
| Venezuelan equine encephalitis TC83 (NDBR 102 lot 4-3) (live, attenuated, lyophilized) | 1971 (1965) | 73 |
| Venezuelan equine encephalitis C-84 (TSI-GSD 205, lot 7-1) (inactivated, dried) | 1981 (1975) | 12 |
| Western equine encephalitis (TSI-GSD 210 lot 3-1-92) (inactivated, dried) | 1992 (1984) | 46 |
| Q fever[d] (NDBR 105 lot 4) (inactivated, dried) | 1970 (1972) | 15 |
| Tularemia (LVS) (NDBR 101 lot 4) (live, attenuated) | 1962 (1965) | 18 |

SOURCE: Boudreau 2010.

[a]Exact number of doses is confidential. Years of supply assumes use by the SIP on the basis of about 4 times the current use rates.

[b]CDC holds the IND.

[c]The inclusion of Rift Valley fever MP-12 in the SIP has been discussed and a draft clinical protocol for its use has been developed. However, the vaccine needs to be revialed into single-dose vials for use in the program (Ellen Boudreau and Judy Pace-Templeton, USAMRIID, personal communication).

[d]Q fever vaccine use is currently limited by skin test availability. There have been Q fever skin test potency issues: Q fever NDBR 105 inactivated vaccine requires prevaccination with the IND Q fever skin test. FDA placed a hold on the skin test because of potency issues. The skin test was remanufactured, and data were submitted to FDA in January 2010, but further documentation was requested from the production facility. One solution is the Australian Q fever vaccine Q-Vax, whose maker has been encouraged to submit a Biologics License Application in the United States. Administration of this vaccine in Australia also makes use of a prevaccination skin test, in this case intradermal administration of diluted vaccine (Gidding et al. 2009).

**TABLE 3.4** Current SIP Vaccines (Licensed)

| Vaccine Against | Product | Manufacturer |
|---|---|---|
| Anthrax | Biothrax® (anthrax vaccine adsorbed) | Emergent BioDefense Operations Lansing Inc. |
| Hepatitis B | Engerix-B® (recombinant)<br>Recombivax® (recombinant) | GlaxoSmithKline<br>Merck |
| Japanese encephalitis | IXIARO® (inactivated virus) | Intercell AG |
| Rabies | Imovax® (inactivated virus)<br>RabAvert® (inactivated virus) | sanofi pasteur<br>Novartis Vaccines and Diagnostics |
| Smallpox | ACAM2000® (live virus) | sanofi pasteur |
| Yellow fever | YF-VAX® (live virus) | sanofi pasteur |

SIP vaccines, respectively, and Table 3.5 provides information on vaccine characteristics. All but one of the IND vaccines in the SIP are lyophilized preparations stored at –20°C ± 10°C. Typically, the time to use of a reconstituted vaccine is within 1–8 h.

The IND vaccines offered through the SIP would be unavailable to researchers and other at-risk personnel outside enrollment in the SIP. The SIP also offers licensed products against hazardous pathogens to provide continuity of care to personnel enrolled in the SIP (Boudreau 2010). Although immunization with licensed vaccines may be available to researchers from sources other than the SIP, access to some of them remains challenging (Pouch Downes 2010). The SIP provides an integrated mechanism for offering immunizations to at-risk researchers in support of occupational health and biosafety. The extensive medical monitoring and follow-up that are part of the SIP may also be an important source of data and allow the SIP to serve as a clinical test bed.

### 3.5.4 Logistics of Administration

The IND vaccines used in the SIP remain in extended Phase II testing, and this poses substantial cost, regulatory, and logistical burdens on SIP staff.

In 1998, 117 extramural sites were administering investigational vaccines under the USAMRMC-held INDs; USAMRIID provided the principal investigators while the extramural sites provided associate principal investigators. In 1999, USAMRMC closed all the extramural sites when they could no longer meet the rigorous current Good Clinical Practice (cGCP) regulatory requirements necessary for monitoring investigational vaccine use. Currently, all SIP immunizations are administered by USAMRIID, and subjects must go to Fort Detrick for this service. Up to 900 people have traveled to USAMRIID, and

**TABLE 3.5** Characteristics of SIP IND Vaccines

| Vaccine Against | Schedule | Immunogenicity | Boost | Systemic Adverse Effects | Injection-Site Adverse Effects |
|---|---|---|---|---|---|
| Botulinum toxoid | Days 0, 14, 84, 180, 365 | Acceptable for serotypes A/B | annual | 10–15% (fever, headache, myalgia) | 20–40%, increasing after boosters |
| EEE | Days 0, 28 | 65–70% primary; 85–90% booster | Mandatory 6 mo, then as needed according to titer (1:40) | 10–15% | 10% |
| Rift Valley fever | Days 0, 7, 28, 180 | 79% primary series; 96% booster response | As needed according to titer (1:40) | 8–10% | 3–5% |
| Rift Valley fever MP12 | Day 0 | 93–95% | As needed according to titer | 30% (headache), 10% (myalgia and fatigue) | 40% |
| VEE TC83 | Day 0 | 75%, lasts 8 yr | VEE C-84 according to titer (1:20) | 50–60% | Rare |
| VEE C-84 | Day 0 VEE TC83 responders; or days 0, 30, 60 for nonresponders | 86–95% | As needed according to titer (1:20) | 20–30% | 10% |
| WEE | Days 0, 7, 28 | Titer > 40 100% primary series (preliminary data) | Mandatory 6 mo | Not available yet | Not available yet |
| Q fever | Day 0 | Assumed to be lifelong | None | 30–35% | Expected response |
| Tularemia | Day 0 | 99% "take" + 98% + microagglutination titer | If initial take negative, every 10 yr | 30–35% | Expected response |

SOURCE: Boudreau 2010.

USAMRMC initially bore the immunization costs of this program. Since 2003, other agencies enrolling employees in the SIP have been required to pay at least a share of the costs, and a fully burdened cost-sharing agreement has been in place since 2004.

For entry into the SIP, a Cooperative Research and Development Agreement (CRDA) is required between USAMRIID, USAMMDA, and nonfederal institutions, and a Memorandum of Agreement (MOA) is required for federal agencies. Those agreements take about 3 months for approval by USAMRMC, USAMRIID, and USAMMDA. A risk assessment is performed by a supervisor and biosafety officer at the referring institutions to establish the potential for exposure to pathogens and toxins and by an SIP physician for medical eligibility. Travel and return visits by extramural participants are required. Three SIP vaccines require only a single dose or a single dose and a booster dose, but five vaccines are administered in multiple doses. As a result, the extent of travel and associated costs depend on the number and type of SIP vaccines needed by an enrollee. Vaccine recipients who live out-of-state must have an occupational health-care provider available to contact to assess any medical problems or adverse events. Such information is communicated to the SIP personnel by telephone or e-mail. For all SIP participants, an annual medical review at USAMRIID, physical examination, and laboratory tests are required, as is the recording of continuing medications, intercurrent illnesses and accidents, and surgical procedures. Compliance is required for shipping of serum specimens to USAMRIID for antibody titers, baseline electrocardiography (ECG), and chest x rays. Recipients of the tularemia live vaccine strain (LVS) vaccine must remain at Fort Detrick for up to 3 days to assess the "take" after scarification. A similar stay is required for a Q fever vaccine[9] and smallpox vaccine.

Although it increases the travel burden on non-USAMRIID participants in the SIP, having one site for the SIP has advantages, including the following:

- It facilitates annual medical review.
- It centralizes physical examinations and laboratory evaluation, baseline ECG, and the taking of chest x rays.
- It facilitates recording of medications, illness, accidents, and surgical operations.
- It allows serum samples to be assayed in the SIP clinical laboratories and reduces the need to ship samples for titers.

### 3.5.5 SIP Vaccine Supply and Stockpile Management

The bulk of the SIP vaccine supply is made up of legacy vaccines manufactured at the Salk Institute vaccine-production plant in Swiftwater, PA, in the

[9]As noted earlier, use of Q fever vaccine is limited by skin test availability.

1960s–1980s. Since the facilities' acquisition by Institut Merieux in 1989 (later Pasteur Merieux Connaught and now sanofi pasteur) and closure of the Salk GSD in 1998, no new lots of those vaccines have been produced. The existing stockpiles of these legacy investigational vaccines are maintained by the DOD Chemical Biological Medical Systems (CBMS). CDC manages the government stockpile of licensed vaccines available through the CDC Drug Service.

Numerous lots are available for most of the SIP investigational vaccines, and conservative estimates of IND vaccine supply range from 10 or 11 years for Rift Valley fever lots to 73 years for some VEE and EEE lots (see Table 3.4). The use of additional lots with confirmed potency by virtue of stability assessments would expand the supply by a factor of 2–10. As vaccines against hazardous pathogens of interest to the SIP have become licensed (for example, vaccines against Japanese encephalitis, hepatitis B, rabies, anthrax, smallpox, and yellow fever), the SIP has continued to purchase these vaccines and administer them to eligible personnel. However, no specific budgetary line provides for this purchase.

No new IND vaccines currently administered in the SIP have been added since 1992 (WEE); most were placed in the program in 1964–1981 (see Table 3.4). Some vaccines are now over 40 years old, but no vaccine has yet been withdrawn because of low potency or failure to meet other stability assessments.[10] With regular testing of the vaccine lots, there has also been some minimal loss of vaccine stock due to loss of vacuum or sterility. To preserve the existing supply of vaccine, revialing of new lots from bulk stocks may be necessary, but this would be an expensive undertaking with no visible source of funding, no clear manufacturer to assume the effort, and uncertain ability to release such materials based on quality assessments.

Requirements for maintaining SIP vaccines under IND status include

- Regulatory reporting.
- Potency testing every 2 years.
- Sterility testing every 3 years.
- Compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for study conduct.
- Intensive documentation and training of personnel.
- Protocol compliance by volunteers and investigators.
- Quality-assurance and quality-control monitoring.

[10]Although no vaccine has been withdrawn, the dosing schedule of pentavalent botulinum toxoid (PBT) was revised in 2004 to include an additional primary series injection and routine annual booster doses "due to (a) a recent decline in PBT immunogenicity and potency noted on the yearly potency testing, and (b) data from a 1998–2000 PBT study found a decrease in antitoxin titers by week 24 (6 months) in approximately two thirds of vaccinees" (U.S. Department of the Army 2007: 345).

From 2000 to 2003, lot release tests were repeated on all SIP vaccines for potency, bacteriostasis and fungistasis, mycoplasma, endotoxin, general safety, residual moisture and product enhanced reverse transcriptase testing, vial integrity (if vacuum-packed), and spark testing or sterility testing (if nitrogen-packed). Potency testing is conducted every 2–3 years and the other lot release tests could be performed if they were requested by the sponsor or FDA. There is no current budget for new lot release testing (Boudreau 2010).

IND vaccines in the SIP remain in prolonged IND status and are unlikely to transition to licensure for several reasons (Boudreau 2010):

- There are no current manufacturers or pharmaceutical companies that can expect a profit in producing the vaccines.
- Vaccine effectiveness and safety studies have been conducted in animal models. Vaccine effectiveness in preventing disease in humans is difficult to test because of ethical or safety concerns in conducting traditional clinical trials for efficacy; the population of at-risk individuals is also small. To date, no vaccine has been approved for licensure under the "animal rule" instituted by FDA in June 2002.
- FDA permits their use under IND protocol, which may also reduce incentives to proceed to further regulatory milestones.

There are disadvantages of maintaining prolonged IND status for these vaccines, including the fact that no or few controlled clinical efficacy trials have been performed in humans, and questions about whether vaccine potency and sterility will continue to be maintained with aging vaccine product (Boudreau 2010). The SIP IND vaccines were also developed using cell culture production practices that might not meet current standards, and as seen in Table 3.5, the levels of reactogenicity and of local and systemic adverse events for some of them may be higher than desirable. Because the vaccines are administered under clinical trials, there is also a need to monitor titers, perform medical assessments, and analyze and submit clinical data to FDA.

In addition, individuals receiving the IND vaccines may experience adverse events, there may be populations of workers ineligible to receive the vaccines, the benefits of the vaccine may be less in cases of high-dose aerosol exposure, and it is possible that receiving the immunization may lead to an unwarranted sense of safety and security that results in lax laboratory practices (Boudreau 2010). Although some of these considerations might apply to licensed vaccines and to vaccines developed using today's technology, these may be greater concerns given that the SIP IND vaccines were largely developed decades ago prior to the establishment of modern cGMP standards.

Despite the cost of their maintenance, the committee noted that IND vaccines can potentially offer additional protection to personnel in the event of inevitable accidents and percutaneous injury. In such situations, the severity of

diseases being covered and the lack of licensed vaccine support consideration of the use of IND vaccines if they are available and considered to be safe. The immune response may be primed before pathogen or toxin exposure (prophylactic use), or the vaccine may in some cases be able to be administered after a potential exposure in an effort to minimize adverse consequences (therapeutic use), as is the case for smallpox vaccine. Alternatively, the presence of a population of immunized people may allow serum isolated from vaccinated people to be used therapeutically if unimmunized people are exposed. In addition, the data on safety and immunogenicity accumulated through the SIP IND clinical trials could be used to enable FDA to make a determination for an Emergency Use Authorization if this is required.

### 3.5.6 Costs of the Special Immunizations Program

According to SIP leadership, entry into the SIP program currently costs about $10,000–15,000 per volunteer per year (depending on the number and type of SIP vaccines needed).[11] That is based on audited costs of operating the program, which include (Boudreau 2010)

- Periodic potency and lot release testing of the product.
- Storage and maintenance of the stockpile.
- Regulatory submissions, including continuing review reports, annual reports, summary reports every 5 years, investigator brochures, periodic safety and serious adverse event reporting, informed-consent form updates, responses to periodic audits, and clinical monitoring visits.
- Intensive physician and nurse efforts because volunteers are enrolled in multiple clinical studies.
- Clinical database and document control compliant with the record-keeping requirements of 21 CFR Part 11.
- Maintenance of the SIP clinical-record archive, which contains information on the last 40 years of the SIP.

Invoices are sent to participating institutions on the basis of those audited costs of operating the program. Payment is required in advance for SIP enrollees.

In addition to the above-mentioned costs, operation of the SIP entails considerable overhead costs, for example, for staffing, facilities, equipment, and product maintenance. Estimates of costs for the SIP provided during the

[11]No charge is assessed for the IND vaccines themselves, which are provided as part of Phase II clinical trials. Expenses associated with program participation relate to the surrounding medical management and regulatory costs.

2004 subgroup review for the single-location SIP serving about 600 enrollees included 79 staff assignments ($8.9 million per year), with enlisted personnel supplementation from outside of the USAMRIID Division of Medicine as needed. Additional estimates of costs provided during the 2004 review for a single-location SIP serving 600 enrollees included $0.8 million for facilities, $0.2 million for equipment, and $6.1 million for product storage, testing, and documentation.[12] Those data indicated a total overhead cost of about $16.0 million per year (Eitzen 2010). It was projected that SIP expenses would increase by about $0.9 million per year over the following 5-year period (Eitzen 2010). Current staffing and related costs appear to be different than those used during the 2004 review, and are discussed in more detail below.

At the time of the 2004 HSC PCC agreement estimating that SIP enrollment would expand to 2,000 subjects, it was projected that such an expanded program would require additional staff costs and facilities costs for the projected regional sites, which would result in an estimated annual cost of $35.6 million. On the basis of projected use by the primary federal government stakeholders, the estimated annual expenses would be $11 million for DOD and $15 million for HHS, with USDA, DHS, other federal agencies, and private users making up the balance. It was also estimated that considerable filling and finishing of existing bulk vaccines would be required for the expanded program at an estimated one-time cost of $28 million for 5 years (Eitzen 2010).

According to SIP leadership, the total number of staff currently in the SIP is about 40–45 at USAMRIID and approximately 8 part-time staff at USAMMDA. They include 10 physicians (5 for the SIP, 4 for after-hours calls for USAMRIID personnel, and 1 medical monitor), 6 registered nurses and 6 licensed practical nurses, 3 administrators, and several vaccine verifiers (enlisted personnel) and vital-signs takers. Management of the vaccination protocols also requires data-entry personnel (4) and data managers (2). In addition, USAMMDA provides 10–15 regulatory personnel, including quality-assurance managers, study monitors, product managers, and managers for product testing (USAMRIID 2009). The cost trend for the present scope of the SIP—including immunizations and medical management of participants at USAMRIID, and regulatory management though USAMMDA Regulatory Affairs—is estimated to be about $9 million per year (Boudreau 2010). CBMS/JVAP contracts with third parties for product storage and potency testing.

The SIP operates on a pay-as-you-go basis, and funding to support the

[12]In generating these cost projections, the 2004 SIP subgroup obtained cost estimates from relevant providers. For example, quotes were provided by SRI, Q-One Biotech, BioReliance, and USAMRIID for product testing; quotes for vaccine storage were provided by JVAP; and quotes for regulatory documentation were obtained from SAIC, USAMRIID, Quintiles, and Parexcel. Personnel numbers and costs used by the 2004 subgroup are different than the current estimates provided by SIP leadership, and, for example, appear to also include personnel in storage and IT (Eitzen 2010).

extensive infrastructure and staffing of the program appears insecure. There is no line item in the USAMRMC budget for the SIP, and each participating stakeholder, whether DOD or non-DOD, pays for SIP immunizations out of discretionary money in its budget. The vaccines are stored at two off-site facilities, and costs of CBMS stockpile management have been estimated at $1.5 million per year (Boudreau 2010). *However, there is no line item in the budget for further vaccine storage and testing. CBMS currently manages these activities on a year-to-year basis; no other office has agreed to undertake this management and no long-term mechanism has yet been identified (Boudreau 2010).*

### 3.5.7 Governance of and Priority-Setting in the Special Immunizations Program

As discussed in Section 3.2, national priorities for military and civilian MCM are currently set separately from the process of governance that determines the current and future capabilities of the SIP. These national MCM priorities include agents of specific interest to the military, agents of interest to civilian authorities such as HHS, and agents of interest to both. In addition to products directed against traditional pathogens and toxins, strategies are being pursued to develop broad-spectrum antivirals and antibiotics and potential countermeasures against genetically modified or novel agents.

Against the backdrop of the national MCM enterprise, there is a need to consider whether the current portfolio of products available in the SIP aligns with national research agendas and whether there is a decision-making process by which a vaccine becomes available to or is removed from the SIP.

Table 3.6 compares the current list of investigational and licensed products in the SIP with several current national priority lists. As can be seen in the table, the SIP continues to contain a subset of investigational vaccines that largely reflect historical R&D efforts in USAMRIID and traditional military biodefense priorities. It does not, for example, include investigational vaccines against the Ebola and Marburg filoviruses, which are of interest to both DOD and HHS, or against pathogens of particular HHS priority, such as Junin and *Burkholderia* species. Initial development and production of seed vaccine stocks for two products against pathogens that may be of interest to civilian researchers, Junin virus and Chikungunya virus, were developed at USAMRIID but have since been transferred to institutions outside the United States and are no longer available in the SIP. The use of those vaccine stocks in other countries is discussed in Chapter 5. The committee believes that this illustrates a general limitation of the current SIP for pathogens having primarily civilian but not military interest.

As discussed in Chapter 5, other relevant countermeasures development efforts may be under way (for example, against Ebola and Marburg viruses) and could be considered for inclusion in the SIP once efforts have reached a suit-

**TABLE 3.6** Comparison of SIP Provision of Vaccines with DOD and HHS Priorities

| SIP | PHEMCE Implementation Plan | JPEO-CBD | Transformational Medical Technologies |
|---|---|---|---|
| *B. anthracis* (anthrax) | Anthrax | Anthrax | Anthrax |
| *C. botulinum* (botulism) | Botulism | Botulism | Botulism |
| *Variola major* (smallpox) | Smallpox | Smallpox | Smallpox |
| *F. tularensis* (tularemia) | Tularemia | Tularemia | Tularemia |
| EEE, VEE, WEE viruses | | EEE, VEE, WEE | EEE, VEE, WEE |
| Rift Valley fever virus | | | |
| *C. burnetii* (Q fever) | | | Q fever |
| Hepatitis B (licensed) | | | |
| Japanese encephalitis virus (licensed) | | | |
| Rabies (licensed) | | | |
| Yellow fever (licensed) | | | |
| | Ebola/Marburg | Ebola/Marburg | Ebola/Marburg |
| | *Burkholderia* spp. | *Burkholderia* spp. | *Burkholderia* spp. |
| | Junin virus | Junin virus | Junin virus |
| | *Yersinia pestis* (plague) | *Yersinia pestis* | *Yersinia pestis* |
| | *Rickettsia prowazekii* (typhus) | | Typhus |
| | | *Brucella* spp. | *Brucella* spp. |
| | | Staphylococcal enterotoxin B | Staphylococcal enterotoxin B |
| | | Ricin | Ricin |
| | | | *Vibrio cholerae* |
| | | | T2 mycotoxin |

SOURCES: HHS 2007; Newmark 2009; Hough 2010; NBSB 2010a.

able stage of development. HHS has also made development and acquisition of vaccines against pandemic influenza strains such as H5N1 a priority. It has solicited requests for proposals for influenza manufacturing capacity (see Section 5.2.4) and a licensed H5N1 vaccine has been produced (sanofi pasteur, licensed in 2007). The vaccine is for pre-pandemic use; it is not included in the SIP.

The process by which DOD sets its priorities for biodefense and infectious disease vaccines and undertakes the R&D and acquisition activities that it supports is complex.[13] As the committee understands the current process of

[13]See, for example, the IOM reports *Protecting our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military* (2002) and *Giving Full Measure to Countermeasures: Addressing Problems in the DOD Program to Develop Medical Countermeasures* (2004), which described the DOD vaccine development and acquisition process in place at the time and recommended creation of a single agency in DOD to streamline matters.

governance of the SIP, for an IND vaccine to be placed into the SIP by DOD there must be a formal document establishing the military need for it. If the need is established, an effort is initiated, and the vaccine must be placed into the category of advanced development. There is no funding for any vaccine that has not achieved those milestones. The DOD vaccine enterprise is focused largely on developing and acquiring licensed products for potential larger-scale use in force protection, not on the more limited role of vaccines (including investigational products that may never progress to full licensure and larger-scale manufacture) for protecting personnel who work to develop next-generation countermeasures.

Within USAMRIID, a Special Immunizations Committee chaired by the chief of the Medical Division is charged with oversight of the SIP program and is able to recommend DOD vaccines for incorporation into the SIP. Its mission is to "outline and evaluate policy and procedure for administration of special immunizations for personnel requiring entry into USAMRIID Biosafety Level 3 and 4 laboratories, and to make immunization policy recommendations to the Commander" (USAMRIID 1995). The current system of SIP oversight and the requirement for a documented military need for a vaccine to be added to the SIP suggest that there is no procedure for placing an investigational vaccine that is deemed critical to the protection of non-DOD laboratory workers into the SIP. Further, the committee could not find evidence of an interagency process for undertaking regular reviews and making broader systematic decisions on vaccines to be included in the SIP. The gap appears particularly noteworthy in the context of the "expanded" SIP agreements implemented since 2004 that include enrollment of at-risk laboratory workers in non-DOD agencies, academe, and industry.

## 3.6 FINDINGS AND CONCLUSIONS ON THE MEDICAL COUNTERMEASURES ENTERPRISE AND THE CURRENT SPECIAL IMMUNIZATIONS PROGRAM

During the last decade, numerous outside reviews of military and civilian biodefense vaccine programs have recommended a substantial increase in the funding of and the priority given to these programs, including the establishment of production facilities and agencies that have oversight functions to direct the efforts. More recently, recommendations have been offered to create incentives for industry and the private sector to establish better collaboration with government and academe and to overcome regulatory obstacles. Previous reviews of the SIP have consistently recommended that the program be open to at-risk researchers beyond USAMRIID and cost-sharing mechanisms to support the additional use.

In this context, the committee concluded that several findings about the SIP are evident:

- *Finding 3:* The SIP remains the only formal program that exists to provide multiple vaccines (both licensed and IND) to at-risk laboratory workers and other occupationally exposed personnel who work with hazardous pathogens.
- *Finding 4:* USAMRMC has the history, personnel, clinic facilities, protocols, standard operating procedures, and regulatory infrastructure to administer, monitor, and document immunizations provided through the SIP.
- *Finding 5:* The SIP generally functions well for USAMRIID customers but has not met the expected need of customers outside of USAMRIID, particularly personnel involved in civilian biodefense countermeasures, public health research, and the veterinary communities.

SIP enrollment remains at about 600–700 per year, rather than the roughly 2,000 projected in 2004, and this suggests a need to reevaluate the potential stakeholders and related customers whose access to the SIP would enhance their biosafety-practices program. Some workers at risk for exposure to dangerous pathogens against which a vaccine exists are able to access the program successfully, but it appears that others are conducting research without the potential protection that a vaccine may provide. Given the current cost structure, potentially relevant users may be unable to afford the price of participation in the program. In the current economic climate, that problem is likely only to worsen. The supply of investigational vaccines in the SIP is sufficient for the immediate term but will be more rapidly depleted if additional participants enter the SIP and require immunizations. The current SIP clinical lots may be unable to accommodate the additional demand from all laboratory workers at risk for exposure. To meet the additional demand, further vialing from bulk stocks may be required, and this would add substantially to the costs of maintaining the SIP in the absence of a clear understanding regarding how these costs would be paid. It is often difficult for stakeholders to obtain the vaccines outside the SIP.

- *Finding 6:* Other than the USAMRIID SIP committee, which is limited to military needs, the SIP appears to lack a governance structure that enables regular strategic review of the investigational and licensed vaccines included in it and to lack mechanisms to address identified gaps.

Further expansion of the SIP to accommodate civilian countermeasure priorities will require a better mechanism for deciding which IND vaccines should be included. Currently, for an IND vaccine to be in the SIP, the DOD process requires the establishment of a military need for a specific vaccine to be developed, and it must reach the end of Phase II testing with an adequate safety profile. IND vaccines developed outside DOD and not required by the military

might well be useful to other stakeholders. A mechanism by which requests to include such vaccines are considered should be implemented.

- *Finding 7:* The SIP lacks consistent funding, including a lack of line items in USAMRIID and other agency budgets to support continued maintenance of the existing stockpiles, vialing additional bulk vaccine from existing stocks, and costs associated with acquiring new vaccines for inclusion in the SIP.

# 4

# Regulations and Other Guidance Pertaining to the Development and Use of Vaccines in the Special Immunizations Program

Reviews of the national countermeasures enterprise consistently highlight challenges in advanced development and manufacturing of new vaccines and therapeutics against hazardous pathogens. Gaps identified in the current SIP also focus largely on the nature and type of vaccines included in the program, options for additional investigational or licensed products that should be considered for inclusion in an expanded SIP, and options for the future supply of SIP vaccines.

As discussed in greater detail in the following chapters the majority of vaccines currently administered within the SIP, with the exception of several licensed products, remain in Phase II clinical trials under Investigatinal New Drug (IND) status and are unlikely to continue on to licensure. The SIP program is designed to serve a small population of laboratory workers and others with potential occupational exposures to highly hazardous pathogens. Even with a potential expansion of the SIP to meet the needs of additional users from the growing community of researchers working on countermeasures against pathogens for which the civilian population may be at risk of exposure, and the incorporation into the SIP of new vaccines against additional pathogens and toxins, the SIP could only continue to serve a relatively small population of lab workers who would benefit from immunization.

The United States continues to undertake strategic planning and to expand investments in the development of countermeasures against hazardous pathogens and toxins for potential use in the civilian population or by the armed forces. Protection of the laboratory personnel working to achieve these mandates will continue to be an important component of this overall enterprise. However, the small scale of SIP vaccination, the nature of the hazardous pathogen vaccines being used in the program, and complications with conducting

human clinical trials on vaccines against highly hazardous pathogens can lead to regulatory and manufacturing challenges. The vaccines required for the SIP have no or extremely limited commercial value and do not attract interest from the biopharmaceutical industry. As a result, there is a need to explore regulatory and manufacturing options. Furthermore, there is a need to consider whether additional vaccines already in use or in development should be considered for inclusion in an expanded SIP.

The following two chapters discuss some of these challenges and options in greater detail in two primary areas: (a) current regulatory pathways applicable to vaccines and how these might apply to the use of vaccines within the SIP (Chapter 4), and (b) the state of vaccine manufacturing and options for the evolution of vaccines currently used in the SIP (Chapter 5).

## 4.1 OVERALL REGULATORY FRAMEWORK FOR VACCINES

In the United States, all vaccines, including those in the SIP, are regulated as biologics by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA). A single set of basic regulatory approval criteria apply to all human vaccines, regardless of the technology used to produce them. CBER's current legal authority for the regulation of vaccines derives primarily from Section 351 of the Public Health Service (PHS) Act and from certain sections of the Federal Food, Drug and Cosmetic (FD&C) Act. The PHS Act is implemented through regulations codified in Title 21 of the *Code of Federal Regulations* (CFR), Parts 600 through 680, which contain regulations specifically applicable to vaccines and other biologics. In addition, because a "vaccine" meets the legal definition of a "drug" under the FD&C Act, sponsors must also comply with current Good Manufacturing Practice (cGMPs) regulations in 21 CFR Parts 210 and 211, and, for all human testing prior to licensure, the Investigational New Drug (IND) regulations in 21 CFR Part 312. Most of the vaccines included in the SIP are directed against pathogens that are now identified as Select Agents (42 CFR Part 72; 42 CFR Part 73; 7 CFR Part 331; 9 CFR Part 121), which can cause life-threatening and/or fatal illness in exposed laboratory workers. As described previously in Chapter 3, the SIP presently consists of eight U.S. licensed vaccines, seven that are administered under active INDs held by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), and one administered under an active IND held by the Centers for Disease Control and Prevention (CDC). Given the large expansion in laboratory research for Select Agents and other existing or emerging pathogens during the past decade, the number of vaccines that might be included in the SIP is expected to grow.

Given this overall regulatory framework, the current objectives of the SIP,

and the potential expansion of the program to provide immunization against additional pathogens, this chapter focuses on four major questions:

- How can the SIP best ensure continuous and convenient availability of appropriate vaccines for prevention of severe disease caused by Select Agents and other high-risk pathogens to which laboratory workers may be exposed?
- What regulatory pathways are available to obtain FDA approval for as many SIP vaccines as possible, both now and in the future?
- How can the evaluation of investigational SIP vaccines administered under IND be improved and extended?
- What are the most expeditious and cost-effective means of bringing additional vaccines into the program?

## 4.2 OPTIONS FOR U.S. LICENSURE

### 4.2.1 Traditional Approval

The most convenient and expeditious mechanism in which researchers and other potential vaccine recipients can be immunized against Select Agents and other pathogens is through the use of licensed products that can be obtained either directly from commercial sources or from another readily available source (with appropriate authorization) such as the CDC Drug Service. As summarized previously, there are, at present, a total of eight licensed vaccines against six diseases included in the SIP, including vaccines against anthrax (Biothrax® [anthrax vaccine adsorbed], Emergent BioDefense Operations Lansing Inc.); smallpox (ACAM2000® [smallpox (Vaccinia) vaccine, live], sanofi pasteur); yellow fever (YF-VAX® [yellow fever vaccine], sanofi pasteur); Japanese encephalitis (IXIARO®, [Japanese encephalitis virus vaccine, inactivated], Intercell AG); hepatitis B (recombinant, Engerix-B®, GlaxoSmithKline; Recombivax®-HB, Merck); and rabies (inactivated virus, Imovax®, sanofi pasteur; RabAvert®, Novartis Vaccines and Diagnostics). Six of these vaccines have commercial markets both domestically and abroad, while the remainder (BioThrax and ACAM2000) are available for use by the military or for emergency use in civilians via the Strategic National Stockpile approval pathway, wherein safety and efficacy (primarily immunogenicity) data were obtained in fairly large, randomized clinical trials, supplemented by post-marketing (Phase 4) safety and/or immunogenicity studies (see Section 5.1 for additional background on this process). In addition, all eight vaccines must continue to meet the requirements specified in the respective product licenses, with any adverse events (including suspected vaccine efficacy failures) to be reported to the Vaccine Adverse Events Reporting System administered jointly by FDA

and CDC. Chronic shortages of these vaccines or withdrawal from the market by the respective manufacturer are not expected in the foreseeable future, such that each will likely remain a part of the SIP.

### 4.2.2 Accelerated Approval

A second regulatory approval pathway that may be applicable to the SIP is accelerated approval (21 CFR Part 601, Subpart E). Such an approval may be granted for certain biological products (including vaccines) that have been studied for their safety and effectiveness in treating *serious* or *life-threatening* illnesses *and* that *provide meaningful therapeutic benefit over existing treatments*. Such an approval is based on adequate and well-controlled clinical trials establishing that the biological product has an effect on a *surrogate endpoint* that is *reasonably likely*, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, *to predict clinical benefit* (21 CFR § 601.41). Approval under this section will be subject to the requirement that the sponsor study the biological product further to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit (21 CFR § 601.41). Post-marketing (Phase 4) studies must also be adequate and well controlled and should be conducted with due diligence (21 CFR § 601.41). The protocols for these studies should be submitted with the original Biologics License Application (BLA). Under an allied provision (21 CFR § 601.42; *Restricted—Approval with restrictions to assure safe use*), FDA may conclude that a biological product shown to be effective can be safely used *only if distribution or use is restricted*. In such instances, FDA will require such post-marketing restrictions as needed to ensure safe use of the biological product. These may include (1) distribution restricted to certain facilities or physicians with special training or experience or (2) distribution conditioned on the performance of specified medical procedures. Limitations imposed will be commensurate with the specific safety concerns presented by the biological product. Recent examples of vaccines approved under this mechanism include Hiberix® (*Haemophilus influenzae* Type b (Hib) conjugate vaccine, GlaxoSmithKline), Fluarix® (inactivated influenza virus vaccine, GlaxoSmithKline), Agriflu® (inactivated influenza virus vaccine, Novartis Vaccines and Diagnostics), and Afluria® (inactivated influenza virus vaccine, CSL Limited), all of which have a surrogate endpoint (pathogen-specific antibody level) that is reasonably likely to predict clinical benefit (i.e., prevention of disease caused by the pathogen to which the vaccine is directed). It is possible that such a pathway might also be followed for one or more investigational vaccines presently utilized within the SIP program (see below), although establishment of an antibody-based endpoint as a valid surrogate of clinical efficacy is highly challenging, especially

for diseases that typically occur sporadically in humans. Such a proposal would need to be discussed with FDA prior to consideration.

### 4.2.3 Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible (21 CFR Part 601 Subpart H, as Well as 21 CFR Part 314, Subpart I, for New Drugs) (67 Fed. Reg. 3,7988 [2002])

The third licensure pathway that is applicable to vaccines utilized under the SIP is known simply as "the Animal Rule." This rule was promulgated in 2002 and designed to permit approval of drugs and biologics (including vaccines) that are intended to reduce or prevent serious or life-threatening conditions caused by exposure to biological, chemical, radiological, or nuclear substances *when human efficacy studies are not ethical* and/or *field trials are not feasible*. While the animal rule has been viewed as critical for bioterrorism preparedness, in practice it has been extraordinarily difficult to utilize as an approval pathway, with only two drugs, pyridostigmine bromide and hydroxocobalamin, having been licensed in the United States through this pathway. Experience has shown that developing animal models that will yield efficacy results expected to be predictive for humans is highly challenging. For example, in the draft guidance document published in 2009, FDA has indicated that:

- The animal studies must be adequate and well-controlled (21 CFR §§ 314.610 and 601.91), and should use the pertinent features of an adequate and well-controlled clinical study, such as a detailed protocol with randomization and adequate blinding and a statistical plan as described in 21 CFR § 314.126.
- The challenge agent must be essentially identical to the agent causing human disease, unless there is very strong evidence that the use of another agent in the animal model would generate human-equivalent disease.
- The pathogenesis and mechanism of toxicity should be the same as those in humans.
- The sponsor must demonstrate the endpoint of interest (i.e., potential for mortality or major morbidity that might be reduced or prevented by a sufficiently effective intervention).
- The route of exposure to the agent must be the same as the anticipated natural human exposure route, and that the quantification of the exposure dose must be equivalent to that anticipated in human disease;
- The response to the etiologic agent (resulting illness or injury) manifested by the animal species exposed to that agent should be similar

to the illness or injury seen in humans. In addition, when comparing the disease in animals with the disease in humans, sponsors should include time to onset of disease/condition; time course of progression of disease; and manifestations, that is, signs and symptoms (severity, progression, clinical and pathologic features, laboratory parameters, the extent of organ involvement, morbidity, and outcome of disease).

- Identification of the trigger for intervention in the animal studies is critical to defining the timing of the intervention. Because animals cannot simulate the health-seeking behavior manifested by humans, the trigger for intervention should be accurately defined in the animal model.
- Animal efficacy studies should reflect the expected clinical use and indication. A particular dosage form may not be suitable for the proposed indication, so the product's dosage form should be considered in planning the development of the product.
- Studies should be designed to mimic the clinical scenario and achieve meaningful outcomes comparable to the endpoints desired in humans. In some instances, supportive care and merciful euthanasia as appropriate should be administered to the animals as part of the study design. In such cases, demonstration of a product's benefit over supportive care (i.e., supportive care plus investigational drug arm should be demonstrated to be superior to the supportive care plus placebo arm) will be necessary for approval or licensure (FDA 2009a).

Because very few pathogens of interest to the SIP have validated animal models of human disease, and because of the high cost and long timelines required for the development of such animal models, licensure of vaccines of major interest to the SIP will not easily be accomplished by means of the Animal Rule, with the possible exception of second-generation anthrax vaccines, third-generation smallpox vaccines, and plague vaccine. At the time that this report was being prepared, FDA and other government agencies are actively considering more practical and feasible ways in which the Animal Rule and its associated guidance may be implemented (FDA 2004, 2007a, 2009b, 2010b,c).

### 4.2.4 Potential Administration of Investigational SIP Vaccines Under Emergency Use Authorization (EUA)

While not considered equivalent to a full (traditional) or accelerated approval for U.S. licensure, there is a fourth mechanism—Emergency Use Authorization (EUA)—that may enable potential recipients to receive an investigational SIP vaccine outside of an IND protocol. Among other provisions, the Project BioShield Act of 2004 (Public Law 108-276) establishes a compre-

hensive program that enables the emergency use of medical products against biological, chemical, radiological, and nuclear attacks or potential attacks for both civilian and military personnel, thereby permitting the FDA Commissioner to approve the emergency use of drugs, vaccines, medical devices, and diagnostics that were not previously licensed for a particular purpose (FDA 2007b). A related act, the Public Readiness and Emergency Preparedness Act of 2005 (Public Law 109-148), provides immunity from liability claims arising from administration and use of covered countermeasures under EUA.

In July 2007, FDA developed a guidance document explaining FDA's policies for authorizing the emergency use of medical products under section 564 of the Federal FD&C Act (FDA 2007b). The guidance is intended to inform industry, government agencies, and FDA staff of the agency's general recommendation and procedures for issuance of EUAs, and includes sections on (1) eligibility determination, (2) the process of requesting consideration for an EUA, (3) FDA processing of an EUA, and (4) conditions for authorization.

Once the secretary of HHS declares an emergency (in consultation with DHS and DOD), the FDA commissioner may issue an EUA only if, after consultation with the director of NIH and the director of CDC (to the extent feasible and appropriate given the circumstances of the emergency), the FDA commissioner concludes that:

1. The agent specified in the declaration of emergency can cause a serious or life-threatening disease or condition.
2. Based on the totality of scientific evidence available, including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing (a) the serious or life-threatening disease or condition; or (b) a serious or life-threatening disease or condition caused by a product authorized under section 564, or approved, cleared, or licensed under the FD&C Act or PHS Act, for diagnosing, treating, or preventing the disease or condition and caused by the agent specified in the declaration of emergency.
3. Known and potential benefits outweigh the known and potential risks of the product when used to diagnose, prevent, or treat the serious or life-threatening disease or condition that is the subject of the declaration.
4. There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating such serious or life-threatening disease or condition.

Experience has already been gained with EUAs, beginning with the emergency use of anthrax vaccine adsorbed (AVA) for prevention of inhalation

anthrax in military personnel in 2004 (terminated in 2006), an EUA for doxycycline hyclate tablet emergency kits for inhalational anthrax (2008), and more recently, a series of EUAs for diagnostic test kits and antiviral agents for the detection and treatment, respectively, of the novel influenza A/H1N1 pandemic strain of 2009 (all terminated as of June 23, 2010).[1] At the present time, the importance and relevance of the EUA provisions to the SIP lie chiefly in the ongoing collection of safety and immunogenicity data under the various active INDs (see below), which may someday provide sufficient evidence of risk/benefit to enable an EUA for a specific vaccine to be used by military personnel and/or civilians should a public health emergency be declared.

### 4.3 ADMINISTRATION OF SIP VACCINES UNDER AN INVESTIGATIONAL NEW DRUG APPLICATION

FDA regulations 21 CFR Part 312 (drugs) and Part 601 (biologics) contain procedures and requirements governing the use of investigational new drugs and biologics. All clinical research projects involving drugs or biologics (including vaccines) that are not FDA-approved for marketing must be reviewed by FDA. This is accomplished by filing an IND for each of the following instances: (1) any use of a drug or biological (including a vaccine) not approved for marketing by FDA, even if no formal study is being conducted; (2) studies involving an approved (i.e., commercially available) drug or biological that is being tested to support a new indication or significant change in labeling of the drug or biologic; and (3) studies involving an approved (i.e., commercially available) drug or biologic that is being used or tested in a new route of administration, new dosage level, or new patient population that may increase the risk of the drug or biologic. All studies conducted under IND must also be in compliance with the requirements for Institutional Review Board (IRB) review and informed consent (21 CFR Part 50 and 21 CFR Part 56, respectively).

There are, at present, four types of IND Applications, all of which apply to the SIP:

- *Conventional (a.k.a. "commercial") IND* (21 CFR § 312.20)—submitted by a sponsor, typically a commercial entity, usually with the intent to market the product at some future date upon FDA approval.
- *Investigator-initiated IND* (21 CFR § 312.22[d])—submitted by a physician who both initiates and conducts an investigation.
- *Individual patients, including for emergency use* (21 CFR § 312.310; formerly 21 CFR 312.36)—issued by FDA to allow the use of an experimental drug or biologic for the treatment of one (so-called "named") patient when (1) the administering physician has determined

[1]For further information, see FDA 2010a.

that the probable risk of the drug (or vaccine) is not greater than the probable risk of disease; and (2) FDA determines that the patient cannot obtain the drug under another IND or protocol. *Research may not be conducted under an emergency use IND.*[2] An emergency use IND exemption may be used one time only for a particular drug or biologic in a particular institution. Subsequent uses require prior IRB review and approval.

- *Treatment IND or treatment protocol* (21 CFR § 312.320; formerly 21 CFR §§ 312.34–35)—submitted for experimental drugs (including vaccines) *already* showing promise in clinical testing for serious or life-threatening conditions, either in an ongoing clinical trial under an existing IND or in instances where all clinical trials have been completed and the sponsor is actively pursuing marketing approval.

### 4.3.1 Conventional IND

As described previously in Chapter 3, a total of eight vaccines are presently being utilized in the SIP under INDs held by USAMRIID or CDC. These vaccines, many of which are in short supply, include botulinum toxoid, eastern equine encephalitis (EEE) virus, RVF virus, VEE virus (strains TC83 and C84), WEE virus, Q fever, and tularemia. A number of other vaccines relevant to laboratory workers are also being studied under IND, but are not currently included in the SIP. A complete listing of such vaccines is not available, although a partial listing based on documents available in the public domain is provided in Chapter 5.

### 4.3.2 Investigator-Initiated IND

Investigator initiated INDs are typically submitted by a single investigator or academic institution, often with the full knowledge and cooperation of the primary (conventional) IND holder. Such INDs are usually submitted to study an investigational vaccine for a different indication (e.g., post-exposure prophylaxis), patient population, schedule, or route of administration. The primary IND sponsor typically provides information (usually via cross-reference to the primary IND) that is not available to the investigator, such as chemistry, manufacturing, and controls (CMC) data; the Investigator's Brochure; or other data relevant to the clinical study proposed by the investigator.

[2] "Research Use": Most use of unapproved devices, drugs, or biologics is part of a systematic clinical trial or other clinical investigation designed to test the safety and/or efficacy of the test article. All such clinical investigations, including pilot studies, require prior IRB review and approval. In addition, almost all clinical studies are conducted under an Investigational Device Exemption (IDE) or an IND exemption obtained from FDA, which require that research protocols be filed with FDA prior to study commencement.

While there are no vaccines presently included in the SIP that are being evaluated under an investigator-initiated IND, this mechanism could be utilized in collaboration with a willing manufacturer and/or primary IND holder. Such a mechanism could be especially relevant to manufacturers who have obtained regulatory approval outside the United States and who may desire potential expansion to the U.S. market (see previous discussion above). These manufacturers could either allow a U.S.-based investigator to cross-reference their IND (if one exists) or they could prepare and submit a Master File that the investigator may cross-reference for relevant CMC, preclinical, and/or clinical information.

### 4.3.3 Emergency Use IND

The need for an investigational vaccine could arise in an emergency situation that does not allow time for submission of a conventional or investigator-initiated IND. For such instances, FDA issued a final rule on August 13, 2009, to facilitate the availability of drugs (including vaccines) to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy in a program known as "expanded access to investigational drugs for treatment use." Among other provisions, the final rule authorizes shipment of the vaccine for a specified use (21 CFR § 312.36). Such authorization is usually conditioned upon the sponsor filing an "Expanded Access Submission" within 15 working days of the original request to FDA.

It is important to appreciate and understand the provisions listed in 21 CFR § 312.300 (general provisions), § 312.305 (requirements for all expanded access uses), and § 312.310 (individual patients, including for emergency use). Under typical circumstances, the following six criteria must be met to comply with federal regulations and IRB policy:

- The patient has a condition that is *serious* or immediately *life-threatening*.
- No standard treatment is available.
- The potential patient benefit justifies the potential risk of the drug (or, in this case, a vaccine), and those potential risks are not unreasonable in the context of the disease to be treated.
- The vaccine cannot be obtained or utilized under another IND or protocol.
- If requested by telephone, the physician or sponsor must explain how the expanded access will meet CFR requirements and must agree to submit a formal Expanded Access Submission within 15 working days of FDA's authorization for use.

Given these circumstances and regulatory requirements, the administration of an investigational vaccine in the SIP under an emergency use IND would be done infrequently, if at all, given the prerequisites of a preexisting IND or

a preexisting study protocol at the requesting institution. The most probable scenario in which this might occur would be a request from the prospective emergency IND holder (e.g., USAMRIID) to an existing IND holder (e.g., domestic or foreign manufacturer) to submit a conventional clinical research protocol to the manufacturer's existing IND. If emergency use of the vaccine is required for a patient who otherwise does not meet entry criteria for the standing protocol, then an emergency IND could be filed by another institution (e.g., USAMRIID), in order to administer the vaccine to that patient. Emergency use of such a vaccine in the SIP setting might also occur as part of a post-exposure prophylaxis scenario in which the vaccine is administered in combination with an antimicrobial treatment and/or passive immune therapy in order to allow sufficient time for a protective immune response to develop. A form of emergency use of an investigational vaccine was employed in Germany in 2009, when a laboratory worker sustained a needlestick while handling Ebola virus. An investigational vaccine developed in Canada and based on vesicular stomatitis virus expressing an Ebola virus envelope glycoprotein was administered to the worker, who did not develop symptoms of disease (Enserink 2009).

### 4.3.4 Treatment IND

A Treatment IND or treatment protocol (21 CFR § 312.320; formerly 21 CFR §§ 312.34–.35) is a mechanism for providing eligible subjects with investigational drugs (including vaccines) for more widespread prevention or treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. In addition to meeting the general criteria for expanded access (21 CFR § 312.305(a)), the following additional criteria must be met:

- The drug (vaccine, in this instance) is either being investigated in a controlled clinical trial under an IND designed to support a marketing application, or all clinical trials of the vaccine have already been completed.
- The sponsor is actively pursuing marketing approval with due diligence.
- For *serious* diseases, there is sufficient evidence of safety and effectiveness (generally Phase III data).
- For *immediately life-threatening* disease, there is sufficient evidence that the vaccine would not pose an unreasonable or significant risk of illness or injury.

Treatment IND studies require prospective IRB review and informed consent. A sponsor may apply for a waiver of local IRB review under a treatment IND if it can be shown to be in the best interest of the subjects, and if a satisfactory alternate mechanism for ensuring the protection of human subjects is available, e.g., review by a central IRB. Such a waiver does not apply to the

informed-consent requirement. An IRB may still opt to review a study even if FDA has granted a waiver.

Based on these considerations, the most likely scenario in which an investigational vaccine would be administered in the SIP under a treatment IND would be during the late stages of a pivotal (Phase III) study (for which the SIP recipient would be ineligible), during the review period of a pending BLA for the vaccine in question, or when very compelling Phase II data were available in the instance of the potential for life-threatening disease. In any of these instances, the SIP would have to obtain permission from the primary IND holder to cross-reference applicable sections.

### 4.3.5 Optimization of IND Program Administration

As discussed previously, an overarching goal of the SIP is to provide more convenient access to existing vaccines included in the program. Ready access has been achieved for the eight licensed vaccines, but remains somewhat cumbersome for laboratory workers outside of DOD to be immunized because of centralized administration of the program at USAMRIID. Although a centralized approach to manage these INDs has a number of important advantages—including detailed knowledge of each IND dossier, complete and careful documentation of adverse event and immunogenicity data, and timely revisions of regulatory documents such as appropriately updated Investigator's Brochures—the requirement that vaccinees must, in nearly all instances, travel to USAMRIID to be vaccinated has appeared to impede participation in the program severely. Therefore, the committee believes that the utilization of other IND mechanisms such as investigator-initiated INDs or treatment INDs held by investigators at other government or academic institutions should be strongly considered, contingent on a continuing strong commitment for complete and standardized data and fulfillment of responsibilities under the IND collection.

## 4.4 OTHER REGULATIONS AND GUIDANCE OFFERING POTENTIAL INCENTIVES TO THE DEVELOPERS OF SIP VACCINES

Because the SIP is directed exclusively at prevention of serious and life threatening disease typically caused by Select Agents or other highly virulent pathogens, FDA regulations have several other provisions designed to speed review and approval of BLAs and/or provide significant financial incentives to developers. These include (1) priority review (which mandates a 6-month FDA review period, rather than the standard 10-month period); (2) fast track (allows for a "rolling" BLA submission); (3) orphan drug designation (which allows for marketing exclusivity for 7 years following BLA approval); and (4)

accelerated approval (which allows for the establishment of efficacy based on surrogate endpoints likely to predict clinical benefit). All four provisions will often apply to most of the pathogens targeted by the SIP, both currently and in the future, and can potentially accelerate and incentivize the approval process in many instances.

In addition to these regulations, FDA published a guidance document in 2008 (FDA 2008) that is intended to provide pharmaceutical manufacturers with further financial incentives to develop drugs (including vaccines) for the prevention and treatment of certain tropical diseases. More specifically, the guidance provides information on the implementation of section 1102 of the FDA Amendments Act of 2007, which adds new section 524 to the Federal FD&C Act (21 U.S.C. § 360n). Section 524 authorizes FDA to award priority review vouchers to sponsors of certain tropical disease product applications that meet the criteria specified by the Act. A priority review voucher may be used by the sponsor who obtains it or another sponsor to obtain a priority review for a different application (typically a product with a very large and/or lucrative marketing potential). Although most of the specific diseases listed in the guidance do not yet apply to the SIP, a few do (e.g., dengue), and importantly, the more general category of "*any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by regulation by the Secretary (section 524(a)(3))*."

## 4.5 REGULATORY CONSIDERATIONS: LOOKING TOWARD THE FUTURE

As described elsewhere, the SIP has, to date, provided substantial benefits for current and future laboratory workers and others exposed to hazardous pathogens. The SIP has maintained, provided, and administered a comprehensive program to support the availability of vaccines that are a key component of a comprehensive strategy to promote the highest standards in biosafety and disease prevention safeguards for protecting these individuals from potentially lethal disease. Moreover, continuing efforts to collect both safety and efficacy data have the potential to contribute further to the advancement of science, including use of existing data to further describe the safety, immunogenicity, and efficacy profiles of the existing SIP vaccines; to consider further development of at least some of them to enable U.S. licensure; to provide an existing platform to benchmark performance for purposes of comparison in the development of the next generation of vaccines; and to better prepare for the possibility of other licensure pathways in the future. With these objectives in mind, the following approaches should be considered to improve the effectiveness of the program with respect to regulatory considerations in the coming decade.

### 4.5.1 Comprehensive Review of Individual SIP Vaccines Tested Under IND

As discussed previously, U.S. licensure has simplified access to and availability of eight vaccines included in the SIP, and, importantly, provides eligible laboratory workers the confidence that these vaccines meet stringent requirements for safety and efficacy. Because of these clear advantages, detailed review of the investigational vaccines included in the SIP should be undertaken to determine whether there would be any possibility of obtaining U.S. licensure. These reviews could consist of, at a minimum:

- Examination of CMC information to determine (1) the extent to which the existing stocks of each vaccine may have met cGMP requirements, and if not, whether remedial compliance actions might be instituted; (2) if the manufacturing process could be replicated in whole or in part to generate new lots for purposes of physical and biochemical characterization and clinical bridging studies; and (3) if the manufacturing process or product cannot meet cGMP standards, whether critical starting materials (e.g., vaccine seed strains) are still available and could be utilized to make additional cGMP-compliant lots.
- Examination of all available clinical data (safety and immunogenicity) available for each SIP vaccine studied under IND, with an assessment of the apparent risk-benefit ratio. For those vaccines with an unfavorable risk-benefit ratio, consider the development of a next-generation replacement vaccine as soon as possible. Also consider the potential withdrawal of current vaccine(s) from the SIP based on the detailed risk-benefit assessments.
- Explore the most likely means of U.S. licensure, which, for the majority (if not all) of the current investigational SIP vaccines, would likely consist of either accelerated approval (if a suitable antibody correlate is available) or full approval under the Animal Rule. In reference to the Animal Rule, a review of existing or potential animal models that might be used to generate efficacy data should be pursued.

### 4.5.2 Exploring the Potential to Expand the SIP Portfolio with Vaccines Developed Outside the United States

Three vaccines against pathogens either already included in the SIP or that could be added in the near-term are currently approved outside the United States: Q-Vax® (whole-cell *Coxiella burnetii* vaccine, CSL Limited, Australia); Encepur® (whole-virus, formaldehyde-inactivated tick-borne encephalitis virus vaccine, Novartis Vaccines and Diagnostics, Germany); and FSME-IMMUN® (whole-virus, formaldehyde-inactivated tick-borne encephalitis vaccine, Baxter BioScience Vaccines, Austria). Because the U.S. market for these vaccines is

highly limited (because of absence of, or extremely low, disease incidence), none of the manufacturers appear to be interested in seeking U.S. licensure, even though it is reasonable to assume that each product would likely meet FDA requirements in terms of manufacturing process, testing and controls, and clinical safety and immunogenicity. It is unknown whether these companies would consider submitting a BLA if sufficient financial and/or other incentives might be made available by the U.S. government.

In addition to the three vaccines made by the three well-established, multinational companies, there are a number of other vaccines potentially applicable to the SIP that are approved in other, more limited regulatory jurisdictions. These include vaccines against hemorrhagic fever with renal syndrome (approved in South Korea and China), Argentine hemorrhagic fever (approved in Argentina), Kyasanur Forest disease (approved in India), Crimean-Congo hemorrhagic fever (approved in Bulgaria), SARS (approved in China), and plague (approved in the former Soviet Union). It is presently unknown whether any of these vaccines could potentially meet FDA requirements for licensure, but if they did, the respective companies may also require an incentive to submit a BLA in the same manner as the multinational companies listed above.

Discussions with the relevant manufacturers as to the potential for BLA submission (for U.S. licensure) and/or biologics Master File submission (to enable incorporation of the vaccines under a U.S. IND held by the U.S. Army Medical Department Office of the Surgeon General or other U.S.-based entity) should be pursued. Similarly, discussions with manufacturers in other regulatory jurisdictions (e.g., China, India, Eastern Europe, and Latin America) might also be considered, especially for those vaccines that have promising safety and immunogenicity profiles. Joint development programs between these and U.S.-based entities might also be a means to accelerate development of additional vaccines of interest to the SIP. Teams of vaccine development experts might also be assembled to carry out on-site reviews, patterned after successful "due diligence" approaches carried out by large pharmaceutical companies and venture capital groups for merger and acquisition and/or in-licensing opportunities for SIP portfolio expansion.

### 4.5.3 New Regulatory Approaches

Because of the unique medical and epidemiologic circumstances surrounding the SIP—that is, (1) the typically very high risk of severe morbidity or death following percutaneous, respiratory, or other exposure to a Select Agent or other highly virulent pathogen; (2) the typically very low risk for exposure to such pathogens among the general population, except for potential instances of biological terrorism; (3) the very low numbers of persons who would be qualified to receive a SIP vaccine (e.g., persons who may be exposed as a consequence of laboratory-based exposure)—typical regulatory pathways gener-

ally do not apply. The most analogous regulatory circumstance pertains to an orphan drug (per the Orphan Drug Act [ODA] of 1983, §§ 525 [360aa] and 526 [360bb]). This legislation, which is intended to provide incentives to the pharmaceutical industry to develop drugs with very small commercial potential, provides benefit from a 50% deduction tax credit for clinical trial expenses and a market exclusivity of 7 years. In addition, protocol assistance in the form of written recommendations from the secretary of HHS for the nonclinical and clinical investigations needed for marketing approval can be obtained to accelerate the approval process. In this respect, a more flexible approach has often been adopted for the development of orphan drugs, such as potential waivers for preclinical toxicologic data, including teratogenicity and/or carcinogenicity studies, so long as the safety to human subjects is not significantly compromised. The legislation also states that the clinical dossier of an orphan drug (including vaccines) should be built on a realistic assessment of the qualitative and quantitative nature of the studies that can realistically be performed. Such an assessment is highly relevant because of the orphan nature of the disease and its low prevalence in the general population—or, in the case of the SIP, low prevalence among laboratory workers and other at-risk populations—may make it difficult to recruit a large enough number of qualified participants for a clinical trial. An important drawback of this approach is that the approval of such a vaccine, if granted, would have a relatively limited amount of safety data when compared with the typical safety database for a vaccine (which often includes a minimum of 4,000–5,000 subjects). Therefore, if an Orphan Drug Designation is pursued as an ancillary regulatory mechanism, attention must be given to the potential concern among SIP vaccine recipients that assurances regarding the safety of the product may be less robust than those for vaccines given to the general population.

An additional approval pathway available in Europe, but not in the United States, is the granting of a marketing authorization "*under exceptional circumstances,*" pursuant to Article 14(8) of the European Commission (EC) Regulation No. 726/2004 (EMA 2005). More specifically, the European Medicines Agency (EMA) has determined that if the applicant (the equivalent of an IND sponsor in the U.S.)

> can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:
>
> 1. the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence; *or*
> 2. in the present state of scientific knowledge, comprehensive information cannot be provided; *or*
> 3. it would be contrary to generally accepted principles of medical ethics to collect such information

> a marketing authorization [equivalent of U.S. licensure] may be granted subject to certain specific obligations.

These obligations, in turn, may include the following:

- "The applicant shall complete an identified program of studies within a time period specified by the competent [regulatory] authority, the results of which shall form the basis of a reassessment of the benefit/risk profile";
- "The medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital"; and
- "The package leaflet [package insert] and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects."

This approval pathway is most analogous to the EUA regulatory provision in the United States (see previous discussion), but has the important advantage of being implemented in the absence of a public health emergency. Such a potential pathway seems especially relevant to vaccines included in the SIP, both now and in the future. Thus, exploration of the possibility of potential new regulatory pathways such as "restricted" or "conditional" licensure (FDA 2010d: 128), which would be relevant to use of a SIP vaccine, should be considered.

In addition to these possibilities, continuing advancements in manufacturing and analytical technologies and biomarkers may eventually mature to the point where the licensure of manufacturing "platforms" might be considered under special circumstances, rather than licensing of individual drug products per se. As discussed in more detail in Chapter 5, platform technologies are applicable to the development of multiple products for different indications based on a single technical approach. The best example in vaccinology is the use of a single vector virus, bacteria, or yeast to deliver foreign genes against the pathogen to which immunity is desired. The same vector backbone, with or without some modifications, could then be reused to deliver other genes. If expression of those genes consistently resulted in, for example, the generation of recombinant viral capsid protein antigens critical to a protective immune response, then the clinical profile of one vaccine might be easily bridged to another, without the need for extensive clinical testing of each recombinant vaccine individually. Experience gained with such a platform could also be leveraged for other pathogens that might be of greater commercial interest, and thus provide a continuous "warm base" for the manufacture of large batches to be used commercially as well as smaller batches to be used as "orphan vaccines" for the SIP or other biodefense purposes. In addition to predictable manufacturing platforms, *ex vivo* testing in the form of appropriate biomarker

generation may also be predictive of a robust antibody response in the absence of any concerning safety signals. If so, rapid approval of new vaccines against Select Agents and other highly virulent pathogens might be further enabled in the coming decades.

The recent Public Health Emergency Medical Countermeasures Enterprise Review (HHS 2010b) includes recommendations to explore and develop new "regulatory innovation, science, and capacity" applicable to the development of medical countermeasures such as vaccines. Efforts undertaken by FDA and others should continue to advance this area in the future, and the committee endorsed these goals.

## 4.6 FINDINGS AND CONCLUSIONS ON REGULATORY PATHWAYS APPLICABLE TO THE SIP

- *Finding 8:* There are provisions within existing FDA regulations that could apply to the SIP and, in particular, that could be used to enable the administration of additional SIP immunizations and/or to enable the use within the SIP of additional IND vaccines (both domestic and foreign).
- *Finding 9:* New regulatory approaches and further development of science to support regulatory approval mechanisms might offer additional options for use of SIP IND vaccines and/or licensure pathways for existing or new vaccines relevant to the SIP.

# 5

# New Vaccine Development and the Future Needs of the Special Immunizations Program

## 5.1 THE PROCESS OF VACCINE DEVELOPMENT

As discussed in detail in Chapter 4, vaccine development and licensure are regulated by the Food and Drug Administration (FDA)'s Center for Biologics Evaluation and Research, according to the regulations contained in Title 21 of the *Code of Federal Regulations*.

Vaccine development leading to a licensed product typically involves a series of steps, starting with initial research, development, and testing for immunogenicity and protective immunity in animal models. After those preclinical studies, investigators submit data to FDA to receive an Investigational New Drug (IND) approval and move into testing in human volunteers. Clinical testing is accomplished in several phases:

- *Phase I.* Testing in relatively small groups of healthy adults to obtain initial safety and human immunogenicity data.
- *Phase II.* Testing in larger groups to continue refining information on safety, efficacy, and dosing.
- *Phase III.* Trials usually conducted in large groups of the likely user population with a focus on obtaining information on infrequent adverse events and on demonstrating efficacy often through measurements of immune correlates of protection.

After obtaining successful results in clinical trials, the sponsor submits a Biologic License Application (BLA) to FDA to seek product licensure. Once a product is licensed, Phase IV, or post-market surveillance, continues to be conducted, and adverse events that occur are reported. Included along the continuum of the process is the need to manufacture a candidate vaccine under

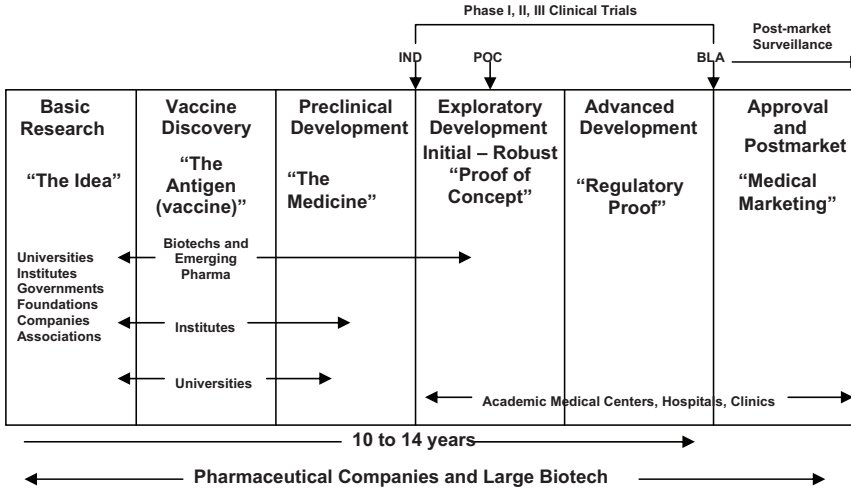



**FIGURE 5.1** Vaccine research from idea to market. SOURCE: Adapted from IOM 2009. IND = Investigational New Drug application; POC = proof of concept; NDA = New Drug Application; Pharma = pharmaceutical companies.

current Good Manufacturing Practices standards on a pilot scale for preclinical testing and early clinical studies and on larger scales for testing in Phase III trials and ultimately for commercial production (Figure 5.1).

Candidates for enrollment in the Special Immunizations Program (SIP) include researchers studying fundamental biology and pathology of highly hazardous pathogens or working in the initial stages of development of new candidate vaccines and medical countermeasures (MCM). Preclinical animal challenge and testing studies also potentially expose laboratory researchers and animal technicians to pathogen infection. And personnel working on the pilot and scale-up manufacturing of a potential vaccine candidate may benefit from SIP vaccination, particularly if at risk of exposure to large quantities of live pathogen strains.

## 5.2 NEW VACCINE DEVELOPMENT AND THE FUTURE NEEDS OF THE SPECIAL IMMUNIZATIONS PROGRAM

Except for several licensed vaccines, the vaccines now used in the SIP are IND products and are no longer being manufactured (information on the available stocks of these vaccines is provided in Chapter 3). At the current rate of use, these stocks will be adequate for a number of years. However, a number of risks are associated with the lack of current manufacture and the current status of SIP vaccines:

- Existing stocks could be found to be out of specification because of loss of potency, contamination with an adventitious agent, appearance of particles, or other product-quality problems.
- There could be a need to increase use in laboratory workers in the event of an expanded research, development, or manufacturing effort associated with a specific threat agent.
- There could be an unexpected need to use the vaccines in a larger number of people because of deployment of military or public health personnel to an area with a natural disease emergence or biological threat.

Such events could necessitate renewed manufacturing. As time passes, and the existing stocks age, there is also increasing concern that degradation might result in changes that are not detected in the stability program but could adversely affect product quality or biological performance or lead to adverse reactions.[1] The committee therefore believes that it may be prudent to have fresh materials prepared for some or all products and to have bridging clinical trials performed. Such a program could be rolled out in order of priority considering aspects such as the amount of available stocks, the likely size of the researcher user population, the age of the vaccine stocks, the vaccine product profile, and concerns about potency or other product-quality issues.

In undertaking such a program, careful consideration should be given to the question of whether the legacy vaccine has a product profile that warrants the effort of new stock manufacture. For example, it is widely known that the attenuated Venezuelan equine encephalitis (VEE) TC-83 vaccine safety and immunogenicity profiles are deficient. Alternative vaccine candidates have already been developed, and clinical data on them are available (for example, the replicon vaccine developed by the U.S. Army Medical Research Institute for Infectious Diseases and AlphaVax, Inc.), so consideration should be given to replacement of VEE TC-83 vaccine in the SIP rather than making new stocks of it. Similarly, as pointed out elsewhere in the report, a licensed Q fever vaccine is manufactured by CSL, Ltd. in Australia and could replace the legacy vaccine now being used in the SIP. Although it is also used with a prevaccination skin test, this has been accomplished by intradermal administration of diluted vaccine (Gidding et al. 2009). The committee believes that the need for new manufacturing of legacy vaccines, priority-setting, improvements in vaccine

[1]Biological products may undergo gradual degradation from enzymes such as proteases or from physical influences such as heating or freezing. In addition, a vaccine based on a live virus or bacteria may die off and become less potent over time. Part of cGMP compliance is the longitudinal monitoring of biological products for parameters such as potency and sterility to ensure that the products will continue to meet requirements throughout their period of use.

manufacture, and replacement vaccines with improved product profiles for given indications should be analyzed case by case as a separate exercise.

As research priorities in biodefense and emerging infectious diseases shift and evolve, researchers may find themselves working with highly hazardous pathogens that are not addressed in the current SIP. Thus, the committee considered the process of new vaccine development and how vaccine development issues might be related to the future of the SIP.

### 5.2.1 Types of Vaccines and Manufacturing Methods

Many technologies are applicable to the development and manufacture of vaccines (see Table 5.1). The risk of adverse reactions to a vaccine is highest for live, attenuated or live-vector vaccines because the full spectrum of reactogenicity cannot be known at an early stage of development and adverse reactions may occur in people who have inherited or acquired susceptibility factors. Those risks are significant, but live vaccines may permit use of very low doses (and thus allow small-scale production of many doses), usually trigger both innate and adaptive immunity, and may confer long-lasting immunity with a single dose. A substantial safety database on such products may be required before they can be included in an immunization program like the SIP. The risk of adverse reactions posed by inactivated or subunit vaccines is inherently lower. However, the inclusion of novel adjuvants with an inactivated or subunit vaccine may increase safety concerns and require additional clinical experience before they can be included in the SIP.

The equipment and facilities used for biomanufacturing are changing, and low-capital, rapid-turnaround, single-use disposable bioreactors and process systems are enabling low-cost manufacture of small volumes of vaccines and other biologics. Although fixed, hard-piped stainless-steel bioreactors and clean-in-place and sterilize-in-place facilities are still important for high-volume or dedicated product manufacture, the use of flexible, single-use equipment can reduce initial investment cost and support rapid manufacture of clinical supplies. For example, Bavarian Nordic manufactures a new investigational modified vaccinia Ankara smallpox vaccine in GE WAVE bioreactor bags. The benefits of single-use bioreactors include lower cost of facility buildout and operations, shorter changeover times, increased productivity, lower risk of bacterial or mold contamination, and less scrap. Single-use process trains can support flexibility in the operation of a multiuse facility. Several companies have developed single-use stirred-tank bioreactors,[2] mixers, and downstream purification systems. The bioreactors are now large enough to meet the needs of almost all vaccines for the Department of Defense (DOD) and the Department

[2]These include Xcellerex, Sartorius, and Hyclone.

of Health and Human Services (HHS). No manufacturer makes a commercial product with these systems yet, but the technology will soon be applied to vaccine production; several large companies are using disposable systems for products in the last stages of development. For SIP products with requirements for small numbers of doses, traditional pilot-scale manufacturing with disposable technology—such as WAVE bioreactor bags, roller bottles, and cell factories—may suffice. However, manufacturing on a pilot scale (for example, 25–1,000 L) initially in a stirred-tank bioreactor with disposable liner bags or in a fixed tank cleaned in place ensures that scale-up can be rapid if the need arises. Roller bottles, WAVE bags, and cell factories may require replication of small units to achieve larger manufacturing capacity or may present a more challenging transition to larger bioreactors.

The requirements (or at least expectations) for product quality, purity, and freedom from animal products in new vaccines are more stringent than they were when the older SIP vaccines were manufactured. Except for vaccines prepared in diploid human cells, residual host-cell DNA concentrations must be less than 10 nanograms per human dose, and the size of residual DNA should be no more than the size of a gene. Host-cell protein concentrations are of less concern, but new vaccines generally contain less than 1 microgram per dose. Other residual contaminants from materials used in or added to the process may need to be measured. There is now a strong preference for avoiding any animal product (such as fetal bovine serum or porcine trypsin) or human blood-derived proteins in the manufacturing process. Tests for adventitious agents are more extensive and complex today than ones that were in place when the older products were made. Porcine circovirus contamination of Vero cells, African green monkey kidney cells used in the manufacture of rotavirus vaccines, is a case in point (Victoria et al. 2010).

Standards for testing for adventitious agents are very different today from when the SIP products were manufactured. Moreover, the cell culture–based SIP vaccines would have been manufactured with fetal bovine serum in the medium used to expand cells before viral infection. As a result, from 2000 to 2003, the SIP repeated complete lot release testing and tracked down the sources of fetal bovine sera to document that the vaccines meet current requirements and to exclude the possibility of bovine spongiform encephalopathy contamination.

Table 5.1 describes a variety of strategies used in the development of vaccines and compares some of their characteristics.

### 5.2.2 Replenishing and Expanding Existing Vaccine Stockpiles

For existing SIP vaccines, developed and made many years ago, there are numerous opportunities to improve on method of manufacture and control, product quality, stability, and potentially even efficacy (for example, by the

**TABLE 5.1** Examples and Characteristics of Major Concepts for Design and Scale-up of New, Improved Vaccines

| Platforms | Whole Microorganisms | Subunits | Bulk Process Complexity | Formulation Complexity | BSL Required | Transmissible to Nonvaccinees | Immunologic Advantages |
|---|---|---|---|---|---|---|---|
| Live attenuated bacterial and viral vaccines (e.g., *S. typhi*, shigella, varicella, measles) | Attenuated wild-type microorganisms | | Minimum complexity; fermentation, cell culture, often without purification | May require lyophilization with stabilizing agents | Minimum BSL-2+ | Yes | Very low dose; innate and adaptive immunity; long duration of immunity |
| Inactivated wild-type bacterial vaccines (e.g., DTP, animal vaccines) | | | Minimum complexity; fermentation, cell culture, followed by inactivation, often without purification | | BSL-2/3 | No | Not infectious; innate and adaptive immunity |
| Inactivated wild-type viral vaccines (e.g., animal vaccines, annual influenza | Egg-adapted current strains; cell culture may use wild type | "Split" vaccines processed to remove core components, leaving surface antigens | Egg-based process—complex; cell-culture process—less complex | | wild-type requires BSL-3; attenuated, egg-adapted, BSL-2/3 | No | Not infectious; innate and adaptive immunity; "split" vaccines may have less severe injection-site reaction |
| Replicating nonpathogenic bacterial vectors (e.g., recombinant commensal bacteria, oral typhoid, animal vaccines, experimental cancer vaccines) | | Recombinant heterologous antigens | Minimum complexity; fermentation | May require lyophilization with stabilizing agents | | Yes | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Replicating nonpathogenic viral vectors (e.g., cancer vaccines, HIV vaccines, animal vaccines) | Recombinant heterologous antigens | | May require lyophilization with stabilizing agents | | Yes | Recombinant-DNA vaccine platforms that stimulate both innate and adaptive immunity; may be very-low-dose systems |
| Nonreplicating viral vectors (e.g., alphavirus replicons, RNA and DNA vaccines) | Recombinant heterologous antigens | | | Infectious wild-type viruses may require BSL-3 | No | Recombinant-DNA vaccine platforms that stimulate both innate and adaptive immunity |
| Particulate vaccines (virus-like particles, bacterial-cell ghosts, self-assembled subunit antigens) | | Moderate to complex | May require stabilants or cross-linking; used in conjunction with adjuvants | | No | Mimic whole-virus vaccines in recruiting innate and adaptive immunity |
| Purified proteins, peptides, polysaccharides | | Moderate to complex | Minimal; many adsorbed to alum | | No | Generally poor immunogens |
| Conjugated proteins, peptides, polysaccharides (e.g., pneumococcal, meningococcal, *H. influenzae* conjugates) | | Complex; two fermentations, isolations, purifications; separate conjugation chemistry and purification steps | Minimal; many adsorbed to alum | | No | Improved immune response to purified antigens |

*continued*

**TABLE 5.1** Continued

| Platforms | Whole Microorganisms | Subunits | Bulk Process Complexity | Formulation Complexity | BSL Required | Transmissible to Nonvaccinees | Immunologic Advantages |
|---|---|---|---|---|---|---|---|
| DNA vaccines | | Typically recombinant genes amplified in bacterial plasmids | Minimum complexity | Minimum to moderate complexity | | No (?) | Can be designed and scaled up in very little time; recruit innate and adaptive immune response; effective as "primer" in "prime-boost" strategies |

SOURCE: Drew 2007.

addition of an adjuvant). The priority for replacing an existing product will be driven by a case-by-case assessment of the following factors:

- Current supply.
- Assessment of future needs (for example, in an expanded SIP program).
- Stability trending data that may indicate a loss of potency.
- Potential issues of product quality (as noted, complete lot release testing was redone in 2000–2003).
- Whether an improved product for the same indication already exists (for example, as a licensed or investigational product) or is in development with an expected timeline for availability within the lifespan of existing vaccine stocks.
- Current product profile versus ideal product profile for a vaccine for the same indication.
- Specific problems and issues with the existing vaccines (for example, substrate acceptability), use of animal products in culture media or manufacturing steps (for example, use of fetal bovine serum or porcine trypsin), incorporation of human-blood–derived materials in the product (for example, human serum albumin), lack of controls for adventitious agents, genetic stability, safety, and immunogenicity, to name a few concerns likely to arise given current manufacturing and regulatory standards.
- Whether there is an existing sponsor for redevelopment and manufacturing of replenishment vaccine.
- Existence and completeness of documentation and materials (for example, seed stocks and analytic reagents) that allow technology transfer to a contract manufacturer.
- Extent of proposed changes in manufacturing and control methods.
- Scope of clinical trials required for bridging past data on safety, immunogenicity, and potential efficacy to a new vaccine stock.

Changes in the manufacture of a biological product must be carefully considered because regulatory approval necessary for human use focuses on control of the process rather than on analysis of the end product (as would be the case for a well-defined chemical entity or drug). Even if a replenished supply of an older vaccine were made with methods as close as possible to the original process, there would be many changes in raw materials, cell banks, and procedures for production and downstream processing. In essence, a redevelopment program would be required to reproduce clinical-trial material with engineering or pilot batches to ensure manufacturability and quality of the product. Depending on whether FDA views changes in the production process or product as material changes, there may need to be additional preclinical

toxicology studies. Certainly, some bridging clinical trials will be necessary to ensure comparability with the original vaccine. The costs of technology transfer, manufacturing, quality control, and bridging studies for new production of an existing SIP vaccine may be substantial and should be carefully weighed case by case against an investment in innovative or improved technology for vaccine development and production.

Some substrates used to produce the original vaccine may not be acceptable for use today, such as guinea pig heart cells in the case of VEE TC-83 vaccine. However, use of a new substrate would constitute a substantial product change. For live, attenuated vaccines, such as tularemia LVS and VEE TC-83, and some other vaccines that might be considered for inclusion in an expanded SIP, such as Chikungunya 181 clone 25, genetic stability may present a challenge for production of new vaccine lots. Molecular tools that allow assessment of genetic stability were not available when these vaccines were originally developed, and genetic variability when new lots are produced would have uncertain regulatory implications. This issue will be a concern, particularly for vaccines against RNA viruses, which have high mutation rates.

### 5.2.3 Near-Term Requirements

Even with the complexities described above, the timeline for manufacturing, releasing, and testing a new supply of an existing product may be far shorter than the timeline for developing a new vaccine to the point where it could be integrated into a program like the SIP. Assuming that there is a need for replenished supply within a short timeline (such as 3 years), new vaccine lots of selected existing investigational vaccines that have a reasonably straightforward manufacturing path and are not likely to be eclipsed by new technology within that period could be made. That applies principally to inactivated vaccines against eastern equine encephalitis (EEE), western equine encephalitis (WEE), VEE, and Rift Valley fever (RVF), and to botulinum toxin. Assuming the availability of batch-production records, cell banks, and seed stocks for the legacy vaccines, it should be possible to bring a new lot of any of them to the point of release in about 12 months. To enable production of existing vaccines, it would be useful to prepare a product-development plan for each product that defines task-specific timelines, resource requirements, and costs.

### 5.2.4 Choice of Manufacturing Site, Methods, Scale, and Scalability

Vaccines in the SIP were manufactured on a small scale in multiuse facilities, such as the Salk Institute Government Services Division (GSD), which is no longer in existence. A number of laboratories are engaged in early-stage research on and development of new vaccines of interest to the SIP, but they are generally small biotechnology companies or academic institutions, and only

a few have the facilities and capability to develop vaccines to the point where they could be included in the SIP or to produce or maintain vaccine supplies over a longer period.

Since closure of the Salk GSD, the DOD has had few options for obtaining vaccine development and production services. Other contractors, for example, declined to compete for the vaccine work that had been done by the Salk Institute, and discussions in 1991 with five commercial vaccine producers confirmed the lack of contractor interest (GAO 1991). In the absence of a commercial market for biodefense vaccines in the United States, commercial vaccine producers have not invested in the construction of the containment facilities needed to produce them. Commercial manufacturers explained that such facilities are expensive to construct and shockingly expensive to operate and maintain and that they would therefore seek a guarantee from the DOD before any construction effort that they would recoup their investments. One official estimated that it would cost about $25 million to construct a facility that could produce 1–2 million doses each of seven or eight vaccines a year (GAO 1991).

In many respects, the Salk GSD, which operated as a nonprofit foundation funded by government contracts, may be one model for future facilities for making vaccines against special pathogens that lack commercial markets. Other groups have called for establishment of government–industry partnerships and the creation of additional incentives to encourage greater industry participation in advanced development and manufacturing of medical countermeasures (IOM 2004; HHS 2010b; NBSB 2010a,b). Recent requests for information and requests for proposals from both HHS and DOD address components of this vaccine manufacturing gap.

In 2009, HHS issued a request for proposals for establishment of new multiuse facilities based on single-use flexible manufacturing formats for developing and manufacturing new vaccines (HHS 2009a). The request focused on a facility to handle the array of preclinical to clinical development of recombinant influenza vaccine and might potentially provide some surge capacity for MCM manufacturing more broadly. The projected costs would be split between government and industry and two contracts have recently been announced for approximately $100 million each. However, the emphasis on production of civilian pandemic influenza vaccine limits the application of such a potential development and manufacturing facility for the SIP. Recently, HHS also issued a request for proposals more explicitly focused on the U.S. MCM program (HHS 2011). The request seeks public–private partnerships in "Centers for Innovation in Advanced Development and Manufacturing" to expand capabilities for producing MCM against potential known or unknown threats, as well as additional pandemic influenza surge production capacity.

DOD has also issued a request for information on the development and manufacture of MCM as an effort complementary to the HHS undertaking

(U.S. Department of the Army, 2010). The request seeks to gather information to enhance the ability to develop countermeasures against threat agents for military needs and may also have some ability to enhance the development of countermeasures for civilian use. The request emphasizes government–industry partnership, a flexible production scale of up to 100 million doses per month, and a focus on innovative technologies and platform development. If the planning for the DOD and HHS facilities moves forward, the committee believes that new vaccines are likely to enter into development for a wider array of pathogens and toxins, including ones against hazardous pathogens of relevance to the SIP. As discussed in Chapter 2, the Army at one time considered expanding the biocontainment facilities at the Pilot Bioproduction Facility of the Walter Reed Army Institute of Research. This facility currently remains at BSL-2, but could potentially also be modified and expanded to increase options for advanced development and manufacturing of small amounts of MCM.

### *5.2.5* New Technologies and Longer-Term Strategies

A number of exciting innovative technologies bear directly on the future objectives of the SIP.

Platform technologies are applicable to the development of multiple products for different indications using a single, foundational technical approach. The best example in vaccinology is the use of a single vector virus, bacterium, or yeast to deliver foreign genes against the pathogen to which immunity is desired. The same vector backbone, with or without some modifications, can be reused to deliver other genes. Such chimeric constructs have been successfully developed with a variety of vector backbones. A common theme is that the vector itself provides important biological functions that are critical for efficacy of the chimeras: the ability to carry large foreign genes or multiple genes, the ability to infect or transduce cells to generate high yields of translated foreign protein, the ability to target the foreign gene to relevant cells (such as dendritic cells) for immunity induction, in some cases the ability to elicit cells that traffic to mucosal sites and induce mucosal immunity, and the ability to enhance the response by activating toll-like receptors. Examples of successful viral vector platforms include adenoviruses, poxvirus, flaviviruses (yellow fever 17D and dengue), alphaviruses (VEE and Sindbis), vesiculoviruses (VSV-Ind and VSV-NJ), measles virus, and lentiviruses. The principal problem in the use of most vectors has been anti-vector immunity, but this has been overcome in many systems, particularly in the alphavirus system, which has been shown to be insensitive to vector immunity. Most of these systems also include technology for rendering the vaccine candidates safe (by gene deletions that prevent replication in vivo or the use of replicons that generate protein or subviral particles.

Several vector platforms are essentially ready for use in generating new candidates that could be used in the SIP against existing and new target indi-

cations, including improved VEE vaccine, and vaccines against Ebola, Marburg, and others. Manufacturing methods have been developed and include well-established complementing cell lines (for example, PerC6 in the case of adenoviruses) or methods for large-scale electroporation of recombinant and helper RNA (e.g., alphavirus replicons). Cell lines used for production are widely available, and multiple products produced with the methods used for manufacturing chimeric viruses have approved INDs and are in clinical trials.

Other important platform technologies for vaccine development include the use of plasmid DNA with or without enhanced delivery systems, including cationic liposomes or electroporation devices. For some indications, it is possible to generate virus-like particles by expressing a single viral protein or by co-expressing the target viral proteins with other molecules that form particulate structures.

Many examples indicate that optimal immune responses may require priming and boosting strategies by using two different modalities. Priming with DNA followed by boosting with a live vector, priming with one vector and boosting with a different vector, or priming with a live vector followed by a protein or subunit boost may elicit the optimal response.

### 5.2.6 H5N1 Avian Influenza Vaccine

H5N1 influenza virus can cause life-threatening human disease and may pose a risk to laboratory workers and the public in the event of an escape of the virus from laboratory containment (via an infected laboratory worker).[3] According to *Biosafety in Microbiological and Medical Laboratories* (*BMBL*), although "LAI [laboratory-acquired infections] have not been routinely documented in the literature . . . informal accounts and published reports indicate that such infections are known to have occurred, particularly when new strains showing antigenic shift or drift are introduced into a laboratory for diagnostic/research purposes" (CDC/NIH 2009). As noted in Section 3.5.7, a licensed, nonadjuvanted H5N1 vaccine is available in the United States, but stocks are controlled by HHS. The vaccine needs to be adjuvanted (for example, with MF59 or AS03 emulsions) for maximal immune responses and several investigational adjuvanted vaccines exist. Personnel working on H5N1 vaccine development and manufacture may be able to gain access to investigational vaccine candidate strains by other mechanisms. H5N1 vaccines are relevant to broader discussions on the use of investigational vaccines against pathogens and

[3] Highly pathogenic strains of influenza virus are included on the U.S. Department of Agriculture Select Agents and Toxins list. In addition to highly pathogenic avian H5N1, a low-pathogenic form of H5N1 exists and circulates among North American birds. *BMBL* recommends biosafety level 2 (BSL-2) containment for standard human influenza and for low-pathogenic avian influenza strains, but BSL-3 is recommended for highly pathogenic influenza strains (CDC/NIH 2009).

toxins for the potential protection of laboratory workers, and vaccines against H5N1 could be considered for inclusion in the SIP as part of multistakeholder strategic discussions on SIP priorities.

## 5.3 THE INTERNATIONAL CONTEXT OF THE SPECIAL IMMUNIZATIONS PROGRAM

Infectious disease research and the development of vaccines are not limited to the United States. Many of the pathogens that are studied in the context of biodefense are exotic pathogens, and some pose public health threats in other countries and have resulted in the production of vaccines for protecting the general population from natural threat of infection. In addition, just as in the United States, a few vaccines have been developed only to an early developmental stage and might be considered for risk amelioration for potential protection of laboratory workers or for emergency response. Examples of these are presented to show the availability of alternatives that might be useful in the context of the SIP.

### 5.3.1 Vaccines Developed in Other Countries

A number of vaccines, approved for use for public health purposes in their countries of origin, have been used in the United States for special immunization purposes in laboratory settings under IND status. They have included vaccines against Japanese encephalitis (JE), tickborne encephalitis (TBE), and Argentine hemorrhagic fever (AHF) vaccines. Vaccines against JE have since been licensed in the United States for use in military and civilian travelers. The TBE vaccine was used briefly under the umbrella of DOD's operations in deployment of forces to Bosnia and is now the subject of an IND held by the National Institutes of Health for use in laboratory workers. TBE and AHF vaccines are no longer available in the SIP program. As a result, some U.S. researchers travel to the countries where those vaccines are available to be vaccinated (for example, TBE vaccine is available in Canada and in many European countries).

As can be seen in the table and the discussions above, numerous vaccine candidates of potential value to the SIP either are under development in the United States or abroad or are already licensed for use in other countries. A partial list of such vaccines, focused on arboviruses, is provided in Table 5.3.

### 5.3.2 Vaccines Developed in the United States and Later Used in Other Countries

Some of the vaccines that were developed at the Salk Institute have proved useful in countries that have endemic diseases and disease emergencies. A vac-

**TABLE 5.2** Vaccines That Are Approved or Have Been Clinically Tested in Other Countries but Not Currently Licensed for Use in the United States

| Pathogen | Disease | Country | Type of Vaccine |
|---|---|---|---|
| *Yersinia pestis* | Plague | Russia | Live, attenuated |
| *Francisella tularensis* | Tularemia | Russia, UK | Live attenuated |
| *Coxiella burnetii* | Q fever | Australia (Ackland et al. 1994) | Inactivated |
| Tickborne encephalitis virus | Tickborne encephalitis | Germany (Novartis), Austria (Baxter) (Fischer et al. 2009) | Inactivated |
| Crimean–Congo hemorrhagic fever virus | Crimean–Congo hemorrhagic fever | Bulgaria (Christova 2009) | Inactivated suckling mouse brain |
| Japanese encephalitis virus | Japanese encephalitis | China, India, South Korea, Nepal, Sri Lanka (PATH 2007) | SA14, tissue culture, modified live |
| Kyasanur Forest disease virus | Kyasanur Forest disease | India | Inactivated suckling mouse |
| Hantaan virus | Hemorrhagic fever with renal syndrome | South Korea, China | Rat brain, tissue culture, inactivated |
| Junin virus | Argentine hemorrhagic fever | Argentina | Live, attenuated |
| Ebola Zaire virus | Ebola hemorrhagic fever | Canada | Vesicular stomatitis virus replicating vector |
| Severe acute respiratory syndrome (SARS) virus | SARS | China | Inactivated cell culture |

cine against Argentine hemorrhagic fever, Junin candidate 1 (Candid 1) vaccine underwent Phase III clinical testing in Argentina (sponsored by DOD), and the vaccine seed stock and manufacturing technology were transferred to an Argentine manufacturer (Instituto Nacional de Enfermedades Virales Humanas, J. I. Maiztegui, Pergamino, Argentina) in the 1990s. In that case, co-development with a foreign government and initial manufacture in the United States resulted in the successful deployment of an investigational vaccine in its endemic area (Maiztegui et al. 1998). The vaccine is now used to immunize the human population in a large area of Argentina in which the disease is endemic and has reduced the number of cases from hundreds to a few cases each year in the endemic area, has effectively controlled the disease, and has saved many lives. Even though the first immunizations in human volunteers occurred in the

**TABLE 5.3** Examples of New Vaccines Under Development That Could Be Considered for Incorporation into the Special Immunizations Program

| Indication | BSL Level | Lab Infections Reported | Vaccine |
|---|---|---|---|
| West Nile | 3 | Many | ChimeriVax-WN (YF/WN chimera, live attenuated) |
| | | | Recombinant subunit-alum |
| | | | Live, attenuated, chimeric DEN4/WN |
| | | | Live, attenuated chimeric DEN2/WN |
| Tick-borne encephalitis | 3 | Many (deaths) | Inactivated whole virus-alum |
| | | | Live, attenuated DEN4/Langat |
| Chikungunya | 3 | Many | Live, attenuated |
| | | | Live, attenuated, chimeric |
| St. Louis encephalitis | 3 | Yes | ChimeriVax-SLE (YF/SLE chimera, live attenuated) |
| Murray Valley encephalitis | 3 | Yes | Imojev® (ChimeriVax-JE, YF/JE chimera, live attenuated) |
| Kyasanur Forest disease | 4 | Many (deaths) | Inactivated whole virus (cell culture) |
| Ross River | 2 | Yes | Inactivated whole virus (cell culture) |
| Dengue | 2 (3 in EU) | Yes | ChimeriVax-DEN |
| | | | Recombinant subunit-alum |
| | | | Live attenuated |
| | | | Live attenuated, chimeric |
| Japanese encephalitis | 3 | | Imojev® (ChimeriVax-JE, YF/JE chimera, live attenuated) |
| EEE | 3 | | Live, attenuated chimeric Sindbis/EEE |
| WEE | 3 | | Live, attenuated chimeric Sindbis/EEE |
| VEE | 3 | | Live, attenuated chimeric Sindbis/EEE |
| Ebola/Marburg | 4 | Yes (deaths) | Ad5 recombinant live vector |
| | | | VSV recombinant live vector |
| | | | VEE replicon |
| Rift Valley fever[a] | 4 | Yes (deaths) | Live attenuated MP12 |

[a]As noted in Chapter 3, the inclusion of Rift Valley fever MP-12 in the SIP has been discussed.

| Company | IND | Development Stage | Comment |
|---|---|---|---|
| sanofi pasteur (Acambis) | Yes | Phase II | |
| Hawaii Biotech | Yes | Phase I | |
| NIH | No | Preclinical | |
| Inviragen | No | Preclinical | |
| Novartis | No | Licensed (Europe) | |
| Baxter | No | Licensed (Europe, Canada) | Previously under IND (Yugoslav conflict) |
| NIH | Yes | Phase I | |
| (USAMRMC) | Inactive | Phase II | Redevelopment, sanofi pasteur |
| (UTMB) | No | Preclinical | |
| sanofi pasteur (Acambis) | No | Preclinical | |
| sanofi pasteur (Acambis) | Yes | In licensure registration | Cross protects against MVE |
| Haffkine Institute (Mumbai) | | Licensed (India) | |
| Baxter | No | Preclinical or Phase I | |
| sanofi pasteur (Acambis) | Yes | Phase III | |
| Hawaii Biotech | Yes | Phase I | monovalent vaccine in clinic) |
| NIH | Yes | Phase I | |
| Inviragen | Yes | Phase I | |
| sanofi pasteur (Acambis) | Yes | In licensure registration | |
| (UTMB) | No | Preclinical | |
| (UTMB) | No | Preclinical | |
| (UTMB) | No | Preclinical | |
| NIH, GenPhar | No | Preclinical | |
| Profectus | No | Preclinical | |
| Alphavax | No | Preclinical | |
| (UTMB) | No | Preclinical | |

United States (Barrera Oro et al. 1988), the product is now being manufactured and used in Argentina and is not available in the United States through the SIP. As a result, U.S. investigators working with the virus travel to Argentina to avail themselves of the vaccine.

In 2005, Chikungunya virus caused large epidemics in countries around the Indian Ocean and ultimately spread to Europe. The Army's Chikungunya vaccine seed stock was transferred to the French National Institute of Health and Medical Research (INSERM) and was under investigation as a potential means of controlling this disease in future outbreaks (Powers and Logue 2007). It was transferred to additional countries and development efforts are being pursued in India (Ellen Boudreau and Judy Pace Templeton, USAMRIID, personal communication).

Another investigational vaccine developed by the U.S. Army, VEE strain TC-83, was instrumental in controlling the extensive epizootic of VEE that occurred in northern South America (Colombia, Ecuador, Peru, and Venezuela), Central America, Mexico, and Texas in 1969–1971. Vaccine stocks produced by Merrell-National Laboratories were used to immunize equids, and the vaccine was transferred to a number of veterinary-vaccine manufacturers in the United States (Jochim et al. 1973). The vaccine was licensed for the vaccination of equids at risk of infection but remained available as an investigational product for human use through the SIP. The investigational formalin-inactivated RVF vaccine developed in the United States was used to help protect laboratory workers in Egypt in the outbreak of 1977–1978 (J.M. Meegan, personal communication) and deployed peacekeepers in the Sinai conflict (Niklasson et al. 1979). RVF vaccine was again requested by and provided to the Kingdom of Saudi Arabia to help protect laboratory workers and other high-risk people in the 2000 outbreak there (CDC, unpublished material). Similarly, Kenyan laboratory and field workers were afforded the use of the vaccine in the 2006–2007 outbreak in East Africa.

Willingness of the United States to provide limited uses of some investigational products has resulted in a great deal of goodwill and has not resulted in any recognized adverse events in the relatively small number of instances of use of the vaccines. The attenuated Junin virus vaccine has yielded the most benefit: the number of cases of this serious disease has been reduced from hundreds to a few each year in the endemic area. The import or export of vaccines requires that FDA be involved.[4] In the examples noted above of the use of some vaccines in epidemic settings, FDA approval of export was necessary, and the materials used in clinical trials required certificates for movement.

[4]Further information on import and export guidance is available from FDA (FDA 2010b).

## 5.4 COOPERATION WITH THE VETERINARY COMMUNITY

Most of the diseases included in the SIP are zoonoses, and many are important diseases of livestock—VEE, EEE, WEE, JE, RVF, anthrax, and Q fever. The animal health industry currently manufactures veterinary vaccines against some of those diseases. The use of a human vaccine (VEE TC-83) in equids in the face of a public health emergency in 1969–1971 has been noted above and the Salk Institute GSD-produced EEE vaccine was tested for potential protection in whooping cranes (Olsen et al. 1997). Moreover, new vaccines against some diseases of possible future interest for inclusion in the SIP (such as new VEE and RVF vaccines, and vaccines against brucellosis and glanders) are of great interest to or are in development by the veterinary community. The committee recognizes the value of closer interactions between the human-health and animal-health scientific communities in the development, production, and testing of effective vaccines against those indications. The Animal Rule for regulatory approval, which relies on animal models of human disease, is an obvious subject for such collaboration. The importance of collaboration between human-health and animal-health research communities is the basis of the One Health Initiative,[5] a worldwide effort to integrate the fields of human medicine and veterinary medicine in ways that improve public health, including industry efforts to develop new medicines and vaccines.

## 5.5 FINDINGS AND CONCLUSIONS RELATED TO FUTURE VACCINE NEEDS IN THE SPECIAL IMMUNIZATIONS PROGRAM

On the basis of the above discussions, the committee offers the following findings related to vaccine development and use in the SIP.

- *Finding 10:* In the absence of such a facility as the previous Salk Government Services Division or establishment of a new government-owned, contractor-operated vaccine facility, vaccines of interest to the SIP are unlikely to be manufactured or replaced, particularly if the pharmaceutical industry is reluctant to commit its resources to them.
- *Finding 11:* Numerous vaccine candidates of potential value to the SIP either are under development in the United States or abroad or are already licensed for use in other countries (for example, Q-Vax, a Q fever vaccine developed in Australia).
- *Finding 12:* Investigational vaccines developed in the United States and initially tested on human volunteers have proved valuable in other countries where the diseases may be endemic. This use of IND vaccines serves a public health goal, is a source of international goodwill,

[5]For further information, see One Health (2011).

and is thus an additional benefit of MCM research. The data on vaccine safety and immunogenicity obtained by immunizing SIP participants with these IND vaccines help to provide the clinical basis for such uses.

The committee concluded that a systematic assessment of the need for new manufacturing of vaccines that are now in the SIP and a systematic assessment of potential candidates that could be entered into the SIP should be undertaken as a separate exercise. Vaccines and vaccine candidates developed in other countries should be considered as part of this assessment process for possible inclusion in the SIP.

Efforts to increase vaccine manufacturing capacity under HHS and DOD contracts appear to be under way. The committee encourages such efforts to include the SIP's current needs and capacities in making decisions on expanding the manufacturing capacity of a comprehensive U.S. MCM effort. The committee also recognizes that manufacturing new stocks of existing SIP vaccines or incorporating some or all of the additional vaccines into the SIP must occur in the context of U.S. regulatory policy, as discussed in Chapter 4.

# 6

# Potential Options for the Special Immunizations Program and for Personnel Immunization

The committee outlined several possible options for the Special Immunizations Program (SIP) during its discussions of the structure of the current program, the role of vaccination for laboratory workers, and potential needs and opportunities. On the basis of its analysis, the committee concluded that a cooperatively governed SIP located at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) would constitute the most effective vaccination program for the community of military and civilian personnel who work with hazardous pathogens while continuing to provide a manageable operational structure (see Option 2, below). The anticipated expansion of facilities as part of the National Interagency Biodefense Campus at Fort Detrick—which will include USAMRIID along with the National Institute of Allergy and Infectious Diseases (NIAID) Integrated Research Facility, the Department of Homeland Security National Biodefense Analysis and Countermeasures Center, and the U.S. Department of Agriculture Agricultural Research Service and Foreign Disease-Weed Science Research Unit—also strengthen the appeal of this option.

The committee recognizes that decisions on the structure of a program like the SIP must take into account multiple factors, some of which are beyond the scope of the committee's charge. A discussion and comparison of the options considered by the committee are presented below to help inform further conversations.

**TABLE 6.1** Summary Comparison of Options

| Option | Greatest Potential Worker Protection | Most Flexibility | Meet DOD Needs | Meet Civilian Needs | Lowest Relative Cost | Greatest Feasibility |
|---|---|---|---|---|---|---|
| 1. Status quo | ○○ | ○○ | ●●● | ○○ | ●●● | ●●● |
| 1a. Status quo with additional funding | ●●● | ○○ | ●●● | ●●● | ○○ | ●●● |
| 1b. Status quo with separate civilian program | ●●● | ●●● | ●●● | ●●● | ○ | ○○ |
| 2. Cooperative governance, based at Ft. Detrick | ●●●● | ●●● | ●●●● | ●●●● | ○○ | ○○ |
| 3. SIP as a central MCM enterprise component | ●●●● | ●●● | ●●●● | ●●●● | ○ | ○ |
| 4. Cancel the SIP | ○ | ○ | ○ | ○ | ●●●● | ●●●● |

Evaluation scale: least to most effective in meeting the objective—
○ - ○○ - ●●● - ●●●

## 6.1 OPTIONS FOR THE FUTURE OF THE SIP

In formulating responses to its statement of task, the committee discussed the implications of several possible options for the SIP program. Criteria on which these options were evaluated include

- *Worker protection.* Does the option provide potential protection to researchers and others who work with hazardous pathogens?
- *Flexibility.* Does the option allow the program to adapt to meet new needs and priorities?
- *Department of Defense (DOD) needs.* Does the option meet the needs of military researchers and other DOD users?
- *Civilian needs.* Does the option meet the needs of civilian users?
- *Cost.* How expensive is the option likely to be in comparison with other options?
- *Feasibility.* How feasible does implementation of the option appear to be in comparison with other options?

Four options and two suboptions are discussed in more detail below, and a comparison of them is summarized in Table 6.1

### 6.1.1 Option 1: Maintain the Special Immunizations Program in Its Present Form (Status Quo)

The current SIP provides a benchmark against which to compare the implications of possible program changes. In its current form, the SIP is operated

by the U.S. Army Medical Research and Materiel Command (USAMRMC) through USAMRIID and USAMMDA, and located at Fort Detrick, MD. The program provides access to licensed vaccines against six diseases and to eight investigational vaccines. The cost for each user to participate in the program is about $10,000–15,000 per year. Approximately 600 participants per year are enrolled: 395, or about 60%, at USAMRIID and an additional 228, about 40%, from other DOD units, other government agencies, and external organizations (Boudreau 2010). The operation of the current SIP is discussed in detail in Chapter 3.

*Worker protection:* The SIP as currently conceived provides an additional layer of biosafety protection for a subset of military and civilian personnel who work with certain highly hazardous pathogens. Those who are most effectively covered under the current SIP are those who are working directly with the pathogens and toxins that are currently included in the SIP and working in an agency or organization that is able to support the costs of their program enrollment. The committee noted that participating agencies at the time of the 2004 Homeland Security Council Policy Coordination Committee decision establishing a cost-sharing arrangement for the SIP estimated that 1,000–5,000 workers in BSL-3 and BSL-4 laboratories might be candidates for occupational vaccination and that NIAID's estimated use alone would grow to 1,800 workers by 2010. In contrast, the committee noted that SIP use has remained relatively constant since 2004 at about 600 users per year; *thus, a number of potential users are not accessing the current program and there may be insufficient worker vaccination coverage of the larger medical countermeasures (MCM) enterprise*. That stasis may reflect such factors as the cost to participate in the SIP program and a misalignment of the current SIP vaccines with the pathogens and toxins of most interest to civilian biodefense researchers.

*Flexibility:* The investigational vaccines currently included in the SIP were manufactured at the Salk GSD facility in Swiftwater, PA, which closed in 1998. The current SIP vaccines largely reflect the needs and priorities of historical DOD biodefense research programs and no new vaccine stocks for the program are being generated. The committee noted that new vaccines have periodically been incorporated into the SIP, particularly as licensed products have become available. The replacement of the previous investigational calf lymph smallpox vaccine with ACAM 2000 in 2007 is a successful example. A vaccine against Junin virus, which causes Argentine hemorrhagic fever, also underwent initial development and human clinical trials at USAMRIID and was produced in pilot lots by the Salk GSD (Maiztegui et al. 1998). However, the Junin vaccine was later removed from the SIP because Junin was not considered a threat of interest to DOD despite its inclusion in the Select Agents and Toxins list, the NIAID Category A pathogens, and its consideration as an HHS priority pathogen for countermeasure development. The development and removal of the Junin vaccine from the SIP appears to reflect a limitation in the current

mandate of the DOD-operated program to meet the vaccination needs of both military and civilian laboratory workers.

The committee noted the recent substantial investments made by the United States in developing MCM to meet military and civilian needs. However, military and civilian pathogen research priorities are likely to evolve over time and are affected by judgments on emerging public health diseases, endemic diseases in regions of potential military deployments, and assessments of probable bioterrorist or bioweapons threats. The committee is not aware of systematic governance mechanisms to evaluate the current portfolio of vaccines in the SIP or of clear processes to add new vaccines in response to shifting military and civilian hazardous pathogen research priorities. As a result, fundamental strategic aspects of the SIP program appear to have remained fairly static over time, despite reviews that have addressed operational needs such as site location and cost (for example, the 2004 review and HSC PCC decision that did not explicitly consider future vaccine or manufacturing issues in the SIP beyond the potential need for production of new clinical lots from existing stocks). The lack of an established process to allow for program evolution, particularly a governance mechanism to include both civilian (HHS and USDA) and military (DOD) stakeholder perspectives, appears to be an important limitation of the current SIP.

*DOD needs:* The SIP has historically operated under DOD and its original mandate was to offer occupational vaccine protection to military biodefense personnel. The vaccines currently included in the SIP largely reflect that history. The SIP clinic and operational home for the program remain at USAMRIID and about 60% of current SIP users are USAMRIID personnel. As a result, those able to benefit most directly from enrollment in the SIP are USAMRIID researchers. Although the current SIP appears to function sufficiently in meeting the current needs of USAMRIID and other DOD programs, the committee noted that this may not remain the case without the ability of the SIP to adapt and evolve. The DOD mandate is primarily to support the development of products that will meet the needs of warfighters. The subset of pathogens of most interest to DOD will continue to include those in the current SIP (such as *Bacillus anthracis*, which causes anthrax), but also others, such as Ebola virus, that are not included in the current SIP. As DOD priorities change and are subject to the natural emergence of new infectious diseases on a global basis, and as DOD researchers focus their efforts on the most current high-priority pathogens and toxins, the ability of the SIP to meet DOD needs as effectively as it has in the past may decrease.

*Civilian needs:* The current SIP framework allows civilian personnel to participate through a cost-sharing arrangement. Civilian researchers thus have access to the benefits provided by the SIP as long as their agency or organization is willing to support the costs of their enrollment. The committee noted that investments in civilian biodefense research have grown substantially during

this period. However, there has not been an equivalent growth in civilian SIP participation, and total SIP enrollment has remained static at about 600 a year. That stasis may reflect multiple factors, including the cost to participate in the SIP program and a misalignment of the current SIP vaccines with the pathogens and toxins of most interest to civilian biodefense researchers. Anecdotally, SIP enrollment costs have discouraged some potential users from considering participation in the program (Pouch Downes 2010).

*Cost:* The most important costs associated with the current SIP include personnel expenses related to clinical trial execution, ongoing medical monitoring and regulatory compliance, vaccine stockpile maintenance and testing, and facilities expenses. The costs total approximately $9 million a year and each SIP enrollee is required to pay about $10,000–15,000. The SIP program is not inexpensive. On the other hand, the investments to maintain the program are small compared with the substantial amounts of money invested in the overall biodefense and MCM efforts.

*Feasibility:* The current SIP is administered from a central location at USAMRIID. Participants must travel to Fort Detrick for vaccine administration, although not all vaccines require multiday stays. In addition to on-site immunization, medical monitoring to document immunologic responses or to report adverse events is also accomplished by a physician associated with the enrollee's home organization. Until 1999, the SIP also included 117 satellite sites. During that period, administration of investigational vaccines to SIP enrollees was considered to be exempt from Investigational New Drug (IND) protocol regulations. However, the requirement in 1997 to meet Food and Drug Administration (FDA) IND regulations would have required recruitment of co-investigators, training, site audits, medical monitoring, and other measures that were beyond the capability of the program without major revisions and increased costs. Because of problems with regulatory documentation and compliance under the former system of multiple sites, the SIP is now operated at a single site.

The current SIP builds on the history and program expertise housed at USAMRIID and USAMMDA, which have demonstrated that they have the operational expertise to manage the program, including administering the vaccines and maintaining compliance with the IND protocols for the investigational products in use. The requirement to travel to a central location is less convenient for non-USAMRIID users and contributes to the cost for these users to participate—a situation that appears to ensure IND compliance but presents barriers for use by the non-USAMRIID institutions that wish to avail themselves of the SIP program

*Conclusions:* The current SIP provides a baseline against which to compare other possible options. It operates as a small, self-contained program that is currently not well integrated into other MCM and biodefense investments. It appears to work most effectively for DOD and USAMRIID workers and for

a relatively small group of researchers unaffiliated with DOD. However, the committee was not convinced that the current program has sufficient adaptability to meet new needs and priorities. It is also not sufficiently integrated into ongoing, strategic discussions of the development and manufacturing of next-generation MCM, and the mandate and user base of the current program do not reach many civilian personnel in both the medical and veterinary fields who work with highly hazardous pathogens and theoretically could make use of this type of occupational immunization program.

### *Option 1a: Maintain the Special Immunizations Program in Its Current Form but with Additional Resources*

The committee also considered the potential outcomes if the SIP were maintained in its current form but were provided with additional financial resources to help supplement the funds raised by the current cost-sharing arrangement. Such resources could be used to meet ongoing expenses for maintenance of the current SIP vaccine stocks, to expand the range of vaccine offerings, or to help support SIP enrollment for additional public health or other civilian researchers who are not enrolled currently due to budgetary constraints (although this would present additional complicating factors in prioritizing which potential users would receive subsidized participation).

However, the committee considered that simply adding money to the current program fails to address more fundamental needs and opportunities for the SIP. For example, such a choice fails to provide a path to better integrate SIP into other biodefense and medical countermeasures development programs and does not address the need for a SIP governance mechanism of regular strategic review and program evolution.

### *Option 1b: Maintain the Special Immunizations Program in Its Current Form and Encourage the Development of a Separate Civilian-Focused Personnel Vaccination Program*

The current SIP appears to best address the needs of USAMRIID users, but does not include robust participation from other civilian and public health workers. The committee also discussed the possibility of two independent worker immunization programs, an option that was also considered by the 2004 SIP subgroup.

Most of the expansion in research and development of medical countermeasures for civilian use, along with increased capacity for public health diagnosis and surveillance against highly hazardous infectious diseases, has been supported by the HHS. As discussed in Chapter 2, the ethical principle of beneficence supports offering workers the option of immunization, if available, as an additional layer of biosafety protection to further reduce the risk to which

they are exposed when working with hazardous pathogens and toxins. HHS thus has an obligation to consider the immunization needs of the researcher community supported by its significant financial investment in these areas. It is also necessary to consider the needs of the veterinary community (lab workers, public health personnel, and veterinary vaccine manufacturers), and to ensure integration of the SIP program with the USDA. The SIP could continue to exist in its current form to meet the needs of the limited, largely USAMRIID-based, population who now benefit from it. A fully independent program could be developed under HHS (and to include USDA) with a mandate to meet the needs of civilian researchers, some of whom may be working on pathogens and toxins that are not covered under the current SIP. Although this option would expand access to personnel vaccination, the committee was concerned that such an option would lead to an inefficient duplication of resources since USAMRIID already possesses the knowledge base to successfully operate a worker immunization program.

### 6.1.2 Option 2: Institute a Cooperatively Governed Special Immunizations Program Based at the U.S. Army Medical Research Institute of Infectious Diseases

The committee considered whether there were alternative ways to envision the SIP, and discussed whether these options might address the perceived limitations in the current program. A reimagined SIP could continue to draw on the operational expertise and history of SIP management by continuing to house the program in USAMRIID. To meet the needs of both military and civilian research communities effectively, however, a more explicit partnership of shared governance could be developed among DOD, HHS, and USDA. The governance mechanism would need to incorporate regular review of the vaccines included in the SIP, periodic assessment of U.S. and international vaccines and medical countermeasures reaching such developmental milestones as IND or licensed status, and recommendations on specific vaccines that should be added to or removed from the program. For example, an external assessment of the SIP in 2002 suggested that the Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) play a role in determining worker immunization policy (Boudreau 2010). ACIP currently makes recommendations on the use of licensed vaccines, including some vaccines of relevance to health-care or laboratory workers, such as anthrax, smallpox, and Japanese encephalitis, but does not address the use of vaccination with IND products. The committee judged that a system of broader stakeholder input into the SIP and shared governance would help to incorporate perspectives from relevant HHS agencies including NIH and CDC. This option would focus on the same fundamental mandate as the current SIP but

seek to recognize and serve the growth in civilian pathogen and MCM research and engage this community more effectively.

*Worker protection:* In the near term, this option would provide potential worker protection equivalent to the current SIP by offering the same suite of vaccines and operating from the existing offices at USAMRIID. Over the longer term, the committee concluded, worker protection would be enhanced by this option. By providing a governance mechanism that engaged DOD, HHS and USDA and a system of strategic program reviews, the option enables the SIP to evolve to ensure that it remains aligned with national research priorities and developments.

*Flexibility:* The option provides greater flexibility than the current SIP because of the proposed system of shared governance, review, and oversight. The committee noted that the current investigational vaccines administered in the SIP are no longer being manufactured. Although the remaining stocks are sufficient to meet current demand for the foreseeable future, they may eventually run low or lose their potency. The current investigational vaccines were produced with older techniques and more limited knowledge of potential immunization targets. As a result, some of the vaccines in the program are more reactogenic and less effective than other vaccine products available outside of the United States or vaccine products that may be developed in the future. As such products are developed, a system needs to be in place to consider whether they should be incorporated into the SIP; if so, a clear pathway needs to be established by which to accomplish and fund these acquisitions.

The committee also considered the utility of a limited expansion of SIP locations to include regional immunization sites (an option that was also proposed by the 2004 SIP subgroup). The committee suggested that a small number of satellite clinic locations could reduce travel and costs for other participating institutions. A limited expansion in close partnership with a central administration at USAMRIID might avoid the compliance issues previously experienced with immunizing at 117 locations and increase the flexibility and use of the program. In the spirit of presenting several possible examples, potential locations for such satellite sites might draw on the network of Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases and Regional Biocontainment Laboratories, or on the eight NIAID Vaccine and Treatment Evaluation Units, although the committee noted that it would be valuable for satellite locations to be sufficiently geographically diverse. Another option might be for SIP personnel to periodically travel to a few regional locations, a model similar to that used occasionally in outbreak responses.

*DOD needs:* This option would allow the SIP to continue to meet DOD needs, and drawing on the current SIP expertise, staff, and facilities through USAMRIID should minimize disruptions. Ensuring that DOD maintains a strong voice in SIP planning should also ensure that the SIP vaccinations

continue to be aligned with the needs and priorities of military researchers and others supported through DOD contracts.

*Civilian needs:* By creating a mechanism for stronger and more direct HHS and USDA engagement in SIP governance, this option should also ensure that the needs of civilian researchers are better addressed by the program.

*Cost:* The program could continue to be operated as the current SIP is with a central administrative base at USAMRIID and a cost-sharing arrangement among the participating agencies. By providing such agencies as HHS and USDA with a mechanism for direct participation in program planning, the option might encourage agencies to be more willing to cover enrollment costs for researchers supported by them. If expansion to a small number of regional sites is implemented, costs would probably increase beyond those of the current program. However, as noted in Chapter 4, there may be additional regulatory options that could be pursued to enable immunizations off-site from USAMRIID (for example, with investigator-initiated IND's cross-referencing a USAMRIID primary IND).

The committee recognizes that implementing a shared DOD-HHS-USDA SIP governance system will probably entail costs and challenges and that this option may be more expensive than the current SIP. For example, there will probably have to be periodic meetings of a review and oversight board to make decisions about new SIP vaccine acquisitions or vaccines to eliminate from the program. If additional vaccines are brought into the program (perhaps purchased from DOD or HHS-contracted vaccine manufacturing facilities), there will be additional costs associated with administering the vaccines, maintaining necessary regulatory documentation, and ensuring vaccine supplies. In contrast, if the program is able to transition to greater use of licensed products (as these are developed through the MCM research pipeline), there may be lower costs associated with administration of licensed vaccines and a decreased need to maintain more burdensome IND protocols.

*Feasibility:* This option will be more complicated than the current SIP because of the need for shared oversight by DOD, HHS, and USDA. However, the committee considered that the current program location at Fort Detrick provides special advantages that make achieving synergy within the SIP more valuable and more feasible. DOD and HHS have already increased their communication and collaboration through the Integrated Portfolio for CBRN Medical Countermeasures (Newmark 2009). Several agencies are also developing new facilities as part of the National Interagency Biodefense Campus at Fort Detrick, which will include USAMRIID and the NIAID Integrated Research Facility, the DHS National Biodefense Analysis and Countermeasures Center, and the USDA Agricultural Research Service and Foreign Disease-Weed Science Research Unit. The committee also noted that certain investigational vaccines of potential interest to the SIP may be available under IND protocols maintained by federal agencies outside of USAMRMC. It may be possible to

consider cooperative options under which laboratory workers needing an immunization for which another agency holds an IND are directed to that agency, a situation that may be made more feasible if agencies such as DOD, HHS, and USDA are collaboratively involved in setting the strategic priorities of the SIP.

*Conclusions:* Although this option suggests the need for substantial changes in the SIP, the committee concluded that the addition of a more structured governance system reflecting the needs of both civilian and military research communities, mechanisms to enable the SIP to evolve as needed and continued operation at USAMRIID and USAMMDA to take advantage of the administrative history and program expertise offer advantages that could counterbalance additional cost and logistical concerns. Such an option may offer a feasible response to many of the current SIP limitations while minimizing program disruptions and building on momentum generated by ongoing, multiagency collaborative projects as part of the overall U.S. MCM enterprise. The committee concluded that USAMRMC may be uniquely positioned to continue to implement the SIP under these circumstances and that this option could best meet the ethical obligation to continue offering immunizations to personnel working with highly hazardous pathogens, to implement a system serving both the military and civilian user communities, and to establish a system that can adapt and evolve over time.

### 6.1.3 Option 3: Position the Special Immunizations Program as a Central Component of the National Preparedness Enterprise

As discussed above, because the SIP is the vehicle that provides occupational vaccines to personnel who work with hazardous pathogens it sits at a clear intersection between military and civilian biodefense enterprises. In addition to the direct potential occupational health benefit that the SIP provides to researchers who handle certain pathogens and toxins, the existence of the SIP contributes to the advancement of science in several broader ways. It is possible to conceive of a SIP that develops those broader missions more explicitly so that it serves a more central role as a test bed in the overall MCM enterprise. For example, the ongoing medical monitoring of those who receive SIP vaccines and the collection of safety and immunogenicity data can be an invaluable resource for

- Identifying safe products.
- Expanding knowledge about human immune responses to immunization.
- Furthering the development of safe and effective vaccines beyond IND status (as part of the documentation needed for FDA approval).
- Providing a benchmark of performance for comparison in the development of the next generation of vaccine products.
- Gathering data in the event of a need for Emergency Use Authorization.

Having a ready supply of vaccines against a variety of Select Agents and other highly hazardous pathogens also means that immunoglobulin can be produced by immunizing healthy plasma donors to produce a treatment for nonimmunized people in the event of an exposure. Key components of a comprehensive national preparedness strategy include the infrastructure and human capital to rapidly respond to needs for vaccine and the deployment of immunized individuals in the event of a bioterror incident. A SIP can provide a clinical test bed that can help to enable rapid and coordinated responses to natural and human-made biological threats to national security.

*Worker protection:* While expanding the mandate of the SIP, this option would continue to meet its core mission of providing immunizations to at-risk researchers. As a result, it would continue to provide an equivalent level of additional potential protection for workers through immunizations as the current SIP.

*Flexibility:* A SIP reconceived as a central component of biodefense and MCM investments, and adequately supported, would be responsive to the future needs of the military and civilian biodefense efforts.

*DOD needs:* As in other options, the SIP would continue to meet DOD needs. Ensuring that DOD maintains a strong voice in SIP planning should also mean that the SIP vaccinations would continue to align with the needs and priorities of military researchers and others supported through DOD contracts

*Civilian needs:* As in option 2, a SIP that included stronger and more direct HHS and USDA engagement should ensure that the program meets the needs of civilian researchers. Such a program would also assure the general public that the nation is better prepared to address natural and human-made biological threats.

*Cost:* Conceiving of the SIP as a central base in the MCM enterprise would require additional resources for management and administration, implementation, and coordination. It seems probable that an occupational immunization program conceived with this type of expanded mission would cost much more than the current SIP.

*Feasibility:* The committee concluded that feasibility would be an important obstacle to implementation of this option. The existing SIP is designed to meet a limited set of needs for a defined user community and is not organized to meet a greatly expanded mission as a central component of the national MCM enterprise. The mandate of developing, testing, and manufacturing new vaccines and medical countermeasures also falls to multiple existing and proposed programs. The committee observed that the SIP has never played the type of central role implied by this option, even within the portfolio of DOD biodefense programs, and that the SIP has struggled to find sufficient financial support to maintain even fundamental components such as current vaccine stockpile management. Over the recent course of its history, the SIP has failed to generate the enthusiasm that would be needed for it to assume a central role

in national preparedness, and the committee judged it extremely unlikely that the SIP would be positioned to become this type of keystone program now.

*Conclusions:* The primary mandate of the SIP has historically been and remains provision of vaccines against a subset of hazardous pathogens to those personnel who are occupationally at risk for infection. The SIP remains a small but well-defined component of the overall U.S. MCM enterprise. Over the previous decade or more of its existence, enrollment in the SIP has remained at roughly 600 users a year and financial and strategic investments in the SIP have been limited. Although the additional vaccine safety and immunogenicity data generated by the SIP, particularly the longer-term follow-up data, constitute a benefit that should be used by vaccine developers and manufacturers to the greatest extent possible, the SIP is unlikely to be in a position to serve as an ambitious central test bed for the larger MCM enterprise. The committee concluded that it is not feasible for the SIP to assume this additional role.

### 6.1.4 Option 4: Cancel the Special Immunizations Program

The committee considered the question of whether a SIP was still needed and what the implications of canceling the program might be. It concluded that cancelling the SIP would lead to avoidable harms.

*Worker protection:* The SIP maintains, provides, and administers a program to support the availability of occupational vaccines, which are a key component of a comprehensive strategy to promote the highest standards in biosafety and disease prevention safeguards for protecting laboratory workers from the risk of disease in handling high-risk pathogens. High-risk pathogens can cause serious, potentially fatal disease through aerosol and percutaneous exposures. Immunization remains a proven part of an overall protection strategy that includes engineering control measures, safety training and the use of personal protective equipment. Despite training in safe laboratory practices, the risk of needlesticks and exposure to other sharp instruments and injury by laboratory animals cannot be entirely eliminated and immunization offers a final level of potential protection for such exposure. As discussed in Chapter 2, offering personnel who work with hazardous pathogens and toxins the option of immunization as a part of a program of biosafety measures remains a standard of best practice and an ethical obligation. Canceling the SIP would leave a gap in worker occupational health protection and would probably shift the medical monitoring currently conducted through the SIP to community physicians or to occupational health programs at the worker's institution who are unfamiliar with the hazardous agents and the vaccine products.

Having a program such as the SIP that provides licensed and investigational vaccines to individual laboratory workers also provides potential social and population-level benefits that would be lost were the program to be canceled. For example, the committee noted that potential laboratory exposures

might lead to infections in a worker that could be spread to family members or to the community. Although uncommon, such a situation is not impossible and transmission of laboratory-acquired *Brucella* infection to a spouse has previously been reported (Ruben et al. 1991). The medical monitoring and collection of blood samples through the SIP may help to identify asymptomatic infections, and the safety and immunogenicity data collected through the SIP might be of use to regulatory authorities both for comparison with newly developed vaccines and in helping to support emergency use of a vaccine should such a situation arise.

In addition, a number of publications have resulted from the data collected by administering investigational vaccines through the SIP. These include studies to investigate details of the human immune response and mechanisms of action of particular vaccines (McClain et al. 1998; Pittman et al. 2005b; Fuller et al. 2007; Rusnak et al. 2011), to examine long-term health trends among recipients of investigational vaccines (Pittman et al. 2004, 2005a), to analyze information on laboratory exposures to pathogens (Rusnak et al. 2004a,b), and others. These studies have provided a wealth of valuable information to the research community.

*Flexibility:* Canceling the program represents an inflexible solution to the limitations perceived in the current SIP. Canceling the program would also result in a loss of the program operational and administrative expertise housed within USAMRIID and USAMMDA while failing to provide a pathway for at-risk personnel working in a biohazardous environment to receive relevant investigational vaccines.

*DOD needs:* As discussed in Chapter 2, the committee judged that offering immunizations to laboratory workers continues to be one component of an overall biosafety program. Canceling the program would not meet the responsibilities of DOD to offer this additional measure of potential protection to its researchers working with hazardous pathogens.

*Civilian needs:* Canceling the program would mean that the needs of civilian researchers who work with hazardous pathogens would not be met.

*Cost:* The committee was unable to conduct a detailed financial assessment of the benefits provided to workers by SIP immunizations, beyond the levels of protection provided by other forms of biosafety, compared with the costs of operating the program. Canceling the SIP is the most cost-favorable option with respect to direct program costs. Eliminating the program and the associated IND maintenance and medical monitoring that are required would save about $9 million per year (see Chapter 3 for discussion of the current cost structure of the SIP). In contrast, if a hazardous pathogen researcher contracted a laboratory-associated infection that might have been prevented through SIP immunization, agencies might face additional costs in treating this infection, in lost worker productivity, and in reassuring the public, costs that could have been saved if the SIP were available (the cost of not having a program). It is

possible that the loss of this resource would result in a reduction in the countermeasure research enterprise, given concerns about liability among employers and personal safety among laboratory workers. In addition, the committee noted that the SIP has value beyond individual worker immunization. The SIP serves as a resource on safety and immunogenicity information of all vaccines used in the program. Such data may have substantial value in a future national biodefense emergency. Publications arising from the SIP have also contributed to biosafety practices.

*Feasibility:* Challenging issues that need to be addressed within the current SIP, such as maintenance of vaccine stocks and compliance with IND regulatory requirements, could be avoided if the SIP were canceled. Although it may be feasible or even tempting to cancel the program, the committee concluded that the issue of the best way to protect the population of personnel working with hazardous pathogens as part of biodefense, MCM, and public health investments will remain and must be addressed in some fashion.

*Conclusions:* As discussed in Chapter 4, the committee noted that access to the licensed vaccines currently included in the SIP would be possible through other mechanisms were the SIP to be canceled. However, canceling the SIP would prevent access to the investigational vaccines it contains, which may offer an additional level of protection to researchers and remain an important component of an overall biosafety program. Despite potential cost savings and the possibility of avoiding challenging strategic questions about SIP governance and evolution, the committee strongly concluded that this option fails to meet an ethical duty to provide the option of immunization to personnel who work with hazardous pathogens where licensed or investigational vaccines are available. In addition, the SIP remains an essential component of our national countermeasure efforts.

## 6.2 CONCLUSION ON POTENTIAL OPTIONS FOR THE SIP

The committee concluded that a cooperatively governed SIP located at USAMRIID would constitute the most effective vaccination program for the community of military and civilian personnel working with hazardous pathogens while continuing to provide a manageable operational structure.

# 7

# Conclusions and Recommendations

Biomedical research on infectious pathogens inescapably carries a small but finite risk of infection. With the widespread adoption of well-engineered biocontainment facilities and equipment, effective personal protective gear, and rigorous training, the frequency and number of serious incidents in the United States have decreased substantially. The committee was charged with examining the role of vaccinations in providing protection, in addition to those measures.

## 7.1 THE ROLE OF VACCINES IN PROTECTING RESEARCH WORKERS

The Special Immunizations Program (SIP) is unique in its mission, filling an important niche in biosafety not currently covered by any other programs in the United States. It is the only mechanism whereby certain vaccines against highly hazardous pathogens and toxins are made available to laboratory-based and field-based workers who may be exposed to these pathogens and toxins. The types of workers for whom SIP vaccination is most relevant include not only laboratory researchers but also animal technicians working to develop next-generation medical countermeasures (MCM) for military and civilian use, personnel engaged in the manufacture of biodefense vaccines and human and veterinary vaccines against zoonotic diseases, and scientists and laboratory technicians engaged in field studies of the ecology and epidemiology of hazardous pathogens. Scientists in public health diagnostic laboratories may be another potential community of SIP users (although currently the New York State Department of Health has the only state health laboratory that participates in the program).

The committee examined historical data on incidents of laboratory-acquired

infections, reports of Select Agent loss and release events, the history of biosafety practices, and lessons learned from occupational health and safety immunization programs such as the SIP. The committee noted that accidents and containment failures can occur even in highly regulated environments with trained personnel, and that some types of procedures (such as those involving sharps or aerosol exposures of animals), and some pathogens (such as those that have particularly low infectious doses) can present the greatest increased risk of infection to workers. The committee endorsed the concept that immunizations are not a substitute for other biosafety practices—such as appropriate training, personal protective equipment, and engineering controls—but that vaccines can serve as an important adjunct. The committee also endorsed the idea that immunizations should be offered to workers when safe and effective products exist and that employers have an ethical mandate to follow best practices in biosafety, including the provision of vaccines where warranted.

The committee considered the use of both licensed and Investigational New Drug (IND) status vaccines in the setting of occupational immunization. Licensed products have generally undergone larger-scale clinical trials, and their safety and efficacy profiles are well known. The IND vaccines used in the SIP remain in extended Phase II clinical trials. However, the clinical protocols under which these vaccines are administered have produced a wealth of data on human safety, immunogenicity, and probable efficacy, including long-term medical monitoring of SIP enrollees. The committee noted that publications analyzing data collected through the SIP have improved the understanding of immune responses to investigational vaccines and have helped to provide guidelines for the safe conduct of pathogen research and the management of laboratory infections. The committee views these publications as an important resource provided by the program, and encourages the SIP to analyze and make such data available to the research community. Although the IND vaccines currently used within the SIP were developed and manufactured largely in the 1970s and 1980s under standards that would probably be different from those applied today, the committee noted that these vaccines may be offered when beneficial to at-risk personnel and when options for immunization with newer or superior vaccines do not exist.

The committee emphasized the importance of conducting appropriate risk assessments and maintaining informed-consent procedures to ensure that IND vaccines are offered only to workers who are both at risk and medically eligible to receive such them. The committee endorsed the view that immunizations with SIP IND vaccines should be given on a voluntary basis. Immunizations with certain IND vaccines, such as those currently offered in the SIP, remain an important component of an overall biosafety program for laboratory workers who are at risk for exposure to hazardous pathogens.

**Recommendation 1: Special Immunizations Program IND vaccines should be offered to laboratory workers on a voluntary basis, subject to risk assessments and informed consent. The use of immunizations should never be a substitute for careful adherence to all biosafety best practices, but should be considered a component of an overall biosafety program**

**Recommendation 2: Federal agency stakeholders should modify the SIP to ensure that immunizations are readily available and accessible to all at-risk research workers, including those working on civilian as well as military projects.**

## 7.2 FOR WHICH PATHOGENS WOULD IT BE HIGHLY DESIRABLE TO HAVE VACCINES, AND WHICH PATHOGENS SHOULD RECEIVE PRIORITY ATTENTION?

The committee examined publicly available priority lists from the Department of Defense (DOD) and the Department of Health and Human Services (HHS) for the development of new medical countermeasures and additional information on vaccines available or in development in the United States and abroad. The committee chose not to attempt to create a prescriptive list of pathogens against which the SIP should acquire new vaccines. Rather, the committee suggested a framework for evaluating which pathogens should receive priority attention for inclusion of a vaccine against them in the SIP. This framework should be based on an evaluation of two core criteria: the characteristics of the pathogen or toxin and the characteristics of the threat that it poses.

The characteristics of the pathogen that should be considered in making the judgment include infectious dose, transmission potential (including aerosol transmission), and case fatality rate, so that pathogens that have low infectious doses, high transmissibility, and substantial morbidity and mortality from infection would receive higher priority. The relevant characteristics of the threat that will influence which pathogens should be included in the SIP include the presence of the pathogen on government priority threat lists (which are largely generated by the intelligence community), which pathogens researchers are most actively working on, the availability or development status of vaccines, and the existence of effective anti-infective therapeutics directed against the pathogen. Historical information about the occurrence of and frequency of laboratory infections with the pathogen should also be considered.

An overarching conclusion reached by the committee is that the SIP lacks clear and sufficient processes for governance, priority-setting, and strategic review to enable it to continue to adapt and evolve as needs change. The committee judged that a strategic review and systematic assessment of vaccines to be included in the SIP based on the above framework and incorporating stake-

holder perspectives of both military and civilian agencies should be undertaken. This detailed assessment was beyond the scope of the present study.

**Recommendation 3: In order to generate a specific list of pathogens for priority attention for inclusion in the SIP, a strategic review and systematic assessment on a pathogen-by-pathogen basis should be undertaken by the government stakeholders. The assessment should consider the characteristics of each pathogen and toxin and the characteristics of the threat posed by it, incorporating both military and civilian stakeholder perspectives. The SIP should not be a static program but instead should be enabled to evolve over time with respect to the vaccines that it offers.**

## 7.3 ADVANTAGES AND DISADVANTAGES OF THE USE OF INVESTIGATIONAL VACCINES AS THEY HAVE BEEN USED IN THE SPECIAL IMMUNIZATIONS PROGRAM

In concept, the use of IND vaccines for protection of at-risk laboratory workers has substantial merit. From the individual laboratory worker's perspective, a vaccine with a good safety profile and strong immunogenicity might well be expected to provide protection despite as yet unproven efficacy in humans. From a societal perspective, use of IND vaccines in laboratory workers permits the collection of safety and immunogenicity data on new vaccines, and these data could someday be of substantial value in a future national biodefense emergency. Although meritorious in concept, the use of IND vaccines currently in the SIP is not ideal for several reasons: the vaccines are older products that have not been produced for many years, the safety and immunogenicity profiles of some of the vaccines are less than optimal (for example, the vaccine against Venezuelan equine encephalitis virus, VEE TC-83, is associated with a demonstrated 20% rate of systemic adverse events [Pittman et al. 1996]), and immunization under the required Phase II clinical trial protocols poses substantial cost and regulatory burdens on the program. The committee observed that it is important to evaluate the use of these SIP IND vaccines carefully case by case, so that they are made available for those researchers for whom the benefits of vaccination outweigh the risks (as judged by appropriately conducted risk assessments). The committee also concluded that if or when newer, safer, or improved vaccines become available against pathogens that are included in the SIP, the replacement vaccines should be incorporated into the program to phase out the older or less efficacious ones. That conclusion reemphasizes the overarching need for the SIP to incorporate clear procedures for undertaking periodic reviews and assessments of the vaccines used in the program, the pathogens against which the vaccines are directed, and the existence and state of development of other relevant MCM products.

**Recommendation 4: The SIP should offer the safest and most effective vaccines available, which would include use of licensed vaccines where available and/or replacing older vaccines in the SIP with newer IND vaccines that have substantially improved manufacturing, quality-control, safety, and immunogenicity profiles. The safety and immunogenicity of all vaccines used in the SIP should be studied carefully, as these data may have substantial value in a potential future national biodefense emergency.**

## 7.4 VACCINE DEVELOPMENT AND SUPPLY WITHIN AND BEYOND THE EXISTING SPECIAL IMMUNIZATIONS PROGRAM

Given its emphasis on the importance of shared governance and program flexibility, the committee went on to consider recent developments in vaccine production and in regulatory processes that might affect the SIP. It noted that the modest scale of the current SIP user base means that only a limited number of immunization doses are required for its immediate needs. Newer pilot manufacturing technologies, such as flexible, single-use bioreactors, may improve the cost and speed of manufacturing such small-scale quantities of vaccines. Flexible platform approaches to vaccine development may, in the future, also reduce the time and expense needed to develop new products and take them through to advanced development and licensure. If a future emerging threat dictates the need for a particular SIP vaccine, the experience gained in the manufacture and human trials of that vaccine candidate product through the SIP may help to shorten the timeline needed to mount a full MCM response.

The committee also observed that potential new vaccines to be included in the SIP could come from national U.S. MCM development efforts (for example, the plague vaccine whose advanced development is being managed by the Joint Vaccine Acquisition Program) or from vaccines that are currently licensed by countries other than the United States.

The committee noted the procurement initiatives put forward by HHS and DOD to support industry partnerships in vaccine development, which potentially include small biotechnology companies and large pharmaceutical manufacturers. The committee encourages the federal agencies, when they are making major U.S. investments in this area, to consider the immunization needs of the SIP and of the frontline biodefense researchers who help to develop these next-generation MCM.

The committee also encourages the Food and Drug Administration (FDA) and other relevant bodies to explore potential new regulatory pathways that might more easily enable use of relevant SIP vaccines to reduce some of the substantial regulatory burden associated with the current IND clinical protocols.

**Recommendation 5: As research on medical countermeasures continues, new vaccine products should be systematically incorporated into the SIP and older or outdated products for similar applications should be considered for removal. Products currently licensed for use in other countries, but not yet in the United States, could also be used to fill gaps in the SIP armamentarium. Such newly developed and/or imported products could replace the older IND products currently administered. These additional products could also expand the SIP to include vaccines against additional infectious pathogens and toxins that reflect evolving national military and civilian medical countermeasures (MCM) priorities.**

**Recommendation 6: The Food and Drug Administration and other relevant regulatory authorities should explore new administrative and regulatory pathways to facilitate the development and licensure of SIP vaccines. Options might include a form of "restricted" or "conditional" licensure or an "exceptional circumstances" pathway (similar to that available in Europe). U.S. government (HHS, DOD) vaccine production and procurement plans should be designed to take full advantage of the SIP program and to consider SIP vaccine needs.**

## 7.5 GENERAL OBSERVATIONS REGARDING THE ROLE OF IMMUNIZATIONS IN THE CONTEXT OF RESEARCH WITH HAZARDOUS PATHOGENS

The committee noted that the SIP is a unique program and is the only immunization program in the United States that supports researchers who work with hazardous pathogens by providing both licensed and IND vaccines. The committee emphasized the value of maintaining a program like the SIP.

The committee also observed that the SIP sits at a critical intersection of military and civilian MCM research and development efforts. However, the committee observed that the SIP, as currently structured and managed, appears to lack a coordinated civilian and military stakeholder perspective on policy, management, and funding:

Indeed, when the full vaccine MCM pathways are considered, there are important synergies but still important differences between the military and civilian programs, as summarized in Table 7.1.

With the expansion of the MCM enterprise and the shifting nature of national security and public health threats, the mandate for countermeasures now extends well beyond DOD to include substantial investments by civilian research and public health agencies. The history and expertise available at U.S. Army Medical Research and Materiel Command (USAMRMC) in establishing and operating the SIP remain extremely valuable and provide a strong foun-

**TABLE 7.1** Synergies and Differences Betweem Military and Civilian Medical Countermeasures Pathways That Affect the Special Immunizations Program

| | R&D | Manufacturing | Regulation | Delivery |
|---|---|---|---|---|
| Military | Historically had primary role | New DOD request for information[a] for biologics-based MCM | Changes made in last two decades to conform to FDA regulations | The SIP is currently housed in and operated by DOD |
| Civilian | Expansion of public bio-preparedness research | New HHS request for proposal[b] focused on influenza production and request for proposal[c] on centers for advanced development | Investigational vaccine use regulated under FDA | There is no independent civilian SIP program |

[a]U.S. Department of the Army 2010.
[b]HHS 2009a.
[c]HHS 2011.

dation that can be built upon to create an effective 21st century occupational immunization program to support hazardous pathogen research.

**Recommendation 7: If the SIP is to serve effectively as an immunization program for all at-risk researchers working with hazardous pathogens, the committee recommends that the governance of the SIP be revised to develop processes for shared priority-setting and operational oversight by key stakeholders from civilian (HHS, USDA) as well as military (DOD) and other agencies. The revised system should build upon the wealth of SIP expertise available at USAMRMC.**

The committee noted that agency demand for research worker vaccination should be proportional to the investments that agencies are making in relevant research, development, diagnostic, and surveillance programs. However, the current structure of the SIP appears inefficient for laboratory workers and public health practitioners who are not affiliated with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). There appears to be limited harmonization with the needs of stakeholders such as the National Institute of Allergy and Infectious Diseases, the Centers for Disease Control and Prevention, the Biomedical Advanced Research and Development Authority (BARDA), the U.S. Department of Agriculture, the Department of Homeland Security, vaccine manufacturers, and the Association of State and Territorial Laboratory Directors. The IND status of many SIP vaccines also increases the regulatory burden and creates complex logistics for program administration, because continuing medical monitoring is required to document safety and immunogenicity. While the program provides a wealth of information, the IND

documentation and reporting requirements greatly increase program costs compared to the costs of administering licensed products. Storage and maintenance of the existing IND vaccine stockpiles present yet another challenge. Although Chemical Biological Medical Systems has been maintaining the stocks on a year-to-year basis, no long-term mechanism has been identified. It is not clear which other organization would take its place, and no funds have been allocated for this expense. Despite previous reviews of the SIP and a 2004 Homeland Security Council Policy Coordinating Committee decision to expand the program under a fully burdened cost-sharing arrangement, the committee expressed concerns about the continuing financial stability of the SIP and about access to SIP immunizations for all at-risk personnel who handle hazardous pathogens.

The committee offers the following suggestions to address aspects of those concerns, although it recognizes that these may present additional costs:

- The committee encourages agencies awarding contracts and grants (by HHS, BARDA, and others) to cover the costs of immunizing personnel in those cases where such SIP immunizations are appropriate on the basis of risk so that the costs are not borne by institutions working on government-supported programs. Costs per person to participate in the SIP include an annual enrollment fee of approximately $10,000, additional program costs that vary depending on the vaccine(s) administered (which range from several hundred to several thousand dollars each, depending on the vaccine and the number of doses required), and travel to USAMRIID to receive medical exams and immunizations.[1] A given laboratory might seek to immunize more than one person, compounding the expense and making cost a potentially significant burden on laboratory budgets.
- The committee noted that the 2004 evaluation undertaken by the SIP subgroup included recommendations for several regional SIP immunization sites throughout the United States. The committee encourages this concept to be revisited. The committee supports the idea of central SIP administration but suggests that a small number of satellite clinic locations could reduce travel and cost issues for other participating institutions. A limited expansion closely administered by USAMRMC would avoid the compliance issues previously experienced when immunizations took place at 117 locations.
- One method to help achieve an expansion of SIP immunization locations is the use of additional IND mechanisms, such as investigator-initiated INDs or treatment INDs, that would be held by investigators at other government or academic institutions, contingent on a continuing strong commitment by the additional investigators for collection

[1]As noted in Chapter 3, no charge is assessed for the IND vaccine itself.

of complete and standardized data and fulfillment of responsibilities under the IND. Alternatively, co-investigators under the USAMRMC IND could be recruited; this would be the equivalent of a multisite clinical trial under a single protocol, a very common practice in the development of vaccines and drugs.

As a result, the committee offers a final recommendation:

**Recommendation 8: All biodefense contracting and granting agencies should consider covering the cost of immunizing at-risk research workers so that this cost is not borne solely by the institutions working on government-supported programs. The committee supports the idea of central SIP administration but recommends that the SIP explore options for having a small number of satellite clinic locations around the country to reduce travel and inconvenience for other participating institutions (provided that they are able to adhere to the IND protocols).**

# References

Ackland, J.R., D.A. Worswick, and B.P. Marmion. 1994. Vaccine prophylaxis of Q fever. A follow-up study of the efficacy of Q-Vax (CSL) 1985-1990. Medical Journal of Australia 160(11):704-708.

Barrera Oro, J.G., J.I. Maiztegui, and C.J. Peters. 1988. Safety and immunogenicity of a live attenuated Junín virus vaccine (Candid-1) in human volunteers. Second International Conference on the Impact of Viral Diseases on the Development of Latin American Countries and the Caribbean Region, Mar del Plata, Argentina.

Barry, M.A. 2005. Report of Pneumonic Tularemia in Three Boston University Researchers: November 2004–March 2005. Boston Public Health Commission.

Birt, C., and G. Lamb. 1899. Mediterranean or Malta fever. Lancet 154(3967):701-706.

Boudreau, E. 2010. Special Immunizations Program, USAMRIID. Presentation at the First Meeting of the Committee on Special Immunizations Program for Laboratory Personnel Engaged in Research on Countermeasures for Select Agents, Mar. 4, 2010, Washington, DC.

Casadevall, A., and L.-A. Pirofski. 1999. Host-pathogen interactions: Redefining the basic concepts of virulence and pathogenicity. Infection and Immunity 67(8):3703-3713.

CBDP (Chemical and Biological Defense Program). 2010. Annual Report to Congress. U.S. Department of Defense Chemical and Biological Defense Program [online]. Available: http://www.acq.osd.mil/cp/cbdreports/cbdpreporttocongress2010.pdf [accessed Mar. 8, 2011].

CDC (Centers for Disease Control and Prevention). 2000. Laboratory-acquired human glanders—Maryland, May 2000. Morbidity and Mortality Weekly Report 49(24):532-535.

CDC. 2002a. Public Health Dispatch: Update: Cutaneous anthrax in a laboratory worker—Texas, 2002. Morbidity and Mortality Weekly Report 51(22):482.

CDC. 2002b. Suspected cutaneous anthrax in a laboratory worker—Texas, 2002. Morbidity and Mortality Weekly Report 51(13):279-281.

CDC. 2008a. Laboratory-acquired brucellosis—Indiana and Minnesota, 2006. Morbidity and Mortality Weekly Report 57(02):39-42.

CDC. 2008b. Laboratory-acquired vaccinia exposures and infections—United States, 2005-2007. Morbidity and Mortality Weekly Report 57(15):401-404.

CDC. 2008c. Update: Potential exposures to attenuated vaccine strain *Brucella abortus* RB51 during a laboratory proficiency test—United States and Canada, 2007. Morbidity and Mortality Weekly Report 57(02):36-39.

CDC 2009. Laboratory-acquired vaccinia virus infection—Virginia, 2008. Morbidity and Mortality Weekly Report 58(29):797-800.

CDC. 2011a. CDC Drug Service [online]. Available: http://www.cdc.gov/laboratory/drugservice/index.html [accessed Apr. 22, 2011].

CDC. 2011b. Fatal laboratory-acquired infection with an attenuated *Yersinia pestis* strain—Chicago, Illinois, 2009. Morbidity and Mortality Weekly Report 60(07):201-205.

CDC/APHIS (Centers for Disease Control and Prevention and Animal and Plant Health Inspection Service). 2008. Select Agents and Toxins: Theft, Loss and Release Information Document. 7 CFR Part 331.19, 9 CFR Part 121.19, 42 CFR Part 73.19. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Division of Select Agents and Toxins, Atlanta, GA, and U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Agriculture Select Agent Program, Riverdale, MD. Jan. 18, 2008 [online]. Available: http://www.selectagents.gov/resources/CDC-APHIS_Theft_Loss_Release_Information_Document.pdf [accessed Mar. 8, 2011].

CDC/NIH (Centers for Disease Control and Prevention and National Institutes of Health). 2009. Biosafety in Microbiological and Biomedical Laboratories, 5th Ed., L.C. Chosewood, and D.E. Wilson, eds. HHS Publication No. (CDC) 21-1112. Washington, DC: U.S. Government Printing Office [online]. Available: http://www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf [accessed Mar. 8, 2011].

Christova, I. 2009. Bulgarian vaccine against CCHFV. Presentation at Arbo-Zoonet Symposium: Interventions against WNV, RVFV and CCHFV: Where are we? Nov. 19-20, 2009, Istambul, Turkey [online]. Available: http://www.arbo-zoo.net/_data/1-Iva_Christova_istanbul09.pdf [accessed Mar. 11, 2011].

Covert, N.M. 2000. Cutting Edge: A History of Fort Detrick, Maryland, 4th Ed. Fort Detrick Public Affairs Office [online]. Available: http://www.detrick.army.mil/cutting_edge/index.cfm [accessed Mar. 8, 2011].

Crumrine, M. 2010. Special Immunizations Program: NIAID perspective. Presentation at the First Meeting of the Committee on Special Immunizations Program for Laboratory Personnel Engaged in Research on Countermeasures for Select Agents, Mar. 4, 2010, Washington, DC.

DOD (U.S. Department of Defense). 2001. Report on Biological Warfare Defense Vaccine Research and Development Programs. U.S. Department of Defense, Washington DC. July 2001 [online]. Available: http://www.defense.gov/pubs/reportonbiologicalwarfaredefensevaccineRDPrgras-July2001.pdf [accessed Mar. 10, 2011].

DOD. 2008. Roles and Responsibilities Associated with the Chemical and Biological Defense (CBD) Program (CBDP). DOD Directive No. 5160.05E, Oct. 9 2008 [online]. Available: http://www.dtic.mil/whs/directives/corres/pdf/516005p.pdf [accessed Mar. 8, 2011].

DOD. 2009. Protocol for Participation in the Special Immunization Program, FY05-15, Amendment No. 4. U.S. Department of Defense, Office of the Human Use Committee. HUC Submission Dec. 10, 2009.

DOD. 2010. Quadrennial Defense Reviews. U.S. Department of Defense [online]. Available: http://www.defense.gov/qdr/ [accessed Mar. 8, 2011].

Drew, S.W. 2007. Platforms for vaccine manufacturing. Pp. 37-54 in WTEC Panel Report on International Assessment of Research and Development in Rapid Vaccine Manufacturing. World Technology Evaluation Center, Inc., Baltimore, MD [online]. Available: http://www.wtec.org/vaccmfg/RapidVaccMfg-finalreport.pdf [accessed Mar. 8, 2011].

DVC LLC (DynPort Vaccine Company LLC). 2011. DynPort Vaccine Company LLC: Case Studies [online]. Available: http://www.csc.com/dvc [accessed Mar. 8, 2011].

Eitzen, E. 2004. Special Immunization Program (SIP) Subgroup—Weapons of Mass Destruction Medical Countermeasures (WMDMCS): Final Policy Recommendations to U.S. Homeland Security Council Policy Coordinating Committee, December 2004.

Eitzen, E. 2010. Special Immunization Program (SIP) Subgroup, Weapons of Mass Destruction Medical Countermeasures (WMDMCS): Decision Brief to U.S. Homeland Security Council PCC, Dec. 16, 2004. Presentation at the First Meeting of the Committee on Special Immunizations Program for Laboratory Personnel Engaged in Research on Countermeasures for Select Agents, Mar. 4, 2010, Washington DC.

EMA (European Medicines Agency). 2005. Guideline on Procedures for the Granting of a Marketing Authorisation Under Exceptional Circumstances, Pursuant to Article 14(8) of Regulation (EC) No. 726/2004. EMEA/357981/2005. Committee for Medicinal Products for Human Use (CHMP). Dec. 15, 2005 [online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004883.pdf [accessed Nov. 2, 2010].

Enserink, M. 2009. Mystery: Did experimental vaccine save Ebola accident victim's life? Science Insider. April 7, 2009 [online]. Available: http://news.sciencemag.org/scienceinsider/2009/04/did-experimenta.html?sms_ss=email&at_xt=4d9619df9577ec5c%2C0.

Fatz, R.J. 2003. Special Immunization Program. Memorandum to Directors of the Army Staff, from Raymond J. Fatz, Deputy Assistant Secretary of the Army (Environment, Safety and Occupational Health), U.S. Department of the Army, Washington, DC. May 27, 2003.

FDA (U.S. Food and Drug Administration). 2004. Public Workshop on Animal Models and Correlates of Protection for Plague Vaccines, Oc. 13, 2004, Gaithersburg, MD. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research [online]. Available: http://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/TranscriptsMinutes/UCM054438.pdf [accessed Dec. 13, 2010].

FDA. 2007a. Anthrax Vaccines: Bridging Correlates of Protection in Animals to Immunogenicity in Humans: Workshop, Nov. 8, 2007, Gaithersburg, MD. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research [online]. Available: http://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/TranscriptsMinutes/UCM054424.pdf [accessed Dec. 13, 2010].

FDA. 2007b. Emergency Use Authorization of Medical Products Guidance—Emergency Use Authorization of Medical Products. U.S. Department of Health and Human Services, Food and Drug Administration, Office of the Commissioner, Office of Counterterrorism Policy and Planning, Rockville, MD. July 2007 [online]. Available: http://www.fda.gov/oc/guidance/emergencyuse.html [accessed July 14, 2010].

FDA. 2008. Guidance for Industry: Tropical Disease Priority Review Vouchers. Draft Guidance. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). October 2008 [online]. Available: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf [accessed July 14, 2010].

FDA. 2009a. Guidance for Industry: Animal Models—Essential Elements to Address Efficacy Under the Animal Rule. Draft Guidance. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). January 2009 [online]. Available: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078923.pdf [accessed July 14, 2010].

FDA. 2009b. Public Meeting on Animal Models—Essential Elements to Address Efficacy Under the Animal Rule; and Reopening of Comment Period. Docket No. FDA-2009-D-000, Nov. 5, 2010 [online]. Available: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm225074.htm [accessed Dec. 13, 2010].

FDA. 2010a. Emergency Use Authorization. U.S. Food and Drug Administration [online]. Available: http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm [accessed July 14, 2010].

FDA. 2010b. Import and Export Guidance Documents. Regulatory Information. U.S. Food and Drug Administration [online]. Available: http://www.fda.gov/RegulatoryInformation/Guidances/ucm122048.htm [accessed Mar. 14, 2011].

FDA. 2010c. Pathway to Licensure for Protective Antigen-based Anthrax Vaccines for a Post-exposure Prophylaxis Indication Using the Animal Rule, Briefing Document for the Vaccines and Related Biological Products Advisory Committee Meeting, Nov. 16, 2010 [online]. Available: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM232400.pdf [accessed Dec. 13, 2010].

FDA. 2010d. Transcript of the November 15, 2010 Meeting of the Science Board to the Food and Drug Administration [online]. Available: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM236313.pdf [accessed Dec. 13, 2010].

Fischer, M., A. Griggs, and J.E. Staples. 2009. Tick-Borne Encephalitis (TBE). Chapter 5 in CDC Information for International Travel 2010 (The Yellow Book). U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, Atlanta, GA [online]. Available: http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-5/tick-borne-encephalitis.aspx [accessed Mar. 11, 2011].

Franco, C., and T.K. Sell. 2010. Federal agency biodefense funding, FY2010-FY2011. Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science 8(2):129-149.

Fuller, C.L., K.C. Brittingham, M.W. Porter, M.J. Hepburn, P.L. Petitt, P.R. Pittman, and S. Bavari. 2007. Transcriptome analysis of human immune responses following live vaccine strain (LVS) *Francisella tularensis* vaccination. Molecular Immunology 44(12):3173-3184.

GAO (U. S. General Accounting Office). 1991. Biological Warfare: Role of Salk Institute in Army's Research Program. GAO/NSIAD-92-33. Washington, DC: U.S. General Accounting Office. December 1991 [online]. Available: http://archive.gao.gov/t2pbat7/145851.pdf [accessed Mar. 8, 2011].

GAO (U.S. Government Accountability Office). 2007. High-Containment Biosafety Laboratories: Preliminary Observations on the Oversight of the Proliferation of BSL-3 and BSL-4 Laboratories in the United States. Testimony Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives. GAO-08-108T. Washington, DC: U.S. Government Accountability Office [online]. Available: http://www.absa.org/leg/0712GAOHighContainmentLabsReport.pdf [accessed Mar. 8, 2011].

GAO. 2009a. High-Containment Laboratories: National Strategy for Oversight Is Needed. GAO-09-574. Washington, DC: U.S. Government Accountability Office. September 2009 [online]. Available: http://www.gao.gov/new.items/d09574.pdf [accessed Mar. 8, 2011].

GAO. 2009b. High-Containment Laboratories: National Strategy for Oversight is Needed. Testimony Before the Subcommittee on Terrorism and Homeland Security, Committee on the Judiciary, Senate. GAO-09-1045T. Washington, DC: U.S. Government Accountability Office [online]. Available: http://www.gao.gov/new.items/d091045t.pdf [accessed Mar. 8, 2011].

Gidding, H., C. Wallace, G.L. Lawrence, and P.B. McIntyre. 2009. Australia's national Q fever vaccination program. Vaccine 27:2037-2041.

Harding, A.L., and K.B. Byers. 2006. Epidemiology of laboratory-associated infections. Pp. 53-80 in Biological Safety Principles and Practices, 4th Ed., D.O. Fleming and D.L. Hunt, eds. Washington, DC: ASM Press.

Henchal, E.A. 2003. Changes in the Special Immunizations Program at the U.S. Army Medical Research Institute of Infectious Diseases. Memorandum for Directors of All Agencies Whose Employees Are Participants in the Special Immunizations Program at the U.S. Army Medical Research Institute of Infectious Diseases. MCMR-UIM-R. Aug. 14, 2003.

HHS (U.S. Department of Health and Human Services). 2007. Public Health Emergency Medical Countermeasure Implementation Plan for Chemical, Biological and Nuclear Threats. U.S. Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Office of Public Health Emergency Medical Countermeasures. April 2007 [online]. Available: http://www.pswrce.uci.edu/pdf/phemce_implplan_041607final.pdf [accessed Mar. 8, 2011].

HHS. 2009a. Advanced Development of Recombinant Influenza Vaccine Products and Manufacturing Capabilities for Pandemic Preparedness. Request for Proposal, Solicitation No. HHS-BARDA-09-32. U.S. Department of Health and Human Services. FedBiz Opps [online]. Available: https://www.fbo.gov/index?s=opportunity&mode=form&id=056306ed6f1b7ef2f79215516c4b8dfe&tab=core&_cview=1 [accessed Mar. 8, 2011].

HHS. 2009b. National Health Security Strategy of the United States of America. U.S. Department of Health and Human Services. December 2009 [online]. Available: http://www.phe.gov/Preparedness/planning/authority/nhss/strategy/Documents/nhss-final.pdf [accessed Mar. 9, 2011].

HHS. 2010a. Biennial Implementation Plan for the National Health Security Strategy of the United States of America. Draft Report, July 19, 2010 [online]. Available: http://www.phe.gov/Preparedness/planning/authority/nhss/comments/Documents/nhssbip-draft-100719.pdf [accessed Mar. 8, 2011].

HHS. 2010b. Public Health Emergency Medical Countermeasure Enterprise Review: Transforming the Enterprise to Meet Long-Range National Needs. U.S. Department of Health and Human Services, Assistant Secretary for Preparedness and Response. August 2010 [online]. Available: https://www.medicalcountermeasures.gov/documents/MCMReviewFinalcover-508.pdf [accessed Mar. 8, 2011].

HHS. 2011. Centers for Innovation in Advanced Development and Manufacturing. Request for Proposal, Solicitation No. 11-100-SOL-00011. U.S. Department of Health and Human Services. FedBiz Opps [online]. Available: https://www.fbo.gov/index?s=opportunity&mode=form&id=d642fcb0614b1558e9c8482f57e327d0&tab=core&_cview=1 [accessed Jun. 6, 2011].

Hornick, R.B., A.T. Dawkins, H.T. Eigelsbach, and J.J. Tulis. 1966. Oral tularemia vaccine in man. Pp. 11-14 in Antimicrobial Agents and Chemotherapy, G.L. Hobby, ed. Bethesda, MD: American Society for Microbiology.

Hough, D.E. 2010. TMT Overview. Presentation at the Transformational Medical Technologies Initiative (TMTI) Partnership Symposium, May 3, 2010, Lansdowne, VA [online]. Available: http://tmt-cbdefense.org/calendar/eventfiles/TMTI%20Program%20Overview.pdf [accessed Mar. 10, 2011].

IOM (Institute of Medicine). 2002. Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military. Washington, DC: National Academies Press.

IOM. 2004. Giving Full Measure to Countermeasures: Addressing Problems in the DOD Program to Develop Medical Countermeasures. Washington, DC: National Academies Press.

IOM. 2009. Conflict of Interest in Medical Research, Education, and Practice. Washington, DC: National Academies Press.

IOM. 2010. Public Health Emergency Countermeasures Enterprise, Innovative Strategies to Enhance Products from Discovery to Approval, Feb. 23-24, 2010, Washington, DC: National Academies Press.

Jahrling, P., C. Rodak, M. Bray, and R.T. Davey. 2009. Triage and management of accidental laboratory exposures to biosafety level-3 and -4 agents. Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science 7(2):135-143.

Jochim, M.M., T.L. Barber, and A.J. Luedke. 1973. Venezuelan equine encephalomyelitis: Antibody response in vaccinated horses and resistance to infection with virulent virus. Journal of the American Veterinary Medical Association 162(4):280-283.

Joint Chiefs. 2010. Joint Biological Warfare Defense Capabilities, Chairman of the Joint Chiefs of Staff Instruction. CJCSI 3112.01A, Feb. 9, 2010 [online]. Available: http://www.dtic.mil/cjcs_directives/cdata/unlimit/3112_01.pdf [accessed Mar. 9, 2011].

JPEO-CBD (Joint Program Executive Office for Chemical and Biological Defense). 2011. Joint Vaccine Acquisition Program (JVAP). Joint Program Executive Office for Chemical and Biological Defense [online]. Available: http://www.jpeocbd.osd.mil/packs/Default.aspx?pg=1208 [accessed Mar. 10, 2011].

Kaiser, J. 2007. Pathogen Work at Texas A&M Suspended. Science Now, July 2, 2007 [online]. Available: http://news.sciencemag.org/sciencenow/2007/07/02-01.html [accessed Mar. 9, 2011].

Kimman, T.G., E. Smit, and M.R. Klein. 2008. Evidence-based biosafety: A review of the principles and effectiveness of microbiological containment measures. Clinical Microbiology Reviews 21(3):403-425.

Kisskalt, K. 1915. Laboratory infections with typhoid bacilli. Zeitschrift fuer Hygiene und Infektionskrankheiten 80:145-162.

Leifer, E., D.J. Gocke, and H. Bourne. 1970. Report of laboratory-acquired infection treated with plasma from a person recently recovered from the disease. American Journal of Tropical Medicine and Hygiene 19:677-679.

Maiztegui, J.I., K.T. McKee, Jr., J.G. Barrera, L.H. Harrison, P.H. Gibbs, M.R. Feuillade, D.A. Enria, A.M. Briggiler, S.C. Levis, A.M. Ambrosio, N.A. Halsey, and C.J. Peters. 1998. Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. Journal of Infectious Diseases 177(2):277-283.

McClain, D.J., P.R. Pittman, H.H. Ramsburg, G.O. Nelson, C.A. Rossi, J.A. Mangiafico, A.L. Schmaljohn, F.J. Malinoski. 1998. Immunologic interference from sequential administration of live attenuated alphavirus vaccines. Journal of Infectious Diseases 177(3):634-741.

Meyer, K.F., and B. Eddie. 1941. Laboratory infections due to *Brucella*. Journal of Infectious Diseases 68(1):24-32.

NBSB (National Biodefense Science Board). 2010a. Optimizing Industrial Involvement in Medical Countermeasure Development. National Biodefense Science Board, February 2010 [online]. Available: http://www.phe.gov/Preparedness/legal/boards/nbsb/meetings/Documents/nbsbrpt-2010.pdf [accessed Mar. 9, 2011].

NBSB. 2010b. Where Are the Countermeasures? Protecting America's Health from CBRN Threats. National Biodefense Science Board, March 2010 [online]. Available: http://www.phe.gov/Preparedness/legal/boards/nbsb/meetings/Documents/nbsb-mcmreport.pdf [accessed Mar. 9, 2011].

Newmark, J. 2009. The Integrated National Biodefense Portfolio Initiative "One-Portfolio, JPEO CBD. Presented at the 2009 DOD Chemical Biological Defense Advance Planning Briefing for Industry (APBI), May 7, 2009 [online]. Available: http://www.jpeocbd.osd.mil/packs/Default.aspx?pg=851 [accessed Jan. 5, 2011].

NIAID (National Institute of Allergy and Infectious Diseases). 2007. NIAID Strategic Plan for Biodefense (2007 Update). U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases [online]. Available: http://www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/Documents/biosp2007.pdf [accessed Mar. 9, 2011].

NIAID. 2009. NIAID Category A, B, and C Priority Pathogens [online]. Available: http://www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/research/Pages/CatA.aspx [accessed Mar. 10, 2011].

NIAID. 2010. Regional Centers of Exellence for Biodefense and Emerging Infectious Diseases (RCEs): Overview [online]. Available: http://www.niaid.nih.gov/labsandresources/resources/rce/pages/introduction.aspx [accessed Mar. 14, 2011].

NIAID. 2011. Resources for Researchers: Current National Biocontainment Laboratories (NBL) and Regional Biocontainment Laboratories (RBL) [online]. Available: http://www.niaid.nih.gov/LabsAndResources/resources/dmid/NBL_RBL/Pages/site.aspx [accessed Mar. 14, 2011].

Niklasson, B., J.M. Meegan, and E. Bengtsson. 1979. Antibodies to Rift Valley fever virus in Swedish U.N. soldiers in Egypt and the Sinai. Scandinavian Journal of Infectious Diseases 11(4):313-314.

NIOSH (National Institute for Occupational Safety and Health). 1999. NIOSH Alert: Preventing Needlestick Injuries in Health Care Settings. Publication No. 2000-108. U.S. Department of Health and Human Services, Public Health Service, Centers for Diseases Control and Prevention, National Institute for Occupational Safety and Health. November 1999 [online]. Available: http://www.cdc.gov/niosh/docs/2000-108/pdfs/2000-108.pdf [accessed Mar. 9, 2011].

NRC (National Research Council). 2009. Responsible Research with Biological Select Agents and Toxins. Washington, DC: National Academies Press.

NRC. 2010. Evaluation of the Health and Safety Risks of the New USAMRIID High Containment Facilities at Fort Detrick, MD. Washington, DC: National Academies Press.

NSC (National Security Council). 2009. National Strategy for Countering Biological Threats. National Security Council, The White House. November 2009 [online]. Available: http://www.whitehouse.gov/sites/default/files/National_Strategy_for_Countering_BioThreats.pdf [accessed Mar. 9, 2011].

Olsen, G.H., M.J. Turell, and B.B. Pagac. 1997. Efficacy of eastern equine encephalitis immunization in whooping cranes. Journal of Wildlife Diseases 33(2):312-315.

One Health. 2010. One Health Initiative [online]. Available: http://www.onehealthinitiative.com/ [accessed Mar. 15, 2011].

PATH. 2007. SA 14-14-2 Japanese Encephalitis (JE) Vaccine. April 2007 [online]. Available: http://www.path.org/vaccineresources/files/SA14142_fact_sheet_15Feb08.pdf [accessed Mar. 14, 2011].

Paweska, J., L. Blumberg, J. Weyer, A. Kemp, P. Leman, B. Archer, D. Nkosi, and R. Swanepoel. 2008. Rift Valley fever outbreak in South Africa. Communicable Diseases Surveillance Bulletin (South Africa) 6(2):1-2.

Pike, R.M. 1976. Laboratory-associated infections: Summary and analysis of 3921 cases. Health Laboratory Science 13(2):105-114.

Pike, R.M. 1978. Past and present hazards of working with infectious agents. Archives of Pathology and Laboratory Medicine 102(7):333-336.

Pike, R.M. 1979. Laboratory-associated infections: Incidence, fatalities, causes, and prevention. Annual Review of Microbiology 33:41-66.

Pittman, P.R., R.S. Makuch, J.A. Mangiafico, T.L. Cannon, P.H. Gibbs, and C.J. Peters. 1996. Long term detectable neutralizing antibodies after administration of live-attenuated VEE vaccine and following booster vaccination with inactivated VEE vaccine. Vaccine 14(4):337-343.

Pittman, P.R., K.M. Coonan, P.H. Gibbs, H.M. Scott, T.L. Cannon, and K.T. McKee, Jr. 2004. Long-term health effects of repeated exposure to multiple vaccines. Vaccine 23(4):525-536.

Pittman, P.R., S.F. Leitman, J.G. Oro, S.L. Norris, N.M. Marano, M.V. Ranadive, B.S. Sink, and K.T. McKee, Jr. 2005a. Protective antigen and toxin neutralization antibody patterns in anthrax vaccinees undergoing serial plasmapheresis. Clinical and Diagnostic Laboratory Immunology 12(6):713-721.

Pittman, P.R., S.L. Norris, K.M. Coonan, and K.T. McKee, Jr. 2005b. An assessment of health status among medical research volunteers who served in the Project Whitecoat program at Fort Detrick, Maryland. Military Medicine 170(3):183-187.

Pouch Downes, F. 2010. Public Health Laboratory Vaccination Needs, Michigan Department of Community Health. Presentation at the Third Meeting on Special Immunizations Program, May 18, 2010, Washington, DC.

Powers, A.M., and C.H. Logue. 2007. Changing patterns of Chikungunya virus: Re-emergence of a zoonotic arbovirus. Journal of General Virology 88(9):2363-2377.

Riesman, D. 1898. Two cases of diphtheria, one from a laboratory infection, and one in an infant eleven days old. Philadelphia Medical Journal 1(10):422-424.

Ruben, B., J.D. Band, P. Wong, and J. Colville. 1991. Person-to-person transmission of *Brucella melitensis*. The Lancet 337(8732):14-15.

Rusnak, J.M., M.G. Kortepeter, J. Aldis, and E. Boudreau. 2004a. Experience in the medical management of potential laboratory exposures to agents of bioterrorism on the basis of risk assessment at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID). Journal of Occupational and Environmental Medicine 46(8):801-811.

Rusnak, J.M., M.G. Kortepeter, R.J. Hawley, A.O. Anderson, E. Boudreau, and E. Eitzen. 2004b. Risk of occupationally acquired illnesses from biological threat agents in unvaccinated laboratory workers. Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science 2(4):281-293.

Rusnak, J.M., M.G. Kortepeter, R.J. Hawley, E. Boudreau, J. Aldis, and P.R. Pittman. 2004c. Management guidelines for laboratory exposures to agents of bioterrorism. Journal of Occupational and Environmental Medicine 46(8):791-800.

Rusnak, J.M., P. Gibbs, E. Boudreau, D.P. Clizbe, and P. Pittman. 2011. Immunogenicity and safety of an inactivated Rift Valley fever vaccine in a 19-year study. Vaccine. 2011 29(17):3222-3229.

sanofi-pasteur. 2010. Company website: Origin [online]. Available: http://www.avpi.org/sanofi-pasteur2/ImageServlet?imageCode=27494&siteCode=SP_CORP [accessed Mar. 9, 2011].

Sawyer, J., A. Bennett, V. Haines, E. Elton, K. Crago, and S. Speight. 2007. The effect of microbiological containment systems on dexterity. Journal of Occupational and Environmental Hygiene 493:166-173.

Sawyer, W.A. 1932. Vaccination against yellow fever with immune serum and virus fixed for mice. Journal of Experimental Medicine 55(6):945-969.

Simpson, A. 2010. An international perspective on immunizing laboratory researchers—UK Position. Presentation at the Second Meeting of the Committee on Special Immunizations Program for Laboratory Personnel Engaged in Research on Countermeasures for Select Agents, May 18, 2010. Washington, DC.

Sjöstedt, A. Laboratory of Molecular Infection Sweden (MIMS). E-mail to Alan Cross. Mar. 23, 2011.

Top, F.H. Jr., J.J. Dingerdissen, W.H. Habig, G.V. Quinnan, Jr., and R.L. Wells. 2000. DoD Acquisition of Vaccine Production: Report to the Secretary of Defense by the Independent Panel of Experts, Nov. 29, 2000. (Appendix D in DOD 2001)[online]. Available: http://www.defense.gov/pubs/reportonbiologicalwarfaredefensevaccineRDPrgras-July2001.pdf [accessed Mar. 10, 2011].

U.S. Department of the Army. 1990. Use of Volunteers as Subjects of Research. Army Regulation 70-25. Headquarters, U.S. Department of the Army, Washington, DC. Jan. 25, 1990 [online]. Available: http://armypubs.army.mil/epubs/pdf/R70_25.PDF [accessed Mar. 14, 2011].

U.S. Department of the Army. 1997. Medical Aspects of Chemical and Biological Warfare, F.R. Sidell, E.T. Takafuji, and D.R. Franz, eds. Textbooks of Military Medicine. Office of the Surgeon General, Boden Institute, Walter Reed Army Medical Center, Washington, DC [online]. Available: http://www.bordeninstitute.army.mil/published_volumes/chemBio/fm.pdf [accessed Mar. 10, 2011].

U.S. Department of the Army. 2007. Medical Aspects of Biological Warfare, Z.F. Dembek, ed. Textbooks of Military Medicine. Office of the Surgeon General, U.S. Army Medical Department Center and School, Boden Institute, Washington, DC [online]. Available: http://www.bordeninstitute.army.mil/published_volumes/biological_warfare/biological.html [accessed Mar. 10, 2011].

U.S. Department of the Army. 2010. Advanced Development and Manufacturing of Biologics-Based Chemical, Biological, Radiological, and Nuclear Defense Medical Countermeasures. Request for Information. Solicitation No.W911QY11XMCMI, U.S. Department of the Army. FedBizOpps [online]. Available: https://www.fbo.gov/index?s=opportunity&mode=form&id=6ad751b397cb963fb32f7d65d061ffdb&tab=core&_cview=0 [accessed Mar. 8, 2011].

USAMRIID (U.S. Army Medical Research Institute of Infectious Disease). 1995. Boards, Commissions and Committees. Regulation 15-1. June 30, 1995.

USAMRIID. 2004. Risk Assessment and Special Immunizations Program Participation Request. Standard Operating Procedure SOP MD-06-06. September 10, 2004.

USAMRIID. 2009. USAMRIID Special Immunizations Program (SIP) Clinic Capabilities. December 15, 2009.

Victoria, J.G., C. Wang, M.S. Jones, C. Jaing, K. McLoughlin, S. Gardner, and E.L. Delwart. 2010. Viral nucleic acids in live-attenuated vaccines: Detection of minority variants and an adventitious virus. Journal of Virology 84(12):6033-6040.

Wedum, A.G. 1996. The Detrick experience as a guide to the probable efficacy of P4 microbiological containment facilities for studies on microbial recombinant DNA molecules. Applied Biosafety 1(1):7-25.

Wedum, A.G., W.E. Barkley, and A. Hellman. 1972. Handling of infectious agents. Journal of the American Veterinary Medical Association 161(11):1557-1567.

White House. 2007. Homeland Security Presidential Directive 18 (HSPD-18). Medical Countermeasures against Weapons of Mass Destruction. January 31, 2007. Available: http://www.dhs.gov/xabout/laws/gc_1219175362551.shtm [accessed Jun. 8, 2011].

White House. 2010. National Security Strategy. May 2010 [online]. Available: http://www.whitehouse.gov/sites/default/files/rss_viewer/national_security_strategy.pdf [accessed Mar. 9, 2011].

Widmer, J. 2000. The Spirit of Swiftwater: 100 Years at the Pocono Labs. Scranton, PA: University of Scranton Press.

WRAIR (Walter Reed Army Institute of Research). 2010. Pilot Bioproduction Facility: Frequently Asked Questions. U.S. Army Medical Research and Materiel Command, Walter Reed Army Institute of Research [online]. Available: http://wrair-www.army.mil/Pilot_Bioproduction_Facility/Welcome/ [accessed Mar. 9, 2011].

# Appendixes

# Appendix A

# Committee Member Biographies

**Donald S. Burke, M.D.** (*Chair*), is the dean of the University of Pittsburgh Graduate School of Public Health, the UPMC-Jonas Salk Professor of Global Health, associate vice chancellor for global health, and director of the Center for Vaccine Research. Before coming to the University of Pittsburgh, Dr. Burke was a professor at the John Hopkins Bloomberg School of Public Health, where he served as associate chair of the Department of International Health and director of the Center for Immunization Research. He also served as principal investigator of National Institutes of Health-supported research projects on HIV vaccines, biodefense, and emerging infectious diseases.

Prior to his tenure at Johns Hopkins, Dr. Burke served 23 years on active duty in the U.S. Army, leading military infectious disease research at the Walter Reed Army Institute of Research in Washington, DC, and at the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand. He retired with the rank of colonel.

In addition to many decorations received while in military service, Dr. Burke has been honored by the scientific community. He is an elected fellow of the American Association for the Advancement of Science, the American Academy of Microbiology, the Royal Society of Tropical Medicine and Hygiene, the American College of Physicians, the Infectious Disease Society of America, and the Institute of Medicine. He served as president of the American Society of Tropical Medicine and Hygiene in 1995–1996.

Dr. Burke has authored or co-authored more than 200 research reports. Recent selections in his bibliography include reports on the evaluation of the likely effectiveness of strategies for containing an emerging pandemic influenza in Southeast Asia, on simulation of the dynamic effects of antibody-dependent enhancement on the fitness of viruses, on detection of traveling waves in the

epidemiology of dengue hemorrhagic fever, and on emergence of unique primate T-lymphotropic viruses among central African bushmeat hunters.

Dr. Burke's career-long mission has been prevention and mitigation of the impact of epidemic infectious diseases of global importance. His research activities have spanned a wide range of science "from the bench to the bush," including development of new diagnostics, population-based field studies, clinical vaccine trials, computational modeling of epidemic control strategies, and policy development and evaluation.

**W. Emmett Barkley, Ph.D.**, is the president of Proven Practices, LLC where he supports environmental health and safety programs at major academic research universities and government agencies. He is the former director of laboratory safety at the Howard Hughes Medical Institute and has recently served on the Committee on Prudent Practices in the Laboratory: An Update. His experience includes 24 years at the National Institutes of Health (NIH), where he served as the founding director of the NIH Division of Safety. Dr. Barkley was a principal contributor to several authoritative guidelines in the fields of biological and chemical safety, including the *NIH Guidelines for the Laboratory Use of Chemical Carcinogens*, the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, and the CDC/NIH publication *Biosafety in Microbiological and Biomedical Laboratories*. He received a bachelor of civil engineering from the University of Virginia and the master of science and doctorate degrees in environmental health from the University of Minnesota.

**Gerardo Chowell, Ph.D.**, is an assistant professor in the School of Human Evolution and Social Change at Arizona State University (ASU). Prior to joining ASU, Dr. Chowell was a director's postdoctoral fellow with the Mathematical Modeling and Analysis Group (Theoretical Division) at the Los Alamos National Laboratory. He performs mathematical modeling of emergent and re-emergent infectious diseases (including SARS, influenza, Ebola, and foot-and-mouth disease) with an emphasis in quantifying the effects of public health interventions. His research interests include agent-based modeling, model validation, and social network analysis. Dr. Chowell received his Ph.D. in biometry from Cornell University and his engineering degree in telematics from the Universidad de Colima, Mexico.

**Alan S. Cross, M.D.**, is professor of medicine at the University of Maryland School of Medicine and researcher at its Center for Vaccine Development. Dr. Cross has three major areas of interest: the development of a vaccine for the prevention and treatment of sepsis, the early interactions of *Bacillus anthracis* with the host immune system, and the role of sialic acid in innate and adaptive immunity. A previous phase I study with a detoxified endotoxin vaccine complexed to group B meningococcal outer membrane protein revealed that while

the vaccine was well-tolerated, it was only weakly immunogenic. Currently, preclinical studies in murine models as well as clinical studies in human subjects are continuing with this vaccine given in conjunction with novel adjuvants. The relative roles of Toll-like receptors and Fc receptors in mediating macrophage killing of *B. anthracis* is another focus of the laboratory. The ability of the various *B. anthracis* structures (spore and vegetative forms and exosporium) to initiate macrophage signaling pathways leading to the killing of the organism is being characterized, and the effects of anthrax toxins on myeloid function are being defined. Finally, Dr. Cross found that the sialidase (neuraminidase) activity of various cells in the immune system is an essential element of innate and adaptive immunity. Currently, the laboratory is focusing on the mechanisms by which human neutrophil sialidase regulates cellular trafficking in both in vivo and in vitro model systems. These studies rely on endothelial cell culture systems as well as murine models of inflammation. Dr. Cross is past president of the International Endotoxin and Innate Immunity Society. Dr. Cross earned his B.A. from Harvard College and his M.D. from the University of Pennsylvania.

**Stephen W. Drew, Ph.D.**, is a former Distinguished Senior Scientist at Merck & Co., Inc., where his responsibilities encompassed the development of new process technologies for biologics and pharmaceutical manufacturing and technology transfer. Since retirement from Merck, he has founded two new companies—Drew Solutions LLC, a direct consulting firm, and Science Partners LLC, an advocacy company for medicines and technologies—that support the biotechnology and pharmaceutical industries. Prior to his retirement, he held vice presidential positions of responsibility at Merck & Co., Inc. as the vice president of Vaccine Science and Technology, the vice president of Vaccine Operations, and the vice president of Technical Operations & Engineering. He joined Merck in 1981 to create the Department of Biochemical Engineering. At Merck, he contributed to the process development and manufacture of several conventional and recombinant microbial products ranging from antibiotics to vaccines. Dr. Drew works in manufacturing processes for human and animal vaccines; recombinant biologics; chemical, biological, and engineering technology for bulk manufacture of pharmaceuticals and biologics; capital project engineering; process engineering; and fermentation, cell culture, isolation, and purification processes for sterile products. Dr. Drew received his B.S. and an M.S. in food science from the University of Illinois, and a Ph.D. in biochemical engineering from the Massachusetts Institute of Technology. He was elected to the National Academy of Engineering in 1993 and is a member of several professional organizations serving interests in chemical engineering, chemistry, and biology. He has held offices in the American Institute of Chemical Engineers, the American Chemical Society, the American Society for Microbiology, and the Society for Industrial Microbiology, and is a Founding Fellow of the American Institute for Medical and Biological Engineering. He has served as chairman of

the advisory committee to the Engineering Directorate of the National Science Foundation. He is a member of two standing committees of the National Research Council and has participated in many National Research Council studies.

**Kathryn Edwards, M.D.**, is the Sarah Sell Professor of Pediatrics, director of the division of Pediatric Clinical Research at the Kennedy Center, Vanderbilt University, and director of the Vanderbilt Vaccine Research Program. Dr. Edwards's work focuses on the evaluation of vaccines for the prevention of infectious diseases in adults and children. She has conducted large efficacy trials of influenza vaccine and has coordinated multicenter trials of vaccines against *Hemophilus influenza* type b, *Bordetella pertussis*, *Streptococcus pneumoniae,* and vaccinia vaccines. She is currently studying dose-sparing strategies for influenza vaccine and avian influenza vaccines. She also conducts active population-based surveillance to monitor the impact of new vaccines on disease burden. Through National Institutes of Health and Centers for Disease Control and Prevention funding Dr. Edwards has performed many of the pivotal studies on vaccine effectiveness, vaccine safety, and vaccine impact in the past three decades. She is actively engaged in mentoring young clinical investigators and in teaching residents, medical students, and fellows. Her clinical work is focused on preventing and managing infectious diseases in children.

**Robert J. Hawley, Ph.D., RBP, CBSP**, is an independent consultant on biological safety, biosecurity and biosurety issues. Before retiring in April 2011, he served as Senior Advisor, Science, for Midwest Research Institute's Mid-Atlantic Operations and was responsible for the technical oversight of all group biosafety, biosecurity, and biosurety projects, and support staff. He performed incident investigations, biosafety threat and risk assessments, and threat and vulnerability and emergency requirements analyses at designated facilities to mitigate security and safety risks regarding the storage and handling of biological threat agents. Dr. Hawley also provided training in biological safety operations, maximum containment, recombinant DNA technology, and the science and safety of microbial agents and toxins for BSL-2, BSL-3, and BSL-4 operations. Before joining MRI in 2003, he worked at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) for 15 years, where he was responsible for formulating, implementing, and interpreting USAMRIID's microbiological and industrial safety policies and procedures. Positions filled during his tenure at USAMRIID include safety and occupational health specialist, safety and occupational health manager, chief of the Safety and Radiation Protection Office, and Command Biological Safety Officer. Dr. Hawley received his master's degree in virology from the Catholic University of America and Ph.D. degree in microbiology from the College of Medicine and Dentistry of New Jersey. He conducted research on mycobacteria and streptococci at the Georgetown University Schools of Medicine and Dentistry, Holy Cross

Hospital, and the University of Maryland before joining USAMRIID. He is a former president of the American Biological Safety Association (ABSA) and its Chesapeake Branch. He received the Council of Principal Scientists Science Award, Midwest Research Institute, in 2006 and the Everett Hanel, Jr. Presidential Award from the American Biological Safety Association in 2005. He was a member of the United Nations Special Commission (UNSCOM) Inspection Team in Iraq (1995); member of the team to sample for *Bacillus anthracis* at Stepnogorsk, Kazakhstan (1997); member of the World Health Organization team tasked to inspect the smallpox facility at the State Research Centre of Virology and Biotechnology in Novosibirsk, Central Siberia (1999, 2002, and 2009), and at the Centers for Disease Control and Prevention (2009). He consulted for the Environmental Protection Agency in Boca Raton, Florida (October 2001) and Washington D.C. (October 2001), for sampling and decontamination of facilities exposed to *Bacillus anthracis* spores. He was a member of the Defense Science Board Task Force on Defense Against Terrorist Use of Biological Weapons, Office of the Secretary of Defense (2002). He is a member of the Editorial Review Board of *Applied Biosafety: Journal of the American Biological Safety Association*; non-affiliated member of the Institutional Biosafety Committee at the University of Maryland, Baltimore, and a member of the Biological Sciences Experts Group, Office of the Director of National Intelligence. He served as a member of the Committee on Laboratory Security and Personnel Reliability Assurance Systems for Laboratories Conducting Research on Biological Select Agents and Toxins, National Academy of Sciences and a member of the Great Lakes Regional Center of Excellence Evaluation Committee (November 2010). He is the author or co-author of more than 250 abstracts, presentations, and publications in the areas of microbial taxonomy, chemistry, and genetics, plasmid-mediated antibiotic resistance, rapid diagnostic technology, medical aspects of AIDS, biological safety, biocontainment and decontamination, protection against biological warfare agents, bioterrorism and biological safety, decontamination, sterilization, disinfection, and antisepsis, biosafety and biosecurity regulatory impact, safety considerations in the BSL-4 (maximum) containment laboratory, and the science and safety of biological toxins.

**Thomas G. Ksiazek, D.V.M., Ph.D.**, is a professor in the departments of Pathology and of Microbiology and Immunology at the University of Texas Medical Branch (UTMB) at Galveston, Texas, senior staff scientist and director of the High Containment Operations Core at Galveston National Laboratory, and director of the University of Texas Medical Branch National Biodefense Training Center. He has previously served as chief of the Special Pathogens Branch, Division of Viral and Rickettsial Diseases (DVRD), National Center for Zoonotic, Vector-borne, and Enteric Diseases, Centers for Disease Control and Prevention (CDC); chief of the Disease Assessment Section, Special Pathogens Branch, DVRD, National Center for Infectious Diseases, CDC (1991–2005);

and chief of the Rapid Diagnosis Department, Disease Assessment Division, U.S. Army Medical Research Institute of Infectious Diseases, Ft. Detrick (1988–1991). Dr. Ksiazek's scientific interests include the epidemiology/ecology and laboratory diagnosis of hemorrhagic fevers and arthropod-borne viral diseases. He has served as a consultant on operational biosafety and facility design to the U.S. Department of Agriculture, UTMB, U.S. Department of Defense, and U.S. Department of Homeland Security, and several international laboratories. Dr. Ksiazek received his D.V.M. from Kansas State University (1970); M.S. from the University of Wisconsin Madison (1976) and Ph.D. from the University of California (1984). He received the Army Surgeon General's Award of an "A" skill identifier (1990); the Department of the Army Research and Development Achievement Award for Technical Achievement (1990), the Pekka Halonen Award for Diagnostic Virology (1993), and four Department of Health and Human Services Secretary's Awards for Distinguished Service. He was the Founders Lector, American College of Veterinary Preventive Medicine (1995); delivered the Stilt Lecture, Association of Military Surgeons of the United States (1995); and is a Snowden Lecture Awardee, Australian Animal Health Laboratory (2009). He is the author or co-author of more than 330 research papers and his international experience includes long-term professional assignments in England, Taiwan, Indonesia, and Egypt as well as extensive outbreak experience in Asia, Africa, and South America.

**Thomas P. Monath, M.D.**, is a partner in the Pandemic and Biodefense Fund of Kleiner Perkins Caufield & Byers. He is also adjunct professor, Harvard School of Public Health. From 1992 to 2006, Dr. Monath was chief scientific officer and an executive director at Acambis (a publicly traded biopharmaceutical company), where he directed R&D on dengue, West Nile, Japanese encephalitis, yellow fever, *Clostridium difficile*, as well as smallpox vaccines for defense against bioterrorism. Dr. Monath received his undergraduate degree from Harvard College and M.D. from Harvard Medical School and trained in internal medicine at the Peter Bent Brigham Hospital, Boston. COL Monath retired from the U.S. Army in 1992 after 24 years in the uniformed services. From 1973–1988, he was director of the Division of Vector-Borne Viral Diseases, Centers for Disease Control, Fort Collins, CO, and from 1989 to 1992 he was chief of the Virology Division, U.S. Army Medical Research Institute of Infectious Diseases. He is on the editorial board of five scientific journals. He received the Nathanial A. Young Award (1984), the Richard M. Taylor Award (1996), and the Walter Reed Medal (2002) from the American Society of Tropical Medicine & Hygiene and was president of that society (2004–2005). He has served on numerous government and international committees on infectious diseases and biosecurity, World Health Organization expert committees, and the National Vaccines Advisory Committee (U.S.). Dr. Monath has published

over 385 papers and edited 6 books on the epidemiology, immunology, and pathogenesis of viruses and on vaccine development.

**Peter A. Patriarca, M.D.**, is senior clinical consultant for the Biologics Consulting Group, Inc. in Bethesda, MD, where he provides a wide range of regulatory advice to various clients in the drug industry, focusing primarily on vaccines and other biological products. Dr. Patriarca's specialties include regulatory strategy, product development strategy, clinical protocol design, submission preparation and review, and Food and Drug Administration (FDA) and Advisory Committee meeting preparation. Prior to working for Biologics Consulting Group, Inc., Dr. Patriarca was the corporate head and vice president of world-wide Regulatory Affairs and Pharmacovigilance for MedImmune, Inc., from 2001 to 2005. He earned his B.S. at the University of Notre Dame, his M.D. at Tulane University School of Medicine, and is a board-certified pediatrician. Dr. Patriarca served as a Commissioned Officer in the U.S. Public Health Service from 1980 to 2000. During some of that time, he worked at the FDA, where he served as director of the Division of Viral Products in the Office of Vaccines Research and Review in the Center for Biologics Evaluation and Research. In that capacity, he worked on quality and consistency of chemistry manufacturing controls and clinical reviews, actively participated in sponsor meetings, and was intimately involved with regulatory decisions and policy affecting the development and approval of numerous investigational products. In his work at the Centers for Disease Control and Prevention, he was a field and clinical investigator, with about 100 peer-reviewed journal publications, and was a major contributor to immunization programs and policy promulgated through the Advisory Committee on Immunization Practices. Dr. Patriarca's product experience includes vaccines, plasma derivatives, monoclonal antibodies, and small molecules. He is an expert on influenza, poliomyelitis, measles, and pertussis and has extensive international experience (including interactions with high-level World Health Organization personnel), vaccine policy experience, and experience as an investigator in epidemiologic research and large-scale vaccine efficacy studies.

**Holly A. Taylor, Ph.D., M.P.H.**, is an assistant professor in the Department of Health Policy and Management, Bloomberg School of Public Health and a core faculty member of the Berman Institute of Bioethics at the Johns Hopkins University. She received her B.A. from Stanford University, her M.P.H. from the School of Public Health at the University of Michigan, and her Ph.D. in health policy with a concentration in bioethics from the Bloomberg School of Public Health, Johns Hopkins University. Before pursuing her doctoral degree, Dr. Taylor was a presidential management intern with the Department of Health and Human Services and spent two years rotating through AIDS-related policy positions at the National AIDS Program Office, National Commission on

AIDS, the San Mateo County Health Department, and the Senate Committee on Labor and Human Resources. After completing her internship, Dr. Taylor spent two years as special assistant to the director of the National Institute of Allergy and Infectious Diseases of the National Institutes of Health. In 1999, Dr. Taylor received a Mentored Scientist Development Award to pursue theoretical and practice aspects of justice in human subject research. She currently serves as associate director for empirical research at the Berman Institute of Bioethics. Dr. Taylor has served on the Institutional Review Boards of the Bloomberg School of Public Health and the Johns Hopkins School of Medicine. Her primary interests are research ethics, local implementation of federal policy relevant to human subject research, HIV/AIDS policy, and qualitative research methods.

**Thomas E. Walton** earned his D.V.M degree from Purdue University in 1964, a Ph.D. degree from Cornell University in virology in 1968, and a D.Sc. (honoris causae) from Purdue University in 1999. He is a diplomate of the American College of Veterinary Microbiologists and a Fellow of the Society for Tropical Veterinary Medicine. He has 31 years of experience in infectious diseases research, research leadership, and research management at the Middle America Research Unit of the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Canal Zone (1968–1972, research veterinarian; equine encephalomyelitides and vesicular stomatitis); the Arthropod-borne Animal Diseases Research Laboratory of the Agricultural Research Service (ARS), U.S. Department of Agriculture (USDA), Denver, CO, and Laramie, WY (1972–1992, research leader, bluetongue, epizootic hemorrhagic disease, equine encephalomyelitides, and vesicular stomatitis); the national program staff, ARS, USDA, Beltsville, MD (1992–1995, national program leader for animal health responsible for animal health program quality and relevance for 13 ARS animal health laboratories); and the National Animal Disease Center, ARS, USDA, Ames, IA (1995–1997, director, research leadership and management for indigenous livestock diseases). In addition, he has 11 years' experience in regulatory veterinary medicine as associate deputy administrator and acting deputy administrator for veterinary services (VS), Animal and Plant Health Inspection Service (APHIS), USDA, Washington, DC, and director of the Centers for Epidemiology and Animal Health, VS, APHIS, USDA, Fort Collins, CO. He is author or co-author of more than 150 scientific publications on infectious disease research with exotic and zoonotic pathogens and regulatory veterinary medicine.

Since retirement in 2006, he has served as a consultant to several companies on the design and environmental assessment of veterinary and human infectious diseases biocontainment laboratories and as a consultant to the Millennium Challenge Corporation and USDA, Foreign Agriculture Service for veterinary medical projects in the Republic of Namibia and in the Republic of Mongolia.

# Appendix B

# Abbreviations and Acronyms

| | |
|---|---|
| **ACIP** | Advisory Committee on Immunization Practices |
| **ASPR** | Assistant Secretary for Preparedness and Response |
| **BARDA** | Biomedical Advanced Research and Development Authority |
| **BDRP** | Biological Defense Research Program |
| **BMBL** | Biosafety in Microbiological and Biomedical Laboratories |
| **BSC** | Biological safety cabinet |
| **BSL** | Biosafety level |
| **CBDP** | Chemical and Biological Defense Program |
| **CBMS** | Chemical Biological Medical Systems |
| **CBMS-JPMO** | Chemical Biological Medical Systems Joint Project Management Office |
| **CBRN** | Chemical, Biological, Radiological, Nuclear |
| **CDC** | Centers for Disease Control and Prevention |
| **CFR** | Code of Federal Regulations |
| **cGCP** | Current Good Clinical Practice |
| **cGMP** | Current Good Manufacturing Practice |
| **CRDA** | Cooperative Research and Development Agreement |
| **DARPA** | Defense Advanced Research Projects Agency |
| **DHS** | Department of Homeland Security |
| **DIA** | Defense Intelligence Agency |
| **DOD** | Department of Defense |
| **DOE** | U.S. Department of Energy |
| **DSAT** | Division of Select Agents and Toxins |

| | |
|---|---|
| **EEE** | Eastern equine encephalitis |
| **EKG** | Electrocardiogram |
| **EMA** | European Medicines Agency |
| **EUA** | Emergency Use Authorization |
| **FDA** | Food and Drug Administration |
| **FFRDC** | Federally Funded Research and Development Center |
| **FSA** | Civilian Federal Security Agency |
| **FY** | Fiscal year |
| **GAO** | U.S. Government Accountability Office |
| **GOCO** | Government-owned, contractor-operated |
| **HBV** | Hepatitis B virus |
| **HHS** | Department of Health and Human Services |
| **HSC** | U.S. Homeland Security Council |
| **IAWG** | U.S. Government Interagency Working Group |
| **ICH** | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| **IND** | Investigational New Drug |
| **IOM** | Institute of Medicine |
| **JPEO-CBD** | Joint Program Executive Office for Chemical/Biological Defense |
| **JRO** | Joint Research Office |
| **JSTO** | Joint Science and Technology Office for Chemical and Biological Defenses |
| **JVAP** | Joint Vaccine Acquisition Program |
| **LAI** | Laboratory-associated infection (laboratory-acquired infection) |
| **LRRI** | Lovelace Respiratory Research Institute |
| **LVS** | Live vaccine strain |
| **MCM** | Medical Countermeasure |
| **MEDCOM** | U.S. Army Medical Command |
| **MOA** | Memorandum of agreement |
| **MOU** | Memorandum of understanding |
| **NBACC** | National Biodefense Analysis and Countermeasures Center |
| **NBFAC** | National Bioforensic Analysis Center |

| | |
|---|---|
| **NBSB** | National Biodefense Science Board |
| **NIAID** | National Institute of Allergy and Infectious Diseases |
| **NIH** | National Institutes of Health |
| **NMRC** | U.S. Navy Naval Medical Research Center |
| **NRC** | National Research Council |
| **OMB** | Office of Management and Budget |
| **OPEO** | Office of Preparedness and Emergency Operations |
| **OSHA** | Occupational Safety and Health Administration |
| **PERT** | Product-enhanced reverse transcriptase |
| **PHEMCE** | Public Health Emergency Medical Countermeasures Enterprise |
| **PI** | Principal investigator |
| **PPE** | Personal protective equipment |
| **PPP** | Public–private partnership |
| **PCC** | Policy Coordinating Committee |
| **R&D** | Research and development |
| **RCE** | Regional Centers of Excellence |
| **SAE** | Serious adverse event |
| **SBCCOM** | U.S. Army Soldier and Biological Chemical Command |
| **SIP** | Special Immunizations Program |
| **SNS** | Strategic National Stockpile |
| **TMT** | Transformational Medical Technologies program |
| **TPP** | Target product profiles |
| **USAMMDA** | U.S. Army Medical Materiel Development Activity |
| **USAMRDC** | U.S. Army Medical Research and Development Command (Subsequently merged with the Medical Material Agency to create USAMRMC) |
| **USAMRIID** | U.S. Army Medical Research Institute of Infectious Diseases |
| **USAMRMC** | U.S. Army Medical Research and Materiel Command |
| **USDA** | U.S. Department of Agriculture |
| **VEE** | Venezuelan equine encephalitis |
| **WEE** | Western equine encephalitis |
| **WMDMC** | Weapons of mass destruction medical countermeasures |
| **WMDMCS** | Weapons of Mass Destruction Medical Countermeasures Subcommittee |
| **WRS** | War Research Service |

# Appendix C

# Glossary

**Adjuvant:** substance (e.g., aluminum salt) that is added during production to increase the body's immune response to a vaccine.

**Adventitious agents:** microorganisms that have been unintentionally introduced into the manufacturing process of a biological product. They include bacteria, fungi, mycoplasmas, rickettsia, protozoa, parasites, transmissible spongiform encephalopathy agents, and viruses.

**Anthrax:** infectious disease of humans and animals caused by the bacterium *Bacillus anthracis*.

**Antibody:** an immune system protein that specifically recognizes a target site on an antigen. Antibodies are also commonly referred to as immunoglobulins (Ig). There are different classes of antibodies produced by different types of immune system cells, at different stages of the immune response, and that serve different immune system functions in response to different types of antigens.

**Antigen:** a substance that triggers the immune system to produce an antibody against it.

**Bacteria (singular: bacterium):** a large group of single-celled, prokaryote (organisms that lack a cell nucleus or any other membrane-bound organelles) microorganisms. Typically a few micrometers in length, bacteria have a wide range of shapes, ranging from spheres to rods and spirals. Bacteria are ubiquitous in every habitat on Earth, growing in soil, acidic hot springs, radioactive waste, water, and deep in the Earth's crust, as well as in organic matter and the live bodies of plants and animals.

**Biocontainment:** concept, also called laboratory biosafety, pertaining to microbiology laboratories in which the physical containment of highly pathogenic organisms (bacteria) or agents (viruses) is required, usually by isolation in environmentally and biologically secure cabinets or rooms, to prevent accidental infection of workers or release into the surrounding community during scientific research.

**Biological agent:** a microorganism or a component of a microorganism, whether natural or synthesized, including bacteria, viruses, fungi, and microbial toxins.

**Biological Safety or Biosafety:** the application of knowledge, techniques, and equipment to prevent personal, laboratory, and environmental exposure to potentially infectious agents or biohazards. Biosafety defines the containment conditions under which infectious agents can be safely manipulated. The objective of containment is to confine biohazards and to reduce the potential exposure of the laboratory worker, persons outside of the laboratory, and the environment to potentially infectious agents. It can be accomplished through the following means:

Primary Containment: Protection of personnel and the immediate laboratory environment through good microbiological technique (laboratory practice) and the use of appropriate safety equipment.

Secondary Containment: Protection of the environment external to the laboratory from exposure to infectious materials through a combination of facility design and operational practices.

Combinations of laboratory practices, containment equipment, and special laboratory design can be made to achieve different levels of physical containment.

The most important element in maintaining a safe work environment is strict adherence to good microbiological and laboratory practices and techniques. Everybody working with infectious agents or potentially infected materials must be aware of the potential risks. In addition, they must be trained and proficient in the practices and techniques required for handling such material. It is the responsibility of the principal investigator or person in charge of the laboratory to provide or arrange for appropriate training of all personnel.

**Biosafety Level (BSL):** the level of the biocontainment precautions required to isolate dangerous biological agents in an enclosed facility. The levels of containment range from the lowest biosafety level 1 to the highest at level 4. In the United States, the Centers for Disease Control and Prevention (CDC) has specified these levels in the publication *Biosafety in Microbiological and Biomedical Laboratories*, 5th Ed. (December 2009).

**Chimera:** an individual organism whose body contains cell populations from different zygotes or an organism that is developed from portions of different embryos. A chimera virus or chimeric virus is defined by the Center for Veterinary Biologics (part of the U.S. Department of Agriculture's Animal and Plant Health Inspection Service) as a "new hybrid microorganism created by joining nucleic acid fragments from two or more different microorganisms in which each of at least two of the fragments contain essential genes necessary for replication.

**Containment:** the combination of personnel practices, procedures, safety equipment, laboratory design, and engineering features to minimize the exposure of workers to hazards or potentially hazardous agent.

**Disease:** an abnormal condition affecting the body of an organism. It is often construed to be a medical condition associated with specific symptoms and signs. It may be caused by external factors, such as infectious disease, or it may be caused by internal dysfunctions, such as autoimmune diseases. In humans, "disease" is often used more broadly to refer to any condition that causes pain, dysfunction, distress, social problems, and/or death to the person afflicted, or similar problems for those in contact with the person.

**Formalin:** an aqueous solution of formaldehyde that is 37% by weight. Formaldehyde is a colorless, gaseous compound that is the simplest aldehyde, used for manufacturing melamine and phenolic resins, fertilizers, dyes, and embalming fluids and in aqueous solution as a preservative and disinfectant, especially in vaccines.

**Genome:** the entirety of an organism's hereditary information. It is encoded either in DNA or, for many types of virus, in RNA. The genome includes both the genes and the non-coding sequences of the DNA/RNA.

**Immunity:** protection against a disease. There are two types of immunity, passive and active. Immunity is indicated by the presence of antibodies in the blood and can usually be determined with a laboratory test. *Active immunity* is the production of antibodies against a specific disease by the immune system. Active immunity can be acquired in two ways, either by contracting the disease or through vaccination. Active immunity is usually permanent, meaning an individual is protected from the disease for the duration of their lives. *Passive immunity* is protection against disease through antibodies produced by another human being or animal. Passive immunity is effective, but protection is generally limited and diminishes over time (usually a few weeks or months). For example, maternal antibodies are passed to the infant prior to birth. These antibodies temporarily protect the baby for the first 4–6 months of life.

**Immunization:** the process of stimulating the immune system to respond to a biological agent. This can be accomplished by exposing the immune system to antigens from the biological agent, such as by injecting live or dead pathogens, in order to provoke the production of antibodies directed against the biological agent (referred to as generating active immunity). Immunization can also be accomplished by transferring antibodies produced by an already immunized individual to a non-immunized one (passive immunity).

**Inactivated vaccine:** a vaccine in which a virus or bacteria has been rendered inactive through chemical or physical processes so that the microorganism can no longer grow and replicate.

**Intercurrent illness:** a disease that develops during the course of another, unrelated illness.

**Investigational vaccine:** a vaccine that has been approved by the Food and Drug Administration (FDA) for use in clinical trials on humans. However, investigational vaccines are still in the testing and evaluation phase and are not licensed for use in the general public.

**Live, attenuated vaccine:** a vaccine in which a live virus or bacteria is weakened through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease. Live, attenuated vaccines currently licensed in the United States include measles, mumps, rubella, polio, yellow fever, and varicella.

**Microorganism (or microbe):** an organism that is unicellular or lives in a colony of cellular organisms. The study of microorganisms is called microbiology, a subject that began with Anton van Leeuwenhoek's discovery of microorganisms in 1675, using a microscope of his own design. Microorganisms are very diverse; they include bacteria, fungi, archaea, and protists; microscopic plants (green algae); and animals such as plankton and the planarian. Some microbiologists also include viruses, but others consider these as nonliving. Most microorganisms are unicellular (single-celled), but this is not universal, since some multicellular organisms are microscopic, while some unicellular protists and bacteria, like *Thiomargarita namibiensis*, are macroscopic and visible to the naked eye.

**Pathogen:** a microorganism, such as a bacterium, virus, or fungus, that is capable of causing disease or host damage, either through the action of the microorganism or through the host immune response to the microorganism.

**Plasmid:** a DNA molecule that is separate from, and can replicate independently of, the chromosomal DNA. They are double stranded and, in many

cases, circular. Plasmids usually occur naturally in bacteria, but are sometimes found in eukaryotic organisms (e.g., the 2-micrometer ring in *Saccharomyces cerevisiae*). Plasmid size varies from 1 to over 1,000 kilobase pairs (kbp). The number of identical plasmids within a single cell can range anywhere from one to even thousands under some circumstances. Plasmids can be considered to be part of the mobilome (the total of all mobile genetic elements in a genome) since they are often associated with conjugation, a mechanism of horizontal gene transfer. The term plasmid was first introduced by the American molecular biologist Joshua Lederberg in 1952. Plasmids are considered transferable genetic elements, or "replicons," capable of autonomous replication within a suitable host.

**Recombinant:** may refer to a recombinant organism, that is, an organism that contains a different combination of alleles from either of its parents, recombinant DNA, that is, a form of artificial DNA; or a recombinant virus, that is, a virus formed by recombining genetic material.

**Replicon:** a DNA molecule or RNA molecule, or a region of DNA or RNA, that replicates from a single origin of replication. For most prokaryotic chromosomes, the replicon is the entire chromosome. The only exceptions found comes from archaea, where two *Sulfolobus* species have been shown to contain three replicons. Plasmids and bacteriophages are usually replicated as single replicons, but large plasmids in Gram-negative bacteria have been shown to carry several replicons. For eukaryotic chromosomes, there are multiple replicons per chromosome. The definition of replicons is somewhat confused with mitochondria, as they use unidirectional replication with two separate origins.

**Risk:** the potential that a chosen action or activity (including the choice of inaction) will lead to a loss (an undesirable outcome). The notion implies that a choice having an influence on the outcome exists (or existed). Potential losses themselves may also be called "risks." Almost any human endeavor carries some risk, but some are much riskier than others.

**Scarification:** a process of immunization that involves scratching or puncturing the skin surface to break it and introduce the antigenic material.

**Select Agent:** an infectious disease-causing pathogen or toxin that is subject to regulation by the U.S. government according to the *Code of Federal Regulations* (42 CFR Part 73 and 9 CFR Part 121). The lists of biological agents subject to the Select Agent regulations are maintained by the Centers for Disease Control and Prevention and the Animal and Plant Health Inspection Service.

**Seroconversion:** the development of antibodies in response to an immunization, indicated by a change from a negative response on a blood test for these antibodies to a positive test response.

**Titer (antibody):** a measure of the concentration of a particular antibody in a sample. Serial dilutions of the sample are made and the highest dilution factor that still yields a positive reading for the presence of the antibody is the titer.

**Toxin:** A toxin is a poisonous substance produced by living cells or organisms. It was the organic chemist Ludwig Brieger (1849–1919) who first used the term "toxin." Toxins can be small molecules, peptides, or proteins that are capable of causing disease on contact with or absorption by body tissues interacting with biological macromolecules such as enzymes or cellular receptors. Toxins vary greatly in their severity, ranging from usually minor and acute (as in a bee sting) to almost immediately deadly (as in botulinum toxin, the toxin from *Clostridium botulinum*).

**Transduce:** to cause transduction in (a cell). Transduction is the transfer of genetic material from one cell to another by means of a virus.

**Vaccination:** A process that originally referred to a particular type of immunization, namely, the inoculation of antigenic material from the cowpox virus in order to generate immune resistance to the related but more lethal disease of smallpox. In current usage, the term is frequently used synonymously with immunization to indicate stimulation of the immune system by delivery of antigens in order to provoke an antibody response.

**Vaccine:** a product that produces immunity, therefore protecting the body from the disease. Vaccines are administered through needle injections, by mouth, and by aerosol.

**Virus:** a small infectious agent that can replicate only inside the living cells of organisms. Most viruses are too small to be seen directly with a light microscope. Viruses infect all types of organisms, from animals and plants to bacteria and archaea. Virus particles (known as virions) consist of two or three parts: the genetic material made from either DNA or RNA, long molecules that carry genetic information; a protein coat that protects these genes; and in some cases an envelope of lipids that surrounds the protein coat when they are outside a cell. The shapes of viruses range from simple helical and icosahedral forms to more complex structures. The average virus is about one one-hundredth the size of the average bacterium.

**Zoonotic disease:** an infectious disease that can be transmitted (in some instances, by a vector) from nonhuman animals, both wild and domestic, to humans or from humans to nonhuman animals (the latter is sometimes called reverse zoonosis or anthroponosis). Of the 1,415 pathogens known to affect humans, 61% are zoonotic.