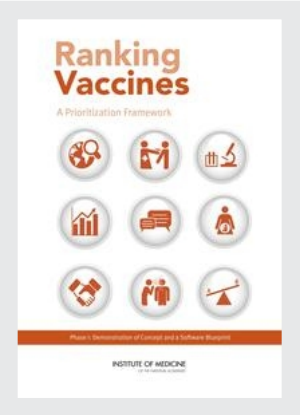

Ranking Vaccines: A Prioritization Framework: Phase I: Demonstration of Concept and a Software Blueprint

DETAILS

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AUTHORS

Guruprasad Madhavan, Kinpritma Sangha, Charles Phelps, Dennis Fryback, Tracy Lieu, Rose Marie Martinez, and Lonnie King, Editors; Committee on Identifying and Prioritizing New Preventive Vaccines for Development; Board on Population Health and Public Health Practice; Board on Global Health; Institute of Medicine

Ranking Vaccines

A Prioritization Framework

Phase I: Demonstration of Concept and a Software Blueprint

Committee on Identifying and Prioritizing
New Preventive Vaccines for Development

Board on Population Health and Public Health Practice
Board on Global Health

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Dennis Fryback, Tracy Lieu, Rose Marie Martinez, and
Lonnie King, *Editors*

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

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VINOD SAHNEY, Senior Fellow, Institute for Health Care Improvement

ROBERT STEINGLASS, Immunization Team Leader, Maternal and Child Health Integrated Program, John Snow, Inc.

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KINPRITMA SANGHA, Research Associate

MALCOLM BILES, Senior Program Assistant

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KATHLEEN STRATTON, Scholar (until September 2011)
AMY PRYZBOCKI, Financial Associate (until December 2011)
SAMANTHA ARNETT, Christine Mirzayan Science and Technology Policy Fellow (Winter 2011)

Consultants, Modeling and Software Development

SCOTT LEVIN, Assistant Professor of Emergency Medicine, Johns Hopkins University
MATTHEW TOERPER, Senior Software Engineer, Johns Hopkins University
PANAYIOTIS KARABETIS, Partner and Lead Information Designer, VIM Interactive
MICHAEL KAPETANOVIC, Partner and Project Manager, Reef Light Interactive

Consultants, Concept Evaluation

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

Yves Bergevin, United Nations Population Fund
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the con-

clusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Stephen Fienberg,** Carnegie Mellon University, and **Alfred Berg,** University of Washington School of Medicine. Appointed by the National Research Council and the Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Foreword

Ranking Vaccines: A Prioritization Framework previews a product that is unique in the annals of the Institute of Medicine: an early-stage decision-support software for prioritizing new vaccines.

Decision makers in the area of vaccine development—including developers, investors, practitioners, and policy makers—are constantly challenged by rapidly changing demographics, epidemiology, economics, technologies, and health systems. Thus, a comprehensive yet adaptable framework is needed to assist decision making. The Strategic Multi-Attribute Ranking Tool for Vaccines, or SMART Vaccines, described in this report, provides one such framework.

SMART Vaccines was conceived with the appreciation that changing circumstances, technological developments, and resource availability influence priorities for new vaccines. This tool should make it possible for decision makers in a variety of circumstances to weigh competing values, test assumptions, and explore alternative scenarios to help guide the priority-setting process. Like all decision tools, SMART Vaccines is an aid for decision making, not a substitute for sound judgment.

Beyond its potential applications in independent and collaborative decision making, SMART Vaccines can facilitate focused and informed discussion among various stakeholders. In this role, it can provide a common platform for diverse constituents to arrive at mutually agreeable priorities and help foster collaborations among them. In addition, SMART Vaccines is being designed so that it can be adapted and configured to help set priorities related to health interventions other than vaccines.

We intend the initial prototype to serve as a springboard to further development. With iterative enhancements, SMART Vaccines should become a dynamic, living guide that can be applied both domestically and internationally and reapplied according to changing health needs, scientific knowledge, and financial constraints.

I congratulate the members and staff of the Committee on Identifying and Prioritizing New Preventive Vaccines for Development for leading this exciting initiative and bringing the project to this promising stage of development.

Harvey V. Fineberg, M.D., Ph.D.
President, Institute of Medicine

Preface

Vaccines have profoundly improved the practice and the quality of public health. New opportunities for developing or improving vaccines are promising, even exciting, in this "decade of vaccines."

However, designing a national and global vaccine development strategy is a Herculean task. Such an effort would involve a concrete, crosscutting understanding of the health, demographic, economic, business, scientific, technological, policy, social, and operational dimensions of vaccines.

The first step toward tackling this complex mission will be to prioritize which vaccines most need to be developed for both domestic and international use. This is a basic task but not an easy one, as the resulting decisions may have significant health, economic, and global consequences. Unfortunately, no universally accepted method or model exists to help guide these important decisions.

To make progress in this area, the Institute of Medicine, at the request of the National Vaccine Program Office of the U.S. Department of Health and Human Services, created a 16-member Committee on Identifying and Prioritizing New Preventive Vaccines for Development. A central commitment of the committee was to ensure that stakeholders were significantly involved in informing the work and the deliberations of the committee.

As part of fulfilling its charge, the committee developed and tested a model designed to assist in the prioritization of new vaccines. The committee also prototyped the beta version of a software named Strategic Multi-Attribute Ranking Tool for Vaccines, or SMART Vaccines. This is a unique product within the National Academies and is expected to be an evolving tool.

In this report we describe the committee's thought process and modeling strategy, and introduce the software blueprint of SMART Vaccines Beta through illustrative screenshots. Since this is a work in progress and subject to additional improvements, we have chosen not to release SMART

Vaccines Beta along with this report. Further work in the next phase of this study is expected to result in SMART Vaccines 1.0, which would be made available for public use.

Through this effort we hope to inspire a community of users who will improve, enhance, and potentially manage the capabilities of this product in an open-source environment and who will generate the required data for operating a multi-stakeholder vaccine prioritization software.

On behalf of the committee, I would like to thank a number of individuals and organizations who gave their time, advice, and expertise to our work.

The committee is indebted to the Institute of Medicine study staff, whose diligence, creativity, and excellent organizational skills were critical to our success. The committee gratefully acknowledges the outstanding work of Guru Madhavan, the study director; the invaluable contributions of Kinpritma Sangha, our research associate; and the able administrative assistance from Malcolm Biles.

We recognize Rose Marie Martinez, director of the Board on Population Health and Public Health Practice; Patrick Kelley, director of the Board on Global Health; and Kathleen Stratton, who skillfully led previous Institute of Medicine studies on vaccines, for their thoughtful insights. We deeply appreciate the wise counsel of Clyde Behney, deputy executive officer of the Institute of Medicine, and Marc Gold, associate general counsel of the National Academy of Sciences, as well as the assistance of other staff members throughout this project.

The committee is very appreciative of our modeling consultants, Scott Levin and Matthew Toerper from the Johns Hopkins University, and our software developers, Pete Karabetis of VIM Interactive and Michael Kapetanovic of Reef Light Interactive. The committee also thanks Robert Pool, Laura DeStefano, and Hannan Braun for their terrific editorial assistance and Samantha Arnett, the National Academies' Christine Mirzayan Science and Technology Policy Fellow, for her research assistance.

Our special thanks go to Jon Andrus, Claire Broome, Joachim Hombach, Philip Hosbach, Robert Lawrence, Adel Mahmoud, Gregory Poland, Jaime Sepulveda, Edward Shortliffe, and Alastair Wood whose thoughtful comments and critical feedback during our concept evaluation sessions have helped us improve SMART Vaccines Beta.

Finally, we would like to thank the National Vaccine Program Office of the Department of Health and Human Services for its sponsorship, support, and encouragement.

Lonnie King, *Chair*
July 2012

Contents

Disclaimer

This report presents SMART Vaccines, a prioritization model and blueprint of associated software in development. This work is being developed by the Institute of Medicine Committee on Identifying and Prioritizing New Preventive Vaccines for Development with the assistance of consultants from Johns Hopkins University and VIM Interactive. This report does not intend to actually provide a ranking of vaccine priorities. It describes the committee's modeling strategy and assumptions in order to demonstrate a proof of concept.

This consensus study is being conducted in two phases. The Phase I statement of task asked for a model to be developed that prioritizes the development of new preventive vaccines, tested with two or three vaccine candidates. In Phase II the committee will obtain feedback from the stakeholders on the Phase I model and use it to enhance SMART Vaccines in addition to adding three test vaccine candidates. Thus this report describes a product that is purposefully midstream in development.

The committee has chosen to employ a modeling approach based on multi-attribute utility theory, supported by a computational engine and a user-friendly interface. SMART Vaccines Beta processes available or expert-informed data for three conditions (influenza, tuberculosis, and group B streptococcus) in two nations (the United States and South Africa). Thus the examples that appear in this report are limited to comparing *hypothetical* vaccines only.

SMART Vaccines is intended to serve only as a decision-support tool for vaccine prioritization and *not* to be used as a decision maker. Final decisions should not be made based on the scores provided by SMART Vaccines. The Institute of Medicine does not warrant the completeness of the model, the accuracy of the software in development, or the reliability of any data presented in this report.

July 2012

Summary

Over the centuries, from Edward Jenner to Bill Gates, as our scientific understanding of diseases has increased, so has the focus on prioritizing new vaccines to help achieve better health. Despite the expanding interest in and support toward improving global health, constraints inherent to vaccine development and delivery present decision makers with difficult choices. Given the lack of effective tools and models to assist the decision-making process, renewed attention is needed to improve the approaches available for priority setting and for guiding investment decisions.

Prioritizing vaccines—"arranging in the order of relative importance"—is a time- and resource-intensive process requiring diverse considerations. Examples of such considerations include the emergence and reemergence of disease threats, limits in the progress of research related to the disease in question, technological feasibility, economic and other resource constraints, possibilities for enhancing vaccine administration methods, and other broader objectives. Decision makers involved in setting priorities come from different constituencies with different perspectives. Therefore, it becomes vitally important to develop not only a practical approach that provides a common language to assist decision making but also a flexible tool that embraces a wide spectrum of inputs and perspectives in efforts to advance vaccine development.

This report, *Ranking Vaccines: A Prioritization Framework*, describes a decision-support model and the blueprint of accompanying software being developed to help prioritize vaccines. The consensus study that produced this report is being carried out in two phases. Phase I work, described in this report, provides the conceptual underpinning of Strategic Multi-Attribute Ranking Tool for Vaccines, or SMART Vaccines. SMART Vaccines Beta, developed by the committee in Phase I, is not available for public use. SMART Vaccines 1.0 is expected to be released at the end of Phase II, when it will be fully operational and capable of guiding discus-

sions about prioritizing the development and introduction of potential new vaccines. In the committee's view, a "new vaccine" (or "vaccine candidate") can refer not only to a completely novel vaccine but also to an existing vaccine given improvements to some of its features, including innovations in its production or delivery methods.

The audience and potential users of SMART Vaccines include those institutions funding and carrying out basic biomedical research, private firms involved in vaccine production, philanthropic foundations with a strong interest in vaccination and global health programs, international health organizations, and high-level decision makers, such as ministers for health, commerce, and finance or senior administrators.

The committee's charge

Phase I of the study was supported by the National Vaccine Program Office of the U.S. Department of Health and Human Services. The Phase I statement of task is presented in Box S-1. Phase II of the study is oriented toward expanding and enhancing the capabilities of the model and transforming SMART Vaccines Beta to SMART Vaccines 1.0.

This report describes the committee's approach toward demonstrating a proof of concept using three *hypothetical* vaccine candidates that have not yet been developed. The committee included a broad range of attributes that represent the various perspectives relating to vaccine development and impact. Some of the data for these attributes are readily available (such as population characteristics), while other data are estimated by the user (e.g., qualitative attributes of the vaccines) or through expert opinion (e.g., disease burden or cold-chain requirements).

Because the data inputs in this report were not intended to be precise, readers should not take any output of SMART Vaccines Beta as the "exact" or "recommended" priority value relating to any particular vaccine; instead the outputs should be seen only as illustrative examples of how the model and beta software currently operate.

Previous Institute of Medicine reports

Previous Institute of Medicine (IOM) studies from 1985–1986 and 2000 that focused on vaccine prioritization provided specific lists of vaccine ranks. The two-volume IOM study *New Vaccine Development*, released in 1985–1986, prioritized vaccines both for the United States and from an

BOX S–1
Committee on Identifying and Prioritizing New Preventive Vaccines for Development

Institute of Medicine
Phase I
Statement of Task

Task 1: Review domestic and global research and development prioritization activities relevant to identifying new preventive vaccine targets.

Task 2: Develop an analytical framework and model for prioritizing vaccines of domestic and global importance. Engage stakeholders to inform the process of the model development and implementation.

Task 3: Test and validate the model using two to three predetermined vaccines, including at least one vaccine candidate of domestic importance and one of global importance.

Task 4: Prepare a report containing the analytical framework and model for evaluating and prioritizing vaccine targets along with recommendations as to how to use the model for reviewing the catalog of preventive vaccines every 2 to 3 years.

international perspective, based on infant mortality equivalents—a proxy measure of health burden.

The 2000 report *Vaccines for the 21st Century* focused entirely on the U.S. population and, unlike the 1985–1986 report, used an efficiency measure for ranking vaccines: incremental cost per incremental quality-adjusted life years saved ($/QALY), a measure derived from a classic welfare economics model. The cost-effectiveness model of the 2000 report represented important progress toward vaccine prioritization, but it did not provide guidance for answering some challenging questions often encountered in decision making. For instance, the model provided no guidance on how to choose between two diseases with equal QALYs when one was a low-impact disease affecting the majority of the population and the other a disease with few cases but with very high mortality and potential large-scale social disruption.

While both of the earlier reports noted that vaccine prioritization can include aspects of social value beyond net costs (or savings) and health burden reduction, these variables were considered to be beyond the scope of the cost-effectiveness or infant-death-equivalents-prevented framework. SMART Vaccines significantly expands the single criterion framework of the earlier prioritization efforts to include a number of additional criteria that influence decision making in vaccine development.

An overview of SMART Vaccines

The committee's principal contributions have been broadening the set of criteria for valuing preventive vaccines and demonstrating how the selection of criteria and data can influence the prioritization process. Users are offered a choice of up to 29 attributes drawn from broad categories which include health burden considerations, economic considerations, demographic considerations, public concerns, scientific and business considerations, programmatic considerations, and policy considerations. Table S-1 presents the general list of attributes influencing the rank of vaccine candidates in SMART Vaccines.

Because decision makers may represent different constituencies, their criteria for prioritizing various vaccine candidates are likely to differ as well. Further, each of these selected criteria can be valued and weighed differently in the prioritization process. Thus, not only does SMART Vaccines broaden the scope of the valuation criteria, but it also allows users to select and weigh criteria according to their values or those of the communities they represent.

From the technical standpoint, SMART Vaccines Beta expands the utility function for evaluating vaccines compared to the models published in the earlier reports. But the fact that different users may make different choices when using SMART Vaccines adds further value: It provides a framework to compare, discuss, and perhaps reconcile differing priorities. Thus, rather than pre-specifying which criteria are used and how they should be weighed, the committee has opted to allow the users to select their own.

Model and software development

The modeling strategy of the committee was based on multi-attribute utility theory. The multi-attribute utility approach has a well-grounded theoretical basis, but employing the theory for SMART Vaccines presented various challenges. The report discusses how the committee sought to tackle

TABLE S-1

Choices of Attributes in SMART Vaccines Beta

Health Considerations	• Premature Deaths Averted per Year • Incident Cases Prevented per Year • QALYs Gained or DALYs Averted
Economic Considerations	• One-Time Costs • Annual Net Direct Costs (Savings) of Vaccine Use • Annual Net Workforce Productivity Gained • Cost-Effectiveness
Demographic Considerations	• Benefits Infants and Children • Benefits Women • Benefits Socioeconomically Disadvantaged • Benefits Military Personnel • Benefits Other Priority Population
Public Concerns	• Availability of Alternative Public Health Measures • Potential Complications Due to Vaccines • Disease Raises Fear and Stigma in the Public • Serious Pandemic Potential
Scientific and Business Considerations	• Likelihood of Financial Profitability for the Manufacturer • Likelihood of Successful Licensure in 10 Years • Demonstrates New Production Platforms • Existing or Adaptable Manufacturing Techniques • Potential Litigation Barriers Beyond Usual • Interests from NGOs and Philanthropic Organizations
Programmatic Considerations	• Potential to Improve Delivery Methods • Fits into Existing Immunization Schedules • Reduces Challenges Relating to Cold-Chain Requirements
Intangible Values	• Eradication or Elimination of the Disease • Vaccine Raises Public Health Awareness
Policy Considerations	• Special Interest for National Security, Preparedness, and Response • Advances Nation's Foreign Policy Goals

these challenges throughout the model and software development and evaluation process.

Early prototypes were modeled after the one presented in the 2000 report. The committee then began the development of a user-friendly software interface to enable data input with the aim of incorporating sensitivity testing, advanced dynamic modeling, and improved visualization of results in the future. As mentioned earlier, this software will be available for public use at the end of Phase II. This report provides illustrative

screenshots of SMART Vaccines Beta, which is currently under development. The committee also engaged consultants to serve as concept evaluators to help improve the design and features of SMART Vaccines from the perspective of potential users.

SMART Vaccines uses two submodels—a computational submodel and a value submodel—to combine the levels of various attributes into a single measure of priority "score" for each vaccine under consideration. The weights used for criteria in the model must satisfy a number of conditions in order for the model to work properly. Normally, satisfying these conditions would require users to make many explicit quantitative value comparisons. To minimize these demands on the user in the current version of the model, the committee adopted the rank order centroid method to approximate additive multi-attribute utility weights. The only requirement that this method places on users is that they rank order the importance of attributes selected for their prioritization model. The rank order information is used to derive numerical weights which are then used in a scoring function. This approach is known to produce weights that are robust and predictive of the users' eventual decisions. SMART Vaccines Beta permits only an ordinal ranking of the vaccine attributes with no tie scores.

The committee selected three diseases for evaluation: influenza, tuberculosis, and group B streptococcus. These diseases were compared between two countries, the United States and South Africa. Representative test results are discussed in this report with the acknowledgement that sensitivity testing and further validation will be required in Phase II of this study.

To demonstrate the extent to which the selection and ranking of attributes affects the priority scores among vaccines generated by the model, the committee conducted a "value experiment" in which committee members and staff selected attributes and provided ranking scores for six hypothetical vaccines: an influenza vaccine with a 1-year immunity; an influenza vaccine with a 5-year immunity; a tuberculosis vaccine with a 3-year immunity; a tuberculosis vaccine with lifetime immunity; an influenza vaccine with a 1-year immunity but with 50 percent increased coverage; and a tuberculosis vaccine with a 3-year immunity but in a setting with a 100-fold increase in disease prevalence. The results of this experiment, as described in this report, show how each user's selection and weighting of attributes shifted the final rankings among these six hypothetical vaccines. The purpose of this experiment was to emphasize both the importance of the attribute-weighting process in the final rankings and the sensitivity of the ranks to preferences inherent in the decision-making process.

Data requirements

SMART Vaccines Beta requires substantial data inputs from users. In some cases, depending on the country for which the model is employed, the data required to drive the model may be sparse or unavailable. The usefulness of SMART Vaccines will rely upon concerted data collection and future software enhancements.

The model requires refined age- and sex-specific population data; these can generally be imported from the World Health Organization and other existing data sources. SMART Vaccines Beta also requires quantitative inputs concerning age- and sex-specific disease burdens to the population of interest, typical patterns of vaccination and health care use (and their costs) for relevant illnesses with and without the availability of a preventive vaccine, and health complications that might arise from the use of a new vaccine. These data are not widely available at this time and will likely have to be provided at least in part by processes led or guided by expert opinion. "Expert opinion" in this context refers to input from someone who is able to provide knowledgeable, informed estimates about the data needed within the country or region of interest. Economic data are also needed on typical wage rates for workers in each age group in order to compute worker productivity gains achieved by reducing or eliminating disease burden—both in workers directly and, indirectly, in children they may care for—through vaccination.

The model's computational engine uses all data and other user-supplied entries to calculate a series of attributes, including cost-effectiveness, premature deaths averted, incident cases prevented, annual health care costs saved, and net annual gains in worker productivity. These quantities are computed through detailed modeling of the disease and its prevention through vaccination in the population over time.

SMART Vaccines Beta also allows users to specify qualitative attributes for each potential new vaccine, features that are not captured within the computed attributes, and add additional new attributes per their choice. These include, by general category, attributes focusing on the ability of existing health infrastructures to deliver the new vaccine; whether the vaccine has the capability of disease eradication; whether the vaccine targets major population health risks (such as pandemic diseases or bioterrorism attacks); and the likelihood of successful development, which in turn hinges on the likelihood of scientific progress and regulatory approval. Potential users of SMART Vaccines will have the option to include or not include any of these attributes in generating their final priority ranking; obviously, if an attribute is not used in generating the priority ranking, that obviates the need to provide related data for the candidate vaccines.

Ways to use (and not to use) SMART Vaccines

By design, SMART Vaccines offers users considerable flexibility in specifying attributes and their rank order to determine the final prioritization score. Among other things, this means that SMART Vaccines does *not* produce one unique list of priorities among vaccine candidates, unlike the techniques in the predecessor IOM reports in 1985–1986 and 2000. The rankings are sensitive to the choice and the order of attributes and to the trade-offs the user is willing to accept in determining priorities.

SMART Vaccines does not "make decisions." *It is intended to be used exclusively as a decision-support tool and only that*. The committee expects that a major use of SMART Vaccines will be to facilitate discussions about attributes and values among diverse users, helping them to converge upon mutually beneficial priorities and collaborations.

The committee envisions that various organizations could use SMART Vaccines independently to guide their efforts in vaccine development and implementation. This might begin at the basic science level in organizations conducting and funding research to break through bottlenecks in vaccine development. Other potential users, such as manufacturers, might be involved directly in the development and eventual production of vaccines and thus may wish to emphasize an entirely different set of vaccine attributes (e.g., profitability, development and regulatory risks) compared to a basic research organization. Still some users (or user consortia) might use SMART Vaccines to enhance market stability (say, through pre-purchase agreements) and hence the likelihood of successful vaccine development.

SMART Vaccines can help diverse users understand *how* and *why* their rankings differ. Variations in rankings due to differing data inputs can be discussed among users to discover common data sources. When the model produces different results as a consequence of differing values, it can motivate discussions relating to individual or inter-institutional priorities among users. SMART Vaccines may also help inform users of the value of strengthening vaccine delivery methods (e.g., by augmenting the cold-chain capacity) and alternative methods of disease control (e.g., clean water supply, mosquito netting, food safety measures, or health-related education). A further expected benefit of using SMART Vaccines is that it will enable users to identify data needs to ultimately improve their vaccine prioritization process. Future data collection activities, surveillance activities, and resource allocation may be informed and planned by use of SMART Vaccines.

Observations and next steps

This report is intended to introduce potential users to the concept of SMART Vaccines and to encourage stakeholders to inform the development of SMART Vaccines 1.0 in Phase II of this study. The committee will next enhance SMART Vaccines Beta, test its use with three additional vaccine candidates of domestic and global importance, and further improve the user interface as part of the development of SMART Vaccines 1.0.

The value of SMART Vaccines will depend, in part, on data that need to be generated as vaccine candidates evolve and as disease epidemiology becomes better characterized in different parts of the world. In the future—beyond Phase II—an active community of users and an open-source environment would likely lead to future enhancement of the SMART Vaccines' capabilities. Potential enhancements could include creation and sharing of databases for populations from different countries, the enhancement of validation tools and user interface, and the development of ways to address the risk and uncertainty surrounding the characterization of vaccines that have not yet been developed. This study is the first step in moving toward these goals.

1

Introduction: From Smallpox to SMART Vaccines

Edward Jenner was an impatient man. He firmly grasped the importance of vaccination. In a pamphlet, *On the Origin of the Vaccine Inoculation*, published in 1801, Jenner famously articulated the vision of immunizing people against smallpox:

> An hundred thousand persons, upon the smallest computation, have been inoculated in these realms. The numbers who have partaken of its benefits throughout Europe and other parts of the Globe are incalculable: and it now becomes too manifest to admit of controversy, that the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice. (Jenner, 1801)

An 1806 letter to Jenner from fellow experimentalist Thomas Jefferson—then the president of the United States—illustrates the reach and impact of Jenner's efforts:

> I have received a copy of the evidence at large respecting the discovery of the vaccine inoculation which you have been pleased to send me, and for which I return you my thanks. Having been among the early converts, in this part of the globe, to its efficiency, I took an early part in recommending it to my countrymen. I avail myself of this occasion of rendering you a portion of the tribute of gratitude due to you from the whole human family. . . . You have erased from the calendar of human afflictions one of its greatest. Yours is the comfortable reflection that mankind can never forget that you have lived. Future nations will know by history only that the loathsome small-pox has existed and by you has been extirpated. (Jefferson, 1806)

We now know far more about how human immune systems work and about ways to create immunity against diseases than Jenner did. And

as science and technology continue to grow in knowledge and capabilities, a major challenge now is to select from among many options the most important disease targets and to develop new or improved vaccines against them—that is, to *prioritize*, a task that Jenner did not face since he had the means to conquer only one disease, smallpox.

In the last two centuries, vaccines—in conjunction with antibiotics, clean water, and good hygiene—have served to eliminate or significantly mitigate many infectious diseases that used to kill hundreds of millions of people. Even though the vaccine enterprise has seen great strides since the 1800s, the basic research and development challenges in vaccinology have remained essentially the same (Stern and Markel, 2005). Additionally, the sluggish and fragile nature of the global economy is stressing the need for prioritized investments across the board, and especially in the realm of health care.

Private industrial and philanthropic forces have begun to play a far more prominent role in the push for new and improved preventive vaccines for diseases. Consider, for example, the $10 billion investment from Bill Gates announced at the 2010 meeting of the World Economic Forum to help fund the research, development, and delivery of vaccines for the world's poorest countries. Gates said then, "I see the next 10 years as the Decade of Vaccines—a time when we will make more progress than ever on immunizations that save lives in the developing world. . . . This work will make it possible to save more than 8 million lives by 2020" (Gates, 2010).

More recently, Gates' additional $750 million donation toward funding the Global Fund to Fight AIDS, Tuberculosis, and Malaria, in association with other philanthropic and operational partners, has highlighted the serious commitment of multinational alliances in tackling vaccine-preventable diseases of domestic and global importance (McNeil, 2012).

The U.S. government launched the 2010 National Vaccine Plan to enhance efforts in the development and delivery of vaccines (HHS, 2011). This plan, released as a living document by the Department of Health and Human Services, lists goals and priorities primarily directed toward developing new and improved vaccines and the related safety, communication, and surveillance systems (see Box 1-1).

Similarly, other countries are designing their own national vaccine plans. For example, in 2011 the Indian government released its national vaccine policy aimed at strengthening the country's framework, infrastructure, and decision-making practices for immunization policies and programs (Government of India, 2011).

Large-scale efforts that began in the early 1970s resulted in the World Health Organization's Expanded Program on Immunization (EPI), created

BOX 1-1
The 2010 National Vaccine Plan
U.S. Department of Health and Human Services

Goals

1. Develop new and improved vaccines.
2. Enhance the vaccine safety system.
3. Support communications to enhance informed vaccine decision making.
4. Ensure a stable supply of, access to, and better use of recommended vaccines in the United States.

Priorities

A. Develop a catalogue of priority vaccine targets of domestic and global health importance.

B. Strengthen the science base for the development and licensure of new vaccines.

C. Enhance timely detection and verification of vaccine safety signals and develop a vaccine safety scientific agenda.

D. Increase awareness of vaccines, vaccine-preventable diseases, and the benefits/risks of immunization among the public, providers, and other stakeholders.

E. Use evidence-based science to enhance vaccine-preventable disease surveillance, measurement of vaccine coverage, and measurement of vaccine effectiveness.

F. Eliminate financial barriers for providers and consumers to facilitate access to routinely recommended vaccines.

G. Create an adequate and stable supply of routinely recommended vaccines and vaccines for public health preparedness.

H. Increase and improve the use of interoperable health information technology and electronic health records.

I. Improve global surveillance for vaccine-preventable diseases and strengthen global health information systems to monitor vaccine coverage, effectiveness, and safety.

J. Support global introduction and availability of new and underutilized vaccines to prevent diseases of public health importance.

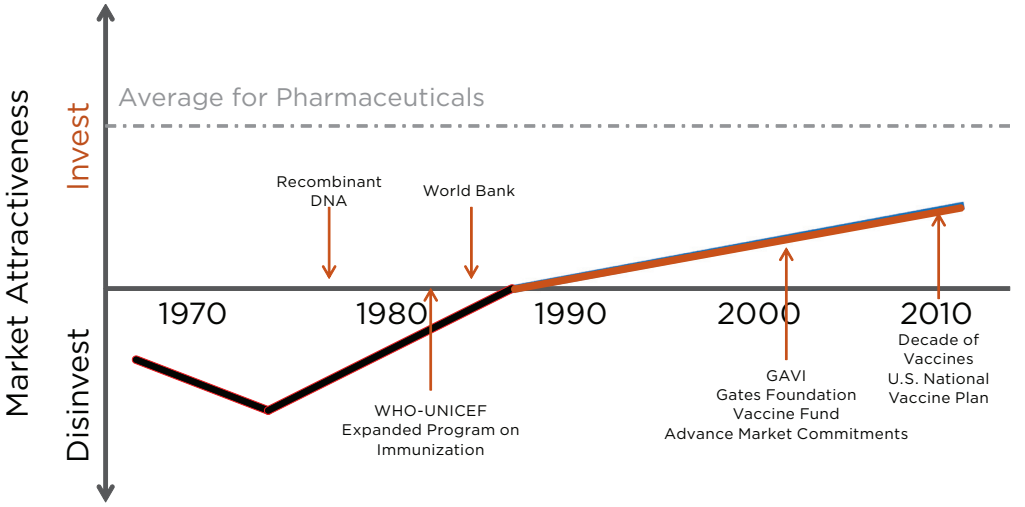


FIGURE 1-1
Historical attractiveness of investments in vaccines. Since the late 1980s significant increases in the efforts and funding relating to vaccine-preventable diseases have made the enterprise attractive for more investments.

SOURCE: Adapted from Rappuoli et al., 2002.

to reduce mortality caused by vaccine-preventable diseases. By partnering with the United Nations Children's Fund (UNICEF) and other organizations, EPI has played a central role in making vaccines available and increasing coverage for children around the world (Keja et al., 1988).

Jenner and his colleagues mostly self-financed their vaccination regimens, as the concept of multinational partnerships was virtually absent during their time. Today, however, there are scores of collaborative ventures that are helping to drive the vaccine enterprise in many countries. The GAVI Alliance, for example, has had multinational support in its efforts to increase access to vaccines in developing countries (GAVI Alliance, 2010).

The explosion of interest, efforts, and new collaborations relating to vaccine-preventable diseases is reflected in the growing attractiveness of investments in vaccines (see Figure 1-1). Coupled with the momentum of the "decade of vaccines," a renewed focus on developing new priority-setting strategies for new vaccine development is timely and critical.

Study scope and process

The first goal of the 2010 National Vaccine Plan is to "develop new and improved vaccines," and the first implementation priority is "to develop a catalogue of priority vaccine targets of domestic and global health importance." To accomplish this task the National Vaccine Program Office (NVPO)

of the Department of Health and Human Services envisions a three-step strategy: The first step is devoted to creating and validating a prioritization model; the second step is focused on populating the model with data; and the third step is to evaluate the model and prioritize vaccines against a catalog of attributes (see Figure 1-2). The current study pertains to Phase I of the first step within NVPO's strategy to help create a model. (The committee's task is presented in Box S-1.) Immediately following its completion of Phase I, the committee is expected to carry out the Phase II work. which will be focused on enhancing and refining the model and adding to its utility and effectiveness.

In early 2011 a 16-member committee was appointed by the Institute of Medicine to conduct this study. (Appendix D contains the biographical information of the committee members.) The committee met five times in 2011 and organized an international stakeholder session as well as a public workshop during its first two meetings. (See Appendix C for a list of speakers.)

In addition to the five committee meetings, four modeling subgroup meetings were also held. The committee engaged several consultants to assist in achieving its goal: two consultants to help with modeling, two for software development, and eleven experts for evaluating the concept of SMART Vaccines Beta.

SMART Vaccines Beta is a result of a modeling effort intended ultimately to help users in making decisions relating to setting vaccine priorities. Potential users of and audiences for this model include decision makers from the institutions funding and pursuing basic research, vaccine manufacturers, and philanthropic organizations with interests in improv-

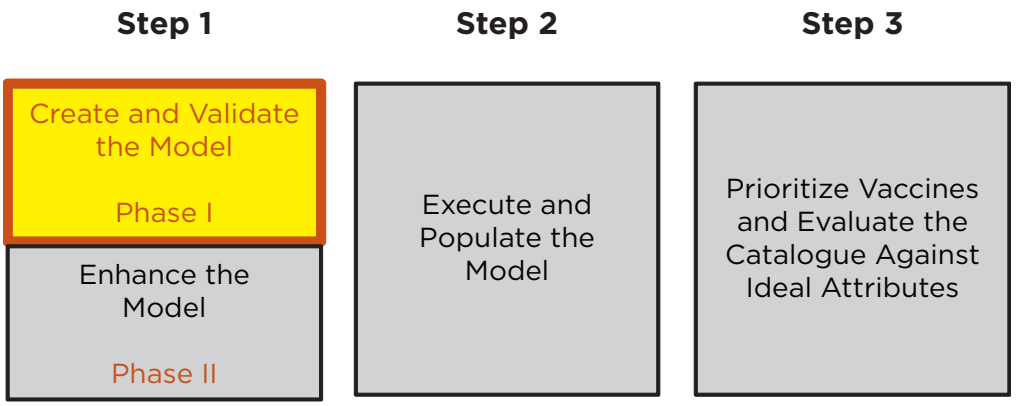


FIGURE 1-2
A three-step vaccine prioritization strategy envisioned by the National Vaccine Program Office. The study described in the current report pertains to Phase I in Step 1.

ing global health; ministers of health, commerce, and finance and other high-level government officials at the country, state, and regional levels; international health agencies; and nongovernmental alliances of interested parties.

Vaccine market dynamics

Until the 1990s vaccines were not considered to be commercially attractive investments, as highlighted in Figure 1-1. Pharmaceutical companies typically considered vaccines as a commodity with high liability risks (or with potentially high costs of litigation), and their business strategy was to exit or to stay away from vaccine development.

A 2008 estimate suggested that the vaccine market had grown 20-fold in the previous two decades and had come to exceed $14 billion, with its sales accounting for between 2 and 3 percent of the global pharmaceutical market, for 40 percent of the market existing in North America, and for 30 percent of the markets in Europe and the rest of the world (Greco and Hessel, 2008). Industrial sources have recently suggested that in 2011 the worldwide vaccine market was around $23 billion, with continued sale growth expected between 5 and 15 percent annually, with the total market possibly reaching $32 billion by 2017.

As the vaccine companies in industrialized countries were consolidating into large pharmaceutical firms, a similar evolution was taking place among the manufacturers in low- and middle-income countries that have begun to obtain World Health Organization (WHO) prequalification and to supply vaccines to UNICEF and GAVI.

Despite the robust growth trends in the vaccine market mentioned above, the fundamental challenges in vaccinology have largely remained unchanged. On the other hand, disease profiles have begun to change, mainly because of major demographic shifts in society. For example, the people for whom vaccines were developed between 1750 and 1850 had an average life expectancy of 35 to 45 years; by contrast, the people for whom most of the current vaccines were developed had a life expectancy of 60 to 65 years, and by 2050 vaccines may need to be developed for people with a life expectancy of as much as 90 to 95 years (see Figure 1-3). Representative vaccines for the 21st century demographics, segmented by age and target population, are shown in Figures 1-4 and 1-5, respectively.

Almost all currently used vaccines were developed in the latter half of the 20th century, with the exception of a few older vaccines such as those developed for such conditions as smallpox, rabies, and typhoid. Figure 1-6, which provides a timeline of vaccine development, shows that

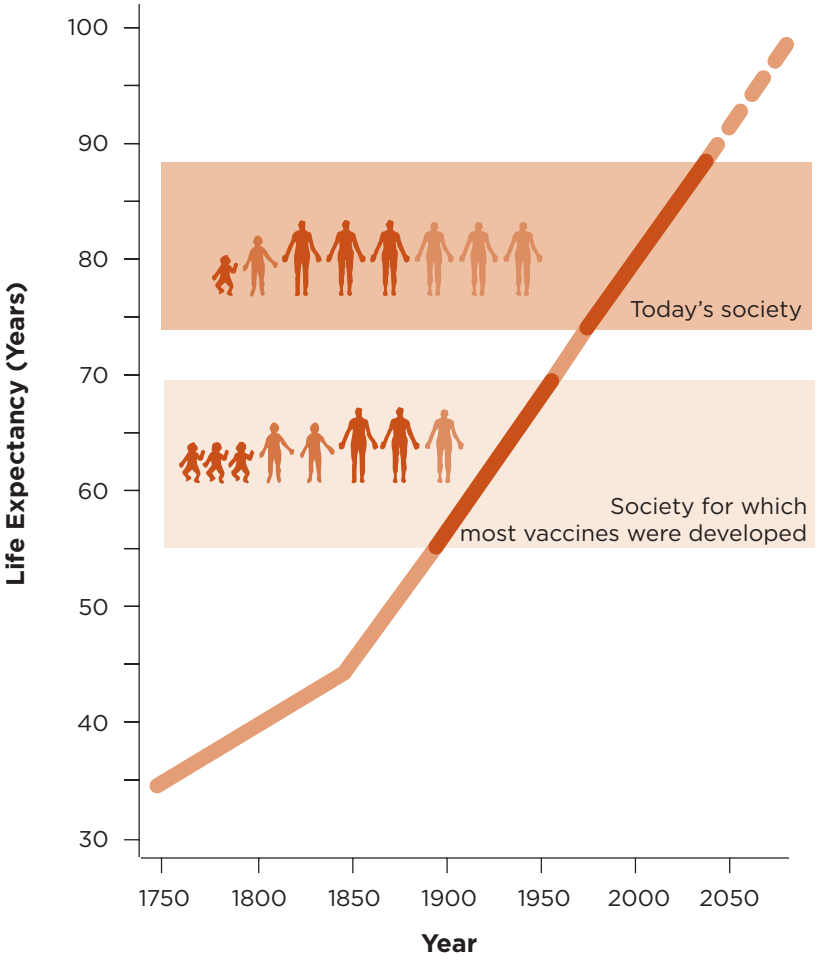


FIGURE 1-3
Increases in life expectancy and longevity since 1750, with projections for the rest of the 21st century. The steady increase clearly shows that the demographic nature of society has changed significantly. The society for which most currently available vaccines were developed had an average life expectancy of 60 to 65 years and was characterized by large numbers of children and young people, which is notably different from today's society, which is characterized by a high proportion of senior citizens and a life expectancy at birth that is more than 80 years in many countries.

SOURCE: Rappuoli et al., 2011.

development activity increased steadily between 1950 and 2010 and that it has now reached a level higher than at any time in history.

Prioritization efforts in the vaccine enterprise

Investment in vaccination as well as in the associated research and production aspects has grown rapidly. The investments are expected to increase

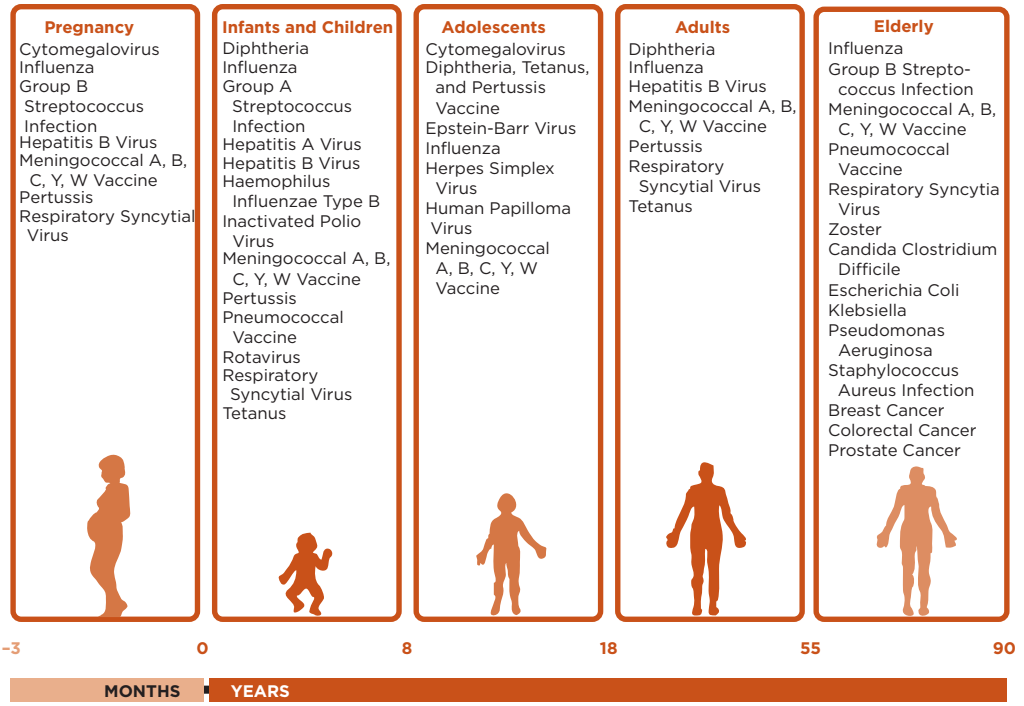


FIGURE 1-4
Target population for vaccines in the 21st century with a listing of representative vaccines for each population segment.

SOURCE: Rappuoli et al., 2011.

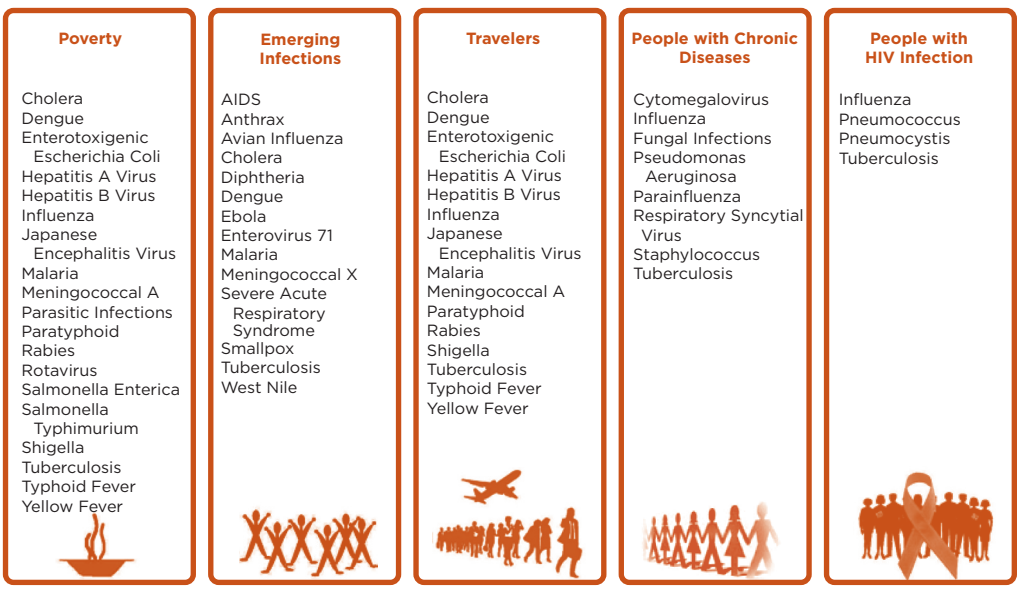


FIGURE 1-5
Special target groups for vaccination in the 21st century with a listing of important representative vaccines for each group.

SOURCE: Rappuoli et al., 2011.

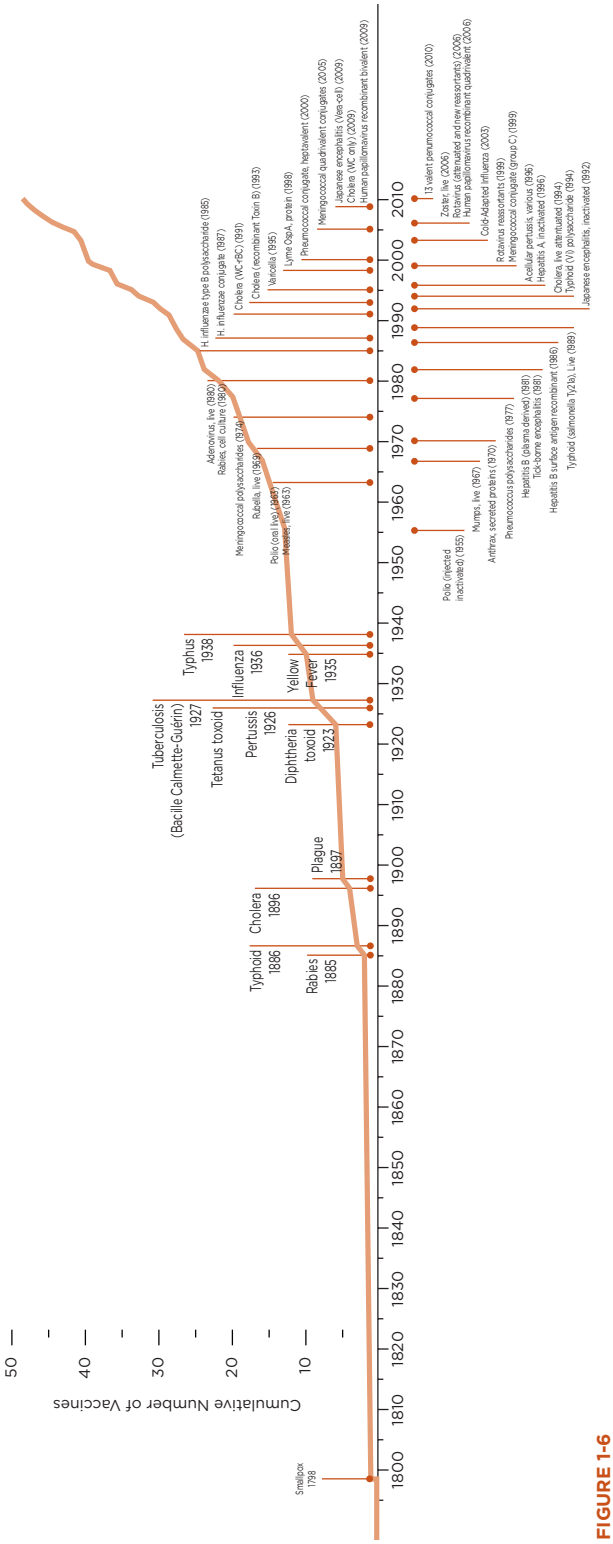


FIGURE 1-6
A timeline of vaccine development illustrating the growing cumulative number of vaccines produced in the 20th and 21st centuries.

SOURCE: Stanley Plotkin, Courtesy of the GAVI Alliance.

even further in response to the economic growth of transitional and developing countries. However, prioritization exercises have not kept up with the pace of spending. Very few published prioritization efforts exist, and organizations' internal mechanisms to set priorities are not well known or publicized. Yet, given the vibrancy of the vaccine enterprise, the need for prioritization plans is tremendous.

The cost of making the best decision on developing a new vaccine may be only a small part of the total health expenditure associated with that vaccine, but significantly large health and economic benefits can be derived. In addition to these health and economic benefits, vaccines also generate broad intangible social benefits that are often underappreciated. All too often health financing and policy decisions are guided mainly by narrowly construed "cost–benefit"[1] analyses which are extended to assessing the introduction and use of vaccines.

In theory, cost–benefit analysis can accommodate a full spectrum of benefits, both monetary and subjective, but the complexities of incorporating non-monetized values often overwhelm the efforts. Since cost–benefit analysis values every benefit in dollars, methods must be devised to estimate these values in situations where no market prices exist. Common approaches to this seek ways to elicit willingness-to-pay measures from appropriate populations and then use these willingness-to-pay estimates to complete the cost–benefit calculations. Thus, for example, willingness-to-pay measures have been used in environmental studies to estimate the value of things such as pollution reduction, reduced traffic congestion, preservation of endangered species, agricultural land, and unique geologic settings. Because these willingness-to-pay approaches are expensive and complicated, many cost–benefit analyses omit such considerations and center more on measurable benefits, such as the value of enhanced water

[1]"Cost–benefit" and "cost-effectiveness are many times used synonymously, but there is a technical difference between these terms. Cost–benefit analysis—derived from economic models to maximize social welfare—is used to compute the net dollar amount represented by the difference in dollar costs and dollar-valued benefits of an investment. The focus is on whether this difference is positive or negative. In contrast, cost-effectiveness refers to an analysis in which net dollar costs of a health care investment are used in the numerator and benefits are measured in the denominator using natural units of health and health benefit, yielding a price per unit of benefit as output. This can be derived from basic principles of maximizing individual utility, subject to a budget constraint (Garber and Phelps, 1997). The price per unit is a measure of how efficient an investment in health care is. The two approaches converge once a decision maker has chosen a critical cutoff value for the cost-effectiveness analysis (Phelps and Mushlin, 1988), although some users object to specifying an exact cutoff and hence report cost-effectiveness ratios without making specific judgments about a specific cutoff.

supply in agriculture, leaving out those facets of a decision that are more difficult to measure, such as the effect on spawning salmon.

Because of the inherent complexity of such analyses, cost–benefit analysis too often becomes reductionist in its approach, resulting in an underestimation of the complex factors involved in vaccines. Whereas economic and health benefits can be captured in a cost–benefit analysis, intangible values are often omitted. Therefore, most economically-focused models (which, so far, are most of those that are available) fail to capture the full return of investment in vaccination. The main reason for this is that it is fairly straightforward to identify and calculate costs of vaccination (e.g., vaccine cost, administration cost, and other costs), but determining all the *benefits* is considerably more difficult.

Capturing the value of vaccination

The overall value of vaccination has not been captured in previous prioritization models for two main reasons. First, the models have looked only at short-term benefits. Second, they do not consider many of the intangible effects related to the long-term benefits of vaccination, including the economic benefits to a country of having a healthier population, the educational benefits due to reduced school absenteeism, the avoidance of potential social disruption caused by a disease with high emotional and political impact (e.g., poliomyelitis or Ebola), and the possibility of preventing or controlling pandemic infections, such as influenza or severe acute respiratory syndrome (SARS). More recent accounts have also called for prioritizing vaccines and other medical interventions according to ethical values and morally just policies (Daniels, 2007; Field and Caplan, 2012; Poland and Marcuse, 2011).

Previous prioritization models have not included the value of vaccination for future generations—that is, getting into the question of "who pays" versus "who benefits." For instance, the costs and benefits of a vaccine developed today are typically calculated for the next year or two, when the cost of the new vaccine will be at its highest. But the price of the vaccine will typically decrease over the next decade, and future generations will inevitably benefit from the reduction of disease by having lower health costs, better quality of life, and longer life expectancy. One way to think about this scenario is as follows: If a prioritization model had computed the cost–benefit of the smallpox vaccine before the eradication of the disease, it would have included costs saved only during the first few years following the vaccination, whereas the value for future generations of a world without smallpox would not be included. Perhaps the value of a smallpox-free

world is so large that it is difficult to capture it numerically. Nonetheless that value should not be ignored.

When performing cost–benefit analyses, different stakeholders may use different assumptions regarding the costs of vaccine development and introduction. Expert estimates and published literature suggest that manufacturers in the high-income countries typically invest between $500 million and $900 million over a period of 10 to 15 years to develop a new vaccine (Greco and Hessel, 2008). The primary criteria for the manufacturers are commonly medical need, the potential market size, and the probability of technical and commercial success.

Individual countries also use cost–benefit analysis when making decisions about vaccine introduction, comparing the benefits of vaccines with the benefits of other interventions. The World Health Organization usually makes high-level recommendations to assist low- and middle-income countries. Other funding organizations, such as the United Nations, the GAVI Alliance, and philanthropic groups, assign their own priorities using criteria such as cost, medical need, and impact on mortality and morbidity.

Previous IOM efforts in vaccine prioritization

The Institute of Medicine (IOM) has previously undertaken two vaccine prioritization exercises. A study in 1985–1986 resulted in the release of *New Vaccine Development: Establishing Priorities*, a report containing two individual volumes, *Diseases of Importance in the United States* (IOM, 1985) and *Diseases of Importance in Developing Countries* (IOM, 1986). This work helped capture both the domestic and the global perspective on vaccine prioritization, using a decision framework based on the expected health benefits from vaccines.

In 2000 the IOM released another consensus study report which contained an updated vaccine prioritization framework and also assessed the barriers to vaccine research and development and recounted the progress that had been made since the 1985–1986 report. That study's focus was on vaccine candidates that had the potential to be developed and used within the next two decades within the United States, so it did not consider the global burden of diseases. The report's analytical criterion was cost-effectiveness, using quality-adjusted life years (QALYs) as the measure of health benefits.

Moreover, the 2000 model used cost-effectiveness analysis only from a societal perspective, hence making the prioritization of limited value to such stakeholders as industry and international vaccine suppliers. Furthermore, the model does not calculate costs (which could be interpreted

differently by different stakeholders) from multiple perspectives (e.g., vaccine development costs, costs of immunization, and vaccine administration costs). While the cost–benefit framework emphasizes the economic impact of vaccines, it often neglects to consider their social impacts, such as possible intergenerational benefits gained when immunizing a pregnant woman.

Previous WHO efforts in vaccine-related prioritization

The World Health Organization's Initiative for Vaccine Research (IVR) recently published *Strategic Plan 2010–2020*, which outlined four high-level strategies in order to highlight the importance of vaccine research in public health practice (WHO, 2010). Of relevance here is the strategy oriented toward the identification of vaccine and vaccination research priorities over the next 10 years, with a special focus on low- and middle-income countries.

The WHO strategy for prioritizing vaccines began by categorizing diseases and then assessing vaccine characteristics. The diseases for which vaccines are still needed were classified into two groups: (1) diseases that have ongoing vaccine development efforts but no license, and (2) diseases with underutilized vaccines. IVR's efforts have principally focused on identifying diseases that are of highest public health importance for vaccine development. Together with disease impact and burden, IVR has also considered economic restraints on developing and using vaccines as well as the ability to contain or prevent diseases through alternative measures.

WHO's Global Immunization Vision and Strategy (GIVS) goes hand in hand with the IVR approach of establishing priorities for vaccines in low- and middle-income countries. The 10-year plan of GIVS, which was released in 2006 jointly by WHO and UNICEF, outlines specific objectives for the control of mortality and morbidity caused by vaccine-preventable conditions (WHO, 2006). As a part of its larger objective to immunize more people with more vaccines, GIVS also aims to strengthen country-level capacity to determine and set policies and priorities for new vaccines. Many countries have adopted GIVS to serve as the framework for their immunization programs and to advance the use of high-priority new vaccines.

The Pan American Health Organization (PAHO) also recently developed a decision-making framework to assist countries in the introduction of new and underused vaccines. PAHO's ProVac Initiative is structured to promote and strengthen evidence-based decision-making capacity for the introduction of new vaccines in WHO's region of the Americas. While the lack of economic analyses and the subsequent absence of successful

immunization policies at the country level is a lingering concern, the ProVac Initiative not only intends to strengthen the economic basis for decision making but also to assess other broad factors that should be considered in making decisions (Andrus et al., 2007). ProVac includes technical, programmatic, operational, and social criteria to help set priorities for the introduction of vaccines in a given region or a country (Andrus et al., 2006, 2007). Finally, PAHO recognizes that the necessary analytical tools and collection of data are needed from the WHO region of the Americas in order to properly evaluate and assess priorities for vaccine introduction in each country.

New technologies and development strategies

As science and engineering progressed in the 21st century, vaccine development methods also evolved. In particular, vaccine development received a boost from the application of state-of-the-art technologies, which led to new and improved products for changing populations. While Pasteur's injunction to "isolate, inactivate, and inject" the microorganism causing the disease is still the mainstay of vaccine development, modern vaccines are also being developed through a number of novel techniques.

The combination of genomics, systems biology, the structure-based design and optimization of immunogens, small molecule adjuvants targeting specific receptors, and sophisticated assays to monitor the immune response is transforming the traditional field of vaccinology into one of today's most dynamic areas of research. Using these methods there is now the real possibility of developing vaccines for diseases that were regarded as not "vaccinable" in the past.

The technologies developed over the past two decades have improved our understanding of the immune system, making it possible to produce vaccines through novel means, and have helped in the development of novel adjuvants. For example, hepatitis B vaccine was developed using recombinant DNA technology, and genomics has made it possible to discover new vaccine candidates through reverse vaccinology, leading to the development of a vaccine against *N. meningitidis* B (Rappuoli et al., 2011).

The development and testing of vaccines requires significant time, money, and effort. The story of vaccine discovery and development proceeded differently in the 1980s than it does today. Then, development was fast, and clinical trials required only a few hundred subjects. Timelines have shifted, however, and it now takes about a decade to develop and commercialize a vaccine. Vaccine licensure itself typically requires tens of thousands of people in clinical trials, with Phase I, Phase II, and Phase III

TABLE 1-1

Representative Stakeholder Priority Areas

Stakeholders	Representative Priorities or Interest Areas
Public Sector: Health agencies; preparedness and response units; public health units; regulatory agencies; basic research divisions; domestic and foreign policy agencies; and military.	• Disease burden and health impact. • Non-market and non-economic benefits of vaccines. • Costs relating to vaccine development and delivery. • Long-term benefits to the vaccine development enterprise, including (a) effective combination vaccines and (b) strategies to optimize existing or new production and delivery platforms. • Ability to produce and administer a vaccine promptly for novel threats. • Innovative methods for administration, including self-administration. • Vaccines with long shelf life and ease of storage and management. • Low number of doses and longevity of protection. • Development of tracking systems from manufacturing plant to recipients in the field. • Development of a scientific base for a new vaccine. • Budgetary constraints for new vaccine research and development. • Programmatic and operational aspects of administering new vaccines. • Fitting new vaccines into existing vaccination schedules. • Building harmony among general public, medical community, public health community, research community, manufacturers, and other international partners. • Identification of disease and vaccine candidates that should not be prioritized.
Private Sector: Vaccine and biopharmaceutical industry.	• Development of desired product profiles that clearly describe target population and subpopulation segments, potential indications, and key product attributes. • Consideration of uncertainty around licensure and identify clinical endpoints that will be used by regulators to assess vaccine efficacy, adjuvants, and key product attributes. • Global need for certain vaccines with volume and price considerations. • Financial burden due to clinical trials and barriers to successful licensing of a vaccine. • Cost of development and projected time to economic return. • Status of competition for a vaccine in developing and developed country markets.

continued

TABLE 1-1

Continued

Stakeholders	Representative Priorities or Interest Areas
Nongovernmental and Other Organizations: International vaccine initiatives, private foundations, and multinational groups.	• Cost-effectiveness and effective implementation for each vaccine. • Special attention for countries with poor resources. • Logistics of vaccine delivery with a regional and local resolution than a national focus. • Consideration of operational criteria for vaccines—availability of cold chain and trained human resources. • Consideration of public perception of risk and the acceptance of vaccines. • Availability of effective surveillance strategies and technologies. • Alternative methods to prevent the disease. • Availability of sufficient number of doses of quality vaccines for distribution.

trials performed sequentially. The requirement for sequential trials further extends the development period and cost.

With the newest technologies, however, the hope is that the development of new vaccines can be accelerated. Systems biology and the adaptive design of clinical trials may help reduce development time by allowing more rapid identification of vaccine candidates and making it possible to conduct the exhaustive and monitored Phase I and Phase II trials in parallel (Rappuoli and Aderem, 2011).

Stakeholder priorities

Various stakeholders are involved in the development and deployment of vaccines. To better understand the different priorities of the public sector, private sector, and nongovernmental groups, the committee organized information-gathering sessions in meetings I and II. Representative priorities and interest areas are listed in Table 1-1.

It became clear to the committee that in order to create a broad-based decision framework that would be relevant to multiple stakeholders and communities, the committee needed to consider not only the vibrancy of the vaccine enterprise but also the specific needs and interests of these stakeholders. The modeling strategy of the committee is discussed in Chapter 2.

2

Modeling Strategy: From Single Attribute to Multiple Attributes

The vaccine prioritization techniques of the earlier Institute of Medicine (IOM) studies published in 1985–1986 and 2000 relied on two criteria: (1) reduction of health burden (IOM, 1985, 1986) and (2) incremental cost or savings (IOM, 2000) due to use of the vaccine in a defined population. More specifically, the 1985–1986 work used only a single attribute—infant deaths averted—for ranking vaccine candidates; it did not consider cost attributes. The 2000 report used an approach based on cost-effectiveness to prioritize vaccines.

Those studies saw the central "modeling task" as numerical estimation of the expected costs and benefits of the vaccines. The principles underlying this approach derive from the economic theory of social welfare as implemented in the classic utility frameworks (Garber and Phelps, 1997). The computational models were the key contributions of the 1985–1986 and 2000 reports. Their work involved many decisions concerning which costs and savings to include and how best to measure health gains.

New Vaccine Development (1985–1986) and *Vaccines for the 21st Century* (2000)

The 1985–1986 report measured health benefits using infant mortality equivalents (IMEs), which involved subjective judgments relating to morbidity and mortality reductions compared to an equivalent number of infant deaths averted. Since the time that report was published, analytical techniques have advanced. Standardized measures of health-related qual-

ity of life (HRQOL) such as the Health Utilities Index Mark 2, or HUI2—a tool to measure morbidity reduction—have been developed using methods of multi-attribute utility theory (Feeny et al., 1996). HUI2 has been combined with actuarial measures of life expectancy changes in order to compute quality-adjusted life years (QALYs) as one of the main health valuation measures.

To derive its vaccine priorities, the 2000 report relied on incremental dollar costs per incremental QALY gained ($/QALY) for both preventive and therapeutic vaccines that are of importance to the United States. In the nearly three decades since the 1985–1986 report was published, the theoretical basis for its calculations has not changed. By contrast, in the years since the 2000 report, the methods of cost-effectiveness analysis have become somewhat more sophisticated when it comes to assessing the effectiveness of $/QALY values for health care technologies.

The self-reported health status data needed for population-based measures such as HUI2 are not available in much of the world. Instead, researchers at the World Health Organization in collaboration with researchers at other institutions developed a similar tool: disability-adjusted life years (DALYs). In calculating DALYs, disability weights are assigned to typical manifestations of a wide variety of diseases; such measures have been used for many countries around the world (Fox-Rushby and Hanson, 2001; Gold et al., 2002; Murray and Lopez, 2000).

Methods to incorporate uncertainties in decision models were undergoing rapid development at the time of the 2000 report. They have since progressed and become more generally applicable (Fenwick et al., 2001; Meckley et al., 2010). There have also been advances in population-based data collection supporting HUI2 and similar indexes of generic health-related quality of life that the 2000 report incorporated (Fryback et al., 2007, 2010; Luo et al., 2005, 2009).

In recent years, advances in complex systems modeling have helped characterize the nature and spread of infections in populations. These dynamical techniques can now be used for estimating the impact of a new vaccine for a specific population (e.g., Epstein et al., 2008). But the underlying decision framework and conceptual approaches to estimating costs and health benefits have essentially remained unchanged.

The previous reports developed a computational model based on two important (but distinctly different) attributes for prioritizing vaccines, although more sophisticated methods could have been used. The main criticism of the 2000 report was related to the basic framework itself: *the system was too limited and considered only costs and aggregated health benefits* (e.g., see Plotkin et al., 2000).

Modeling beyond cost-effectiveness

The committee revisited the assumptions and limitations of the 1985–1986 and 2000 approaches. Instead of taking the path of developing a de novo computational model, the committee chose to significantly expand the previous IOM works by using a multi-attribute utility framework and develop a novel software application. In this work, therefore, some aggregate measure of health benefits (such as infant deaths averted) or an efficiency criterion (such as cost-effectiveness) has simply become one among the many criteria—rather than the only criterion—that influence vaccine prioritization.

The committee took on the task of expanding the list of attributes characterizing vaccine candidates and developing a prototype software—SMART Vaccines Beta—to weigh not only economic and health attributes but also demographic, scientific, business, programmatic (field-level logistics), social, and policy aspects relating to new vaccine development. The short-listing of 29 attributes used in SMART Vaccines Beta was informed by stakeholder and concept evaluator feedback, committee discussions, and literature review (Burchett et al., 2011).

Values and objectives in priority setting

Priority setting means assigning values and objectives. If the main objective of a new preventive vaccine is to minimize the disease burden in the target population, then assuming that all else is equal, the highest priority typically would be given to the vaccine candidate expected to produce the largest health benefit compared to other candidates, and a set of vaccine candidates would be prioritized according to their expected health benefits, going from most expected benefits to least.

But all else is *not* equal. Priorities must also reflect such considerations as the fact that resources are constrained. Such a limited-resources constraint points to a different objective: to minimize the costs associated with bringing a vaccine to licensure and then administering it in the target population. If minimizing costs is the main objective, then the program with the lowest development and implementation costs would be favored, and priorities would simply be ordered according to the increasing costs of the different programs. These two objectives—maximizing health benefits and minimizing costs—are often in conflict. One vaccine candidate may potentially have a very large aggregate impact on health burden but also have greater expected costs than a vaccine addressing a different disease where the effect on health burden may be smaller.

When objectives are in conflict, decision makers often deal with trade-offs. In this case, each vaccine candidate is associated with expected health benefits and costs. Expressing a priority order among candidates requires us to weigh the extent to which each vaccine candidate achieves the two objectives jointly, perhaps preferring one objective over the other. In this case, cost-effectiveness analysis is appropriate and may be used to prioritize vaccine candidates when there are trade-offs between these two important attributes.

But several other objectives could also influence the ranking of vaccine candidates under consideration. These objectives depend on whose priorities are being expressed toward maximizing the overall value of the vaccines. For example, decision makers may want to represent a public desire to minimize the burden of disease in specific target populations such as women, infants, and children; the socioeconomically disadvantaged; or military personnel. There may be certain diseases that raise special concerns or fear in the public mind—for example, a rare but particularly gruesome condition, an unrelenting infection, or a terribly disfiguring disease. Extra priority may be given to a vaccine that prevents such a disease, escalating its priority despite high costs or a relatively small aggregate health burden imposed by the disease in the population compared to a vaccine preventing a condition that is more common but that has a relatively minor health burden.

Other objectives are also possible. One might wish, for instance, to maximize the benefit to future generations by investing in a vaccine that could eliminate a particular disease altogether or mitigate its epidemic potential. Similarly, one might wish to prioritize a vaccine that has the potential to significantly advance the scientific base, including new production, preservation, and delivery methods.

A prioritization exercise starts with a set of vaccine candidates, each of which is expected to meet, to a greater or lesser degree, a number of desired objectives. The basic purpose of prioritization is to place these candidates in order from "most preferred" to "least preferred" in accordance with values held by or represented in proxy by the decision maker. The methods used to accomplish this task in a rigorous fashion fall generally under the rubric "multi-criteria decision making."

Multi-criteria decision-making methods

From the family of multi-criteria decision-making models, the committee chose to use a version of multi-attribute utility theory. As a starting point, the committee limited the models under consideration to those

that included multiple attributes. The committee heard from a number of stakeholders that the narrow range of attributes used to rank vaccine priorities in previous IOM studies significantly limited their value and applications. Thus, the committee reviewed three multiple-attribute modeling approaches (listed in the order of historical development): (1) mathematical programming (or optimization), (2) multi-attribute utility theory, and (3) analytical hierarchy process. The approaches were evaluated against four criteria: axiomatic foundation; priority scaling; sensitivity analysis; and transparency.

Axiomatic foundation

Multi-attribute utility theory and mathematical programming are based on axiomatic theory—the former being derived from principles of utility maximization (Krantz et al., 1971), and the latter being based on mathematical optimization. The analytical hierarchy process has an axiomatic base that the committee considered incomplete. To elaborate, the issue of independence from irrelevant alternatives (IIA) was of particular importance to the committee's considerations. IIA means the following: Given a particular set of options (candidate vaccines) in which candidate A is preferred to candidate B, if an additional candidate C—unrelated to A and B—is added to the option set, then A continues to be preferred over B.

Consider, for example, a comparison of vaccines to prevent tuberculosis and malaria, ranked with one preferred to the other. Now suppose that the science and technology evolves to allow a new vaccine against dengue fever. IIA would mean that the ranking of vaccine candidates for tuberculosis and malaria remains unchanged when the dengue fever vaccine is added to the mix for consideration. The new dengue fever vaccine may be more or less preferred than either tuberculosis or malaria or both vaccines, but the rankings of tuberculosis and malaria vaccines with respect to each other must remain unchanged. Since the appearance of new candidate vaccines can be anticipated over time, the committee concluded that IIA was particularly important to consider.

Priority scaling

The 1985–1986 and 2000 IOM reports relating to vaccine prioritization and the international stakeholder testimonies made it very clear that this committee's work would need to offer greater value in terms of allowing different users to apply their individual preferences in a prioritization model. The committee defines the term "prioritize" consistently with the stan-

dard dictionary definition "to arrange in the order of relative importance." Thus, prioritization at a minimum requires an ordinal ranking and nothing more—simply stating an order of preference. The three modeling methods considered by the committee all provide additional information beyond an ordinal scale—either interval or ratio scale numbers assigned to vaccine candidates to represent relative priority.

To use an analogy relating to temperature measurement, with interval scales the difference between two values has the same meaning at different points along the scale. For example, the difference between 20°C and 40°C has the same meaning as the difference between 30°C and 50°C. But 40°C is not twice as hot as 20°C. Ratio scales also provide information about relative values, thus requiring identification of true "zero" on the scale. Kelvin temperature allows for this: 300K is twice as hot as 150K, whereas statements about ratios of temperatures are incorrect in either °C or °F scales—but ratios of *differences* in temperatures are the same on K, °C, and °F scales. Since only ordinal ranking is required in prioritization, any modeling approach providing interval or ratio scaling is sufficient.

Sensitivity analysis

The committee also wanted to allow users to conduct sensitivity analysis on their results. This sensitivity analysis has several purposes, including (a) enhancing understanding of the inputs to which the results were most sensitive, (b) pointing toward areas where improved data have the greatest value, and hence potentially (c) spurring efforts and investments in data generation. All three modeling approaches had the capability for ably supporting sensitivity analyses.

Transparency

Another important criteria for the committee was transparency. In the committee's view, the multi-attribute utility approach was more transparent than other possible approaches. In mathematical programming, for example, one could subtly alter the constraint set (in ways very difficult for others to see) so as to eliminate some candidates from the solution set in favor of others, or else modify the way the objective function was specified. In analytic hierarchy process, the value weights emerge only after a long series of pair-wise comparisons have been recorded and modified through normalization processes involving complex matrix manipulations. By contrast, in multi-attribute utility theory the weights and data are available for everybody to see and use. In that regard, multi-attribute utility theory was

found to be the best fit for satisfying the transparency requirement. Indeed, the committee saw this as a strength of the SMART Vaccines, highlighting its potential in promoting cross-comparison of different users' rationale and conclusions and leading to more informed discussions about priorities among different stakeholders. Each modeling alternative is summarized in the following sections.

Mathematical programming or optimization

Mathematical programming (linear programming, nonlinear programming, stochastic programming, and more complex optimization algorithms) has been widely and successfully employed in many areas to tackle complex challenges. In concept, mathematical programming is an appropriate method for vaccine prioritization. Its optimization characteristics are well understood (Rardin, 1997). In various formulations, it can provide output of at least ordinal nature (ranking) and, in many formulations, interval or ratio scale output, and software to carry out such calculations is widely available in numerous commercial and free-ware environments. It is also amenable to sensitivity analyses.

The primary uses of mathematical programming involve optimization of some value function (specified by the user) subject to a set of constraints which are often highly complex and frequently nonlinear. In classical linear and nonlinear programming, the values of relevant components of the model are known (e.g., cost, consumer preferences, and other factors). Stochastic programming emerged to provide optimization tools when uncertainty exists about certain components of the system under consideration. But, in general, the value of mathematical programming appears when there are many possible solutions (perhaps an infinite number) within the constraint set.

Prioritization of vaccines differs considerably from the usual uses of mathematical programming. Typically, only a small number of alternatives are considered in the set of potential vaccines (dozens, perhaps, but seldom hundreds, almost never thousands, and certainly not an infinite set of options). Separately, unless a customized stochastic programming method or some equivalent method is developed and used, the dearth of data in regards to new vaccines problem would likely render the optimization capabilities of mathematical programming questionable for the application.

Another issue also deterred the full consideration of mathematical programming for vaccine prioritization: Mathematical programming requires a pre-specification of the value function. This is a crucial issue,

since many users and stakeholders would not be able to competently specify a value function for such reasons as a lack of a quantitative background. Furthermore, there are no well-developed and tested methods for value elicitation associated with mathematical programming methods.

Analytic hierarchy process

The analytic hierarchy process has many desirable attributes. It is widely used by people in business and other settings to assist in decision making, often under the tutelage of professional consultants. It provides a ratio-scale value function, which is more than sufficient for the committee's ranking process. It has a well-developed process for eliciting values from users, based on a large set of pair-wise comparisons of different alternatives along the various attribute dimensions. The user must make a sizeable number (typically in the hundreds) of paired comparison assessments. For each pair of candidates (e.g., vaccines) A and B, and for each attribute, x_j, the decision maker rates the comparison of x_{aj} versus x_{bj} using a scale of 9, 7, 5, 3, 1, 1/3, 1/5, 1/7, 1/9 to describe how much better A is than B on that attribute, where the numbers are meant to convey a ratio scale of relative performance. Although, in principle, any user can program the calculations necessary for deriving priorities[1] from an analytic hierarchy process, most analysts use one of a number of proprietary software packages currently available. These packages lead users through the necessary steps and provide internal consistency checks for many of the comparative assessments.

Besides the complexity associated with value elicitation process, two other features make this analytic hierarchy process less friendly for vaccine prioritization. Perhaps most important, the analytic hierarchy process does not maintain IIA, a fact that is widely understood among both proponents and opponents of this method (Dyer, 1990; Saaty, 1987). Proponents of analytic hierarchy process cite this as a beneficial feature, noting that many real world decisions also do not have IIA. But the committee, for reasons stated previously, views IIA as a critical factor in vaccine prioritization.

[1]Among the users of analytic hierarchy process the word "priority" has a specific technical meaning (relating to a normalized eigenvector used in the model) that does not match the standard definition of priority mentioned earlier and used in this report. Thus, one should not confuse the specific analytic hierarchy process definition of priority with the one used by the committee.

Multi-attribute utility theory

A multi-attribute utility-based prioritization exercise consists of several steps. First, the set of vaccine candidates to be considered must be identified. Next, a set of objectives that underpin the valuation of candidates must be listed. For each objective there must be a specific measure—called an "attribute"—developed. The attributes may be natural scales (such as expected net present value of annualized dollar costs or savings), well-established indexes (such as net annualized increase in QALYs due to the vaccine), or customized categorical scales.

If we denote each candidate vaccine by x_i, then the outcome attributes characterizing that vaccine may be viewed as a vector, $c_i = (x_{i1}, x_{i2}, \ldots, x_{in})$, where n is the number of attributes being considered when setting priorities, and x_{ij} is the value of the scale for the jth attribute for the ith vaccine candidate. Multi-attribute utility models can combine attributes of each type, whether continuous or categorical.

Keeney and Raiffa (1976) as well as a number of others (Barron and Barrett, 1996; Edwards and Barron, 1994; Edwards and Newman, 1982; von Winterfeldt and Edwards, 1986) have described methods to specify n single-attribute functions, $0 \le u_j(x_j) \le 1$, and a global utility function, $U(c_i) = f(u_1(x_{i1}), u_2(x_{i2}), \ldots, u_n(x_{in}))$, such that $0 \le U(c_i) \le 1$. The function U is constructed so that c_a is preferred to c_b if and only if $U(c_a) > U(c_b)$.

Often the function f is additive, $U(c_i) = w_1 u_1(x_{i1}) + w_2 u_2(x_{i2}) + \ldots + w_n u_n(x_{in})$, where the w_js are constants that sum to 1. The ratios w_j/w_k reflect the change in value achieved by changing the jth attribute from its minimum to maximum level in the set of vaccine candidates versus making the corresponding change in the kth attribute. Although there are strong arguments for using an additive function as a first approximation (Edwards and Barron, 1994; Keeney and von Winterfeldt, 2007; von Winterfeldt and Edwards, 1986), in some cases a multiplicative function or multi-linear function might be more appropriate in order to account for interactions among the attributes based on user preferences (Keeney and Raiffa, 1976). Additive functions are often satisfactory for broad policy purposes. The committee employs an additive version of multi-attribute utility method in SMART Vaccines Beta.

Determining what weights $(w_1, w_2, \ldots, w_n)$ to use is a separate problem from that of choosing the functional form (e.g., additive or multiplicative). Edwards and Barron (1994) proposed a method to approximate the w_js using the decision maker's rank order of the relative importance of the attributes. In particular, they proposed using the rank order centroid method to derive weights for a set of attributes, a method that was later extensively evaluated by Barron and Barrett (1996).

The rank order centroid approximation

The decision maker's major input is to produce a rank order of the relative importance of the attributes in order to differentiate the priority of the vaccine candidates. This induces a rank order on the weights in the additive model. Suppose that the rank order is $w_1 \geq w_2 \geq \ldots \geq w_n$ for n attributes. The rank order centroid approximation for the constants in an additive model would then be as follows:

$$w_1 = \left(\frac{1 + \frac{1}{2} + \frac{1}{3} + \ldots + \frac{1}{n}}{n} \right)$$

$$w_2 = \left(\frac{0 + \frac{1}{2} + \frac{1}{3} + \ldots + \frac{1}{n}}{n} \right)$$

$$w_3 = \left(\frac{0 + 0 + \frac{1}{3} + \ldots + \frac{1}{n}}{n} \right)$$

$$w_n = \left(\frac{0 + 0 + 0 + \ldots + \frac{1}{n}}{n} \right)$$

More compactly the weights can be expressed by

$$w_i = \sum_{j=i}^{n} \frac{1}{j} \qquad i = 1 \cdots n$$

Barron and Barrett showed this rank order centroid approximation for weights to be superior to other often-proposed methods, such as the normalized sum of ranks. It is important to realize that rank order centroid weights are not essential to the multi-attribute utility models; rather they are an approximation used to reduce the workload of the potential user.

In SMART Vaccines Beta, the rank order centroid-based weighting approach was employed in order to speed up development of other parts of the model. In many policy settings using multi-attribute utility theory, these weights are developed with experts guiding the process of decision makers elucidating their preferred weights (Keeney and Raiffa, 1976; von Winterfeld and Edwards, 1986).

The multi-attribute decision techniques (or related proprietary software packages) have been used in practical applications in a number of

public policy settings, including to evaluate alternative plans to desegregate schools (Edwards, 1979), to plan wastewater treatment facilities (Keeney et al., 1996), to evaluate accounting regulations for control of nuclear materials (Keeney and Smith, 1982), and to evaluate homeland security decisions (Keeney and von Winterfeld, 2011). Additional applications have been reviewed by Keefer and colleagues (2004).

Data demands

The multi-attribute utility approach places considerable data demands on users. The committee continually sought to balance the model's capabilities and complexity with the data demands it would place on users. The challenge, however, spans every approach considered by the committee. It is intrinsic not to the multi-attribute utility approach itself, but rather to the underlying complexity of prioritization and how to model it. Had mathematical programming or analytic hierarchy process been adopted, a level of data demands similar to those in the multi-attribute utility theory would have been required. The only way to reduce data demands is to have limited capabilities in SMART Vaccines.

A parallel issue relates to how the necessary data must be structured. In the committee's view, the data inputs necessary for the multi-attribute approach are at least as simple—and often simpler—for users to understand than would be the case in alternative models. For example, many formulations of mathematical programming have inequality constraints, a concept that could seem alien to many potential users of our software.

The modeling framework for SMART Vaccines Beta

Multi-attribute utility theory provides the analytical framework that underpins the committee's work, and the specific model within this framework is an additive multi-attribute utility model. A schematic diagram of the model's organization is presented in Figure 2-1.

Within the multi-attribute utility framework, a vaccine candidate is viewed as a *means* to achieve an *end* in a specified population. The various objectives that the development and delivery of a new vaccine may address include

- enhancing public health by reducing the burden due to a particular disease or condition;
- minimizing the societal costs of the disease, and its prevention and treatment;

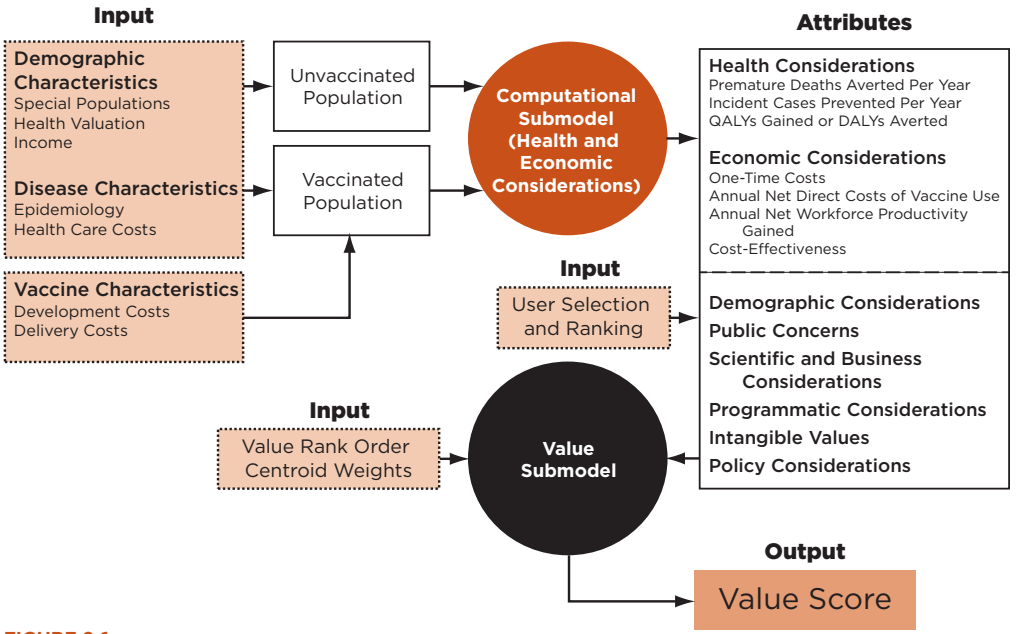


FIGURE 2-1
The modeling framework for SMART Vaccines Beta. The computational and value submodels cooperate to produce a value score based on user inputs and various attributes compared in populations with and without the vaccination against a particular condition.

- addressing public concerns relating to the target disease;
- improving the health of specific, priority populations such as infants and children and economically disadvantaged persons; and
- advancing national security by immunizing military personnel from specific diseases and addressing domestic and foreign policy concerns.

This list is illustrative and not meant to be all-inclusive. Many of these objectives were suggested to the committee during public sessions in which stakeholders from both U.S. and international organizations were invited to discuss their ideas concerning what objectives should be reflected in priorities for new vaccine development.

The 29 attributes in Table 2-1 include both quantitative and qualitative attributes which can be potentially important for many groups of stakeholders. This list is meant to offer a smorgasbord of choices from which stakeholders can select in accordance with their objectives. The committee tried to err on the side of "too much" rather than "too little" and to take the possible interests of various constituencies into account. The quantitative attributes are measures that are "computed" using the demographic,

economic, and new vaccine information provided by the user concerning a particular disease.

Figure 2-1 shows the inputs for the computational submodel that simulates the disease in a target population both in the absence and in the presence of a new vaccine. The output of this computation is the estimated impact of the vaccine on various measures of health burden in the population as well as on the costs associated with the disease, including disease care expenditure.

Table 2-1 contains three attributes describing simulated health impacts of the vaccine and four attributes related to the economic impacts of the condition. Six of these seven attributes are calculated using the computational submodel, which is described in the following section. The remaining 23 attributes for the candidate vaccines are directly scored by users based on their preferences and opinions. The result of the computations and user scores is a vector of attribute levels describing the relative achievement of each candidate vaccine on each of the 29 attributes.

Users are not required to include all 29 attributes when they run SMART Vaccines. In fact, the committee expects that users may not want to include all of the attributes as part of their prioritization process but will include only those that are most relevant to maximizing the value of new vaccines from their particular point of view. SMART Vaccines will be able to help determine the priorities among vaccine candidates for users only on the basis of the attributes they select and rank, which are expected to be different across the users. Stakeholders who use the same subset of attributes to determine priorities may very well weigh them differently per their values and constituencies.

Foundation for the computational submodel

Most of the attributes in Table 2-1 (e.g., whether or not the vaccine primarily targets health burden among infants and children) are qualitative assessments to be made by users in order to characterize aspects of the vaccine candidates that are beyond the capabilities of the computational submodel. But there are six attributes that quantify the impact of the vaccine on mortality and morbidity in the population and the costs of achieving these impacts.

The effects of vaccines in populations are complex functions of relatively well-known inputs. Thus in SMART Vaccines Beta these attributes are estimated using simulation modeling. The simulation model decomposes a complex quantitative issue into smaller parameters so as to allow specific data and targeted expert knowledge about population demography

TABLE 2-1

List of Possible Attributes in SMART Vaccines and Categorizations of the Measures for Domestic and International Comparisons

Attribute	Definition	Categories: Level 1 = Highest Priority	
		For International Comparisons	For Domestic Comparisons
1. Health Considerations[a]			
Premature Deaths Averted per Year	The difference in the number of deaths in 1 year, assuming no routine vaccine use and assuming routine vaccine use against the disease in the population.[b]	Level 1: >1,000,000 Level 2: 500,000–999,999 Level 3: 100,000–499,999 Level 4: <100,000	Level 1: >20,000 Level 2: 5,000–19,999 Level 3: 1,000–4,999 Level 4: <1,000
Incident Cases Prevented per Year	The difference in the number of incident cases of disease in one year, assuming no routine vaccine use and assuming routine vaccine use against the disease in the population.[c]	Level 1: >10 million Level 2: 1–10 million Level 3: 250,000–1 million Level 4: <250,000	Level 1: >75,000 Level 2: 50,000–74,999 Level 3: 10,000–49,999 Level 4: <10,000
QALYs Gained or DALYs Averted	Net increase in QALYs gained or DALYs lost in the population vaccinated.[d] Computed as a difference between QALYs or DALYs experienced in stationary population followed until all have died, assuming vaccination versus assuming no vaccination.	Level 1: >25 million DALYs Level 2: 10–25 million DALYs Level 3: 500,000–10 million DALYs Level 4: <500,000 DALYs	Level 1: >50,000 QALYs Level 2: 20,000–49,999 QALYs Level 3: 5,000–19,999 QALYs Level 4: <5,000 QALYs
2. Economic Considerations			
One-Time Costs	Sum of development plus licensure plus start-up costs. This attribute represents the magnitude of the financial barriers to bringing the vaccine to use in the population.[e]	Level 1: <$100 million Level 2: $100–$500 million Level 3: $500 million–$1 billion Level 4: >$1 billion	Level 1: <$100 million Level 2: $100–$500 million Level 3: $500 million–$1 billion Level 4: >$1 billion

Annual Net Direct Costs (Savings) of Vaccine Use	The difference in the total health care costs without the vaccine and the health care costs with the vaccine and the vaccine administration costs for 1 year, assuming a steady-state population.[f]	Level 1: <$0 (cost saving) Level 2: $0–$100 million Level 3: $100–$300 million Level 4: >$300 million	Level 1: <$0 (cost saving) Level 2: $0–$50 million Level 3: $50–$150 million Level 4: >$150 million
Annual Net Workforce Productivity Gained	Net workforce productivity gained is the difference in the annual productivity loss under the assumption of no vaccine use and annual productivity loss under the assumption of routine vaccine use.[g]	Level 1: >$10 billion Level 2: $5–$10 billion Level 3: $1–$5 billion Level 4: <$1 billion	Level 1: >$10 billion Level 2: $5–$10 billion Level 3: $1–$5 billion Level 4: <$1 billion
Cost-Effectiveness	$/QALY gained or $/DALY avoided.	Level 1: <$0 (cost saving) Level 2: <$50,000 Level 3: $50,000–$150,000 Level 4: >$150,000	Level 1: <$0 (cost saving) Level 2: <$50,000 Level 3: $50, 000–$150,000 Level 4: >$150,000
3. Demographic Considerations			
Benefits Infants and Children	Vaccine targets a disease occurring primarily among infants and children to prevent a serious disease with notable associated mortality and/or that often results in long-lasting serious morbidity. Examples: rotavirus, polio.	Level 1: Yes Level 2: No	
Benefits Women	Vaccine targets a disease primarily affecting women. Example: HPV-caused cervical cancer.	Level 1: Yes Level 2: No	

continued

TABLE 2-1

Continued

Attribute	Definition	Categories: Level 1 = Highest Priority	
		For International Comparisons	For Domestic Comparisons
Benefits Socioeconomically Disadvantaged	Vaccine targets a disease affecting economically disadvantaged population *disproportionately*. Example: malaria, tuberculosis, rotavirus.	Level 1: Yes Level 2: No	
Benefits Military Personnel	Vaccine protects military personnel from a particular deadly disease.	Level 1: Yes Level 2: No	
Benefits Other Priority Population	Vaccine targets a disease particularly prevalent in, say, immunocompromised individuals or other priority populations.	Level 1: Yes Level 2: No	
4. Public Concerns			
Availability of Alternative Public Health Measures	Do relatively effective and inexpensive public health measures to reduce the impact of the target disease already exist? Example: bed nets for malaria.	Level 1: No Level 2: Yes	
Potential Complications Due to Vaccines	Is there an expectation *beyond what would be usual* of potential risks of complications due to the vaccine? This might be inferred from similar vaccines produced using same platform. Example: high-risk live vaccines.	Level 1: No Level 2: Yes	

Disease Raises Fear and Stigma in the Public	Vaccine targets a new or re-emergent disease that raises fear in the public mind and brings public and political calls for prevention. Examples: meningococcal disease, Ebola, SARS.	Level 1: Yes Level 2: No	
Serious Pandemic Potential	Vaccine targets a disease with serious pandemic potential and socioeconomic disruption. Example: A human-to-human transmissible H5N1 influenza.	Level 1: Yes Level 2: No	
5. Scientific and Business Considerations			
Likelihood of Financial Profitability for the Manufacturer	Is the vaccine likely to be a financially profitable endeavor for the producer?[h]	Level 1: Almost certainly will be profitable Level 2 Level 3 Level 4 Level 5: Almost certainly will not be profitable	
Likelihood of Successful Licensure in 10 Years	Probability of successful licensure for the target populations in the next 10 years.	Level 1: Almost certainly will be licensed within 10 years Level 2 Level 3 Level 4 Level 5: Almost certainly will not be licensed within 10 years	
Demonstrates New Production Platforms	Will this vaccine demonstrate a novel vaccine concept or platform technology to inform future vaccine science?	Level 1: Yes Level 2: No	

continued

TABLE 2-1

Continued

Attribute	Definition	Categories: Level 1 = Highest Priority	
		For International Comparisons	For Domestic Comparisons
Existing or Adaptable Manufacturing Techniques	Could this vaccine be developed using existing or adaptable manufacturing techniques?	Level 1: Yes Level 2: No	
Potential Litigation Barriers Beyond Usual	From a manufacturer's perspective, could this vaccine encounter potential litigation barriers beyond the usual?	Level 1: No Level 2: Yes	
Interests from NGOs and Philanthropic Organizations	Could this vaccine generate interests from NGOs and other philanthropic and charitable organizations?	Level 1: Yes Level 2: No	
6. Programmatic Considerations			
Potential to Improve Delivery Methods	Does the vaccine development have the potential to improve delivery methods or stimulate novel approaches to deliver vaccines?	Level 1: Yes Level 2: No	
Fits into Existing Immunization Schedules	Could this vaccine fit into existing immunization schedules?	Level 1: Yes Level 2: No	
Reduces Challenges Relating to Cold-Chain Requirements	Does the vaccine development have the potential to reduce challenges relating to cold-chain storage and related packaging and other requirements?	Level 1: Yes Level 2: No	

7. Intangible Values			
Eradication or Elimination of the Disease	Vaccine presents potential for either global eradication of a serious disease entirely (e.g., smallpox, polio, measles) or elimination of the disease's effects among humans. Example: anthrax, generic flu, malaria—diseases where the reservoir will not be eliminated and each new human generation will need to be vaccinated.	Level 1: Potential Eradication of the Disease Level 2: Potential Elimination from Humans Level 3: Neither of the above	
Vaccine Raises Public Health Awareness	Could this vaccine help improve public health awareness and induce potential public behavioral change? (Example: HPV and safe sex.)	Level 1: Yes Level 2: No	
8. Policy Considerations			
Special Interest for National Security, Preparedness, and Response	Is the development of this vaccine of special interest for reasons of national security?	Level 1: Yes Level 2: No	
Advances Nation's Foreign Policy Goals	Is the development of this vaccine of special interest for reasons of foreign policy, foreign assistance, or diplomatic goals?	Level 1: Yes Level 2: No	

Categories must be consistent and kept constant across vaccine candidates for a particular comparison. The "domestic" values for categorization refer to the United States. The "international" values refer to the remainder of the world in aggregate. If priorities are to be set solely within one country, they can be adjusted to levels meaningful for that country. Value scores are meaningful only among vaccine candidates compared on the same categorizations of variables. Categories for the United States are suggested for comparisons of vaccine candidates within and for the United States. Levels are assigned so that Level 1 is highest priority to be consistent with numbering in the 2000 report.

[a]Either QALYs or DALYs must be selected to apply to all alternatives being prioritized.

continued

[b]Benchmarks for deaths averted per year:

- In 2009, 1.35 million deaths from tuberculosis in non-HIV infected persons (http://bit.ly/bZL4nh)
- In 2010, malaria caused 655,000 deaths worldwide (http://bit.ly/b5frdR)
- Rotavirus caused 352,000–592,000 deaths worldwide (http://1.usa.gov/GVqTKp)
- U.S. influenza deaths: 27,100–55,700 deaths (http://bit.ly/fPDqpf)
- U.S. septicemia deaths: 34,800 in 2007; U.S. bacterial sepsis of newborn deaths: 820 in 2007 (http://1.usa.gov/rbLHiL)
- U.S. hepatitis C deaths in 2007: rate of 4.58 per 100,000 or 1,400 in population of 300 million (http://1.usa.gov/GRlhnA)

These mortality levels may be overstated by large amount as we did not adjust for effectiveness. If on average we presume any program has 50 percent effectiveness then perhaps these boundaries should be cut by 50 percent to spread vaccine candidates more effectively across the categories.

[c]Case incidence:

- U.S. congenital CMV: 30,000/yr in newborns (http://bit.ly/hvVDz)
- U.S. influenza hospitalizations: 42,000 in 2009–2010 season (http://1.usa.gov/GKxQw7)
- U.S. influenza lab-tested specimens positive for influenza: 157,000 of 757,000 tested in 2009–2010 (a high-incidence season—pandemic level). Usual season level about 25 percent of this, or 39,000. Since lab specimens are collected in office visits, influenza-like illness generated at least 757,000 office visits (http://1.usa.gov/GKxQw7)
- U.S. influenza cases estimated at 24.7 million (2003 population) (Molinari et al., 2007)
- U.S. hepatitis C: estimated 2,600 new cases in 2009, with decreasing incidence over time (http://1.usa.gov/GJg90E)
- Worldwide incidence malaria: an estimated 225 million cases in 2009 (http://bit.ly/syqsq5)

[d]DALYs averted and QALYs saved:

- DALYs by cause globally:
  - 72.6 million DALYs due to diarrheal diseases lost in 2004 worldwide
  - 34.2 million DALYs due to tuberculosis worldwide in 2004
  - 33.9 million DALYs worldwide in 2004 due to malaria
  - 9.9 million pertussis, 14.8 million measles, 173,000 diphtheria, 5.3 million tetanus, 1.7 million schistosomiasis, 1.0 million hookworm disease cases
  - WHO data spreadsheet available at http://bit.ly/bmeNUc
- The diseases above seem to fall into four groups (>50 million, 20–50 million, 1–20 million, and <1 million); the DALY cutoffs have been set to reflect these groupings. Net DALYs averted may be considerably less since figures above assume 100 percent effectiveness with no DALYs due to side effects; boundaries between categories have been set assuming 50 percent net effectiveness.
- QALYs for United States by cause for benchmarks:
  - Universal influenza vaccination might save 34,000 QALYs (http://bit.ly/jgyd14)
- QALY boundaries have been set to reflect a very large amount of saved QALYs as in a pandemic, an average flu-year sized program, something smaller than flu, and a program which is quite small in overall QALY benefit.

[e]One-time costs based on expert judgment of the committee. We do not assume these differ for vaccines produced for global use versus for use in the United States.

[f]Net direct costs boundaries should be set to divide the universe of viable vaccine candidates that do not actually produce savings into about tertiles. The boundaries here are set considering U.S. net costs and then doubling these for global vaccines. It is important to remember these net costs are the costs of vaccination net of the costs of health care for the disease in absence of the proposed vaccine (or net over an existing vaccine upon which it is desired to improve with the new vaccine). As of this writing, these boundaries have no empirical basis.

[g]Productivity gains are notoriously hard to estimate. For example, in a 2007 paper published in Vaccine, Molinari et al. estimate $16.3 billion lost annually due to illness and loss of life because of influenza in the United States, based on estimated 24.7 million cases (2003 demographics: 294 million population). The authors used an average $145 per day wage rate and discounted future years of wages lost to present value (Molinari et al., 2007). Boundaries for categories in the United States were set to emphasize large, medium, small, and very small wage loss using influenza as high-impact disease. Global categories have been set equal to the United States because U.S. productivity costs represent a substantial fraction of world productivity. Global losses to tuberculosis estimated at $12 billion in 2011 due to illness and to premature deaths (http://bit.ly/GJUHJ9). Given that this is roughly on same order of magnitude as influenza in the United States, we choose to set these categories the same until better data are at hand.

[h]Note that the computational model does not compute profits as producer costs are not included.

and disease epidemiology to be brought to bear on the issue at hand. The model then uses these components to compute quantities for which we do not have data and which are less accessible to expert opinion.

Five of the six attributes calculated by the computational submodel are *annual* quantities:

1. Annual number of premature deaths averted
2. Annual number of incident cases prevented
3. QALYs gained (or DALYs averted) per year
4. Annual net direct costs (savings) due to the vaccine
5. Annual net workforce productivity gained (in dollar-equivalents)

The sixth quantitative attribute is cost-effectiveness: the net present value of current and future costs of using the vaccine divided by the net present value of gains in QALYs due to the vaccine (or net reduction in DALYs). The cost-effectiveness ratio is an indicator of the efficiency of investing in the vaccine as a method to produce gains in QALYs (Gold et al., 1996). Although related to the annual measures above, the cost-effectiveness ratio considers both present and future benefits and costs of the vaccine to members of the population and is not derived directly from those quantities and is not redundant with information in those quantities.

The computational submodel in SMART Vaccines may be thought of principally as a population simulation run over time in 1-year cycles. The submodel is run twice, once assuming that the vaccine is not available and once assuming that the vaccine is in routine use in the population.

Parameters for this second run are set to reflect the assumption that the vaccine is at its steady state of use in the population. This assumption is used to avoid the transient effects caused by the start up and propagation of the vaccine through the age cohorts of the population until the point of full benefit for the population has been reached; by not including these transient effects, the computed annualized variables reflect the average benefit of the vaccine in steady state.

Consider the following example: Human papilloma virus (HPV) preventive vaccine is given to adolescent girls with the intent of conferring lifelong immunity in the target population. In the computational submodel the steady state assumption is used to set the parameters so that women in *all* age cohorts are assumed to have been offered HPV vaccination when they were adolescents. This assumption is used to evaluate the vaccine's impact as if the present population has had it available for steady-state use over the long term. This would otherwise require using a dynamic population model over a long period of time to simulate vaccination in each suc-

cessive age cohort of adolescents until the members of the first cohort have aged through their lifetimes.

Annual Number of Premature Deaths and Incident Cases Prevented

The computational submodel uses a life-table to simulate all-cause mortality in the current population. Data about case fatalities associated with the target disease are used to estimate all-cause mortality in the absence of the target disease. Data about age-specific health-related quality of life in the population serve as the baseline data for the no-vaccine simulation run.

Data about the target disease incidence and morbidity—including by age and by sex where such data are available—are entered for computation. Data from the literature and expert opinion are used to approximate the quality of life and health care costs for typical manifestations of the disease during its course. The assumed characteristics of the vaccine in use—such as coverage in the population, effectiveness, and duration of immunity—are inputs based on expert user judgments concerning the vaccine candidate being targeted for development.

With these data and assumptions, the difference between the number of deaths in the simulated population observed in the two runs—one run assuming no vaccine and one assuming vaccine use in steady state—is used to measure the attribute "Premature deaths averted per year." Similarly, the difference between the incident cases of the target disease in the two runs is used to measure the attribute "Incident cases prevented annually." These two attributes allow the user to see the estimated consequences of having the vaccine's benefits available to the current population. These are, of course, hypothetical benefits, but they should be meaningful measures that allow users to understand what the benefits of the vaccine candidates would be if the vaccines were widely used today.

In SMART Vaccines Beta, the committee converted the continuous scales of deaths averted per year and incident cases prevented per year into categorical scales for two reasons. First, the computations in SMART Vaccines Beta are just approximations, and the committee does not wish to have users over-interpret the precision of the computational submodel's output. A second, technical reason for categorization is that the range through which attributes vary can affect their effective weights in the multi-attribute utility model. Until the characteristics of the set of vaccine candidates to be appraised by the model are known, treating the quantitative attributes as categorical rather than continuous variables ameliorates the challenges in assigning weights.

The committee has attempted to set the categorical boundaries in a

meaningful fashion. As noted in the footnotes to Table 2-1, the boundaries are benchmarked against known causes of death and case incidences. The topmost level for each attribute is set such that it represents the largest number of deaths (or incident cases) caused by vaccine-preventable diseases and subsequent categories with decreasing number of deaths. If one were to use a baseball analogy, it could be suggested that Level 1 of the attributes would represent a "home run" and once the ball is over the wall it does not matter how far it goes beyond the wall. Levels 2, 3, and 4 represent smaller and smaller accomplishments. Users should consider the relative difference in achievement between Level 1 and Level 4 when ranking the importance of the attribute.

QALYs Gained or DALYs Averted per Year

The third annualized quantitative attribute, QALYs gained or DALYs averted, is also computed using the difference between the two 1-year runs of the simulation. The HRQOL values for manifestations of a typical course of the targeted disease are input as deviations ("tolls") from usual age-specific HRQOL, along with the duration of the deviation.

For example, in the United States the disutility toll for influenza illness with an outpatient visit to a doctor is estimated to be 0.13 on the HUI2 scale and to have duration of 5 days (0.0137 years) (see Appendix B). Forty percent of influenza cases are assumed to have this level of disutility. One-half of 1 percent of cases are hospitalized, with an estimated disutility toll of 0.2 and an estimated duration of 0.0137 years. The remaining 59.5 percent of cases are people with a sufficiently mild case of the disease that they do not have an outpatient visit, and they are estimated to have disutility toll of 0.09 for the same duration. Based on U.S. national data, a man aged 45–49 averages HRQOL of 0.86 each year, as measured by the HUI2. All men of this age in the simulation who suffer influenza during the 1-year run of the model average a HRQOL change of 0.107 QALYs (that is, (0.4)(–0.13) + (0.005)(–0.2) + (0.595)(0.09)). So instead of an average of 0.86 QALYs accrued during the year, a man this age would accrue 0.75 QALYs (that is, 0.86–0.107) during the year in which he had influenza.

In the current version, SMART Vaccines Beta does not allow the same person to have influenza more than one time per year. In the simulation run with vaccine present, this same person will have a reduced chance of having influenza depending on vaccine coverage and effectiveness, so the QALYs loss will be less on average. Of course there are small chances of vaccine-related morbidity, and the disutility tolls for this are averaged into the calculations for people who are vaccinated.

Disease- and vaccine-related mortality are both presumed to occur at

mid-year, so instances of mortality in the simulation incur a loss of one-half of the potential age-specific QALYs to be accrued for that year. We anticipate the QALYs loss due to the disease to be more without the vaccine than with the vaccine in steady-state use, and the difference in average QALYs loss between the two runs of the simulation gives the QALYs gained in the population as a result of having the vaccine available.

DALYs express the sum of years of life lost (YLL) due to premature mortality plus years lived with disability (YLD). YLL is obtained by calculating the difference between life expectancy of the target population—currently around 90 years, based on the life expectancy of longest-lived Japanese women—and the life expectancy in the actual population. The difference between the target and actual life expectancy in any population is years of life lost (YLL). To calculate YLD, the number of years lived with disability is multiplied by a weight factor that reflects the severity of the disease, where a value of 0 means "perfect health" and 1 means "dead." However, unlike QALY weights, DALY weights are determined by a panel of experts and not derived from patient populations (Murray and Lopez, 1996).

Also, depending on a person's age, the DALYs indicate various weights on the outcome that are designed to reflect workplace productivity. Persons in peak productivity years (approximately 20–40 years) receive higher weights than young children and persons over 80. Representative DALY weights for various conditions include 0.105 for diarrhea, 0.229 for deafness, 0.271 for fractured leg, 0.552 for diabetes with blindness, and 0.666 for Alzheimer's disease (WHO, 2004). For tuberculosis, DALYs are estimated to be 0.271.

Annual Net Direct Costs (Savings) and Net Workforce Productivity Gained

Inputs such as average health care costs and frequencies of health care usage are used to compute health care costs of the disease in absence of the vaccine for the first run of the simulation. Because the number of cases will be reduced when the vaccine is in stable use, the computed total costs of health care for the disease will be less in the second run of the simulation.

But in the second run, with the vaccine in stable use, there will be costs of administering the vaccine and taking care of adverse events associated with the vaccine that must be taken into account. These costs are added to the health care costs of caring for the disease in the second run. The difference between the total costs in the two simulation runs is the annual net health care cost of preventing and treating the disease, the attribute entered into the MAU value model (if selected by the user). If the costs

in the vaccine run are less than the costs in the no-vaccine run, then the difference represents a net savings.

The annual net gain in workforce productivity is computed in a similar fashion. For persons older than 15 the time lost to the illness is valued at the national average age-specific wage rate. For children aged 15 or younger (those most likely to have an adult take time away from work to care for them), the time lost to the illness is valued at the national average age-specific wage rate for one person who is the average age of a parent for the particular age of the child. The net gain in workforce productivity is then the average reduction in dollar-valued time lost due to the disease between the two runs of the simulation.

Cost-Effectiveness

The cost-effectiveness attribute of the vaccine is computed differently. SMART Vaccines Beta uses U.S. guidelines for computing the cost-effectiveness of a health intervention in a population (Gold et al., 1996). In the simulation model this is done by age cohort in the current population, assuming benefits of having the vaccine available begin now for each cohort. The simulation is run for each age cohort until all members of that cohort reach age 100 or have died. This is done twice, once assuming that no vaccine is available, and once assuming the vaccine to be in stable use at the start of the simulation.

In the simulation the costs of vaccination are incurred according to a schedule of vaccination determined by assumed length of immunity. For example, if immunity is presumed to last 10 years, then one-tenth of the cohort is immunized in each year. For each cohort in each year of the simulation, the net health benefits measured as QALYs gained or DALYs averted are computed in the same manner as the annual measure described earlier. Similarly, the net health care costs are computed in each year of the simulation in a manner similar to the annual measures. But here the similarity to the annual measures ends.

From "now"—the start of the two simulations for each age cohort—and into the future until all persons in that cohort are aged 100 or deceased, the net health care costs are arranged as a time series into the future, with one entry per year. If "now" is time 0, and each year into the future is labeled 1, 2, 3, . . . , up to n, the final year of the simulation for that cohort, then we let the net cost in year i be NC_i for i=1, . . ., n. The present value (PV) of NC_i is the amount that, if set aside now at an annual interest rate r, would be worth NC_i i years into the future.

$$PV(NC_i) = \frac{NC_i}{(1+r)^i}$$

Another way to say this is that the amount NC_i to be received *i* years in the future has been discounted at a rate *r* to present value. The stream of net costs, NC_1, NC_2, . . ., NC_n, is discounted to present value with each cost being discounted the appropriate number of years, and the costs are then summed to get the net present value of lifetime health care costs (or savings) for each age cohort. This sum is the numerator of the cost-effectiveness ratio.

The denominator of the cost-effectiveness ratio is the sum of the corresponding stream of net QALY gains, one for each year into the future, where each of these annual gains is also discounted to present value at the *same* discount rate as were the costs in the numerator. In their guides to cost-effectiveness computations, Keeler and Cretin (1983) and Gold et al. (1996) discuss the rationale and importance for using the same discount rate in the numerator and denominator of the cost-effectiveness ratio. Using different discount rates—especially for preventive health care, where costs may be incurred years before benefits—can lead to incorrect and paradoxical results. The discount rate is an input to the model. In the United States the currently recommended discount rate is 3 percent for standardized cost-effectiveness models of health care.

If the numerator of the cost-effectiveness ratio is negative—that is, if the program is producing savings—then the new vaccine is a good investment indeed. However even if it is not cost-saving—and many health care interventions are not—it may still offer health benefits to the population. These benefits are measured in QALYs gained, and the cost-effectiveness ratio measures the anticipated cost per QALYs gained by individuals in the population, a measure of the efficiency with which the investment "buys" health.

In SMART Vaccines Beta this is a simple simulation, equivalent to running one simulation of the full population with all cohorts together until all members are age 100 or deceased. The figure of 100 was used as a cutoff because so few people live past that age and also because the number offered the committee a stopping point for the beta model simulation.

As noted earlier, the IOM report *Vaccines for the 21st Century*, issued in 2000, used only one of the 29 attributes—cost-effectiveness—to establish four priority groups. That report specified the highest priority, Level I (most favorable), as including those vaccine candidates projected to save money and to produce QALYs. In the remaining cases, where vaccination programs did not help save money, candidate vaccines were grouped according to efficiency of the investment: Level II (more favorable) included those where $/QALY < $10,000, Level III (favorable) included those candidates

for which \$10,000 < \$/QALY < \$100,000, and Level IV (less favorable) was for candidates for which \$/QALY > \$100,000 for the vaccine.

Since that report there has been debate about which points to use as cost-effectiveness thresholds. Much of the cost-effectiveness literature in the United States since the early 1990s has used a threshold of \$50,000/QALY to distinguish between medical interventions that are attractive and unattractive investments. Similarly, in the United Kingdom, the National Institute for Clinical Excellence has used an explicit threshold of £30,000/QALY. In the United States it has been argued recently that the threshold should be closer to \$200,000/QALY. The World Health Organization has proposed using a threshold in developing countries of three times the per-capita gross domestic product (Braithwaite et al., 2008; Commission on Macroeconomics and Health, 2001). The committee used larger thresholds for efficiency than the previous report in order to reflect the more recent literature, but this is still a matter of great subjectivity and debate (Weinstein, 2008).

Foundation for the value submodel

The value submodel uses the subset of attributes selected by the user from the 29 attributes listed in Table 2-1. Let us assume that the user has selected $K < 29$ of the attributes. We renumber these K attributes to reflect the rank order of importance that has been given to the attributes by the user: $A_1, A_2, \ldots, A_K$, where A_1 is the most important and A_K the least important in the set of attributes. Some of these attributes may be among the quantitative attributes and some among the qualitative.

In SMART Vaccines Beta, each of these attributes has between 2 and 5 levels, depending on the attribute. Each level of each attribute is assigned a single-attribute utility score between 0 (the least preferred level) and 1 (the most preferred level). The specific single-attribute scores for the various levels of an attribute with a given numbers of levels are shown in Table 2-2.

Let $i = 1, 2, \ldots, M$ and V_i be vaccine candidate i, one among a set of M vaccines being ranked. If the level describing vaccine V_i on attribute A_j is denoted as L_{ij} then each vaccine is fully described for the model as a vector of K levels:

$$V_i = (L_{i1}, L_{i2}, \ldots, L_{iK})$$

There is a vector of single attribute scores, SV_i, corresponding to the vector of levels, with the scores taken from the corresponding entries in Table 2-2:

$$SV_i = (S_{i1}, S_{i2}, \ldots, S_{iK})$$

As described earlier, the rank order centroid method is used in SMART Vaccines Beta to compute a weight for each attribute, w_i, i=1, 2, . . . , K (example weights are shown in Table 2-3). Finally, the value submodel computes a value score for V_i by using the weights to form a weighted sum of the single-attribute scores for the levels:

$$Value\ Score(V_i) = 100 \sum_{j=1}^{K} w_j S_{ij}$$

S_{ij} scores are from the vector of scores above, which in turn represent the achievement of V_i on each attribute the user has selected. These are weighted by the importance given to each attribute by the user, and then summed. Because the single attribute scores for each attribute range from 0 to 1.0, and because the weights across the attributes sum to 1.0, the weighted sum of scores varies from 0 to 1.0. This weighted sum is multiplied by 100 to produce a range from 0 to 100.

If a vaccine were "perfect"—that is, the vaccine achieved the most preferred level (a single attribute score of 1.0) for each attribute selected—then it would receive a value score of 100. If it achieved the least preferred level on each attribute, it would have a single attribute value score of 0 on every attribute and thus a weighted sum of 0.

Of course, no vaccine candidate will be the most preferred or least preferred on every attribute. Depending on its level of achievement on the selected attributes and depending on the weights given to the attributes by the user, vaccines will have value scores between 0 and 100. The rank order of vaccines according to their value scores is the priority order of the vaccine candidates under the logic of the multi-attribute utility framework as implemented here.

TABLE 2-2

Single-Attribute Utility Scores for the Levels of Attributes with Varying Numbers of Levels

Number of Levels	Scores for the Attribute Levels				
	Level 1 (most preferred)	Level 2	Level 3	Level 4	Level 5 (least preferred)
2 levels	1.0	0.0	N/A	N/A	N/A
3 levels	1.0	0.5	0.0	N/A	N/A
4 levels	1.0	0.67	0.33	0.0	N/A
5 levels	1.0	0.75	0.5	0.25	0.0

TABLE 2-3

Attribute Weighting Using Rank Order Centroid Method

	Number of Attributes Selected													
Rank	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
1*	0.750	0.611	0.521	0.457	0.408	0.370	0.340	0.314	0.293	0.275	0.259	0.245	0.232	0.221
2	0.250	0.278	0.271	0.257	0.242	0.228	0.215	0.203	0.193	0.184	0.175	0.168	0.161	0.155
3		0.111	0.146	0.157	0.158	0.156	0.152	0.148	0.143	0.138	0.134	0.129	0.125	0.121
4			0.063	0.090	0.103	0.109	0.111	0.111	0.110	0.108	0.106	0.104	0.101	0.099
5				0.040	0.061	0.073	0.079	0.083	0.085	0.085	0.085	0.084	0.083	0.082
6					0.028	0.044	0.054	0.061	0.065	0.067	0.068	0.069	0.069	0.069
7						0.020	0.033	0.042	0.048	0.052	0.054	0.056	0.057	0.058
8							0.016	0.026	0.034	0.039	0.043	0.045	0.047	0.048
9								0.012	0.021	0.027	0.032	0.036	0.038	0.040
10									0.010	0.017	0.023	0.027	0.030	0.033
11										0.008	0.015	0.019	0.023	0.026
12											0.007	0.012	0.017	0.020
13												0.006	0.011	0.014
14													0.005	0.009
15														0.004
Total**	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

*Highest rank = 1.

**Totals may not add to 1.00 due to rounding.

In SMART Vaccines Beta, the weights are computed from a strict rank order of attributes supplied by the user. In future versions, the committee expects that this approximation will be replaced by a more elaborate elicitation of weights, perhaps using a hierarchical clustering of the selected attributes, and based at least in part on direct ratio estimates of the importance of the ranges of value described by each attribute. This elaboration will require considerable attention to the user interface design and was beyond the current demonstration of concept exercise.

Appendix B lists the computations described in this chapter.

User entries and prioritization categories

It is important that all of the vaccine candidates to be prioritized are assessed using the same criteria and measures. At the very outset the user must make two choices that must apply to all vaccine candidates in the set of candidates to be prioritized. The first choice is which metric will be used to measure health benefits—QALYs gained or DALYs averted. The second choice is the selection of attributes by which the value of the vaccines to be compared and prioritized will be measured in the SMART Vaccines Beta.

The reason that these choices, once made, are fixed across all vaccine candidates is that the priorities must be determined using the same criteria and measures for each alternative vaccine. The value scores computed for the alternative vaccines are only meaningful relative to one another. These scores have no intrinsic meaning per se, and they gain validity for comparisons only through the fact that exactly the same basis for evaluation is used for all the alternatives being considered.

Demographic inputs

The computational submodel requires knowledge of the target population for the vaccine. If vaccines are being prioritized for one country, then that country's population is the one for which data are needed. If vaccines are being prioritized across a region with more than one country (say, a "supernation" entity such as the Pan American Health Organization, which has dozens of member countries), the combined population of the region is the target. SMART Vaccines cannot at this time aggregate data across countries, although the current model can deal with multiple populations that have been aggregated a priori and then entered into SMART Vaccines as a new "region."

The population is segmented by age groups—infants, children aged 1 to 4, and then 5-year age bins up to age 99—and also divided into males and

females. The average population is represented by the most recent available census data, with the number living in each age range and a standard life table.

Age-specific average health-related quality-of-life (HUI2) weights and average hourly wage rates (parental wage rates for persons aged less than 15) are also used in the software. In the United States, the life table data are available from the National Center for Health Statistics and the U.S. Census Bureau; the HUI2 data are available from population surveys (see, for example, Fryback et al., 2007; Luo et al., 2009); and the wage data are available from the Bureau of Labor Statistics.

International population data, which are available through the World Health Organization, have been used to pre-populate the data fields and are selectable by country. In the current version of the software, data for hypothetical vaccines for three conditions in South Africa and the United States have been entered. Vaccine selection criteria are discussed in Chapter 3. HUI2 data are not generally available outside of the United States and Canada unless special surveys have been completed, and DALY weights may be used instead. Wage data outside of developed countries where these statistics are usually maintained will have to be estimated subjectively.

SMART Vaccines Beta allows assumptions to be tailored for subgroups of special interest or priority. For example, among persons with tuberculosis the subgroup with HIV infections is of special interest both because immunization may not be effective and because tuberculosis incidence is higher in this subgroup.

Infants and children or military personnel might also be the special targets of particular vaccination programs. The impact of the immunization program in a special population is controlled by different input constants than those used for the "usual" male and female populations. If a special population is specified, it must be subtracted from the general male and female populations so that the total population is the sum of the three parts; in SMART Vaccines Beta, this subtraction must be done outside the program before inputting data.

Disease epidemiology and clinical inputs

The computational submodel requires information on the incidence of the disease by sex and by age range as well as case fatality proportions. The time course of the disease is modeled by inputting time-limited states of illness without outpatient visits, of illness with outpatient visits, and of illness with hospitalization; the fraction of cases experiencing each of these; and the time that a typical person experiencing these states would spend in

the state. Permanent disability is modeled as a separate outcome, and the percent of cases experiencing permanent disability is entered.

Economic inputs

The aggregate incremental costs of vaccination versus treatment of the disease are computed in the computational submodel shown in Figure 2-1. This submodel estimates the net incremental costs (or savings) of having a vaccine program versus not having one. The estimation is done by simulating the incidence of disease cases and then simulating the utilization of the units of care, such as visits to a physician's office, a day of hospitalization, medications, and so forth.

To compute the costs of treatment for the target disease, common events in the care of patients, such as over-the-counter medications, a visit to a physician's office, emergency department visits, and days of hospitalization, are needed as inputs. To compute the costs of vaccination, it is necessary to input the number of doses needed, the cost per dose for vaccine, and the cost per dose to administer the vaccine. Estimates for one-time costs are also entered: research costs for development of the vaccine, costs of the trials and data needed for licensure, and any one-time start-up costs for the initiation of a vaccination program.

The committee recognizes that the modeling of costs is at best a broad-brush approximation. But it is simply not possible—especially for hypothetical vaccines—to carry out a microscopic costing of all possible inputs, modeling the various intricacies of the vaccine delivery process. Accordingly, this model allows users to specify the main components of cost in a summary form common to all vaccines. It will require users to roll many aspects of costs into a few generic slots. For example, cost per dose will need to account for manufacturing, storage, transportation, and suitable profits for all private entities involved in these steps, all in one input number. Sophisticated cost-effectiveness models used to evaluate existing vaccines may break this one input into many subparts in the future, but for now SMART Vaccines Beta uses rough estimates for hypothetical new vaccines.

Vaccine inputs

The health impacts of vaccination are modeled using estimated duration of immunity conferred, incidence of the disease, and vaccine-associated complications that may be experienced. The effectiveness of the vaccine is modeled by inputs quantifying anticipated uptake or coverage in the vari-

ous age groups targeted for vaccination. These estimates should take into account public perceptions of the disease; anticipated vaccine-induced complications, including potential deaths resulting due to the vaccine; and how well the vaccination schedule and doses required fit existing schedules in the health system. The herd immunity threshold is set at 100 percent in SMART Vaccines.

Disease burden summary measures

A number of measures of the health burden of disease are incorporated in the model. Some users may prefer to use premature deaths averted or cases prevented. Others may prefer measures such as DALYs averted or QALYs gained—measures that combine the effects of both mortality and morbidity into one number.

To compute QALYs, the model must know about the age-specific average health-related quality-of-life (HRQOL) as measured in the population. The impacts of the disease that could be prevented by vaccination are modeled by assessing a decrement, or "toll," from the age-specific average for the various health states that an affected person might experience. The reduced HRQOL is then weighted by the length of time that the person is affected in order to get QALYs lost to the disease. SMART Vaccines Beta uses the Health Utilities Index Mark 2 (HUI2) to measure HRQOL, as did the 2000 IOM report.

The age- and sex-specific average population baseline HUI2 weights are input as population characteristics. For example, an average observed HUI2 weight of 0.81 is reported for women aged 60 to 64 years in the United States. The HRQOL tolls for the health states associated with the disease must be estimated. For example, using data from the U.S. National Health Measurement Study (Fryback, 2009), the estimated average decrement in HUI2 weight for adults who report "cough" versus those who do not report "cough," age-adjusted, is –0.09. This is used as the daily decrement, or toll, from the population average for each day with influenza not requiring an outpatient health care visit. The decrement is –0.13 for those reporting fever, which is used as the daily toll in HUI2 weight for persons requiring an outpatient visit for influenza.

Cough and fever are not adjusted here for co-occurrence of other symptoms but rather are used as markers for health states that could be equivalent, on average, to the corresponding influenza health states. A day of hospitalization incurs a toll of –0.2 based on cost–utility analyses from the literature that involve acute illness hospitalization. The 2000 report from the IOM study used subjective role playing by committee members

using the HUI2 scales to record their level of functioning and symptoms for health states they were imagining. In the decade since that report more data sources have appeared, such as the National Health Measurement Study and published analyses, from which to estimate HUI2 tolls to model the time course of diseases.

Similarly, HUI2 weights must be estimated for permanent disabilities resulting from disease- and vaccine-related complications. Estimating the quantities needed for the computational submodel can be vexing, as the needed data are rarely available or reported in the literature. This is further discussed in Chapter 3. If the user elects to compute using DALYs, then similar average health and disability weights must be estimated for disease states.

Other attributes

If the user selects any other attributes listed in Table 2-1, then appropriate levels of the attributes for each vaccine candidate should be entered by the user. All of these attributes are categorical in nature, with some requiring a simple "yes" or "no" entry. The users will need to make subjective assessments where necessary to make the appropriate categorizations.

Attribute selection and ranking is accomplished by a drag-and-drop interface (which can be seen in the screenshots of the SMART Vaccines Beta found in Chapter 3). Attributes are selected one at a time and dropped into the ranking box. The selection and ranking of attributes is done once, and all the vaccine candidates are evaluated using the same criteria with fixed weights. This does not prohibit the user from entertaining "What if?" scenarios by changing the attribute selection or the rankings—or both—to see how the value score is affected. But any one set of priorities for vaccine candidates should be based on only one set of attributes and weights.

Ranking method

In SMART Vaccines Beta the user-selected attributes are not all equally important in establishing priorities. As discussed earlier in this chapter, the rank order of attributes is used to create a set of weights for the factors—the w_js in the equation that is used to compute priority value scores for the vaccines using the Edwards and Barron additive multi-attribute approach (Edwards and Barron, 1994).

This method for using the number and rank order of attributes to determine the weights gives most of the weight to the first few attributes in the rank order. The weights are assigned by an approximation algorithm—

rank order centroids—as discussed earlier in this chapter. Weights in the additive multi-attribute model are each bounded by 0 and 1, and they collectively sum to 1.

A vector of *n* weights, each a number between 0 and 1, may be viewed as a point in the *n*-dimension cube. Suppose a proper rank order of the set of weights is specified. Consider the subspace of the *n*-dimension cube formed by the set of all weight vectors that are consistent with the specified rank order and that sum to 1. The vertices (extreme points) of this subset form a simplex, and averaging the coordinates of the *n* vertices gives the centroid of the simplex. The rank order centroid algorithm takes this centroid as the set of weights to be used in the additive multi-attribute model for computing priority scores. It can be thought of as the average of all sets of weights consistent with the user-specified rank order; it is also the mean of a uniform probability distribution over the simplex bounded by the *n* vertices. Given no other information than the rank order of weights, the rank order centroid is the best statistical estimator for the vector of weights for the additive multi-attribute utility model.

Further development of SMART Vaccines can allow users to modify this set of weights by increasing or decreasing single attribute weights while maintaining the rank order. This would give selected attributes slightly more or less importance in the priority calculations. The rank order centroid can be easily extended to include ties in the rank order. But, as discussed by Barron and Barrett (1996), the key information is contained in the rank ordering, and refinements to the weights consistent with the rank order provide, at most, second-order changes.

There is one important factor that influences the weights: the *number* of attributes selected. Table 2-3 displays examples of rank order centroid weights for various numbers of attributes in the model. The first few attributes receive most of the total weight using this method, and adding more factors to the prioritization problem has a decreasing effect on the final priority ordering of vaccine candidates.

The committee considered limiting the number of weights to some arbitrary number (e.g., seven attributes). After considering this, the committee concluded that introducing a limit on the number of allowed weights would not affect the model much one way or the other, but proceeding without a limit would satisfy those users who really did wish to add a large number of attributes to the model. Users should be aware (see Table 2-3) that once 10 attributes are included, the weight on each subsequent weight is smaller than 0.01 (1 percent) and is extremely unlikely to affect rankings meaningfully. Indeed, even with just five attributes ranked, the weight on the fifth is only 0.04, and with seven attributes, the weight on the seventh is

only 0.02. In both cases, the final attribute has little effect on final rankings unless candidate vaccines diverge dramatically on the ranked dimension.

Moreover, the current model does not allow for ties in attributes because of the programming complexity in allowing ties in the rank order centroid process. Subsequent modifications to the software will allow users to establish their own rankings independent of this process, including the possibility of beginning with the rank order centroid weights and then altering pairs of them to allow for ties. For example, if users had five items ranked and wished to establish the top two as having equal weights, then the weights (say, 0.457 and 0.257) created by the rank order centroid method could be averaged as 0.357.

The meaning and interpretation of weights

This chapter would not be complete without a discussion of the meaning of the weights in the additive multi-attribute utility model. It is tempting to say, as indicated above, that these represent the importance of the different attributes in the prioritization problem. This is a common, but not technically accurate understanding.

The mathematical use of the weights is to change the natural attribute scales into a common unit of value. For each attribute in Table 2-1, there is a "most preferred" and "least preferred" level or category of the attribute, where "most preferred" means leading to the highest contribution to the priority value of the vaccine candidate. These most and least preferred categories define the range of value through which that attribute can change.

If the user defines a single-attribute value function, then each attribute will be equal to 1.0 for the most preferred category and to 0.0 for the least preferred one. Other categories between these are scaled linearly between these end values of the scale. A two-level attribute is simply scaled 1 or 0. A three-level attribute is scaled 1.0, 0.5, and 0.0. A four-level attribute will be scored as 1.0 if the attribute is in the highest category, 0.67 if in the second most preferred, 0.33 in the next lower category, and 0.0 in the lowest category. And, a five-level attribute is scaled 1.0, 0.75, 0.50, 0.25, and 0.0 from the most to the least preferred category.

Again, these linear scales are an approximation used to simplify the model for users. The next step in modeling is to allow users to specify the spacing between the categories on these single-attribute scales.

Consider two attributes in Table 2-1, say Cost-Effectiveness (CE) and Serious Pandemic Potential (SPP). The least-preferred level of CE is Level 4, and the least-preferred level of SPP is Level 2. Suppose there is a vaccine

candidate that has CE of Level 4 and SPP of Level 2. To determine which should have the higher weight—CE or SPP—the question arises: Which change improves the overall priority of the vaccine by the larger amount, changing CE to its Level 1 or changing SPP to its Level 1? If the answer is to change CE, then the weight assigned to CE should be larger than the weight assigned to SPP, and vice versa.

In the attribute selection and weighting phase of this model, the user is asked to pick those attributes from Table 2-1 that should serve as the basis of comparison for all vaccine candidates. The most- and least-preferred levels of each attribute are displayed to aid this choice. The user is instructed to pick the subset of attributes for which a change from lowest to highest level marks a significant change in priority of a vaccine. This subset is then to be rank ordered using exactly the same question as above—sorting the attributes pair-wise according to how much change in priority is implied by changing attributes from least to most preferred levels. The attribute at the top of the user's rank order should have the largest implied change in overall priority when it changes from least to most preferred, and the attribute at the bottom of the user's rank order will result in the least change in priority when it changes from the least- to the most-preferred level.

Selecting more than seven or eight attributes results in diminished or negligible weights for attributes ranked below 8 (see Table 2-3). This is not to say that the user is restricted from selecting all of the 29 attributes in Table 2-1. But it is true that a handful of attributes generally contain the most weight in establishing priorities. Adding additional attributes beyond seven or eight is unlikely to lead to a decisive change in the priority order of the vaccine candidates. However, Edwards, in an extended case study using multi-attribute utility theory to rank different desegregation plans for the Los Angeles school district (Edwards, 1979), observed that if a number of groups holding strong opinions are attempting to negotiate differences and agree on a ranking of decision alternatives, then one can end up including many attributes to make sure that each group sees all attributes of importance to its viewpoint in the final model. Edwards ended up using more than 100 attributes to tackle this challenge. But such efforts are very rare. Five to fifteen attributes in the final model is much more common (von Winterfeldt and Edwards, 1986).

The risk of double counting

The committee understands that the model (as presented) carries some risk of double counting some attributes. Double counting in multi-attribute

utility theory means putting weight on a pair (or a larger set) of attributes that are highly correlated. The higher the correlation between the attributes, the higher is the chance for double counting. The consequence of double counting is that users who include highly correlated attributes will (perhaps inadvertently) put more weight on the "concept" measured by these attributes than intended. The effect on final value scores will depend in part on how many attributes are included by the user and how high the correlated attributes are placed in the user's ranking. If the user includes 10 to 15 attributes and places the highly correlated ones near the bottom of the list, the rankings will not change much, since they will receive little weight anyway. However, placing two highly correlated attributes at the top of a short list in the value function can lead to greater emphasis on that underlying concept than perhaps intended.

To avoid double counting, the committee selected for inclusion only those value attributes that are intended to capture something desirable about a vaccine that (because of limitations to the sub-sectioning of population variables) could not be captured directly in computed attributes. Thus the committee sought to exclude from consideration qualitative attributes that were otherwise used in the computation of quantitative attributes.

For example, the rate of uptake of a vaccine and a vaccine's efficacy rate are used in the calculation of the number of persons effectively vaccinated (and hence in the calculation of reduced disease burden). Thus to include the rate of uptake or the efficacy rate as separate qualitative attributes would create the risk of double counting, and hence they are omitted.

The most obvious of these double-counting risks would involve the use of DALY or QALY measures of health gains (or losses). While they are not exact mirror images of one another, the DALY and QALY measures are sufficiently similar that the SMART Vaccines software blocks the simultaneous use of both as indicated attributes. If users select an efficiency measure, they can use $/DALY or $/QALY, but not both.

There still remains some potential for double counting. For example, deaths averted contains some of the same information as DALYs averted (or QALYs gained), but these measures do contain independent information about the disease burden. Deaths averted would implicitly count each life saved as the same, no matter what the age of the individual. Life years saved or the more sophisticated QALYs saved contain the additional dimension of duration of the saved life. The 1985–1986 IOM study used infant mortality equivalents prevented for a similar reason—to account for the longevity of the surviving persons.

Similarly, combinations of one or more computed quantitative variables can closely correlate with other computed variables. For example,

premature deaths averted per year can be closely approximated by the combination of incident cases prevented per year and fatality proportions. Thus including all three of these variables would lead to double counting. These are not identical in the case where a disease has lingering side effects that cause mortality in later years. An example would be an infection that created a chronic condition with some later-year mortality risk. Presently, the software does not take into account such nuances of double counting. However, the committee's approach to dealing with these double-counting risks will necessarily involve more sophisticated programming in future versions of SMART Vaccines.

Discounting and inflation

Discounting involves making events that occur in the future commensurate with those that occur in the present. Future events are brought to a "present value" by discounting them at a pre-selected annual rate. The default value in SMART Vaccines Beta is set at a discount rate of 3 percent, which is presently the standard rate in the U.S. cost-effectiveness literature for health and medicine (see Gold et al., 1996; Ramsey et al., 2005), but the user can alter this at any point. With discounting at 3 percent, an event that occurs 1 year into the future—cost or benefit—carries only 97 percent as much value as one occurring in the present year. An event occurring 2 years into the future as a present value is weighted at 0.97^2, or 0.9409. One occurring 3 years later would have a present value weight of 0.97^3, or 0.9127. The greater the discount rate—for example, 5 percent instead of 3 percent—the faster these present-value weights diminish over time.

Perhaps most important, SMART Vaccines Beta discounts both costs and benefits at the same rate. The logic for this comes from an extended discussion in the literature of cost-effectiveness analysis that generally concludes that discounting benefits and costs at the same rate is the only appropriate strategy (Keeler and Cretin, 1983). In its current version, SMART Vaccines Beta does not allow for different discount rates for costs and benefits.

The user must use the same discount rate for all candidate vaccines that are being compared. Using different discount rates could seriously distort the comparisons between vaccines. However, a feature that allows one to specify different discount rates for different vaccines has been included in SMART Vaccines Beta.

A separate issue remains regarding the handling of anticipated inflation rates within the economy in which the vaccine comparisons are being made. This is a challenge that is distinct from the question of discounting.

Many cost–benefit analyses presume some background rate of inflation in the economy—for example, 2 percent per year—so that $1 million in costs this year becomes $1.02 million in costs the following year. Adjusting for inflation before discounting is equivalent to simply computing all future economic costs and benefits in today's dollars at today's prices and not worrying about what inflation might be in the future. This is the approach taken by the current model. This is done to avoid questions concerning what inflation rate is appropriate—consumer price inflation, monetary inflation, or sectoral inflation confined to health care. For example the inflationary growth in wages, used to measure worker productivity losses and gains, is quite different from inflation in the costs of health care, which itself is a market basket of services and durable goods with different rates of inflation.

Time horizon and uncertainty

This model always operates within a fixed 100-year time horizon. This has been done to simplify the software programming and to reduce the potential for coding errors. SMART Vaccines Beta does not include the ability to set distributions on the input parameters to reflect uncertainties relating to the disease or vaccine data. Therefore, in its current version the multi-attribute output values do not have standard errors. A dynamic sensitivity analysis may be required to detect changes in the priority score with changes in key values. These possibilities, along with others, are discussed in Chapter 3.

The committee's prototyping and testing efforts are described in Chapter 3, which also provides representative screenshots of SMART Vaccines Beta.

3

Data Evaluation and Software Development

The computational and the value submodels were developed in parallel and then integrated over a software platform that allows users to interact with and understand the relationships between the model input and output. The model development and interface development occurred concurrently. The committee received and adjusted its software development strategy based on feedback received from consultant concept evaluators.

In the following sections we describe the selection of vaccine candidates and of the related data to be fed into the model and then the actual model development and evaluation process.

Selection of vaccine candidates

The committee considered several hypothetical vaccine candidates from the perspectives of the United States and of a developing country. The committee agreed on South Africa as the particular developing country for this process since its income profile, its population, and its health, economic, and social priorities are vastly different from those of the United States. A second reason for selecting South Africa was the availability of input data for disease burden and vaccine estimates, which were necessary to populate and test the model.

The five hypothetical candidate vaccines chosen were a universal influenza vaccine plus vaccines against tuberculosis, group B streptococcus, malaria, and rotavirus. However, as the work of assembling the data for the first vaccines began, it became clear that the present scope of work

made it feasible to complete testing for only three of the candidate vaccines. The committee chose the universal influenza vaccine, the tuberculosis vaccine, and the group B streptococcal vaccine for this phase for a collection of reasons related to how the candidate vaccines helped capture various health, economic, and vaccine attributes.

For example, the universal influenza vaccine addresses a disease that is important in both high- and low-income countries, and the convenience of a single vaccine for all influenza strains would make it readily useful for all parts of the world. Furthermore, influenza affects all age groups and causes widespread morbidity worldwide. In contrast, tuberculosis does not pose a significant threat in high-income nations, thus a vaccine for tuberculosis would likely be of most use in the low- and middle-income countries. And group B streptococcus vaccine would be pertinent for both low- and high-income countries but is designed for administration to pregnant women (a special population) and would confer benefits to their infants. Additional information on the impact of influenza, tuberculosis, and group B streptococcus can be found in Boxes B-1, B-2, and B-3 in Appendix B.

Data sourcing and analysis

In its data-gathering process, the committee did not attempt to develop the best or most detailed estimates about each disease. The objective was instead to obtain reasonable data that could help the committee evaluate the model rather than to generate precise projections about specific vaccines.

The committee chose to develop reasonable estimates for data based on literature reviews and expert opinion, and it sometimes also relied upon committee-generated assumptions because much of the information required for the model, especially information concerning South Africa, was not available. It is thus reasonable to view the data inputs as characterizing hypothetical vaccines against influenza-like, tuberculosis-like, and group B streptococcus–like syndromes.

The estimates and assumptions used in this model were based upon literature reviews, publicly available data provided by international agencies such as the World Health Organization (WHO), and publications of various other organizations, such as the Agency for Healthcare Research and Quality (AHRQ) and the Healthcare Cost and Utilization Project (HCUP) in the United States.

For each candidate vaccine, the model used several categories of inputs (see Table 3-1 for specifics):

TABLE 3-1

Data Entries, Sources, and Methods of Analysis

Data	Parameters	Sources	Method of Analysis	Notes
Demographic Variables	**Life Tables**	• The country life tables are available from WHO, Global Health Observatory Data Repository (http://bit.ly/H5iYNC) • Standard life expectancy depicts the life expectancy for the Japanese population. Also available through WHO, Global Health Observatory Data Repository (http://bit.ly/Ho2VI3)		*Total Population*, *N*, data was used from a separate document provided by WHO officials.
	HUI-2	• Fryback et al. (2007). U.S. norms for six generic health-related quality-of-life indexes from the National Health Measurement study. *Medical Care* 45(12):1162–1170.	HUI-2 scores are derived from the literature. Due to the lack of HUI-2 data for South Africa, values for the United States are used.	
	Wage Rate	• Hourly wage rate is gathered from the Bureau of Labor Statistics. Parents' wage rate is used for children under the age of 15 years.	The BLS Current Population Survey data were used for wage rates.	*Wage Rate for South Africa* was crudely estimated by converting the United States wage rate to South African wage based on the prevailing exchange rate.

continued

TABLE 3-1

Continued

Data	Parameters	Sources	Method of Analysis	Notes
Disease Burden	**Target Population**	• Obtained from the total population data used in the "demographics" section.		Specific group from the entire population suited for the vaccine.
	Annual Incidence Rate	• CDC, WHO • Published literature		See disease and vaccine tables in Appendix C for details.
	Case Fatality Rate	• Published literature • Expert opinion		
	Vaccine Coverage			
	Vaccine Effectiveness			
	Herd Immunity Threshold			Assumed to be 100 percent due to infectious nature of each disease.
Vaccine Characteristics	**Length of Immunity**	• Published literature • Expert opinion		
	Doses Required per Person			
	Cost per Dose	• CDC		
	Research Costs	• Expert opinion		
	Licensure Costs			
	Start-Up Costs			
	Time to Adoption			

Disease Morbidities	**Percent of Cases** **Disutility (Toll)** **Disability Weight** **Duration**	• Published literature • Expert opinion	In cases, where information on exact conditions was not available in HUI-2 index and DALY weights, proxies were used to estimate values for tolls and disability weights.	See disease and vaccine tables in Appendix C for details.
Vaccine-Related Complications	**Morbidity** **Probability per Dose** **Disutility (Toll)** **Disability Weight** **Duration**	• Published literature • Expert opinion		See disease and vaccine tables in Appendix C for details.
Health Care Services	**Services Used for the Treatment of Disease and Potential Complications Caused by the Vaccine**	• Healthcare Cost and Utilization Project (HCUP) • WHO-CHOICE (Choosing Interventions that are Cost Effective) tables of costs and prices (WHO, 2003)		See disease and vaccine tables in Appendix C for details.

- *Population characteristics*, including the number of persons in the population and age and sex distributions. The underlying population characteristics for both the United States and South Africa were imported from country life tables provided by WHO through its Global Health Observatory Data Repository.
- *Disease characteristics*, including annual incidence rate, case-fatality proportion, and complications. For the United States, disease-burden data were obtained primarily from the literature and reports by the Centers for Disease Control and Prevention (CDC), such as Morbidity and Mortality Weekly Reports (MMWR) and National Vital Statistical Reports (NVSR). Comparable information for South Africa was not as readily available. Statistics South Africa and SA Health Info were helpful in providing approximate data, which were adapted to best fit the model parameters.
- *Health characteristics*, including disability-adjusted life years (DALYs) and quality-adjusted life years (QALYs), were obtained from the available literature. DALYs were calculated by assigning DALY weights from the Global Burden of Disease study (Mathers et al., 2006). Similarly, HUI-2 was used as a measure to calculate QALYs. When the exact condition of concern was not categorized in DALY and HUI-2 weights, proxies were used. Appendix C provides a listing of the data used in the model.
- *Vaccine characteristics*, including the number of years to full adoption, population coverage rate, effectiveness, length of immunity, doses required per person, costs of administration, and research and development costs. Vaccine traits were a combination of factual data and expert panel judgments. Vaccine efficacy, vaccine-associated complications, coverage, and the number of doses required for immunity were estimated from the literature, whereas time to adopt a vaccine within an immunization scheme, development risk, and innovation for new delivery methods were guided by expert opinions. Data on health care costs for disease and vaccine candidates were obtained from both a literature review and governmental Web sites such as those for HCUP and CDC for the United States and WHO's Choosing Interventions that are Cost-Effective (CHOICE) project for estimates of health care services costs in South Africa.

For each of the selected vaccines, assembling the data needed for the model presented a different set of challenges.

Tuberculosis poses a significant health challenge in South Africa, and published literature concerning the magnitude of the disease is available.

But accurate epidemiologic and health care cost estimates are difficult to obtain. Some assumptions about disease burden were made to generalize available information to South African populations when age-specific data were not available. By comparison, tuberculosis incidence and health care cost records are available for the United States; thus data for the disease in the United States can be considered fairly accurate.

Group B streptococcal infection is a serious disease in infants. Regardless of the disease burden posed in this vulnerable population, comprehensive surveillance is lacking throughout the world. Additionally, locating data for economic analyses is a daunting task in light of the limited resources available for this estimation. Thus, it was very difficult to populate all the model parameters for group B streptococcus, and many fields of data entry are informed assumptions.

Information for influenza, for example, was fairly accessible through U.S. and international flu surveillance modules, and literature on flu vaccines is abundant, given the global prevalence of the illness.

SMART Vaccines submodels

SMART Vaccines includes two submodels—the computational submodel and the value submodel. As previously shown (Figure 2-1), the computational submodel calculates multiple health and economic measures associated with new vaccine candidates. Many of these measures build upon the work presented in the 2000 IOM report. The computational submodel evolved with the improvements in the health and economic attribute listing for the model. The desire for interpretable health and economic attributes drove much of the computational submodel design.

Early prototypes strongly resembled the model presented in the 2000 report. Those prototypes were tested using the same input information and were determined to reliably replicate the results of the 2000 report. However, this initial prototyping highlighted several limitations in the analytical structure of the 2000 report, specifically in the context of accommodating the following features:

- Computations for all desired health and economic attributes.
- Variations in timing between vaccine administration and onset of disease or death.
- Differences between vaccines that protected for different lengths of time (i.e., 5-year universal influenza vaccine versus 1-year seasonal influenza vaccine).

- Potential future improvements accounting for disease or population dynamics.

Limitations in flexibility directed the modeling efforts toward a population process model whose technical aspects are presented in Appendix A.

The computational submodel comprises seven computed attributes derived from health, vaccine, and economic inputs. The remaining 22 attributes, called "qualitative attributes," were defined in an iterative process by the committee. After formal definitions were developed, levels of assessment were specified (Table 2-1).

The health and economic attribute measures were stratified by category (e.g., Level 2 = $/QALY between $0 and $10,000) so as to not overspecify computational model results, given the inherent uncertainty in input information. Determining the appropriate categories for health and economic measures that are to be generalized across populations of varying size, disease incidence, and mortality rates is a complex process. The categorization of the health and economic attributes needs to be conducted through a thorough evaluation of the model, supported by epidemiologic and economic evidence. This categorization has yet to be completed, but the preliminary assessment resulted in an initial set of categories to use as examples. The qualitative attributes not generated by the computational model are directly assessed by users. Definitions of categories for direct assessment were developed in an iterative process and then finalized. After finalizing the attribute definitions and assessment categories, the committee incorporated the multi-attribute weighting approach. The committee chose the rank order centroid method described in Chapter 2 for ease of use and reliability.

Development of the computational submodel

The computational submodel contains expressions for health and economic values that are based on a population process model. The process model is initialized at year $i = 0$ for a stationary population with: no vaccine (i.e., the baseline population); the vaccine in steady state delivery; and the vaccine first being introduced.

Annualized health and economic values are calculated by comparing a population with a vaccine in steady state to a baseline population after aging 1 year. Values capturing the efficiency of the investment (i.e., cost-effectiveness) are calculated by comparing a population where the vaccine is first introduced to a baseline population after aging 100 years. The following are further relevant details about the three types of populations:

1. The baseline population may have received no vaccine for the disease target. However, the baseline population may include the current vaccination state as a reference against which to compare a newly developed vaccine with different (i.e., more desirable) characteristics targeting the same disease.
2. When the vaccine is administered to the steady state population, individuals of all ages are assumed to have had the opportunity (i.e., accounting for coverage) to receive the vaccine at model initialization. For example, for a vaccine that is solely targeted for infants, individuals of all ages are assumed to have had the opportunity for vaccination. Achieving steady state for this vaccine would require many years, as compared with a vaccine designed for delivery to all ages.
3. The vaccine first being introduced to a population assumes that the vaccine is delivered solely to the target population (i.e., accounting for coverage) at model initialization.

The age-specific population process model simulates measures of population size for the total population, the target population, the vaccinated immune members of the populations, the vaccinated susceptible members, the not-vaccinated immune members (i.e., those who have indirect protection through herd immunity), and the not-vaccinated susceptible members. Simulated health measures include incident cases, deaths by disease, vaccine complications, all-cause deaths, and cause-deleted deaths. Mathematical expressions for these process measures may be found in Tables A-1 and A-2 in Appendix A.

Health and economic attributes are calculated from the population process model with mostly linear expressions (as shown in Tables A-1 and A-2) to serve as a starting point for the committee's modeling effort. Annualized measures are differentiated over the first year $i = 1$ between a population with no vaccine and a population with the vaccine in steady state. These annualized measures include deaths averted, cases prevented, QALYs gained, DALYs averted, net direct costs, workforce productivity (i.e., indirect costs), and one-time costs. The length of time associated with the annualized health and economic attributes associated with death and permanent impairment is assumed to be 6 months, as this is the average time of death between year $i = 0$ and year $i = 1$. Within these tables, vaccine populations for annualized measures refer to the vaccine-in-steady-state populations.

Alternatively, calculations on cost-effectiveness measures (i.e., $/QALY or $/DALY) are performed over 100 years. Time durations incor-

porated within QALYs and DALYs (i.e., included in cost-effectiveness only) associated with death and permanent impairment are assumed to be future life expectancy. Life expectancy is adjusted for baseline health utility indices (i.e., HUI2) for QALYs only. Life expectancy is discounted for both QALYs and DALYs when a discount factor is introduced. Expressions for cost-effectiveness measures may be found in Tables A-1 and A-2. Within these tables, vaccine population references are assumed to be the populations where the vaccine is first introduced.

Evaluation of the computational submodel

The computational submodel has been evaluated using four base cases for preventative vaccine candidates. These cases, given in Table 3-2, are for seasonal influenza, group B streptococcus, and tuberculosis within the United States (2009) and for tuberculosis within South Africa (2009).

Table 3-2 presents input assumptions for the target population, the duration of immunity, the cost to administer, the herd immunity threshold, and coverage. It also displays annualized health and economic attribute measures applicable to a vaccine in a steady state population and efficiency measures for a population in which a vaccine is first introduced. These measures are summed over 100 years and discounted at three percent. These evaluations allow for a constructive comparison of characteristics across base cases.

The model identifies the vaccine for seasonal influenza (i.e., with 1-year duration of immunity) having the largest health impact in terms of averting deaths, preventing cases, and increasing health-adjusted life years within the United States. Direct costs are notably high because annual administration (i.e., delivery costs) to an assumed undifferentiated target population of all ages is much more expensive than delivering the vaccine solely to infants. However, given improvements in health-adjusted quality of life, the cost-effectiveness is greater for the seasonal influenza vaccine than for other candidates in the United States.

The evaluation of the base cases demonstrates major differences between targeting tuberculosis in the United States and in South Africa. The health and efficiency attribute measures are improved within the South African population, where disease incidence is much higher. In South Africa administering the vaccine in steady state is cost-saving (i.e., net direct costs <0). It is important to note that the corresponding efficiency measures do not demonstrate cost savings (i.e., cost per QALY or DALY >0). This highlights a difference between examining vaccine candidates in steady state and the standard computations of cost-effectiveness

TABLE 3-2

Computational Submodel Evaluations for Baseline Cases

Demographic Attributes	Influenza, United States 2009	Group B Streptococcus, United States 2009	Tuberculosis, United States 2009	Tuberculosis, South Africa 2009
Target Population	All ages	Infants	Infants	Infants
Duration of Immunity	1 year	Life	Life	Life
Cost per Dose	$13	$100	$50	$25
Herd Immunity Threshold	None	None	None	None
Coverage (Average)	38%	85%	85%	50%
Health Attributes (per Year)	Vaccine Steady State			
Premature Deaths Averted	12,095	1,248	671	28,973
Incident Cases Prevented	6,123,612	14,841	7,451	140,239
QALYs Gained	21,011	3,571	1,373	40,680
DALYs Averted	8,665	1,170	622	21,421
Economic Attributes (per Year)	Vaccine Steady State			
Net Direct Costs (Delivery—Health Care)	$1,929,730,356	$274,313,238	$253,174,240	–$95,357,702
Vaccine Delivery Costs	$2,691,438,051	$570,970,118	$285,485,059	$15,278,835
Health Care Costs Averted	$761,707,695	$296,656,880	$32,310,819	$110,636,537
Workforce Productivity Gained	$4,619,173,825	$102,210,335	$28,345,945	$285,934,338
One-Time Costs (Research + Licensure)	$150,100,000	$810,000,000	$610,000,000	$610,000,000
Cost Effectiveness (100 Years)	Vaccine First Introduced			
$/QALY	$7,389	$40,539	$801,122	$204
$/DALY	$14,130	$54,992	$1,195,821	$270

for *introducing* a vaccine to a stationary population. For new candidate vaccines, a ramp-up phase may exist, which likely depends upon the timing of the desired vaccine administration (i.e., age of delivery) and the onset of disease. During this phase, the efficiency (i.e., health-adjusted life years and net direct costs) may be different than in a steady state. Furthermore, vaccine delivery schedules and target populations may be designed differently, based on the objectives for each phase.

The base cases were altered to test the relationship between the input information and the health and economic attribute measures (i.e., outputs). This verification process was performed across all inputs with example test cases shown in Table 3-3.

For example, the seasonal influenza vaccine (i.e., with 1-year duration of immunity) was altered to reflect a hypothetical universal vaccine that would provide protection for 10 years. A projected increase in the administrative costs was also included. These changes resulted in a decrease in delivery costs and improved efficiency because of less frequent administration compared to the seasonal base case. However, the improvements are substantially mitigated by the projected increases in the cost of vaccine.

Similarly, the reductions in cost to administer the group B streptococcus vaccine demonstrate more desirable economic measures. Herd immunity threshold was set at 80 percent for tuberculosis in the U.S. test case. Intuitively, the resulting health attribute measures should increase as a result of the indirect protection associated with herd immunity. Finally, the vaccine coverage for tuberculosis in the South Africa base case was increased. This resulted in proportional increases in the health and economic attribute measures. The health impact is greater; however, the cost-effectiveness remains constant compared to the base case.

Simulation of the value submodel

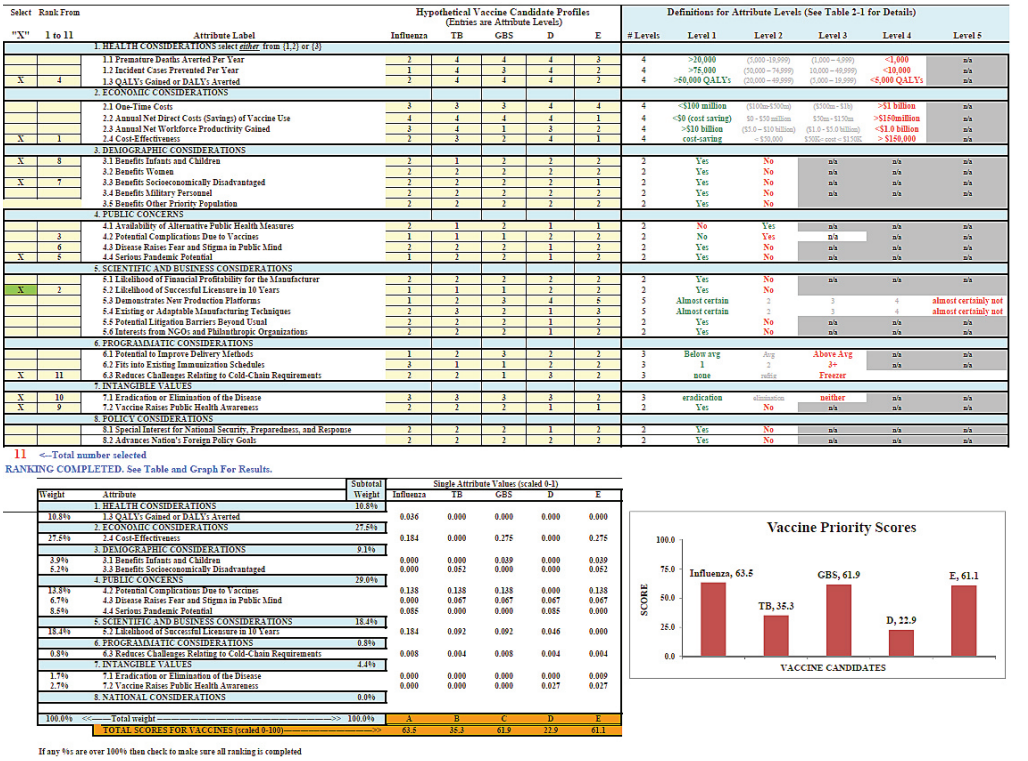
The committee also developed an iterative version of the value submodel in a worksheet in order to simulate and understand the variations in user preferences of attributes. Figure 3-1 displays a screenshot of the user worksheet. Two large blocks and one graph make up the screen. In the top block there are four columns; from left to right these are:

1. Two yellow columns in which the user selects and rank orders the subset of attributes to be used in the multi-attribute utility model.
2. A white area listing the 8 categories of attributes, with a total of 29 attributes.

TABLE 3-3

Computational Submodel Evaluations for Test Cases (Input Changes Indicated by *Bold Orange Italics*)

Demographic Attributes	Influenza, United States 2009	Group B Streptococcus, United States 2009	Tuberculosis, United States 2009	Tuberculosis, South Africa 2009
Target Population	All ages	Infants	Infants	Infants
Duration of Immunity	***10 years***	Life	Life	Life
Cost per Dose	***$65***	***$50***	$50	$25
Herd Immunity Threshold	None	None	***80%***	None
Coverage (Average)	38%	85%	85%	75%
Health Attributes (per Year)	Vaccine Steady State			
Premature Deaths Averted	12,095	1,248	838	43,459
Incident Cases Prevented	6,123,612	14,841	9,314	210,358
QALYs Gained	21,011	3,571	1,719	61,020
DALYs Averted	8,665	1,170	777	32,131
Economic Attributes (per Year)	Vaccine Steady State			
Net Direct Costs (Delivery—Health Care)	$232,954,193	$83,989,865	$242,021,811	–$143,036,554
Vaccine Delivery Costs	$994,661,888	$380,646,745	$285,485,059	$22,918,253
Health Care Costs Averted	$761,707,695	$296,656,880	$43,463,248	$165,954,807
Workforce Productivity Gained	$4,619,173,825	$102,210,335	$41,522,924	$428,901,508
One-Time Costs (Research + Licensure)	$705,000,000	$810,000,000	$610,000,000	$610,000,000
Cost Effectiveness (100 Years)	Vaccine First Introduced			
$/QALY	$1,062	$14,212	$639,232	$204
$/DALY	$2,030	$19,279	$952,630	$270



Select "X"	Rank From 1 to 11	Attribute Label	Hypothetical Vaccine Candidate Profiles (Entries are Attribute Levels) Influenza	TB	GBS	D	E	Definitions for Attribute Levels (See Table 2-1 for Details) # Levels	Level 1	Level 2	Level 3	Level 4	Level 5
		1. HEALTH CONSIDERATIONS select *either* from (1,2) or (3)											
		1.1 Premature Deaths Averted Per Year	2	4	4	4	3	4	>20,000	(5,000-19,999)	(1,000 – 4,999)	<1,000	n/a
		1.2 Incident Cases Prevented Per Year	1	4	3	4	2	4	>75,000	(50,000 – 74,999)	10,000 – 49,999)	<10,000	n/a
X	4	1.3 QALYs Gained or DALYs Averted	2	4	4	4	2	4	>60,000 QALYs	(20,000 – 49,999)	(5,000 – 19,999)	<5,000 QALYs	n/a
		2. ECONOMIC CONSIDERATIONS											
		2.1 One-Time Costs	3	3	3	4	4	4	<$100 million	($100m-$500m)	($500m - $1b)	>$1 billion	n/a
		2.2 Annual Net Direct Costs (Savings) of Vaccine Use	4	4	4	4	1	4	<$0 (cost saving)	$0 – $50 million	$50m – $150m	>$150million	n/a
		2.3 Annual Net Workforce Productivity Gained	3	4	1	3	2	4	>$10 billion	($3.0 – $10 billion)	($1.0 – $3.0 billion)	<$1.0 billion	n/a
X	1	2.4 Cost-Effectiveness	2	3	2	4	1	4	cost-saving	< $30,000	$30K< cost < $170K	> $150,000	n/a
		3. DEMOGRAPHIC CONSIDERATIONS											
X	8	3.1 Benefits Infants and Children	2	1	2	2	2	2	Yes	No	n/a	n/a	n/a
		3.2 Benefits Women	2	2	2	2	2	2	Yes	No	n/a	n/a	n/a
X	7	3.3 Benefits Socioeconomically Disadvantaged	2	2	2	2	1	2	Yes	No	n/a	n/a	n/a
		3.4 Benefits Military Personnel	2	2	2	2	2	2	Yes	No	n/a	n/a	n/a
		3.5 Benefits Other Priority Population	2	2	2	2	2	2	Yes	No			
		4. PUBLIC CONCERNS											
		4.1 Availability of Alternative Public Health Measures	2	1	2	1	1	2	No	Yes	n/a	n/a	n/a
	3	4.2 Potential Complications Due to Vaccines	1	1	1	2	2	2	No	Yes	n/a	n/a	n/a
	6	4.3 Disease Raises Fear and Stigma in Public Mind	2	2	2	1	2	2	Yes	No	n/a	n/a	n/a
X	5	4.4 Serious Pandemic Potential	1	2	2	1	2	2	Yes	No	n/a	n/a	n/a
		5. SCIENTIFIC AND BUSINESS CONSIDERATIONS											
		5.1 Likelihood of Financial Profitability for the Manufacturer	2	2	2	2	2	2	Yes	No	n/a	n/a	n/a
X	2	5.2 Likelihood of Successful Licensure in 10 Years	1	1	1	2	2	2	Yes	No			
		5.3 Demonstrates New Production Platforms	1	2	3	4	5	5	Almost certain	2	3	4	almost certainly not
		5.4 Existing or Adaptable Manufacturing Techniques	2	3	2	1	3	5	Almost certain	2	3	4	almost certainly not
		5.5 Potential Litigation Barriers Beyond Usual	2	2	2	1	2	2	Yes	No	n/a	n/a	n/a
		5.6 Interests from NGOs and Philanthropic Organizations	2	2	2	1	2	2	Yes	No	n/a	n/a	n/a
		6. PROGRAMMATIC CONSIDERATIONS											
		6.1 Potential to Improve Delivery Methods	1	2	3	2	2	3	Below avg	Avg	Above Avg	n/a	n/a
		6.2 Fits into Existing Immunization Schedules	3	1	1	2	2	3	1	2	3+	n/a	n/a
X	11	6.3 Reduces Challenges Relating to Cold-Chain Requirements	2	2	1	3	2	3	none	refrig	Freezer		
		7. INTANGIBLE VALUES											
X	10	7.1 Eradication or Elimination of the Disease	3	3	3	3	2	3	eradication	elimination	neither	n/a	n/a
X	9	7.2 Vaccine Raises Public Health Awareness	2	2	2	1	1	2	Yes	No	n/a	n/a	n/a
		8. POLICY CONSIDERATIONS											
		8.1 Special Interest for National Security, Preparedness, and Response	2	2	2	1	2	2	Yes	No	n/a	n/a	n/a
		8.2 Advances Nation's Foreign Policy Goals	2	2	2	2	2	2	Yes	No	n/a	n/a	n/a

11 <--Total number selected

RANKING COMPLETED. See Table and Graph For Results.

Weight	Attribute	Subtotal Weight	Single Attribute Values (scaled 0-1) Influenza	TB	GBS	D	E
	1. HEALTH CONSIDERATIONS	10.8%					
10.8%	1.3 QALYs Gained or DALYs Averted		0.036	0.000	0.000	0.000	0.000
	2. ECONOMIC CONSIDERATIONS	27.5%					
27.5%	2.4 Cost-Effectiveness		0.184	0.000	0.275	0.000	0.275
	3. DEMOGRAPHIC CONSIDERATIONS	9.1%					
3.9%	3.1 Benefits Infants and Children		0.000	0.000	0.039	0.000	0.039
5.2%	3.3 Benefits Socioeconomically Disadvantaged		0.000	0.052	0.000	0.000	0.052
	4. PUBLIC CONCERNS	29.0%					
13.8%	4.2 Potential Complications Due to Vaccines		0.138	0.138	0.138	0.000	0.138
6.7%	4.3 Disease Raises Fear and Stigma in Public Mind		0.000	0.067	0.067	0.067	0.067
8.5%	4.4 Serious Pandemic Potential		0.085	0.000	0.000	0.085	0.000
	5. SCIENTIFIC AND BUSINESS CONSIDERATIONS	18.4%					
18.4%	5.2 Likelihood of Successful Licensure in 10 Years		0.184	0.092	0.092	0.046	0.000
	6. PROGRAMMATIC CONSIDERATIONS	0.8%					
0.8%	6.3 Reduces Challenges Relating to Cold-Chain Requirements		0.008	0.004	0.008	0.004	0.004
	7. INTANGIBLE VALUES	4.4%					
1.7%	7.1 Eradication or Elimination of the Disease		0.000	0.000	0.000	0.000	0.009
2.7%	7.2 Vaccine Raises Public Health Awareness		0.000	0.000	0.000	0.027	0.027
	8. NATIONAL CONSIDERATIONS	0.0%					
100.0%	<<—— Total weight ——>>	100.0%	A	B	C	D	E
	TOTAL SCORES FOR VACCINES (scaled 0-100) ——>		63.5	35.3	61.9	22.9	61.1

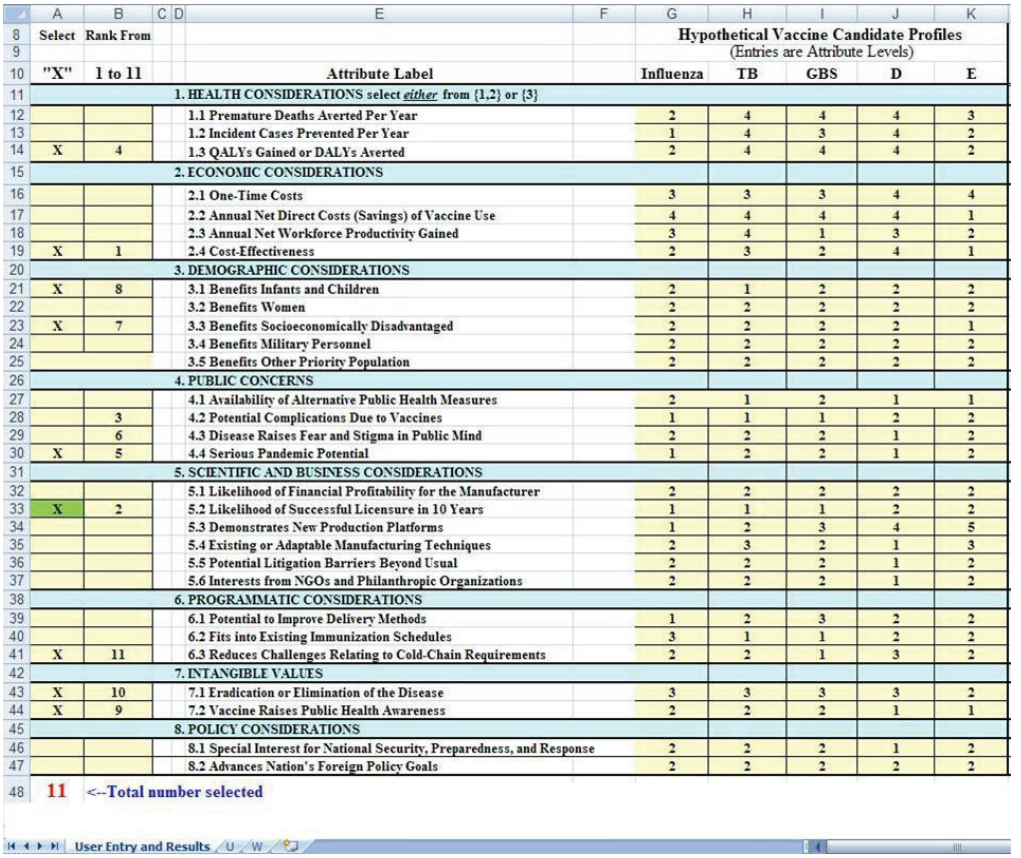
If any %s are over 100% then check to make sure all ranking is completed

FIGURE 3-1
Prototype value submodel simulation worksheet with user attributes and graphical display of vaccine priority scores.

3. A yellow area into which the user enters achievement levels for up to 5 hypothetical vaccines (labeled at the top) for each of the 29 attributes.
4. A white and gray area defining the potential achievement level categories for each of the attributes.

The lower block and the bar chart display outputs of the multi-attribute model. The selected attributes from the upper areas have been assigned weights, the categorical achievement levels on each attribute have been scaled with the weights, and the scaled weights have been summed to display a total priority score for each of the five vaccines at the bottom in the orange colored rows. These scores are displayed in the form of a bar chart showing the scores for each vaccine.

Figure 3-2 shows a closer view of the user input areas. Five hypothetical vaccines are shown in the right-hand yellow columns. The hypothetical influenza vaccine is conceived of as a modest improvement on an existing annual influenza vaccine. Reading down the column titled Influenza,



Select	Rank From	Attribute Label	Hypothetical Vaccine Candidate Profiles (Entries are Attribute Levels)				
"X"	1 to 11		Influenza	TB	GBS	D	E
		1. HEALTH CONSIDERATIONS select *either* from {1,2} or {3}					
		1.1 Premature Deaths Averted Per Year	2	4	4	4	3
		1.2 Incident Cases Prevented Per Year	1	4	3	4	2
X	4	1.3 QALYs Gained or DALYs Averted	2	4	4	4	2
		2. ECONOMIC CONSIDERATIONS					
		2.1 One-Time Costs	3	3	3	4	4
		2.2 Annual Net Direct Costs (Savings) of Vaccine Use	4	4	4	4	1
		2.3 Annual Net Workforce Productivity Gained	3	4	1	3	2
X	1	2.4 Cost-Effectiveness	2	3	2	4	1
		3. DEMOGRAPHIC CONSIDERATIONS					
X	8	3.1 Benefits Infants and Children	2	1	2	2	2
		3.2 Benefits Women	2	2	2	2	2
X	7	3.3 Benefits Socioeconomically Disadvantaged	2	2	2	2	1
		3.4 Benefits Military Personnel	2	2	2	2	2
		3.5 Benefits Other Priority Population	2	2	2	2	2
		4. PUBLIC CONCERNS					
		4.1 Availability of Alternative Public Health Measures	2	1	2	1	1
	3	4.2 Potential Complications Due to Vaccines	1	1	1	2	2
	6	4.3 Disease Raises Fear and Stigma in Public Mind	2	2	2	1	2
X	5	4.4 Serious Pandemic Potential	1	2	2	1	2
		5. SCIENTIFIC AND BUSINESS CONSIDERATIONS					
		5.1 Likelihood of Financial Profitability for the Manufacturer	2	2	2	2	2
X	2	5.2 Likelihood of Successful Licensure in 10 Years	1	1	1	2	2
		5.3 Demonstrates New Production Platforms	1	2	3	4	5
		5.4 Existing or Adaptable Manufacturing Techniques	2	3	2	1	3
		5.5 Potential Litigation Barriers Beyond Usual	2	2	2	1	2
		5.6 Interests from NGOs and Philanthropic Organizations	2	2	2	1	2
		6. PROGRAMMATIC CONSIDERATIONS					
		6.1 Potential to Improve Delivery Methods	1	2	3	2	2
		6.2 Fits into Existing Immunization Schedules	3	1	1	2	2
X	11	6.3 Reduces Challenges Relating to Cold-Chain Requirements	2	2	1	3	2
		7. INTANGIBLE VALUES					
X	10	7.1 Eradication or Elimination of the Disease	3	3	3	3	2
X	9	7.2 Vaccine Raises Public Health Awareness	2	2	2	1	1
		8. POLICY CONSIDERATIONS					
		8.1 Special Interest for National Security, Preparedness, and Response	2	2	2	1	2
		8.2 Advances Nation's Foreign Policy Goals	2	2	2	2	2
11	<--Total number selected						

FIGURE 3-2
A closer view of the user input areas in the value submodel simulation worksheet.

one can see that it is rated as Level 2 on the attribute Premature Deaths Averted per Year (Attribute 1.1), as Level 1 on Incident Cases Prevented per Year (Attribute 1.2), and so forth down the column. The figure shows the levels entered for five hypothetical vaccines. Levels for each attribute are defined in the worksheet (Figure 3-1) and in Table 2-1.

The purpose of this spreadsheet was to allow the committee to experiment with the value computations part of the SMART Vaccines model. This permitted the committee to do "What if?" modeling quickly. But it also required the committee to estimate or fabricate entries for the hypothetical vaccines outside of the computations of the formal model.

Figure 3-2 shows a situation in which the user has selected 11 attributes with which to evaluate the vaccines. The submodel requires that Likelihood of Successful Licensure (Attribute 5.2) be selected in order to ensure that the user considers this factor. This requirement was added after some concept evaluators of SMART Vaccines Beta strongly endorsed

the importance of this factor. The Likelihood of Successful Licensure in 10 Years will depend greatly on specific scientific and immunologic advances and constraints, and different users may have different levels of knowledge about this area.

Users indicate factors to be considered by placing an "x" in the left-most column. The spreadsheet counts the "x" boxes and notes in red colored count at the bottom how many have been selected. This total is also reflected in the message at the top of the second column where the instruction reads, "Rank from 1 to 11." If only six boxes had an "x," then this message would read "Rank from 1 to 6," and so forth.

To demonstrate how perspectives might affect ranking choices, two hypothetical perspectives are presented: a vaccine producer and a health minister of a developing country. In this example, the user (say, a vaccine manufacturer) has entered numbers from 1 to 11 in the second column to indicate the rank order of importance of the selected attributes, with 1 being most important and 11 being the least important. Once the ranking is completed, the output of the value model is shown in the lower block (Figure 3-3) and the graph (Figure 3-1).

Figure 3-3 shows the tabular output from the simulated value submodel spreadsheet. The tabular output displays, from left to right, the weights associated with each of the selected attributes, the attribute labels, the subtotal percentage weight in the model assigned to each of the eight logical groupings of attributes, and the single attribute weighted score for

		Subtotal	Single Attribute Values (scaled 0-1)				
Weight	Attribute	Weight	Influenza	TB	GBS	D	E
	1. HEALTH CONSIDERATIONS	10.8%					
10.8%	1.3 QALYs Gained or DALYs Averted		0.036	0.000	0.000	0.000	0.000
	2. ECONOMIC CONSIDERATIONS	27.5%					
27.5%	2.4 Cost-Effectiveness		0.184	0.000	0.275	0.000	0.275
	3. DEMOGRAPHIC CONSIDERATIONS	9.1%					
3.9%	3.1 Benefits Infants and Children		0.000	0.000	0.039	0.000	0.039
5.2%	3.3 Benefits Socioeconomically Disadvantaged		0.000	0.052	0.000	0.000	0.052
	4. PUBLIC CONCERNS	29.0%					
13.8%	4.2 Potential Complications Due to Vaccines		0.138	0.138	0.138	0.000	0.138
6.7%	4.3 Disease Raises Fear and Stigma in Public Mind		0.000	0.067	0.067	0.067	0.067
8.5%	4.4 Serious Pandemic Potential		0.085	0.000	0.000	0.085	0.000
	5. SCIENTIFIC AND BUSINESS CONSIDERATIONS	18.4%					
18.4%	5.2 Likelihood of Successful Licensure in 10 Years		0.184	0.092	0.092	0.046	0.000
	6. PROGRAMMATIC CONSIDERATIONS	0.8%					
0.8%	6.3 Reduces Challenges Relating to Cold-Chain Requirements		0.008	0.004	0.008	0.004	0.004
	7. INTANGIBLE VALUES	4.4%					
1.7%	7.1 Eradication or Elimination of the Disease		0.000	0.000	0.000	0.000	0.009
2.7%	7.2 Vaccine Raises Public Health Awareness		0.000	0.000	0.000	0.027	0.027
	8. NATIONAL CONSIDERATIONS	0.0%					
100.0%	<<-------Total weight ----------	100.0%	Influenza	TB	GBS	D	E
	TOTAL SCORES FOR VACCINES (scaled 0-100)----------		63.5	35.3	61.9	22.9	61.1
If any %s are over 100% then check to make sure all ranking is completed							

FIGURE 3-3
Output of the simulated value submodel.

each of the vaccines. At the bottom of the table in orange are the total scores for the five vaccines (scaled from 0 to 100).

The attribute ranked as most important by the hypothetical vaccine manufacturer, Attribute 2.4, Cost-Effectiveness, received 27.5 percent of the weight; the next most important, Attribute 5.2, Likelihood of Successful Licensure in 10 Years, received 18.4 percent of the weight. The category Public Concerns received a total of 29.0 percent of the weight (summing across the three attributes selected in this group). Reading down the GBS column, representing a hypothetical group B streptococcus vaccine, Attribute 1.3 contributed nothing to its total score because the rating on that attribute was only a Level 4, or the lowest level possible. By contrast, Attribute 2.4 contributed 0.275 to the total score.

Summing down the columns, the maximum possible total is 1.0—which is achieved only if the vaccine is rated at Level 1 (the best level) for each of the selected attributes. The minimum score is 0, which would be achieved only if the vaccine was rated at the lowest (worst) possible level for every one of the selected attributes. The sums in the table have been multiplied by 100 to scale them from 0 to 100. In the figure, the influenza vaccine scored a total of 0.635, which multiplied by 100 is 63.5; the tuberculosis vaccine scored 35.3, the group B streptococcus vaccine scored 61.9, and vaccines D and E scored 22.9 and 61.1, respectively.

The weights in the table are assigned using the rank order centroid method described in Chapter 2. They are displayed as percentages of the total weight in the model. If the user were to re-rank the attributes, the weights would change, as would the subscores and the total scores for the vaccines. If the user were to change the achievement levels for the hypothetical vaccines in the yellow area in Figure 3-2, these scores would change. This output table shows the detailed effects on the priority scores of the achievement levels of vaccines on the attributes, of the user's attribute selection, and of the user's ranking of attributes.

Now, let us assume the perspective of a health minister from an emerging South American country who may wish to place the priorities for a new vaccine in the following order:

1. QALYs Gained or DALYs Averted
2. Benefits Infants and Children
3. Reduces Challenges Relating to Cold-Chain Requirements
4. Cost-Effectiveness
5. Likelihood of Successful Licensure in 10 Years

Based on this order, QALYs Gained or DALYs Averted (Attribute 1.3) receives the highest weight of 45.7 percent. In contrast to the hypothetical vaccine manufacturer who selected 11 attributes, the health official only selected five, thus distributing the weights among fewer selections. The second important attribute for the health official—Benefits Infants and Children (Attribute 3.1)—receives 25.7 percent weight followed by "Reduces Challenges Relating to Cold-Chain Requirements" (Attribute 6.3) with 15.7 percent of the weight. Cost-Effectiveness (Attribute 2.4) and Likelihood of Successful Licensure in 10 Years (Attribute 5.2) receive 15.7 percent and 4 percent, respectively. The final ranking of vaccine candidates are the TB vaccine with a score of 54.6, followed by the GBS vaccine at 54.3, vaccine D at 47.5, the influenza vaccine at 40.6, and vaccine E at 1.0.

These examples illustrate the flexibility of the value submodel in response to the preferences set by the user. The final ranking scores of the vaccine manufacturer and the health minister are quite different because of their differing priorities, which highlights the potential of SMART Vaccines to facilitate discussions among parties and helping them reach mutually desired objectives.

The value experiment and scenarios

To further illustrate the effect of—and sensitivity to—different choices in the multi-attribute utility model, a simple exercise was performed, called the "value experiment." Six vaccines, for use against one or the other of two diseases, were considered; some of the vaccines actually exist, and some were fictitious, created for use in the experiment. The value experiment was designed to test and illustrate the process of selecting values and to generate sample sets of values that would then be assigned weights and used to test the model. This experiment was conducted while the prototyping of the model was ongoing, so the vaccines evaluated and the assumptions were slightly different from the completed SMART Vaccines Beta.

The committee members and staff ranked the following six vaccines:

1. influenza with 1-year efficacy;
2. influenza with 5-year efficacy;
3. tuberculosis with 3-year efficacy;
4. tuberculosis with lifetime efficacy;
5. influenza with 50 percent increase in efficacy for those receiving vaccination; and
6. tuberculosis with 3-year efficacy, but with a 100-fold increase in incidence in the population risk.

Participants were asked to think about the candidate vaccines for the United States and for low-income countries. Half the participants ranked these vaccine characteristics from the perspective of the United States and half from the perspective of low-income countries. They were provided with a list of an earlier draft attributes deemed important for vaccine prioritization (see Table 2-1). The participants then selected up to five attributes of highest importance to them and ranked them based on their own perspectives. The group included individuals with diverse perspectives, from infectious disease epidemiologists and authorities on health care in low-income countries to experts in health economics, systems engineering, and decision sciences.

The weights were then applied against the vaccines under consideration through SMART Vaccines Beta to calculate each person's priority score for the vaccine and disease combinations. The participants ranked the priorities in the following order:

1. Premature deaths averted per year
2. Incident cases prevented per year
3. Likelihood of successful licensure in 10 years
4. QALYs gained or DALYs averted (DALYs were #4, and QALYs were #6)
5. Cost-effectiveness ($/QALYs)

This experiment shows how weights can have a significant effect on the priority scores. Table 3-4 shows the results for participants A through N. Compare, for example, rankings produced by the multi-attribute utility weights of persons A and B. The weights specified by A led to the highest value (priority score) being placed on the influenza vaccines, the order being quite understandable intuitively (highest for a 1-year with 50 percent increase in efficacy, then the 5-year vaccine, followed by the 1-year vaccine), with the two tuberculosis vaccines running considerably behind. The weights specified by B, however, gave quite a different ranking. That participant gave the highest value to the hypothetical tuberculosis vaccine with 3-year immunity in a population with 100 times higher incidence.

Two other observations emerge from examining this table. First, one cannot meaningfully compare numerical scores across different raters. Person B's score of 44 (tuberculosis with lifetime immunity) has no relationship to person K's score of 44 (influenza with 5-year immunity). To equate these two scores would be to make a mistake similar to saying that 65°F and 65°C were the same temperature. To compare values across similar or different vaccine scenarios for two persons is faulty because the priority

TABLE 3-4

Scores from the Value Experiment

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	Aggregate
Influenza, 1-year immunity	72	42	36	68	61	43	56	61	52	54	36	63	36	49	64
Influenza, 5-year immunity	76	52	36	70	69	47	57	77	54	66	44	69	47	67	67
Tuberculosis, 3-year immunity	34	22	35	24	46	14	13	21	10	18	28	27	11	20	18
Tuberculosis, lifetime immunity	43	44	35	29	47	20	13	58	10	28	29	42	26	42	24
Influenza, 1-year immunity, 50% increased coverage	86	42	36	89	69	55	77	69	73	70	44	76	41	58	84
Tuberculosis, 3-year immunity, 100 times increased incidence	49	87	92	66	80	89	70	65	58	53	57	58	71	59	59

values are different for each individual. Person A's values for choosing the given scenarios are completely different from person B's value selections.

Second, the scores do not have importance relative to their size. Person K's score of 57 for the high-risk tuberculosis scenario is not "twice as much" as K's rating of 28 for the 3-year tuberculosis immunization, nor is person B's rating of 87 (tuberculosis scenario with 100 times increased incidence) twice as large as B's rating of 44 for lifetime immunity against tuberculosis.

This raises the issue of the meaning of the scale of utility in the multi-attribute utility value models. The issue, as discussed in Chapter 2, is the same as encountered when using a temperature scale such as fahrenheit or centigrade; one may be tempted to say that one temperature is "twice as warm" as another, but 20°C is not twice as warm as 10°C, nor is 90°F twice as warm as 45°F. Using the temperature analogy, the multi-attribute value function does not begin at "absolute zero," and hence 80 is not twice as high as 40.

What do the scores mean? The most important result they offer is to provide rank orderings. Furthermore, for a given person, it is generally the case that differences in scores have meaning, so that the difference between 20 and 40 in a priority score has the same meaning as a difference between 50°F and 70°F. This is just the same as saying that the difference between 50°F and 70°F is the same as the difference between 20°F and 40°F—both represent a difference of 20°F, nothing more and nothing less.

Since each rating process is unique, based on the user's perspectives, different rankings will produce different values for users. A multinational health organization will have different weights and priorities than a minister of health or finance from a developing country. The Pan American Health Organization, for example, may choose values that lead to a rank for tuberculosis higher than for influenza, whereas a vaccine manufacturer might have different weights, thus producing different rankings. Similarly, a basic research institution such as the National Institutes of Health (NIH) may have different priorities than a private company. A manufacturer is likely to be interested in return on investment and securing a market for its product, therefore assigning different values than an NIH official who may be interested in scientific advancement that may also apply to other vaccines. The flexibility to accommodate multiple priorities from many users is an asset, as it allows the many sectors within the vaccine enterprise to enlist in the broader discussion that is important in vaccine development and prioritization.

In short, SMART Vaccines allows users to rank attributes to reflect their value preferences. Once users have ranked the set of attributes for the

candidate vaccines under consideration and have received a priority score, they can go back and change the ranks of their original selection to see which of them affect the score the most. Users can then decide to retain or modify their rank order.

Software development: Operational features of SMART Vaccines Beta

This section of the report presents screenshots of SMART Vaccines Beta to illustrate its current features. The intention is to provide readers with an understanding of the conceptual flow of the model in a software platform, the data needs of the program, and the current user interface and navigation, which has potential for further improvement. SMART Vaccines Beta was developed using three software tools: MATLAB for algorithm development and testing, JAVA Servlets for the middleware, and Axure for visual prototyping and interface development. The preliminary database was managed using Microsoft SQL Server.

In its current version SMART Vaccines Beta has a six-step process for producing a value score for vaccine candidates. All the data and the results shown in the screenshots are hypothetical and should not be interpreted as any form of endorsement by the committee or the Institute of Medicine.

Step 0: Terms of Agreement

Figure 3-4 shows the disclaimer page (Step 0) of the software, which requires the user's agreement to the terms. All of a user's work can be saved for future use and modified and re-saved to allow variants in baseline data conditions. User accounts with password protection are possible options.

Step 1: Values

The values page (Figure 3-5) introduces the user to the overall program structure and navigation. Every page has a similar panel of six tabs at the top (with this page having "Values" highlighted). Typically users will move sequentially through these tabs. Every page the user visits will have, in the upper right corner, a pop-up window for a glossary of terms and instructions. The advanced mode (presented in all the screenshots) allows the user to enter data in order to consider attributes beyond health and economic factors. The basic mode, by contrast, has options relating only to health and economic attributes in case the user has a predetermined attribute (say,

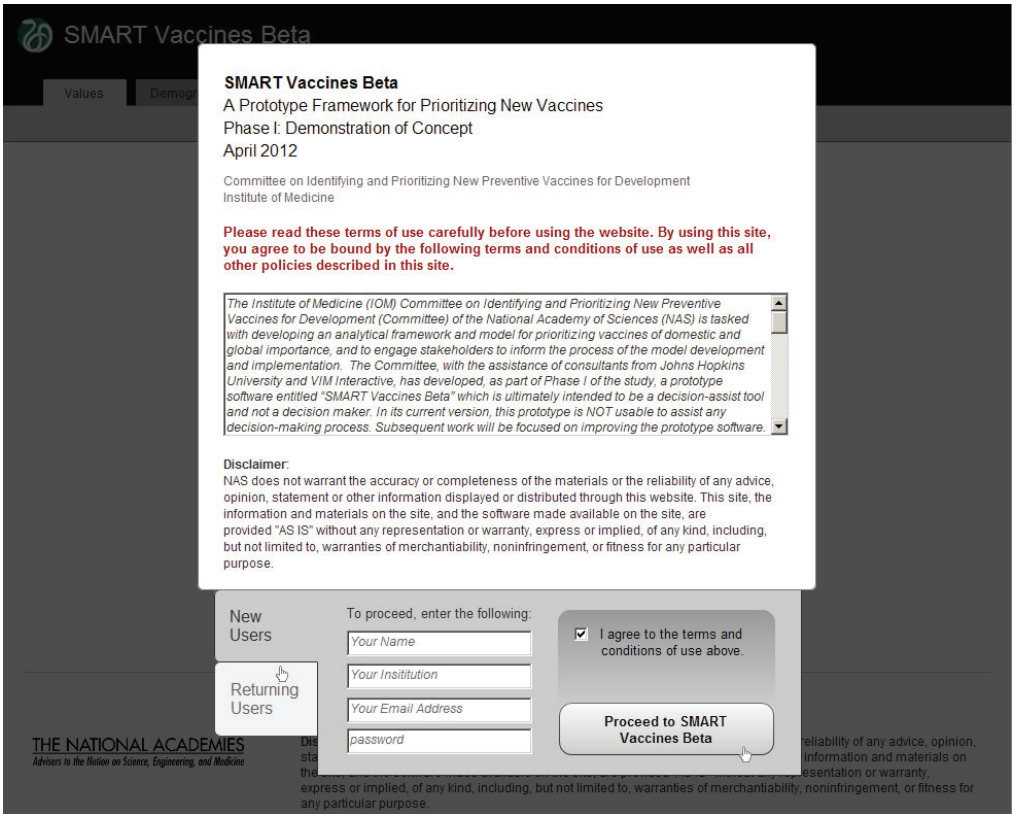


FIGURE 3-4
Terms of agreement page for SMART Vaccines Beta showing options for users to create accounts.

premature deaths averted) in mind on which to base the ranking of his or her set of vaccine candidates.

Step 1 in the process has the user specify the attributes of importance toward the ultimate ranking of candidate vaccines. This feature, wholly novel to the SMART Vaccines approach, makes it possible for users not only to specify which attributes of candidate vaccines are important but also to move them around in rank order. All of this occurs with a drag-and-drop feature, using a pointing device to highlight and drag individual items, including shifting them around in sequence. Users can later alter the list and the ranking of attributes and see immediately what effect this has on final value score.

Attributes fall into eight different categories, and users can select from as many categories as they wish and—in all but a few cases—select multiple attributes from each category. In order to avoid double-counting, the software does not permit the use of highly similar attributes, so, for example, the user must choose either QALYs or DALYs for ranking, and

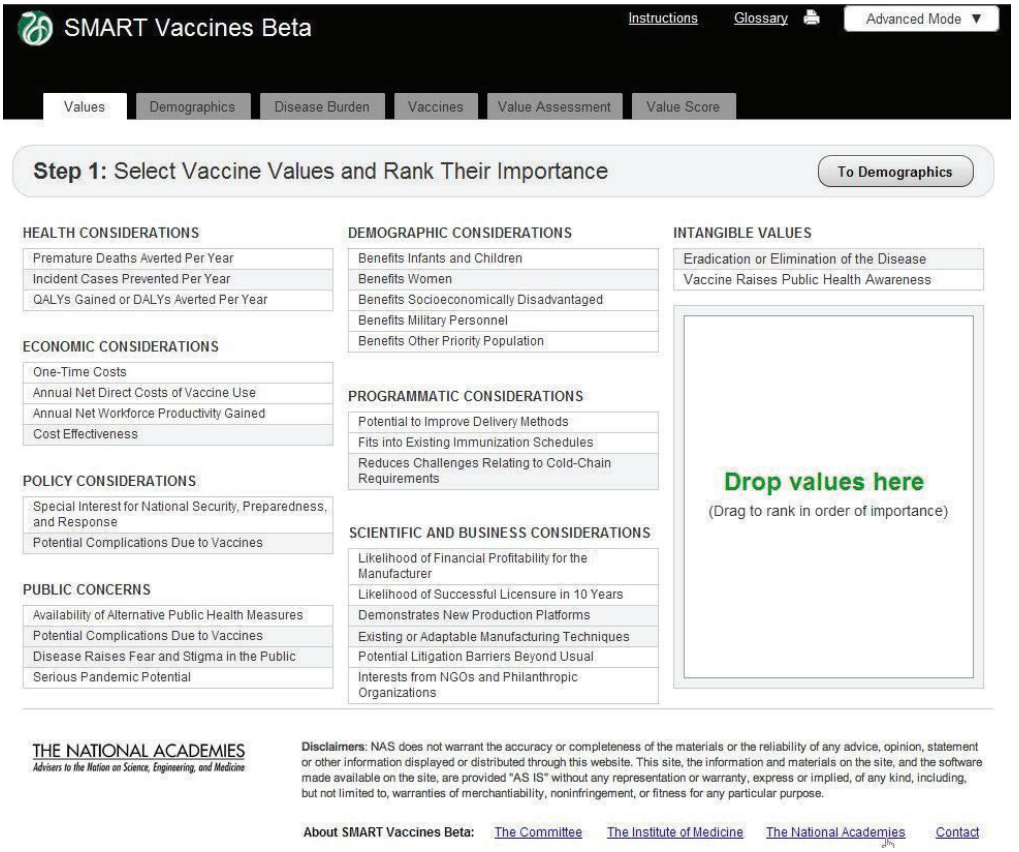


FIGURE 3-5
The SMART Vaccines Beta Values screen allows the user to specify the attributes of importance toward the ranking of candidate vaccines.

the appropriate cost-effectiveness criterion will automatically be used to coincide with the choice of QALYs or DALYs.

SMART Vaccines Beta converts the rank order of attributes selected in the drag-and-drop box into numerical weights to be used in the multi-attribute value model. Chapter 2 described this process and provides references to justify this approach. Later versions of SMART Vaccines should be able to incorporate the direct entry of value weights by the user.

Step 2: Demographics

Figure 3-6 shows the demographics screen in which the user enters population data. The user can either pull up pre-specified populations (such as those of the United States or South Africa in the lower left panel) or begin with a blank template and fill in data for an entirely new population. The

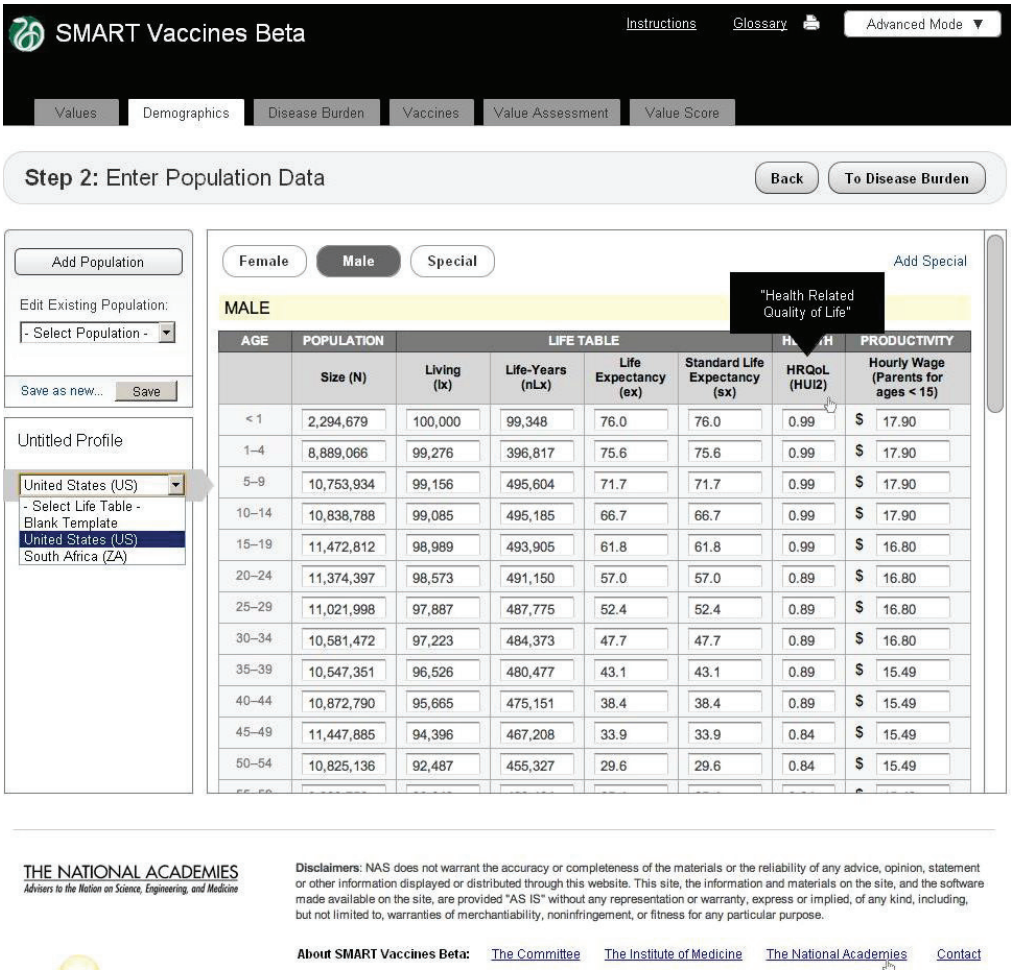


FIGURE 3-6
The SMART Vaccines Beta Demographics screen allows the user to specify the population (by age and sex) to be used for ranking candidate vaccines.

software requires complete templates for males and females, provided in 5-year age intervals for adults and more refined for children. While the data demands in this step seem considerable, the data can be readily imported from available databases at the World Health Organization for most populations around the world.

Average wage rates for children and adolescents are assigned based on the parents' wage rates, on the logic that a sick child will divert a parent from his or her normal productive activity. Market wage rates are used as a proxy for the value of people who may be in nontraditional settings, such as stay-at-home parents. The scroll bar on the right side of the screen

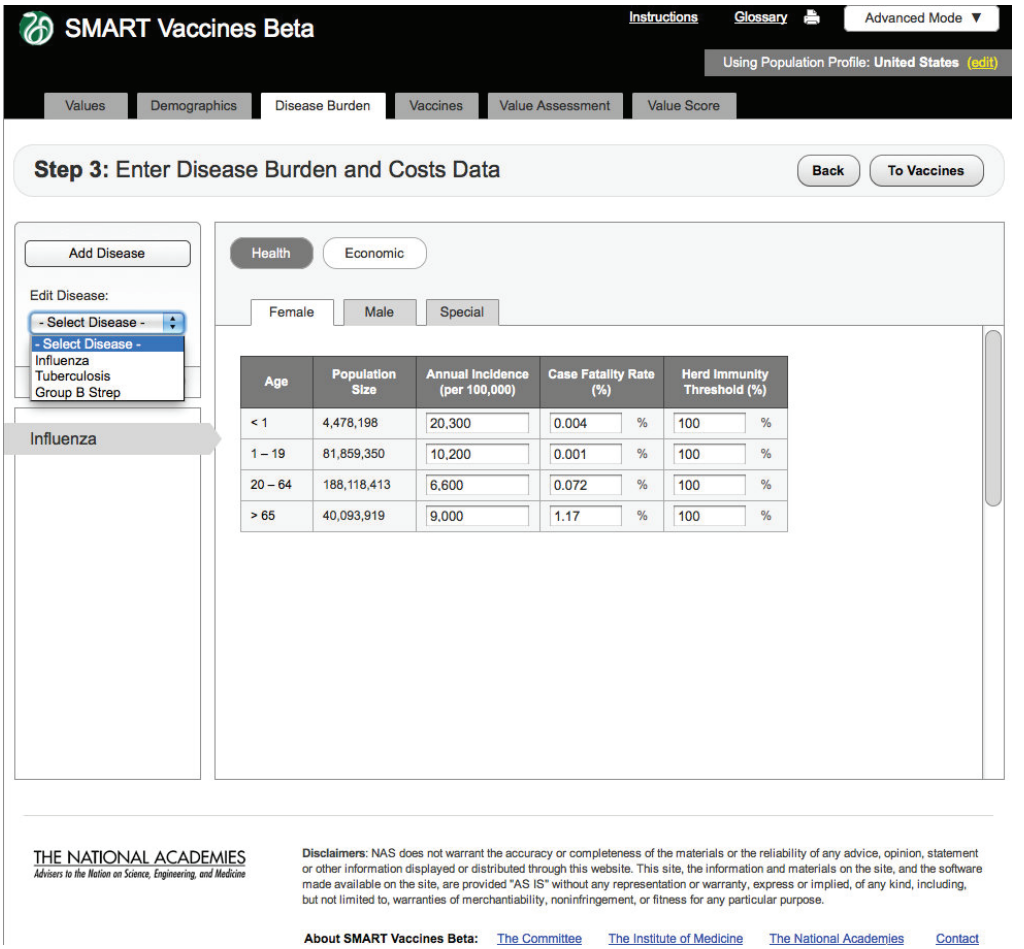


FIGURE 3-7
The SMART Vaccines Beta Disease Burden (health) screen allows the user to enter incidence and case fatality rates for the particular disease.

takes the user to population age groups above those shown (e.g., ages 65 and older).

Step 3: Disease Burden

Step 3 takes the reader into the specification of disease burden (Figure 3-7). Unlike Steps 1 and 2, Step 3 must be filled out separately for each disease that might be prevented by a candidate vaccine (e.g., influenza, tuberculosis, or group B streptococcus), and, as shown below, subsequent screens apply to each candidate vaccine, and there may be more than one candidate vaccine per disease.

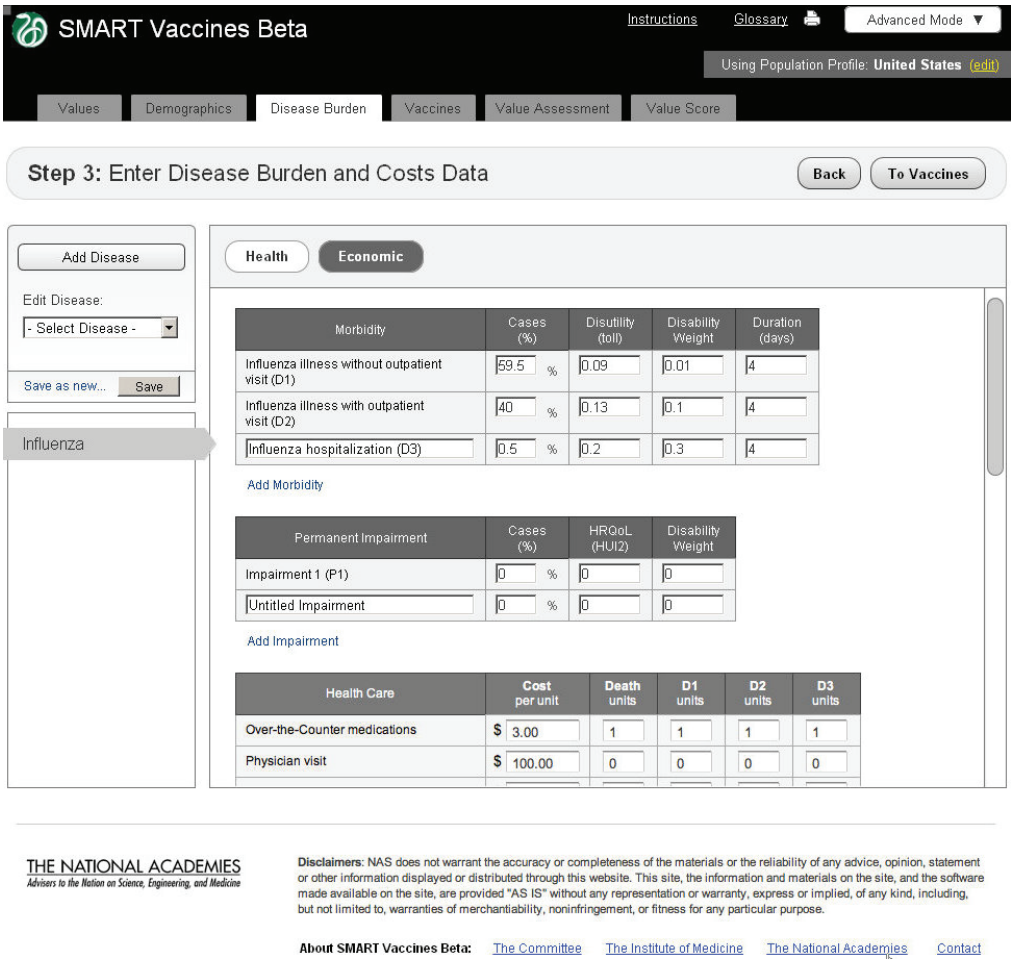


FIGURE 3-8
The SMART Vaccines Beta Disease Burden (economic) screen allows the user to enter morbidity scenarios and associated quality-of-life score values.

Health

SMART Vaccines Beta automatically fills in the population size in each relevant population group from data shown at Step 2, so the user must fill in population-specific information about the annual disease incidence per 100,000 persons in each age group, the case-fatality proportion, and the herd immunity threshold.

The herd immunity threshold provides a simple way to specify whether there is any meaningful herd immunity effect from the vaccine. Some diseases have no person-to-person transmission (e.g., tetanus), in which case the herd immunity level should be set at 100 percent (that is, 100 percent of the population must be vaccinated to achieve 100 percent

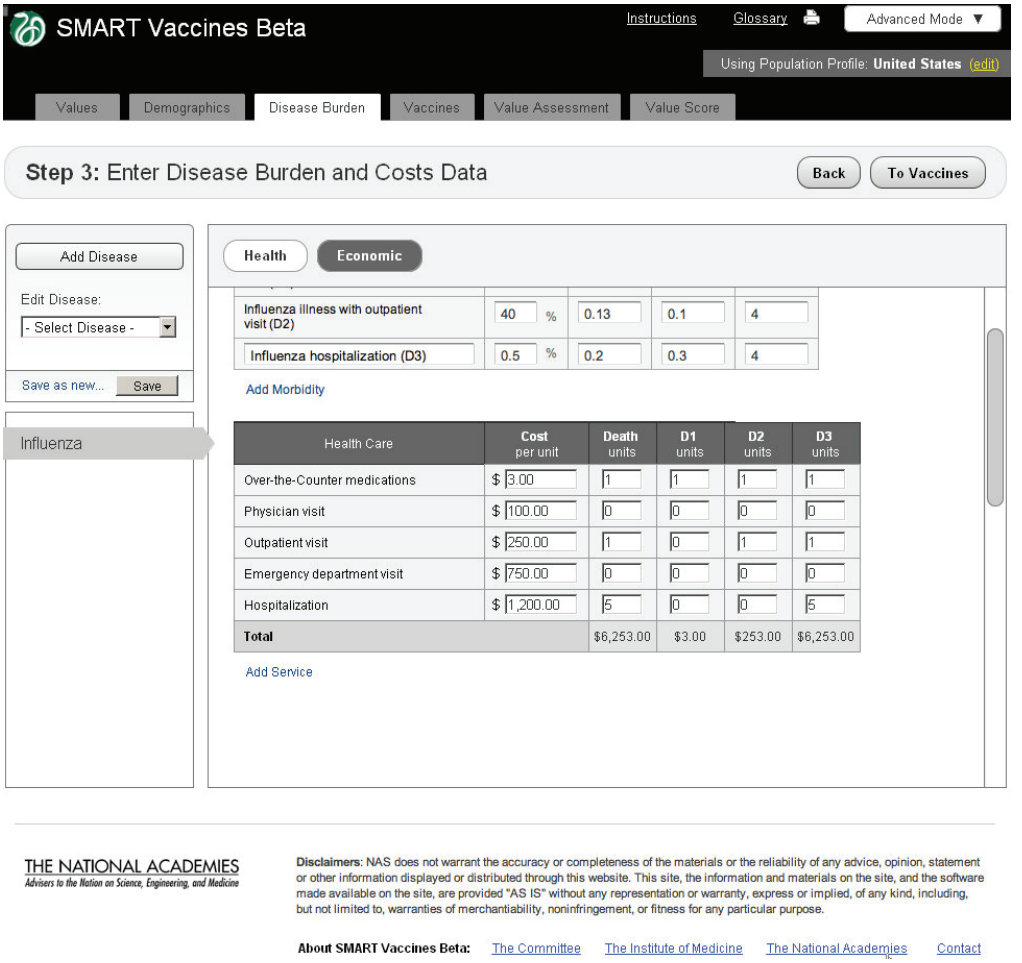


FIGURE 3-9
The SMART Vaccines Beta Disease Burden (economic) screen allows the user to enter health care costs and economic implications for the disease.

immunity). With transmissible diseases such as influenza, one could set the herd immunity threshold at, say, 80 percent, indicating that once 80 percent of the population has achieved immunity, the remaining population gain protection through herd immunity. This is, of course, a highly simplified treatment of the complex dynamics of herd immunity. Later versions of SMART Vaccines will be able to accommodate more sophisticated dynamic models of herd immunity.

Future versions will also be able to allow the user to specify more finely grained populations for the disease burden. This version uses only four categories—infants, children, adults, and adults over 65—to minimize

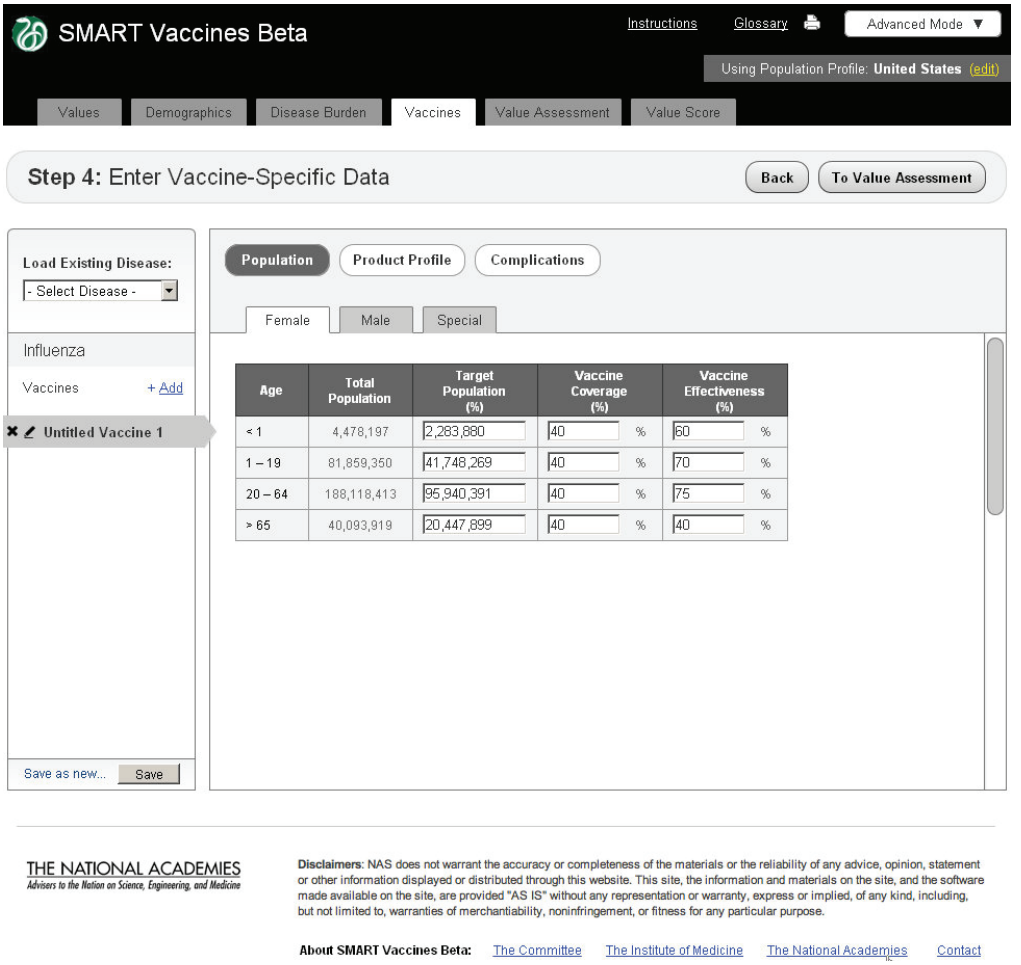


FIGURE 3-10
The SMART Vaccines Beta Vaccines (population) screen allows the user to estimate coverage and effectiveness of a vaccine candidate in a target population.

data-entry burdens. Ultimately the age categories in Step 3 will be able to take on the same level of refinement as the population data in Step 2.

This step also allows for definition of special populations—perhaps those infected by HIV or some other special group, although use of the "special population" tab requires that equivalent numbers of people be removed from the female and male populations to keep population totals accurate.

Economic

In the Economic tab of Step 3 (Figure 3-8), users specify typical treatment patterns for each disease in question and the costs of each type of treat-

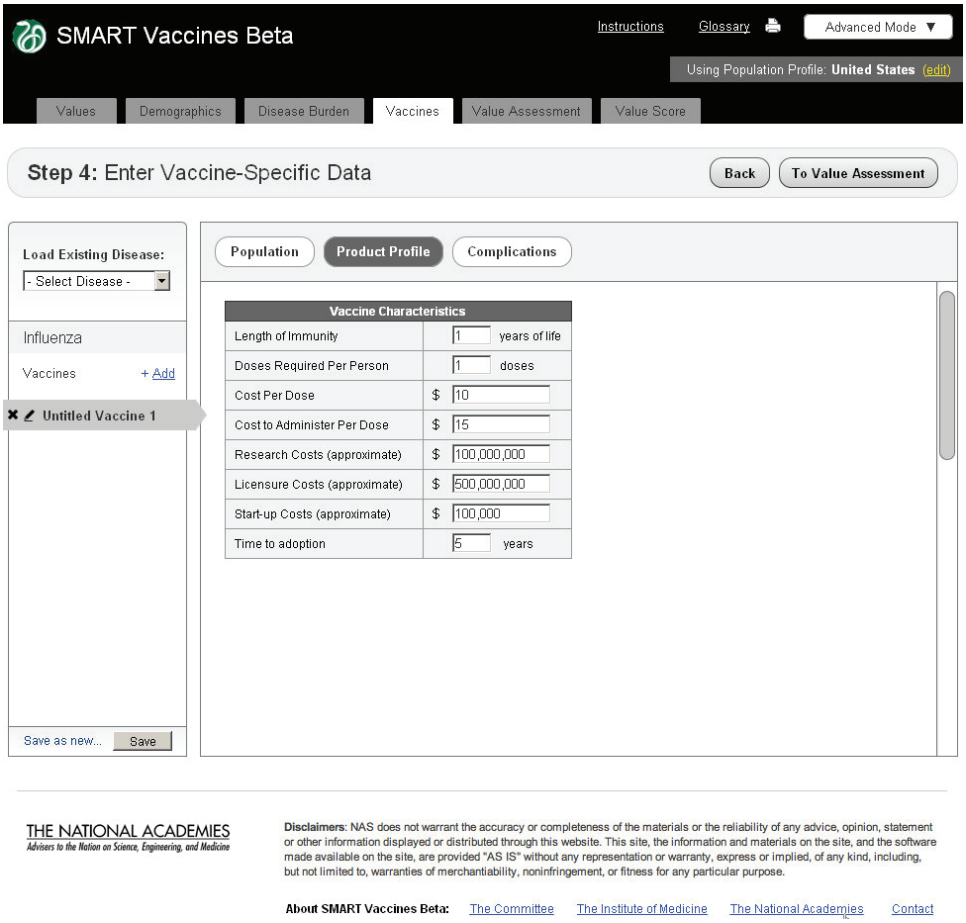


FIGURE 3-11
The SMART Vaccines Beta Vaccines (product profile) screen asks the user to enter vaccine coverage characteristics such as length of immunity, research, licensure, and start-up costs.

ment. These data serve as the basis for calculating the medical costs saved through prevention. This step also requires that users specify the disutility toll for each disease for this specific population (used in the calculation of QALYs) and the disability weight (used in the calculation of DALYs). Disutility tolls are available for some populations through household survey and related studies. DALY disability weights are normally drawn from expert opinion, and typically users find related DALY weights in publications from the developers of the DALYs approach.

In this example screen (influenza in the United States), the user has specified that 59.5 percent of those infected do not visit a doctor, 40 percent have an outpatient visit, and 0.5 percent are hospitalized, but none have permanent impairment. Other diseases would obviously have different patterns. The user may specify additional categories of morbidity or

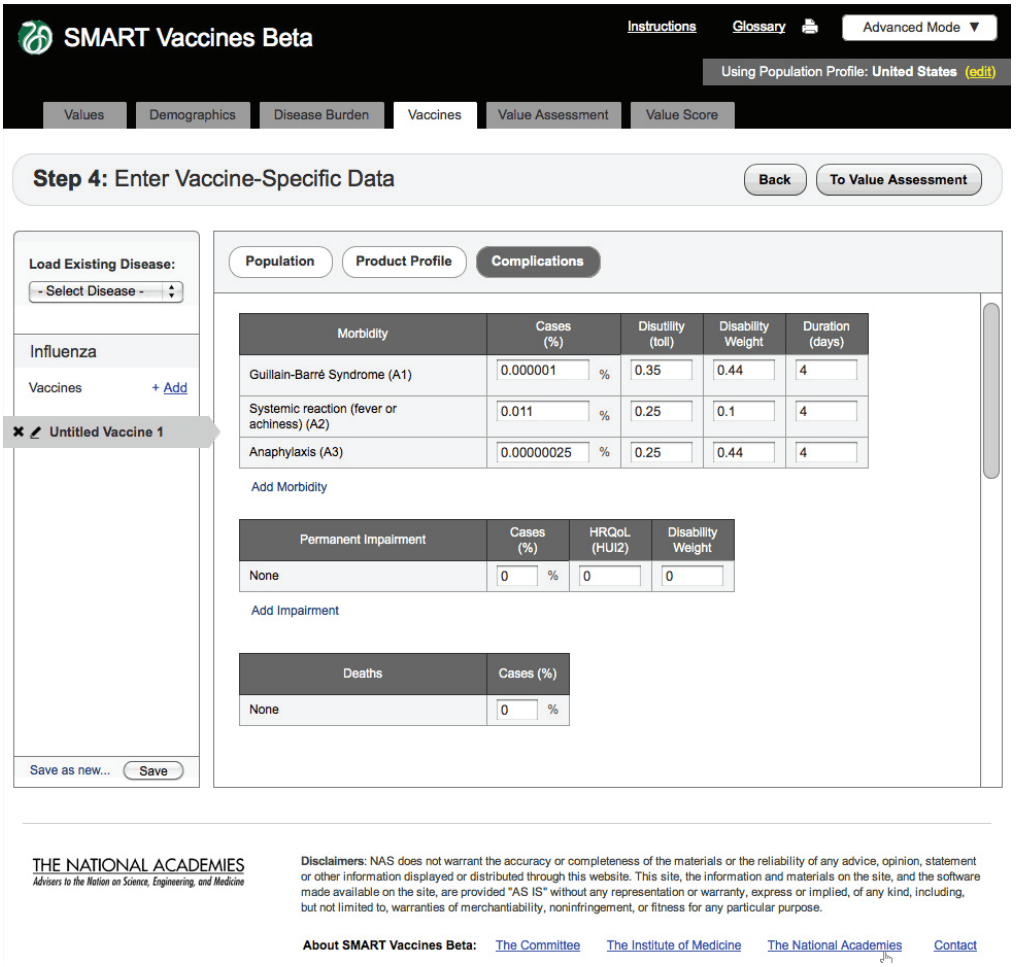


FIGURE 3-12
The SMART Vaccines Beta Vaccines (complications) screen asks the user to enter information relating to expected vaccine-induced complications, permanent impairments, and deaths.

impairment as appropriate for each disease. These categories of morbidity are combined with the cost of each type of treatment (see bottom of Step 3 screen) to estimate the costs of treating unprevented disease. Figure 3-9 shows the lower half of this screen, using the scroll bar on the right side of the screen. This feature is common to most pages of SMART Vaccines.

Step 4: Vaccines

Population

In Step 4 users enter vaccine-specific data (Figure 3-10). Each potential disease under consideration (in this example, influenza, tuberculosis, or

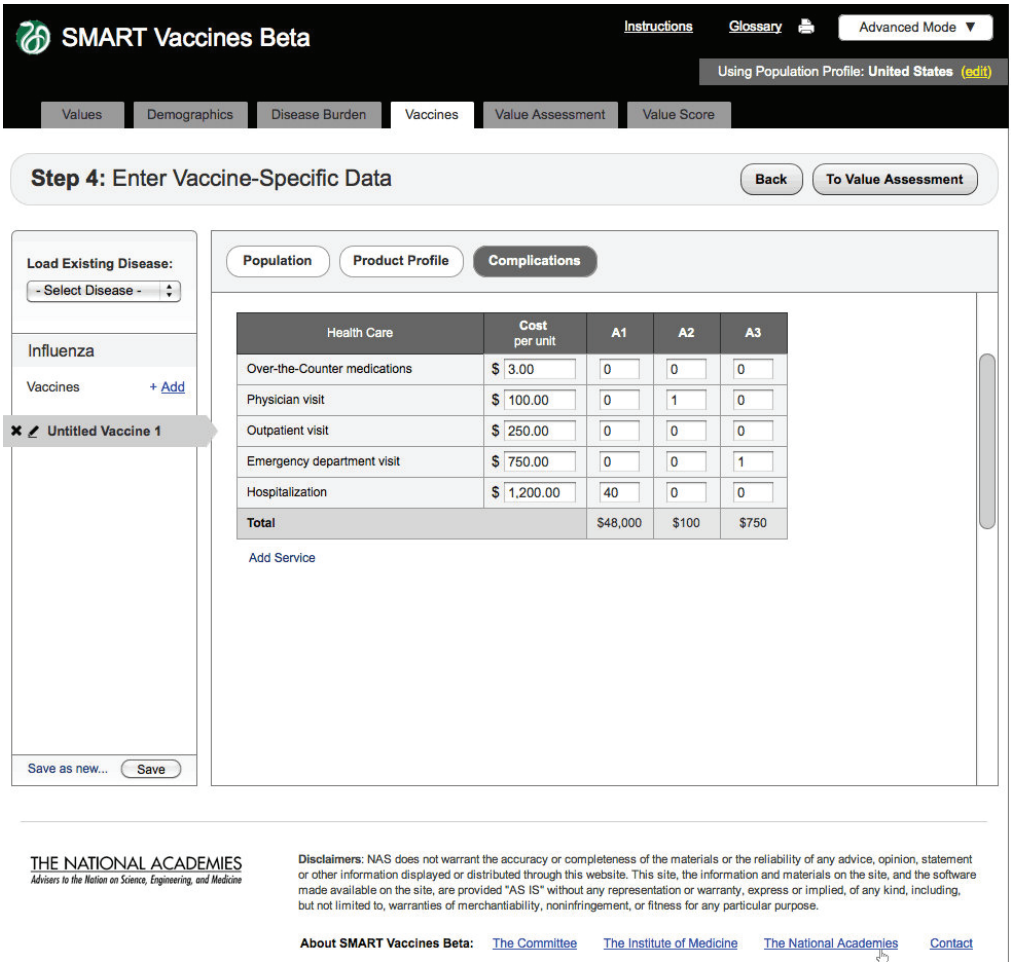


FIGURE 3-13
The SMART Vaccines Beta vaccines (complications) screen further asks the user to enter estimated costs associated with vaccine-related complications.

group B streptococcus) might have multiple vaccine candidates. Users can build up the data for a single vaccine, save it (e.g., as "TB Vaccine A"), modify the input data to reflect another candidate vaccine's characteristics, and save it as another vaccine (e.g., "TB Vaccine B").

As with the disease burden data, these data currently have only four age groups but will be expandable in future versions. Here, the user specifies age-specific vaccine coverage (the percent of the population receiving the vaccine) and effectiveness (among those being vaccinated). SMART Vaccines Beta automatically fills in the population numbers for each age group. These data show, for example, that the user expects 40 percent of

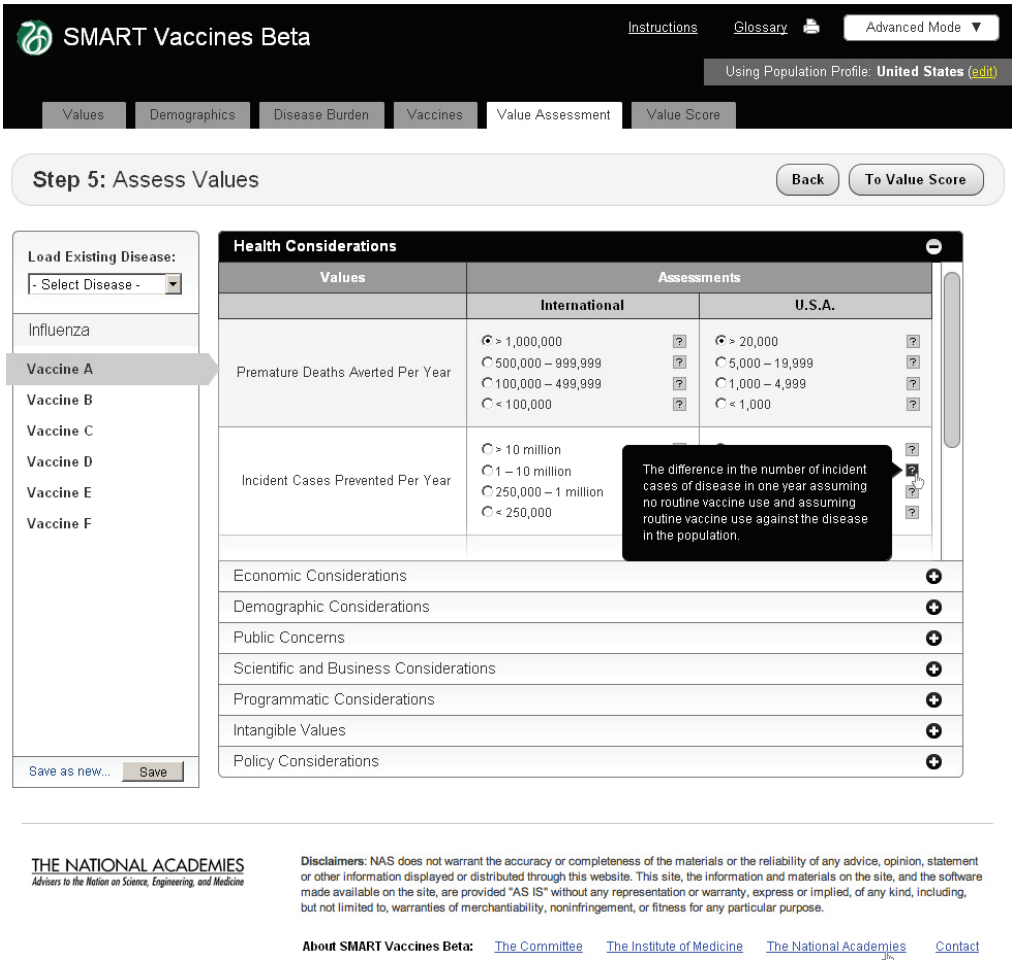


FIGURE 3-14
The SMART Vaccines Beta Value Assessment page allows the user to enter information in eight categories, from health to policy considerations. Each category on this page expands and collapses like an accordion menu.

adults to be vaccinated with a 75 percent effectiveness so that 30 percent of the adult population becomes immune.

Product Profile

In this step the user specifies the potential attributes of a specific vaccine (Figure 3-11). Of course, these are not known with certainty before actual development, so users must use expert opinion to conjecture about the candidate vaccines. These attributes are central to the issues of vaccine prioritization because they include basic aspects of the vaccine (e.g., how many doses and costs per dose to purchase and administer), research and development costs, licensing costs, and expected time to adoption. The

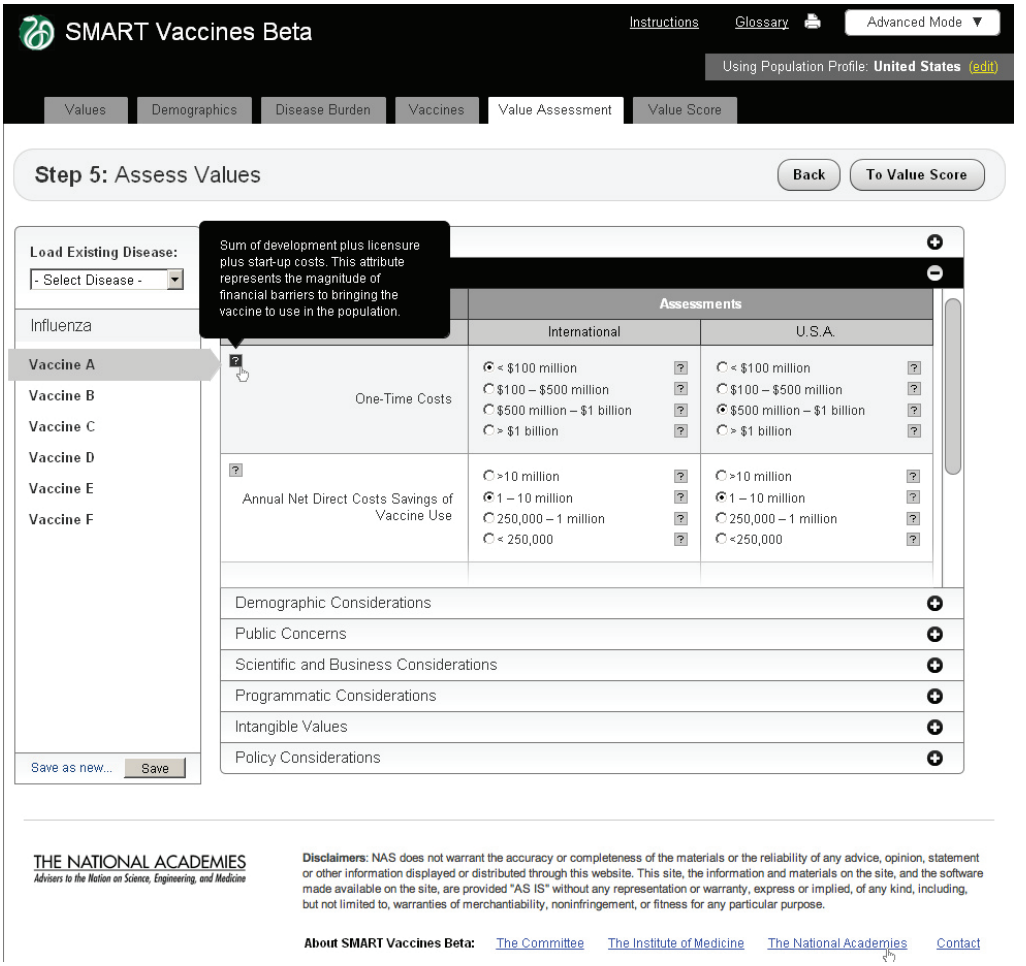


FIGURE 3-15
The SMART Vaccines Beta Value Assessment page showing economic entries from the user with pop-up help menus containing definitions of terms.

user can subsequently change these product profile attributes and see (on a concurrent view of Step 6) how the computed attributes and the priority score have changed. This gives an "on the fly" capability to see how these attributes affect rankings and their computed components, and it allows users to consider trade-offs between attributes as they focus product development efforts—for example, choosing larger research and development costs but reducing the costs to administer by removing cold-chain requirements or product shelf-space demands.

Complications

Step 4 also includes an entry screen for potential complications that a new vaccine may cause (Figure 3-12). These data are similar in concept to those

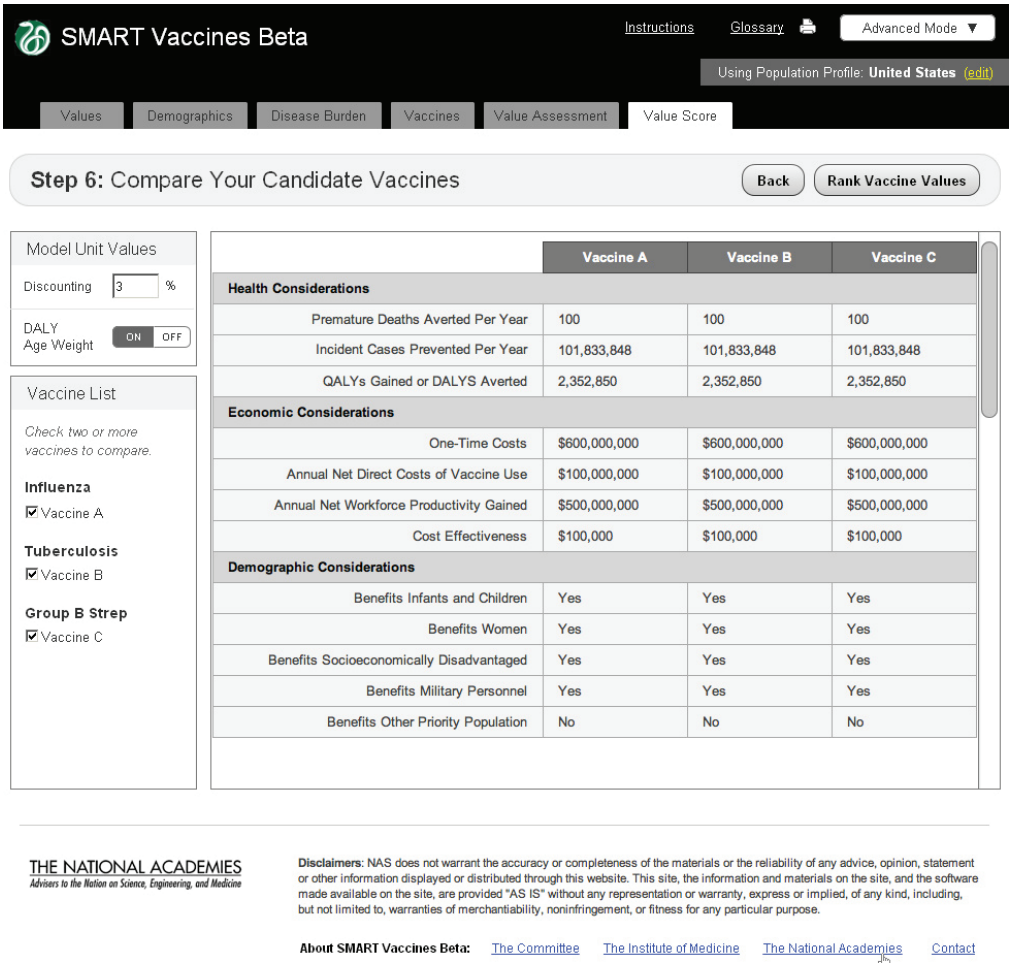


FIGURE 3-16
The SMART Vaccines Beta Value Score (dashboard screen) presents the final values for each vaccine attribute, given the information entered by the user in the earlier steps.

in Step 3 (Disease Burden), but in this case they refer to complications of a candidate vaccine rather than to the consequences of unprevented disease. Users need to specify each possible complication and all associated data. Since these complications are unknown until a vaccine is fully field tested (or used widely so as to detect rare complications), users will necessarily draw on expert opinion and work by analogy from vaccines with similar characteristics (e.g., live or inactivated virus or types of adjuvants). Figure 3-13 shows the bottom of the Complication page using the scroll bar at the screen's right side.

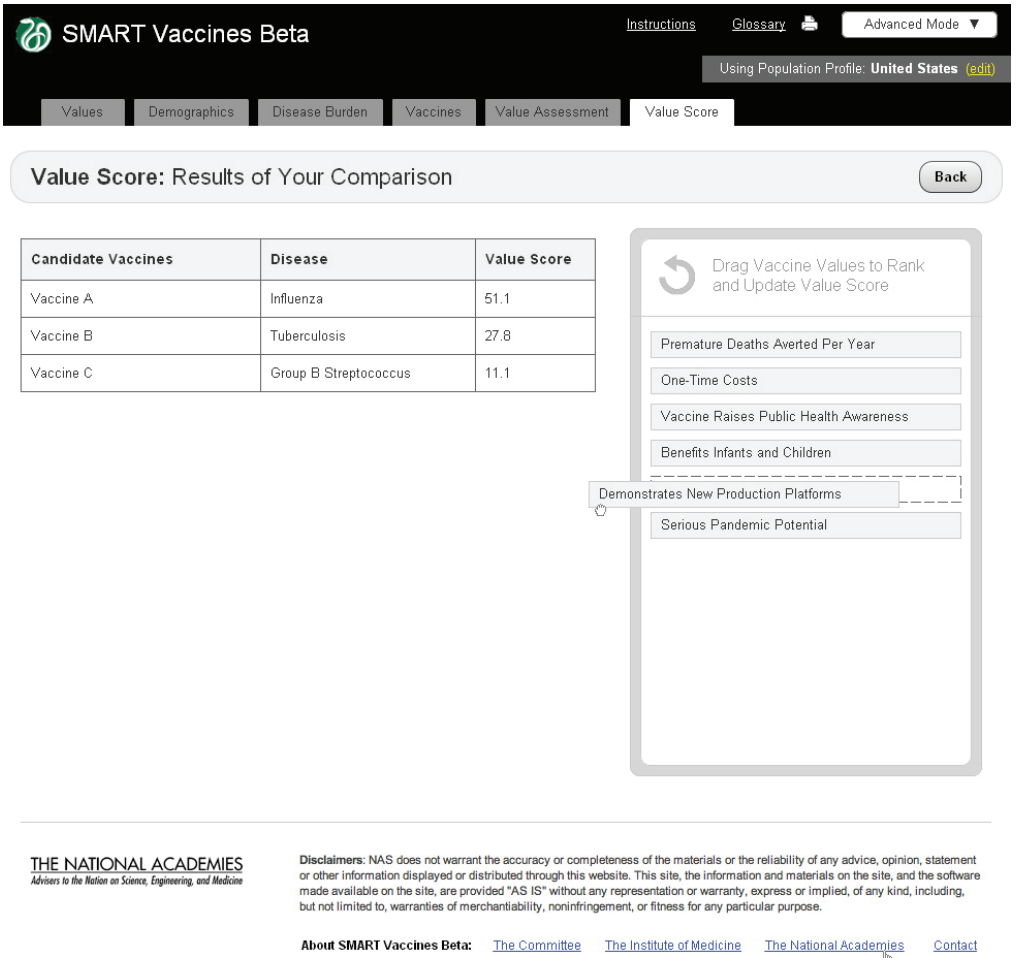


FIGURE 3-17
The SMART Vaccines Beta Value Score screen shows a side-by-side comparison of all vaccine candidates. The top priority areas selected by the user are presented in the Drag Vaccine Values to Rank box for reference to enable re-ranking if necessary.

Step 5: Value Assessment

Step 5 asks users to enter qualitative information about each vaccine. These come in eight categories, as previously shown in Table 2-1. Each one of these categories opens up like an accordion menu to show all of the qualitative attributes associated with any vaccine, whereupon the user checks the appropriate category for each attribute. Each category has a pop-up bubble associated with it to describe to the user the committee's intent or definition regarding a particular categorical choice for each attribute (each indicated by a ? symbol). The user need not fill out these data queries if the attributes in question have not been selected in the value choices (Step 1). Figure 3-14 shows this step with the Health Considerations bar opened up,

and Figure 3-15 shows the same step with the Economic Considerations bar opened up.

Step 6: Value Assessment and Score

The screen at Step 6 shows values for all of the calculated attributes for each vaccine under consideration (Figure 3-16). This provides a single "dashboard" point that shows what all of the previous data entries lead to in calculated attributes. For example, Premature Deaths Averted per Year uses data on population size by age, disease incidence by age, vaccination rate by age, vaccine efficacy rate by age, and the case mortality rate to compute the number of premature deaths averted per year. A similar computation creates the Incident Cases Prevented per Year. Calculation of QALYs gained and DALYs averted also include information (entered at Step 2) regarding disease burden.

As noted before, users may select either DALY or QALY measures, but not both. If a user selects the DALY measure, he or she has the option (at the upper left of the Step 6 screen) to use or avoid the associated age-weights. The calculated illustrative value scores are shown in Figure 3-17.

Consideration of uncertainty

In this phase, the committee was unable to explicitly model issues relating to uncertainty in SMART Vaccines Beta. In Phase II the committee will consider various elements of uncertainty to be included in SMART Vaccines 1.0. Sources of uncertainty and how they affect SMART Vaccines are briefly discussed, along with some possible methods to address these issues in Phase II.

Uncertainty About the Likelihood of Successful Licensure

SMART Vaccines Beta includes one uncertainty component but instead of listing it as a probability the committee characterized it as a value attribute: "Likelihood of Successful Licensure in 10 Years" under "Scientific and Business Considerations" (Table 2-1). The uncertainty related to the time the vaccine may become available for public use affects judgments about priority.

Otherwise, some possible ways to address the issue of uncertainty include programming the uncertainty component into the computational submodel as a delay between "now"—the time when the priorities are being set—and the time when the health benefits due to vaccination might

be expected to accrue, and the time when net costs begin to include the vaccination costs.

Earlier, in the 2000 report, each vaccine candidate under consideration was assigned to one of three development intervals: 3 years, 7 years, or 15 years. An additional 5-year post-licensure delay was assumed before the vaccine was actually made available for public use. The vaccine candidates in this study were assigned to the respective development intervals based on the 2000 "committee's assessment of the current state of the vaccine's development" (IOM, 2000). Once the interval was assigned, no further consideration of uncertainty was made. Costs and benefits were discounted in accordance to the chosen time intervals.

SMART Vaccines Beta addresses this uncertainty in a different way consistent with the programming resources available in this phase of the study. The computational submodel computes the health benefit and economic consequences on an annual basis *as if* the vaccine is presently available. The committee added the attribute "Likelihood of Successful Licensure in 10 Years" to reflect the increase in value of a vaccine that may be developed in the near future versus sometime in the distant future. This attribute requires a subjective assessment by users in the same manner as the 2000 report's subjective assignment of the development interval.

In SMART Vaccines Beta, users are asked to assess the state of the science and market to support the development and licensure of the new vaccine candidate according to a five-point Likert scale (1 reflecting "almost certainly will be licensed within 10 years"; 5 reflecting "almost certainly will not be licensed within 10 years"). This attribute increases the overall priority score of the vaccine as a function of higher likelihood of licensure. The committee determined that 10 years was a reasonable limit for the purpose of modeling.

Another possible way to implement this concept as an attribute would be a direct assessment of expected time to vaccine licensure and availability, but this would then not include a sense of uncertainty around this assessment. The effect of using such an attribute in the value submodel is functionally equivalent to including a direct estimate in the computational submodel—vaccine candidates that are expected to be licensed sooner will receive higher scores and those not expected to be licensed soon will receive lower scores when everything else is equal.

There are advantages to embedding this uncertainty component in the value submodel. Typically, users think about vaccine benefits and costs *as if* the vaccine were available, not as if they were discounted to the future. If the time to availability were embedded in the computational submodel, the definitions of certain attributes relating to the benefits and costs must be changed. The user entries would then need to be averaged out as a func-

tion of the subjective distribution of the estimated licensure time supplied by the users. Although economists are used to thinking in terms of discounted quantities, the average user may not be.

There are also possible disadvantages to this approach. Because users may not appreciate the exponential effect of discounting benefits delayed to the future, they may underweight the value attribute relating to the likelihood of successful licensure in 10 years. The committee discussed making selection of this particular attribute mandatory among the 29 attributes in part to reflect the concern about underweighting. In Phase II, the committee will revisit how to better represent this uncertainty component in SMART Vaccines 1.0.

Other Uncertainties

Manning and colleagues (1996) identify three sources of uncertainty in cost-effectiveness models (that otherwise affect any computational model such as SMART Vaccines): (1) parameter uncertainty; (2) model structure uncertainty; and (3) model process uncertainty.

Parameter Uncertainty

The computational submodel in SMART Vaccines Beta, although simplistic in its current form, is a function of many parameters: population modeling, estimates of health burden and benefits, and estimates of health care costs. Each of these parameters has components of uncertainty surrounding it.

The current model does not incorporate uncertainty about these parameters in its computations. The most straightforward method to do so would be to specify a distribution surrounding each parameter and then use Monte Carlo simulation to sample from the distributions and compute results for each sample. Then a distribution for each of the computational outputs could be built, and these, in turn, could be used to determine an overall distribution on the priority score.

The committee elected not to do this for SMART Vaccines Beta due to two concerns. The first relates to the source of the distributions for input parameters. Some parameters may affect all vaccine candidates, such as population life tables, while others are specific to an attribute or a vaccine candidate. It is well known that life tables are built from population sample data and thus have uncertainty concerning every age-specific mortality rate or life expectancy. Whether these uncertainties should be incorporated in the computational submodel is an open question; many models such as these take population and life-table values as "given" without incorporating any uncertainty surrounding them. In any case, with additional effort, these uncertainties could be represented in the computational submodel.

More concerning are uncertainties about health-related quality of life tolls and disability weights for various disease states. These are, in part, based on data and expert opinion. The disability weights used in DALY models are also, in part, based on expert opinion while disutility weight for QALY models can also use results elicited from studies of relevant populations. In the case of low-income countries, the committee anticipates that only sparse data, at best, will assist users in specifying disutilities or (even more challenging) the distributions around them. Additional uncertainty relates to the economic estimates in SMART Vaccines Beta. These too will come from combinations of sparse data and expert opinion.

Incorporating uncertainty about these parameters requires a separate module within SMART Vaccines that is able to elicit subjective distributions for each parameter—a task that the committee will consider in Phase II. The committee can, however, envision what this module may incorporate. It is unlikely that parameters will be estimated from data because most users will not have access to primary data needed for statistical estimation of parameters and their distributions.

Instead, the committee may use a subjective estimation approach similar to a Bayesian estimation to elicit distribution. In Phase II, the committee expects to identify a distribution for each parameter. For example, if the parameter is a probability, then a statistical beta distribution may be employed to describe uncertainty about it. Costs may be better described by a distribution bounded below by zero and having a tail to the right. Health utility tolls are bounded and might well be described by statistical beta distributions.

Credible interval estimation (used in conjunction with direct estimation of means in some cases), specifying equivalent data samples (used in specifying beta distributions) is one way to describe uncertain quantities in the computational submodel. Other parameters in the model whose uncertainty may be best addressed with sensitivity analysis include vaccine effectiveness and the duration of immunity.

Computation of outputs which are functions of uncertain inputs can be accomplished either by Monte Carlo simulation, or using Markov Chain Monte Carlo simulation to build a pseudo-distribution for the outputs if simple independent sampling of parameters is not realistic within the computational submodel. The committee intends to consider these challenges in the Phase II effort.

Another challenge is to determine the rank order *distributions* for vaccine candidates. Perhaps this would require a secondary Monte Carlo sampling module within SMART Vaccines where the distribution for each of the n vaccine candidates is input to this module and the output is

n distributions over position in the rank order for each of the candidates. Because these distributions may involve codependency of some candidates on uncertainties about certain diseases and assumptions about health utility tolls and costs, the output may not be just a simple independent sampling of priority score distributions. Obviously this is a complicated task that the committee will consider in Phase II.

Model Uncertainty

Manning and colleagues (1996) also identify model uncertainty as uncertainty about whether the computational model itself is an adequate representation of the process that is being investigated. In regards to SMART Vaccines Beta, this uncertainty concerns whether the structure of the computational submodel is adequate. There are only two approaches to incorporating this uncertainty: one is sensitivity analysis where model structure is varied, and the other is to construct a set of alternative models and then to make some weighted combination of them. Either of these is beyond the scope of Phase I or Phase II work of the committee.

Model Process Uncertainty

This final source of uncertainty stems from the fact that SMART Vaccines Beta was constructed by a particular committee tackling a prioritization exercise. If a different set of individuals were to do the same task under the same constraints, the model that would result would differ and could well arrive at somewhat different results.

Manning and colleagues (1996) have called for research concerning model process uncertainty to be a priority for further research. The National Cancer Institute has used the multiple modeling team approach to study simulation models of various cancers (e.g., Berry et al., 2005). They found different modeling approaches lead to results that were quantitatively distinct but qualitatively similar. Similar multiple model approaches are used in climate forecasting (Knutti et al., 2010). The multi-groups or multi-models approach is very expensive and time consuming.

The committee judged the consideration of both the model uncertainty and model process uncertainty to be far beyond the scope of either Phase I or II development of SMART Vaccines.

Current capability for sensitivity analysis

SMART Vaccines Beta has the capability to permit variations in attributes to observe the consequences in the final utility score. This sensitivity analysis can be conducted manually in the current version, and indeed, differ-

ent versions of a single vaccine candidate (with different attributes) can be saved and then compared directly one against another as well as with competing vaccines.

For example, suppose a new vaccine against tuberculosis with some predefined set of attributes is entered by a user as TB Vaccine 1. The multi-attribute utility model will create a value score for this vaccine, and the user can save this specific vaccine as one among many.

Now let the user alter one or more of the attributes for the same tuberculosis vaccine and save the results as TB Vaccine 2. This can be compared against TB Vaccine 1 and other versions. This process thereby allows the user a choice among alternative intensities and distributions if necessary data have been provided by the user.

Phase II enhancements could incorporate, for example, "tornado diagrams" showing how much each candidate vaccine's score changes in response to, say, a doubling or halving of each attribute's value. These diagrams give an immediate visual representation of the extent to which the outcomes strongly depend on the value of inputs. The committee will also consider the possibilities to expand and automate the sensitivity analyses in Phase II.

Beta concept evaluation

Following the development of SMART Vaccines Beta, a concept evaluation session was organized to obtain feedback from potential users. Each of the 11 consultant evaluators participated in a webinar led by a committee member and staff; four similar webinars were held, with two to four evaluators participating in each session. The evaluators were asked to provide feedback regarding the basic concept, software design, technical features, potential applications, and audiences. In general, the overall concept of SMART Vaccines Beta was received positively, even enthusiastically, with the exception of one evaluator who shared concerns regarding the basis and extension of the work. Many of the features of SMART Vaccines Beta have already been updated in response to the comments from concept evaluators. More important, many features have the potential to be upgraded in Phase II of this study.

The committee's observations and views on the next steps in the enhancement of SMART Vaccines Beta are presented in Chapter 4.

4

Observations and Looking Forward

SMART Vaccines is intended to help set relative priorities among candidate vaccines based on user preferences, within the context of health, economic, demographic, scientific and business, programmatic, and policy considerations as well as public concerns. SMART Vaccines integrates computed attributes with qualitative attributes to provide a value score that compares one vaccine opportunity against another. Because SMART Vaccines is built from a complex model, the committee chose to develop user-friendly software to better assist decision makers.

The charge for this study did not call for producing a list of ranked vaccine candidates; instead it asked for the development of a conceptual prioritization model for new preventive vaccines and for that model to be tested against two to three vaccine candidates, at least one of which had an international focus. Thus, the committee wished not only to make sure that the model performed as specified, but also to show that the data were meaningful and, to the extent verifiable, accurate. This section describes the steps the committee took to assure the accuracy of both the model and the data used to exercise the model.

Data requirements

SMART Vaccines requires four types of data for computing and valuing the vaccine attributes.

1. The first type of data used in the model relates to demographics and is verifiable from established sources. Some data sources, however, dif-

fer in their final numbers even for such apparently clear-cut characteristics as the age distribution of the population of the United States for the year 2009. In collecting U.S. population data, for example, at least three potential sources were consulted: the United Nations Population Division, the World Health Organization (WHO), and the U.S. Census Bureau, all of which contain age-specific estimates of the U.S. population (and of the populations of many other nations) by gender. However, the sources differ in minor ways even for such apparently simple data. The United States conducts a complete census only once a decade, and many other nations do so even less frequently. The U.S. Census Bureau often adjusts final estimates to allow for under-reporting by various groups. Thus, even such apparently "hard" data as population demographics may have differences across sources. For example, data are adjusted differently and may be either extrapolated or interpolated differently across years. As part of its testing, the committee used population data for the United States and South Africa drawn from the WHO Global Health Observatory Data Repository (see Appendix B), even though these data differ in some detail from U.S. Census Bureau data.

2. The second type of data relate to disease burden and costs. These data will have a relatively "hard" basis in some nations based on various survey programs, surveillance systems, and one-time research efforts. The committee used such sources to estimate disease burden and treatment costs for the United States and South Africa (see related data tables and sources in Appendix B). For many other settings, especially developing countries, such data will be unavailable immediately and will likely be supplied by a process that relies primarily on expert opinion. Given the uncertainties about these key assumptions, sensitivity analyses will be important to test the robustness of the model's results. Committee members often relied on their own areas of expertise and judgment to identify potential errors in the data, with the result being a reevaluation of the data checked against the original sources. Because the focus of this study is the development and testing of the model, the committee did not use other possible methods of checking data accuracy; however, the committee acknowledges the value of further data verification to optimize the use and accuracy of the model.
3. The third type of data contains assumptions about the characteristics of each vaccine, including efficacy under ideal circumstances, effectiveness in real-life settings, duration of immunity, and risk of adverse events. Some of these characteristics are approximations.

Vaccine-induced immunity, for example, wanes over time and is highly variable across individuals in a population. The current version of SMART Vaccines does not attempt to incorporate data about the pattern or variability in the waning of immunity; this could be incorporated in future refinements.

4. The fourth type of data is not subject to verification since the data describe mostly qualitative attributes of vaccines that do not yet exist. They will be determined by users, presumably often guided by expert opinion. Hence these data cannot be described as either accurate or inaccurate because they reflect the users' own judgments about each candidate vaccine. However, these attributes allow diverse users to consider broader perspectives and dimensions of assessment that will permit a more customized and relevant tool for decision makers worldwide.

SMART Vaccines combines data from all three levels to create a series of calculated variables, all of which are reported to the user in the "dashboard" output interface (see Figure 3-16). To ensure rigorous testing, the committee validated the computations both by hand and via spreadsheets to determine the accuracy of the computations. Appendix B presents the data the committee used.

Looking ahead

To further enhance and improve SMART Vaccines, the committee will undertake three related sets of activities to advance model and software development. For Phase II of this study, the committee will demonstrate the current version of SMART Vaccines to a wide range of stakeholders and potential users and obtain their feedback about the usefulness of the software. Afterwards, the committee will enhance the model, its functionalities, and the user interface underpinning SMART Vaccines as part of moving the software from the beta stage to version 1.0. Three additional vaccine candidates will be tested in the next phase in order to exercise the model and to expand the data library contained within the software. The next phase of this study is expected to begin immediately.

Model Attributes

For further refinement of SMART Vaccines attributes, it will be necessary to obtain feedback from potential users in at least three areas in the Phase II of this study.

First, the rank order centroid method used to acquire and compute weights for the attributes is an approximation. It is a method for reducing the potential workload of the user. Many multi-attribute utility analysts who work one on one with decision makers use extensive questionnaires to elicit weights to represent the decision maker's values more precisely. In order for the committee to provide users with the flexibility to revise their weights according to their values, additional feedback will be required.

Second, the representation of the attributes themselves can improve with experience. Currently they are presented as a list as shown in Table 2-1. One potential area for refining the attribute representation would be to consider reorganizing the way that they are classified.

Third, the categories that are used to represent quantitative attributes need to be reappraised to ensure that they are sensible and meaningful to users and consistent with their values.

Model Evaluation

The committee's model evaluation process included the following steps:

- verification of the software code by modeling consultants;
- exercising the model by the committee and staff to determine if the output changed in meaningful ways;
- replication of results from the 2000 IOM report on vaccine prioritization using its data and specifying a multi-attribute value function that used only $/QALY as the decision rule; and
- construction of a worksheet "simulacrum" of the value model, as discussed in Chapter 3.

As is common with software development, the most reliable method for checking the software's reliability is to place it in the hands of a user community and provide a process for error reporting and creating fixes for known defects.

Trade-Off Considerations

The SMART Vaccines framework is based on trade-offs. The trade-offs are determined by the users' ordering of attributes: Disadvantages on one criterion (e.g., higher costs to vaccinate the target population) may be outweighed by advantages on a different criterion (e.g., long-term health benefits or the demonstration of a new vaccine delivery or production platform).

In this context SMART Vaccines has the potential not only to guide

discussions regarding intra- and inter-institutional vaccine goals, but also to provide a common language for determining priority areas of national and global interests. Appreciating the trade-offs inherent in priority setting exercises may well serve to motivate and focus new vaccine development.

Enhancing the Software Capabilities

The value of SMART Vaccines will depend, in part, on data that need to be generated as candidate vaccines evolve and as disease epidemiology becomes better characterized in different parts of the world. In the future (beyond Phase II), an active community of users and an open-source environment could likely lead to enhancement of the software's capabilities through creation and sharing of databases for populations from different countries, generation of data collection templates, refinement of the attributes and the attribute selection process, enhancement of validation tools and the user interface, and other ways to address the risk and uncertainty surrounding the characterization of vaccines that have not yet been developed. This study is the first step in moving toward these goals.

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A

Mathematical Functions

TABLE A-1

Stationary Population Process Model for Population Age *j* at Year *i*

Measure	Formulation
1. Population Size (N)	For year $i = 1$: $N_{ij} = age - specific\ population\ size$ For year $i > 1$: $N_{ij} = N_{i-1,j-1} - DW_{i-1,j-1} - CP_{i-1,\,j-1}$
2. Target Population (T)	**No Vaccine:** $T_{ij} = N_{ij} \times Proportion\ Target_{ij}$ where $Proportion\ Target_{ij} = 0$ *Vaccine Steady State for year* $i = 1$: $T_{ij} = N_{ij} \times Proportion\ Target_{ij}$ where $Proportion\ Target_{ij} = 1$ **Vaccine Introduced:** $T_{ij} = N_{ij} \times Proportion\ Target_{ij}$ with $Proportion\ Target_{ij} = Input$ (% of $N)_{ij}$
3. Vaccinated Immune (V)	$V_{ij} = T_{ij} \times coverage\ rate_{ij} \times effectiveness_{ij}$
4. Vaccinated Susceptible (VS)	$VS_{ij} = T_{ij} \times coverage\ rate_{ij} \times (1 - effectiveness_{ij})$
5. Not Vaccinated Immune (B)	$B_{ij} = (V_{ij} / herd\ immunity_{ij}) - V_{ij}$
6. Not Vaccinated Susceptible (BS)	$BS_{ij} = N_{ij} - V_{ij} - VS_{ij} - B_{ij}$
7. Total Cases (C)	$C_{ij} = (VS_{ij} + BS_{ij}) \times incidence\ rate$
8. Deaths by Disease (D)	$D_{ij} = C_{ij} \times case\ fatality\ rate$

Measure	Formulation
9. Cases: Impairment (CP)	$CP_{ij} = (C_{ij} - D_{ij}) \times$ *proportion cases impaired*
10. Cases: Morbidity (CM)	$CM_{ij} = C_{ij} - D_{ij} - CP_{ij}$
11. Vaccine Complications (A)	$A_{ij} = (V_{ij} + VS_{ij}) \times$ *vaccine complications rate*
12. All Cause Deaths (DA) Including Disease	**No Vaccine:** $DA_{ij} = N_{ij} \times$ *all cause mortality rate* **Vaccine Steady State:** $DA_{ij} = (N_{ij} \times$ *all cause mortality rate*$) -$ *Deaths averted by vaccine* **Deaths averted by vaccine = Vaccine Steady State D_{ij} – No Vaccine D_{ij}* **Vaccine Introduced:** $DA_{ij} = (N_{ij} \times$ *all cause mortality rate*$) -$ *Deaths averted by vaccine* **Deaths averted by vaccine = Vaccine Introduced D_{ij} – No Vaccine D_{ij}*
13. Cause Deleted Deaths (DE) Excluding Disease	$DE_{ij} = DA_{ij} - D_{ij}$

TABLE A-2

Health and Economic Values for Population Age *j* at Year *i*

1. Premature Deaths Averted per Year	$\sum_{i=1}^{n=1}(\text{No Vaccine } (D_{ij}) - \text{Vaccine } (D_{ij}))$
2. Incident Cases Prevented per Year	$\sum_{i=1}^{n=1}(\text{No Vaccine } (C_{ij}) - \text{Vaccine } (C_{ij}))$
3. Quality-Adjusted Life Years (QALYs) Gained	$\sum_{i=1}^{n=100}(\text{No Vaccine } (QALYs_{ij\ (\text{Death + Impairment + Morbidity − Complications (Impairment + Morbidity))}} - \text{Vaccine } (QALYs_{ij\ (\text{Death + Impairment + Morbidity − Complications (Impairment + Morbidity))}}))$
4. Disability-Adjusted Life Years (DALYs) Gained[a]	$\sum_{i=1}^{n=100}(\text{No Vaccine } (DALYs_{ij\ (\text{Death + Impairment + Morbidity − Complications (Impairment + Morbidity))}} - \text{Vaccine } (QALYs_{ij\ (\text{Death + Impairment + Morbidity − Complications (Impairment + Morbidity))}}))$
5. Net Direct Costs	$\sum_{i=1}^{n=100}(\text{Delivery Costs}_{ij} - \text{Healthcare Costs}_{ij})$
6. Delivery Costs	$\sum_{i=1}^{n=100}\frac{\left(\begin{array}{l}(\text{Vaccine}(V_{ij}+VS_{ij}) - \text{NoVaccine}(V_{ij}+VS_{ij}))\\ \times \text{doses} \times (\text{cost per dose} + \text{cost to administer})\end{array}\right)}{\text{length of immunity}}$
7. Health Care Costs (HC) Averted	$\sum_{i=1}^{n=100}(\text{No Vaccine } (HC_{ij\ (\text{Death + Impairment + Morbidity − Complications (Impairment + Morbidity))}} - \text{Vaccine } (QALYs_{ij\ (\text{Death + Impairment + Morbidity − Complications (Impairment + Morbidity))}}))$
8. Workforce Productivity (WP) Gained per Year	$\sum_{i=1}^{n=1}(\text{No Vaccine } (WP_{ij\ (\text{Death + Impairment + Morbidity − Complications (Impairment + Morbidity))}} - \text{Vaccine } (WP_{ij\ (\text{Death + Impairment + Morbidity − Complications (Impairment + Morbidity))}}))$
9. One-Time Costs	$\text{Cost Research} + \text{Cost Licensure} + \text{Cost Start Up}$

[a]Fox-Rushby, J. A., and Hanson, K. 2001. Calculating and presenting disability-adjusted life years (DALYs) in cost-effectiveness analysis. *Health Policy and Planning* 16(3):326–331.

TABLE A-3

Detailed Expressions (in Reference to Table A-1 and Table A-2)

Measure	Formulation
All Cause Mortality Rate (Derived by Life Table Over Interval)[a]	$1 - e^{\left(\frac{1_x - 1_{x+1}}{1x \times n}\right)}$
$QALYs_{Death}$	$\sum_{i=1}^{n=100} (No\ Vaccine\ (D_{ij}) - Vaccine\ (Dij)) \times Duration_{ij}$
$QALYs_{Impairment\ by\ disease\ or\ complication}$	$\sum_{i=1}^{n=100} (No\ Vaccine\ (CP_{ij}) - Vaccine\ (CP_{ij})) \times (1 - HUI2_{Impairment}) \times Duration_{ij}$
$QALYs_{Morbidity\ by\ disease\ or\ complication}$	$\sum_{i=1}^{n=100} (No\ Vaccine\ (CM_{ij}) - Vaccine\ (CM_{ij})) \times Toll \times Duration$
Disability-Adjusted Life Years (DALYs) Generalization[b]	*Years of Life Lost (YLL) + Years of Life Lived with Disability (YLD)*
YLD or YLL ($W = 1$)	$W\left\{\frac{KFe^{rj}}{(r+G)^2}\left\{\begin{matrix} e^{-(r+G)(L+j)}\left[-(r+G)(L_j)-1\right] \\ -e^{-(r+G)j}\left[-(r+G)j-1\right] \end{matrix}\right\} + \frac{1-K}{r}\left(1-e^{rL}\right)\right\}$
DALYs Variables	K = *age weight modulation factor* (0 = off, 1 = on) F = *constant* (0.1658) r = *discount rate* j = *age of death (YLL) or age of onset of disability (YLD)* G = *parameter form the age weighting function* (0.04) L = *standard expectation of life at age a (YLL) or duration of disability (YLD)* W = *disability weight (YLD)*
$DALYs_{Death}$	$\sum_{i=1}^{n=100} (No\ Vaccine\ (D_{ij}) - Vaccine\ (D_{ij})) \times YLL_{ij}$
$DALYs_{Impairment\ by\ disease\ or\ complication}$	$\sum_{i=1}^{n=100} (No\ Vaccine\ (CP_{ij}) - Vaccine\ (CP_{ij})) \times YLD_{ij}$
$DALYs_{Morbidity\ by\ disease\ or\ complication}$	$\sum_{i=1}^{n=100} (No\ Vaccine\ (CM_{ij}) - Vaccine\ (CM_{ij})) \times YLD_{ij}$
$Health\ Care\ Costs\ (HC)_{Death}$	$\sum_{i=1}^{n=100} (No\ Vaccine\ (D_{ij}) - Vaccine\ (D_{ij})) \times HC\ Service\ Units_{Death} \times Cost\ of\ Services$
$HC_{Impairments\ by\ disease\ or\ complication}$	$\sum_{i=1}^{n=100} (No\ Vaccine\ (CP_{ij}) - Vaccine\ (CP_{ij})) \times HC\ Service\ Units_{Impairment} \times Cost\ of\ Services \times Duration_{ij}$
$HC_{Morbidity\ by\ disease\ or\ complication}$	$\sum_{i=1}^{n=100} (No\ Vaccine\ (CM_{ij}) - Vaccine\ (CM_{ij})) \times HC\ Service\ Units_{Morbidity} \times Cost\ of\ Services \times Duration$

Measure	Formulation
Workforce Productivity (WP) Gained $_{Death}$	$\sum_{i=1}^{n=1}(No\ Vaccine\ (D_{ij}) - Vaccine\ (D_{ij})) \times Hourly\ Wage_j \times 2000\ \text{hours} \times Duration$
$WP_{Impairment\ by\ disease\ or\ complication}$	$\sum_{i=1}^{n=1}(No\ Vaccine\ (CP_{ij}) - Vaccine\ (CP_{ij})) \times Hourly\ Wage_j \times 2000\ \text{hours} \times Duration$
$WP_{Morbidity\ by\ disease\ or\ complication}$	$\sum_{i=1}^{n=1}(No\ Vaccine\ (CM_{ij}) - Vaccine\ (CM_{ij})) \times Hourly\ Wage_j \times 2000\ \text{hours} \times Duration$

[a]Preston, S., P. Heuveline, and M. Guillot. 2000. *Demography: Measuring and modeling population processes*. Chapter 3: The Life Table and Single Decrement Process. P. 46.

[b]Fox-Rushby, J. A., and K. Hanson. 2001. Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. *Health Policy and Planning* 16(3):326–331.

B

Candidate Disease Profiles and Data

Influenza disease profile

BOX B-1
Influenza

Infectious Agent: Orthomyxoviruses, RNA viruses that infect birds and mammals. Three genera cause influenza: Influenza A, which is the most common cause of disease and has varying serotypes; Influenza B, which has only one serotype; and Influenza C, the least common.

Routes of Transmission: Airborne aerosols and direct contact with secretions or contaminated surfaces.

Health Effects: Influenza illness typically begins with chills or fever. The illness often involves cough, sore throat, nasal congestion, muscle aches, headache, and fatigue. It typically lasts for several days. In contrast with common colds, influenza usually has high fever with sudden onset and extreme fatigue. Influenza can also cause pneumonia either directly or through secondary bacterial infection.

Incidence, Prevalence, and Mortality: Influenza causes annual seasonal epidemics throughout the world as well as periodic pandemics. In the United States influenza has been estimated to cause an average of approximately 36,000 annual deaths during 1990–1999 and 226,000 annual hospitalizations during 1979–2001.

The incidence (or attack rate) varies from year to year and is highest in children aged 0 to 4 years old and in the elderly aged 65 years and older. One paper from the Centers for Disease Control and Prevention estimated seasonal influenza attack rates in the United States ranging from 6.6 percent in healthy young adults to 20 percent in the youngest children.

The 2009 pandemic influenza virus A (H1N1) infected an estimated 11 to 21 percent of the populations where the incidence could be studied. The highest incidence (34–43 percent) occurred in school-aged children. The severity of the disease, in terms of hospitalizations and pneumonia, was similar to that of recent seasonal influenza strains.

Prevention and Treatment: Annual influenza vaccination is the primary tool for prevention. The vaccine is reformulated each year to prevent the strains of the virus that the World Health Organization predicts will be most prevalent during the coming year. In addition, antiviral treatment is most effective when initiated within 48 hours of symptom onset and has typically been directed to persons at high risk of complications due to influenza.

Vaccine: In the United States, vaccination has been recommended for all persons 6 months and older since 2006. Two types of vaccines are produced: inactivated (for intramuscular administration) and live attenuated (for intranasal administration).

Tuberculosis disease profile

BOX B-2
Tuberculosis

Infectious Agent: Mycobacteria in the *M. tuberculosis* complex, primarily *M. tuberculosis*, *M. bovis*, and *M. africanum.*

Routes of Transmission: Inhaling droplet nuclei in airborne aerosols generated by coughing or sneezing by individuals with pulmonary tuberculosis and consuming contaminated, unpasteurized cow's milk.

Health Effects: In a small proportion of newly infected individuals, especially infants, initial infection progresses rapidly—in weeks to months—to primary tuberculosis, which often disseminates to blood, bone, and other distant sites. Pulmonary tuberculosis produces cough, fever, night sweats, fatigue, and weight loss; it often goes undiagnosed for a number of months, during which time infection is transmitted to others, especially to close contacts, such as household members. However, infection in the lung can be contained by the immune system and remains latent; fewer than 10 percent of latently infected individuals subsequently develop reactivation pulmonary tuberculosis, generally when age, malnutrition, HIV infection, or other conditions suppress the immune system and thereby allow latent infection to reactivate.

Incidence, Prevalence, and Mortality: Approximately one-third of the world's population is estimated to be latently infected with *M. tuberculosis*, but only a small proportion of these individuals will develop tuberculosis. WHO estimated that in 2010, 8.8 million people developed tuberculosis worldwide, yielding an incidence of 128 cases per 100,000 people. About 650,000 cases were caused by multi-drug-resistant strains of *M. tuberculosis*, and 1.4 million with tuberculosis died of the

disease. The incidence rate, number of cases, and deaths from tuberculosis has been declining in recent years, mainly due to increased attention and resources devoted to diagnosing cases and assuring that patients receive and complete the lengthy treatment regimen.

Prevention: In most wealthy countries with low incidence rates, prevention of tuberculosis primarily rests on prompt diagnosis, correct multidrug treatment, and ensuring completion of treatment among those with pulmonary tuberculosis. Latent infected individuals are also treated with drugs, especially those at high risk of reactivation tuberculosis, such as HIV-infected individuals. In poor countries with high incidence rates of tuberculosis, prevention of tuberculosis, while also dependent on prompt diagnosis, correct treatment, and ensuring completion of treatment, primarily rests on targeting all infants with a single dose of the vaccine, given shortly after birth.

Treatment: Successful treatment of tuberculosis requires multiple drugs (at least three) given for a lengthy time period (9 to 12 months), even though the patient is usually asymptomatic (and non-infectious) after a few weeks of treatment. Treatment of latently infected individuals to prevent reactivation tuberculosis is generally accomplished with a single drug (example, isoniazid), also given for an extended period of time (6 to 12 months).

Vaccine: Bacille Calmette-Guerin (BCG) vaccine is widely used at birth throughout South Africa, where there is a high burden of pediatric HIV infection. BCG is given to all newborns as soon as possible after birth to protect infants infected with tuberculosis from progressing to the more dangerous forms of meningeal and miliary tuberculosis.

Group B streptococcus disease profile

BOX B-3
Group B Streptococcus

Infectious Agent: Group B Streptococcus (*Streptococcus agalactiae*) is a gram-positive organism found as a normal inhabitant of the gastrointestinal and genital tract of humans. The majority of the disease is caused by five serotypes.

Routes of Transmission: Transmission from mother to infant occurs in utero or at the time of delivery. Exposure to GBS in the hospital, at home, or in the community may result in late-onset disease.

Health Effects: Group B Streptococcus (*Streptococcus agalactiae*) is a leading cause of disease in young children. There are two distinct presentations: *Early-onset disease* (days of life 0–6) is the result of vertical transmission from a colonized mother, and *late-onset disease* (days of life 7–89) is acquired from either the mother or environmental sources. Early-onset disease is characterized by sepsis or meningitis with a high mortality rate. Late-onset disease often presents as meningitis with a somewhat lower mortality rate but with prominent sequelae.

Incidence, Prevalence, and Mortality: Group B Streptococcus is the most common cause of sepsis and meningitis in infants from developed countries and one of the most common causes in infants globally. The mean invasive GBS disease incidence is 0.53 per 1,000 live births. The mean incidence of early-onset disease is 0.43 per 1,000 live births, with

the highest incidence reported from Africa: 0.53 per 1,000 live births. The mean incidence of late-onset disease (7–89 days) is 0.24 per 1,000 live births. Incidence is again highest in Africa, at 0.7 per 1,000 live births. Typically, early-onset disease is more likely to cause mortality (case fatality rate of 12.1 percent) than the late-onset disease (case fatality rate of 6.8 percent).

Prevention: Currently, to control group B streptococcus intrapartum antibitotics are administered to pregnant women with either known risk factors for group B streptococcos or documented carriage of the bacteria. This approach was widely adopted in the United States and many developed countries and resulted in substantial declines in disease in infants younger than 7 days. In the United States, culture-based screening is used to identify candidates for chemoprophylaxis, but implementing this strategy has been a difficult in low- and middle-income countries.

Treatment: Supportive care and antibiotics are needed for the successful treatment of GBS in infants. Benzylpenicillin or amoxicillin combined with aminoglycosides is the mainstay of therapy at the onset when GBS is suspected. When GBS is confirmed, benzylpenicillin or amoxicillin can be used as a single agent. Treatment duration for sepsis is generally 10 days, but meningitis is treated for a minimum of 14 days, with more prolonged therapy in complicated cases.

Vaccine: A vaccine is not currently available for group B streptococcal infection.

U.S. Population Data

Female[a]							
	Population	Life Table				Health	Productivity
Age Group	N	Living (lx)	Life Years (nLx)	Life Expectancy (ex)	Standard Life Expectancy[b] (ex)	HUI2[c]	Hourly Wage Rate[d] *(<15 parents)
<1	2,183,518	100,000	99,452	80.9	86.5	0.99	$17.90
1–4	8,456,004	99,391	397,326	80.4	85.7	0.99	$17.97
5–9	10,228,540	99,292	496,309	76.5	81.7	0.99	$23.50
10–14	10,309,899	99,232	495,991	71.6	76.8	0.99	$24.57
15–19	10,910,307	99,164	495,387	66.6	71.8	0.99	$8.45
20–24	10,862,866	98,991	494,371	61.7	66.9	0.99	$10.90
25–29	10,634,528	98,758	493,104	56.9	62	0.95	$16.40
30–34	10,326,394	98,484	491,541	52	57.1	0.90	$16.47
35–39	10,441,258	98,133	489,384	47.2	52.2	0.86	$18.20
40–44	10,944,157	97,621	486,111	42.4	47.3	0.86	$18.20
45–49	11,697,857	96,823	481,067	37.7	42.5	0.84	$18.50
50–54	11,270,132	95,603	473,634	33.2	37.8	0.84	$18.50
55–59	9,904,308	93,850	463,085	28.8	33.1	0.81	$18.70
60–64	8,297,733	91,384	447,776	24.5	28.5	0.81	$18.70
65–69	6,266,131	87,726	425,003	20.4	24	0.83	$16.07
70–74	4,919,414	82,275	391,682	16.6	19.7	0.83	$16.00
75–79	4,159,980	74,398	344,041	13.1	15.5	0.82	$16.00
80–84	3,493,449	63,218	278,259	9.9	11.8	0.82	$16.00
85–89	2,397,331	48,086	195,937	7.3	8.5	0.82	$16.00
90–94	1,194,178	30,289	104,147	5.1	5.8	0.82	$15.00
95–99	422,524	14,523	38,597	3.4	3.8	0.82	$15.00

Male[a]							
	Population	Life Table				Health	Productivity
Age Group	N	Living (lx)	Life Years (nLx)	Life Expectancy (ex)	Standard Life Expectancy[b] (ex)	HUI2[c]	Hourly Wage Rate[d] *(<15 parents)
<1	2,294,679	100,000	99,348	76	79.6	0.99	$17.90
1–4	8,889,066	99,276	396,817	75.6	78.8	0.99	$17.97
5–9	10,753,934	99,156	495,604	71.7	74.9	0.99	$23.50
10–14	10,838,788	99,085	495,185	66.7	69.9	0.99	$24.57
15–19	11,472,812	98,989	493,905	61.8	65	0.99	$9.25
20–24	11,374,397	98,573	491,150	57	60.1	0.99	$11.45
25–29	11,021,998	97,887	487,775	52.4	55.2	0.95	$17.90
30–34	10,581,472	97,223	484,373	47.7	50.4	0.92	$17.97
35–39	10,547,351	96,526	480,477	43.1	45.6	0.88	$23.50
40–44	10,872,790	95,665	475,151	38.4	40.8	0.88	$23.50
45–49	11,447,885	94,396	467,208	33.9	36.1	0.86	$24.57
50–54	10,825,136	92,487	455,327	29.6	31.5	0.86	$24.57
55–59	9,393,752	89,643	438,424	25.4	27.1	0.83	$24.62
60–64	7,674,399	85,726	415,226	21.5	23	0.83	$24.65
65–69	5,587,609	80,364	383,132	17.7	18.9	0.86	$20.90
70–74	4,156,592	72,889	339,373	14.3	15.2	0.86	$19.00
75–79	3,219,109	62,860	281,766	11.2	11.7	0.84	$19.00
80–84	2,359,608	49,846	209,856	8.4	8.7	0.84	$19.00
85–89	1,318,716	34,096	131,028	6.2	6.3	0.84	$19.00
90–94	486,989	18,315	58,224	4.4	4.4	0.84	$18.00
95–99	112,289	7,198	17,589	3	3	0.84	$18.00

[a]The country life tables are available from WHO Global Health Observatory Data Repository (http://bit.ly/HyByvk).

[b]Standard life expectancy depicts the life expectancy for the Japanese population. Data available through WHO Global Health Observatory Data Repository (http://bit.ly/Ho2VI3).

[c]HUI-2 scores are derived from: Fryback, D. G., N. C. Dunham, M. Palta, J. Hanmer, J. Buechner, D. Cherepanov, S. Herrington, R. D. Hays, R. M. Kaplan, and T. G. Ganiats. 2007. U.S. norms for six generic health-related quality-of-life indexes from the National Health Measurement study. *Medical Care* 45(12):1162–1170.

[d]Hourly wage rate was gathered from the Bureau of Labor Statistics Wages. The parents' wage rate was used for children under the age of 15 years.

U.S. data for influenza

Disease Burden

Female							
Age Groups	Population (N)	Target Population (% of N)	Annual Incidence Rate[a] (per 100,000)	Case Fatality Rate[a] (%)	Vaccine Coverage (%)	Vaccine Effectiveness[b] (%)	Herd Immunity Threshold[c] (%)
(<1)	2,183,518	100%	20,300	0.004	30%	60%	100%
(1–19)	39,904,750	100%	11,947	0.002	20%	70%	100%
(20–64)	94,379,233	100%	6,600	0.05	40%	75%	100%
(>65)	22,853,007	100%	9,000	1.17	60%	40%	100%
Male							
Age Groups	Population (N)	Target Population (% of N)	Annual Incidence Rate[a] (per 100,000)	Case Fatality Rate[a] (%)	Vaccine Coverage (%)	Vaccine Effectiveness[b] (%)	Herd Immunity Threshold[c] (%)
(<1)	2,294,679	100%	20,300	0.004	30%	60%	100%
(1–19)	41,954,600	100%	11,947	0.002	20%	70%	100%
(20–64)	93,739,180	100%	6,600	0.05	40%	75%	100%
(>65)	17,240,912	100%	9,000	1.17	60%	40%	100%

[a]Molinari, N. A., I. R. Ortega-Sanchez, M. L. Messonnier, W. W. Thompson, P. M. Wortley, E. Weintraub, C. B. and Bridges. 2007. The annual impact of seasonal influenza in the US: Measuring disease burden and costs. *Vaccine* 25(27):5086–5096.

[b]Allison, M. A., M. F. Daley, L. A. Crane, J. Barrow, B. L. Beaty, N. Allred, S. Berman, and A. Kempe. 2006. Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003–2004 season. *Journal of Pediatrics* 149(6):755–762. e751; Nichol, K. L. 2003. The efficacy, effectiveness and cost-effectiveness of inactivated influenza virus vaccines. *Vaccine* 21(16):1769–1775; Vu, T., S. Farish, M. Jenkins, H. and Kelly. 2002. A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community. *Vaccine* 20(13–14):1831–1836.

[c]Herd immunity threshold is assumed to be at 100 percent due to the infectious nature of Influenza.

Disease Morbidity and Vaccine Complications

Disease Morbidity	Percent of Cases	Disutility[a] (Toll)	Disability Weight[b]	Duration[c] (Years)
Influenza Illness Without Outpatient Visit	59.5%	0.09	0.01	0.0137
Influenza Illness With Outpatient Visit	40.0%	0.13	0.1	0.0137
Influenza Hospitalization	0.5%	0.2	0.3	0.0137

Vaccine Complications	Probability per Dose	Disutility[a] (Toll)	Disability Weight[b]	Duration[c] (Years)
Guillain-Barré Syndrome	0.000001	0.35	0.44	0.137
Systemic Reaction (Fever or Achiness)	0.011	0.25	0.1	0.0027
Anaphylaxis	0.00000025	0.25	0.44	0.0027

[a]Disutility (toll) is the one-time disutility associated with the specific health state. Fryback, D. G., N. C. Dunham, M. Palta, J. Hanmer, J. Buechner, D. Cherepanov, S. Herrington, R. D. Hays, R. M. Kaplan, and T. G. Ganiats. 2007. U.S. norms for six generic health-related quality-of-life indexes from the National Health Measurement study. *Medical Care* 45(12):1162–1170.

[b]Mathers, C. D., A. D. Lopez, C. J. L. and Murray. 2006. The burden of disease and mortality by condition: data, methods, and results for 2001. Global burden of disease and risk factors. Table 3A.6. *Global burden of disease 2004 update: Disability weights for diseases and conditions* 1:45–93.

[c]Committee's expert opinion.

Costs

Health Care Services	Cost	Disease Morbidity				Vaccine Complications		
		Death	Influenza Without Outpatient Visit	Influenza With Outpatient Visit	Influenza With Hospitalization	Guillain-Barré Syndrome	Systemic Reaction	Anaphylaxis
Over-the-counter medications[a]	$3	1	1	1	1	0	0	0
Physician visit[a]	$200	0	0	0	0	0	1	0
Outpatient visit[a]	$250	1	0	1	1	0	0	0
Emergency department visit[b]	$750	0	0	0	0	0	0	1
Hospitalization[b]	$1,200	5	0	0	5	40	0	0

[a]Prosser, L. A., M. A. O'Brien, N. A. Molinari, K. H. Hohman, K. L. Nichol, M. L. Messonnier, and T. A. Lieu. 2008. Non-traditional settings for influenza vaccination of adults: Costs and cost effectiveness. *Pharmacoeconomics* 26(2):163–178.

[b]Committee's expert opinion and estimates from the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample Data. 2009 national statistics for principal diagnosis of influenza only.

Vaccine Characteristics

Length of immunity[a]	1	years or life
Doses required per person[a]	1	doses
Cost per dose[b]	$13	$
Cost to administer per dose[c]	$10	$
Research costs[c]	$50,000,000	$
Licensure costs[c]	$100,000,000	$
Start-up costs[c]	$100,000	$
Time to adoption[c]	5	years

[a]CDC recommends an influenza shot every year (http://1.usa.gov/tEA0Mg).

[b]Cost is approximated using CDC prices for cost per dose (http://1.usa.gov/26Xjuj).

[c]Committee's expert opinion.

U.S. data for tuberculosis

Disease Burden

Age Groups	Population (N)	Target Population (% of N)	Annual Incidence Rate[a] (per 100,000)	Case Fatality Rate[b] (%)	Vaccine Coverage[c] (%)	Vaccine Effectiveness[c] (%)	Herd Immunity Threshold (%)
Female							
<1	2,183,518	100%	1.68	9	85%	65%	100%
1–19	39,904,750	0%	1.15	9	85%	65%	100%
20–64	94,379,233	0%	3.35	9	85%	65%	100%
>65	22,853,007	0%	4.54	9	85%	65%	100%
Male							
<1	2,294,679	100%	3.31	9	85%	65%	100%
1–19	41,954,600	0%	2.27	9	85%	65%	100%
20–64	93,739,180	0%	6.63	9	85%	65%	100%
>65	17,240,912	0%	8.97	9	85%	65%	100%

[a]Centers for Disease Control and Prevention. 2011. Summary of notifiable diseases—United States, 2009. *Morbidity and Mortality Weekly Report* 58(53):1–100.

[b]The committee assigned the value for Case Fatality Rate after consulting with several tuberculosis experts.

[c]Since BCG is not administered in the United States, the committee assumed a potential new vaccine will be 65 percent effective with 85 percent coverage.

Disease Morbidity and Vaccine Complications

Disease Morbidity	Percent of Cases	Disutility[a] (Toll)	Disability Weight[b]	Duration[c] (Years)
Pulmonary Tuberculosis (with Inpatient Treatment)	40.0%	0.30	0.28	0.06
Pulmonary Tuberculosis (with Outpatient Treatment)	20.0%	0.08	0.27	0.16
Latent Tuberculosis (with Treatment)	8.0%	0.00	0.00	0.00
Extrapulmonary Tuberculosis (with Inpatient Treatment)	22.0%	0.30	0.29	0.06
Vaccine Complications	**Probability per Dose**	**Disutility[a] (Toll)**	**Disability Weight[b]**	**Duration[c] (Years)**
Injection Site Abscess	0.000010	0.050000	0.100000	0.082100
Lymphadenitis	0.000010	0.050000	0.010000	0.043000
Severe Local Reaction	0.000050	0.050000	0.100000	0.008200

[a]Disutility (toll) is the one-time disutility associated with the specific health state. Guo, N., F. Marra, and C. A. Marra. 2009. Measuring health-related quality of life in tuberculosis: A systematic review. *Health and Quality of Life Outcomes* 7:14.

[b]Mathers, C. D., A. D. Lopez, and C. J. L. Murray. 2006. The burden of disease and mortality by condition: data, methods, and results for 2001. Global burden of disease and risk factors. Table 3A.6. *Global burden of disease 2004 update: Disability weights for diseases and conditions* 1:45–93.

[c]Committee's expert opinion.

Costs

Health Care Services	Cost[a]	Disease Morbidity					
		Death	Pulmonary Tuberculosis (Inpatient)	Pulmonary Tuberculosis (Outpatient)	Latent Tuberculosis (with Treatment)	Extrapulmonary Tuberculosis	Lung Impairment
Direct Observed Therapy (DOT) Drugs[b]	$0	0	0	0	9	0	0
Outpatient Treatment[c]	$400	0	0	1	0	0	0
Inpatient Treatment[c]	$760	1	11	0	0	3	0
Hospitalization[d]	$1,300	15	0	0	0	0	5

Health Care Services	Cost[a]	Vaccine Complications		
		Injection Site Abscess	Lymphadenitis	Severe Local Reaction
Direct Observed Therapy (DOT) Drugs[b]	$0	0	0	0
Outpatient Treatment[c]	$400	1	1	0
Inpatient Treatment[c]	$760	0	0	1
Hospitalization[d]	$1,300	0	0	0

[a]Costs associated with the health care services used to treat morbidity caused by the disease and vaccine.

[b]Blumberg, H. M., M. K. Leonard, and R. M. Jasmer. 2005. Update on the treatment of tuberculosis and latent tuberculosis infection. *JAMA* 293(22):2776–2784.

[c]Holland, D. P., G. D. Sanders, C. D. Hamilton, and J. E. Stout. 2009. Costs and cost effectiveness of four treatment regimens for latent tuberculosis infection. *American Journal of Respiratory and Critical Care Medicine* 179(11):1055–1060.

[d]HCUP Brief #60. 2008. Tuberculosis stays in U.S. hospitals, 2006.

Vaccine Characteristics

Length of immunity[a]	life	years or life
Doses required per person[a]	1	doses
Cost per dose[a]	$50	$
Cost to administer per dose[a]	$25	$
Research costs[a]	$100,000,000	$
Licensure costs[a]	$500,000,000	$
Start-up costs[a]	$10,000,000	$
Time to adoption[a]	5	years

[a]Since BCG is not administered in the United States, these values are based on expert opinion.

U.S. data for Group B streptococcus

Disease Burden

Female							
Age Groups	Population (N)	Target Population (% of N)	Annual Incidence Rate[a] (per 100,000)	Case Fatality Rate[a] (%)	Vaccine Coverage (%)	Vaccine Effectiveness[b] (%)	Herd Immunity Threshold[c] (%)
(<1)	2,183,518	100%	35.00	3.8	85%	90%	100%
(1–19)	39,904,750	0%	1.37	6.3	85%	90%	100%
(20–64)	94,379,233	0%	4.60	6.0	85%	80%	100%
(>65)	22,853,007	0%	25.30	11.4	85%	80%	100%
Male							
Age Groups	Population (N)	Target Population (% of N)	Annual Incidence Rate[a] (per 100,000)	Case Fatality Rate[a] (%)	Vaccine Coverage (%)	Vaccine Effectiveness[b] (%)	Herd Immunity Threshold[c] (%)
(<1)	2,294,679	100%	35.00	3.8	85%	90%	100%
(1–19)	41,954,600	0%	1.37	6.3	85%	90%	100%
(20–64)	93,739,180	0%	4.60	6.0	85%	80%	100%
(>65)	17,240,912	0%	25.30	11.4	85%	80%	100%

[a]Phares, C. R., R. Lynfield, M. M. Farley, J. Mohle-Boetani, L. H. Harrison, S. Petit, A. S. Craig, W. Schaffner, S. M. Zansky, and K. Gershman, 2008. Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. *JAMA* 299(17):2056–2065.

[b]Since a vaccine for group B streptococcus is not available currently, the effectiveness values are derived from expert opinions.

[c]A herd immunity threshold of 100 percent is assigned for all age groups.

Disease Morbidity

	Percent of Cases	Disutility[a] (Toll)	Disability Weight[b]	Duration[c] (Years)
Meningitis	25%	0.70	0.61	0.04
Pneumonia	20%	0.13	0.15	0.04
Respiratory distress	15%	0.13	0.14	0.02
Sepsis	15%	0.09	0.09	0.03
Neurological impairment	25%	0.35	0.4	

[a]Fryback, D. G., N. C. Dunham, M. Palta, J. Hanmer, J. Buechner, D. Cherepanov, S. Herrington, R. D. Hays, R. M. Kaplan, and T. G. Ganiats. 2007. U.S. norms for six generic health-related quality-of-life indexes from the National Health Measurement study. *Medical Care* 45(12):1162–1170.

[b]Mathers, C. D., A. D. Lopez, and C. J. L. Murray. 2006. The burden of disease and mortality by condition: data, methods, and results for 2001. Global burden of disease and risk factors. Table 3A.6. *Global burden of disease 2004 update: Disability weights for diseases and conditions* 1: 45–93.

[c]Committee's expert opinion.

Costs

Health Care Services	Cost	Disease					
		Death	Meningitis	Pneumonia	Respiratory Distress	Sepsis	Neurological Impairment
Hospitalization[a]	$2,100	7	14	7	7	2	14

[a]Committee's expert opinion and the HCUP Nationwide Inpatient Sample Data, 2009.

Vaccine Characteristics

Length of immunity[a]	life	years or life
Doses required per person[a]	1	doses
Cost per dose[a]	$100	$
Cost to administer per dose[a]	$50	$
Research costs[a]	$200,000,000	$
Licensure costs[a]	$600,000,000	$
Start-up costs[a]	$10,000,000	$
Time to adoption[a]	5	years

[a]Since a vaccine for group B streptococcus does not currently exist, these values are based on expert opinion.

South Africa Population Data

Female[a]							
	Population	Life Table				Health	Productivity
Age Group	N	Living (lx)	Life Years (nLx)	Life Expectancy (ex)	Standard Life Expectancy[b] (ex)	HUI2[c]	Hourly Wage Rate[d] *(<15 parents)
<1	504,851	100,000	97,376	54.9	86.5	0.99	$4.48
1–4	2,061,888	96,251	381,263	56	85.7	0.99	$4.49
5–9	2,556,786	94,692	471,476	52.9	81.7	0.99	$5.88
10–14	2,475,823	93,899	467,978	48.3	76.8	0.99	$6.14
15–19	2,498,988	93,293	463,506	43.6	71.8	0.99	$2.11
20–24	2,518,633	92,109	450,195	39.1	66.9	0.99	$2.73
25–29	2,300,308	87,968	420,123	35.9	62	0.95	$4.10
30–34	1,904,419	80,081	378,913	34.1	57.1	0.90	$4.12
35–39	1,623,918	71,485	342,388	32.9	52.2	0.86	$4.55
40–44	1,432,625	65,471	317,762	30.7	47.3	0.86	$4.55
45–49	1,290,971	61,634	298,340	27.5	42.5	0.84	$4.63
50–54	1,169,991	57,702	277,578	24.2	37.8	0.84	$4.63
55–59	960,397	53,329	254,939	21	33.1	0.81	$4.68
60–64	727,265	48,647	230,430	17.8	28.5	0.81	$4.68
65–69	556,744	43,525	199,866	14.6	24	0.83	$4.02
70–74	385,054	36,421	162,843	11.9	19.7	0.83	$4.00
75–79	239,133	28,716	120,284	9.4	15.5	0.82	$4.00
80–84	124,578	19,397	78,061	7.8	11.8	0.82	$4.00
85–89	52,649	11,827	44,731	6.1	8.5	0.82	$4.00
90–94	16,257	6,066	19,618	4.6	5.8	0.82	$3.75
95–99	2,969	2,496	6,380	3.2	3.8	0.82	$3.75

Male[a]							
	Population	Life Table				Health	Productivity
Age Group	N	Living (lx)	Life Years (nLx)	Life Expectancy (ex)	Standard Life Expectancy[b] (ex)	HUI2[c]	Hourly Wage Rate[d] *(<15 parents)
<1	513,738	100,000	96,596	53.9	79.6	0.99	$4.48
1–4	2,094,078	95,137	375,325	55.6	78.8	0.99	$4.49
5–9	2,587,325	92,961	463,390	52.9	74.9	0.99	$5.88
10–14	2,495,950	92,395	460,642	48.2	69.9	0.99	$6.14
15–19	2,514,105	91,862	457,000	43.4	65	0.99	$2.31
20–24	2,542,121	90,938	450,001	38.8	60.1	0.99	$2.86
25–29	2,384,897	89,062	437,942	34.6	55.2	0.95	$4.48
30–34	2,053,143	86,115	416,874	30.7	50.4	0.92	$4.49
35–39	1,700,601	80,634	386,196	27.6	45.6	0.88	$5.88
40–44	1,372,882	73,844	350,118	24.9	40.8	0.88	$5.88
45–49	1,157,933	66,203	312,525	22.5	36.1	0.86	$6.14
50–54	1,004,315	58,807	275,919	20.1	31.5	0.86	$6.14
55–59	814,859	51,561	238,876	17.5	27.1	0.83	$6.16
60–64	598,768	43,989	202,138	15.1	23	0.83	$6.16
65–69	413,005	36,866	163,729	12.5	18.9	0.86	$5.23
70–74	246,008	28,626	124,506	10.4	15.2	0.86	$4.75
75–79	131,479	21,177	86,228	8.2	11.7	0.84	$4.75
80–84	57,263	13,315	51,119	6.6	8.7	0.84	$4.75
85–89	18,099	7,133	25,265	5.1	6.3	0.84	$4.75
90–94	4,082	2,973	8,783	3.8	4.4	0.84	$4.50
95–99	550	946	2,185	2.8	3	0.84	$4.50

[a]The country life tables are available from WHO, Global Health Observatory Data Repository (http://bit.ly/HyByvk).

[b]Standard life expectancy depicts the life expectancy for the Japanese population. Also available through WHO, Global Health Observatory Data Repository (http://bit.ly/Ho2VI3).

[c]HUI-2 scores are derived from: Fryback, D. G., N. C. Dunham, M. Palta, J. Hanmer, J. Buechner, D. Cherepanov, S. Herrington, R. D. Hays, R. M. Kaplan, and T. G. Ganiats. 2007. U.S. norms for six generic health-related quality-of-life indexes from the National Health Measurement study. *Medical Care*. 45(12):1162–1170. Due to the lack of data for HUI-2 within South Africa, estimates for the United States are used.

[d]Wage Rate for South Africa was crudely estimated by converting the United States wage rate to a South African wage based on the prevailing exchange rate.

South Africa Data for Tuberculosis

Disease Burden

Female							
Age Groups	Population (N)	Target Population (% of N)	Annual Incidence Rate[a] (per 100,000)	Case Fatality Rate[b] (%)	Vaccine Coverage[c] (%)	Vaccine Effectiveness[d] (%)	Herd Immunity Threshold (%)
<1	50,4851	100%	800	19	50%	60%	100%
1–19	9,593,485	0%	900	19	50%	60%	100%
20–64	13,928,527	0%	1100	22	50%	50%	100%
>65	1,377,384	0%	981	20	50%	40%	100%
Male							
Age Groups	Population (N)	Target Population (% of N)	Annual Incidence Rate[a] (per 100,000)	Case Fatality Rate[b] (%)	Vaccine Coverage[c] (%)	Vaccine Effectiveness[d] (%)	Herd Immunity Threshold (%)
<1	513,738	100%	800	19	50%	60%	100%
1–19	9,691,458	0%	973	19	50%	60%	100%
20–64	13,629,519	0%	1200	22	50%	50%	100%
>65	870,486	0%	981	20	50%	40%	100%

[a]WHO. 2011. *Global Tuberculosis Control 2011.*

[b]Corbett, E. L., C. J. Watt, N. Walker, D. Maher, B. G. Williams, M. C. Raviglione, and C. Dye. 2003. The growing burden of tuberculosis: Global trends and interactions with the HIV epidemic. *Archives of Internal Medicine* 163(9):1009–1021.

[c]Vaccine coverage assumed to be 50 percent.

[d]Colditz, G. A., T. F. Brewer, C. S. Berkey, M. E. Wilson, E. Burdick, H. V. Fineberg, and F. Mosteller. 1994. Efficacy of BCG vaccine in the prevention of tuberculosis. *JAMA* 271(9):698–702; Rahman, M., M. Sekimoto, I. Takamatsu, K. Hira, T. Shimbo, K. Toyoshima, and T. Fuku. 2001. Economic evaluation of universal BCG vaccination of Japanese infants. *International Journal of Epidemiology* 30(2):380–385; Rodrigues, L. C., V. K. Diwan, and J. G. Wheeler. 1993. Protective effect of BCG against tuberculous, meningitis, and miliary tuberculosis: A meta-analysis. *International Journal of Epidemiology* 22(6):1154–1158.

Disease Morbidity and Vaccine Complications

Disease Morbidity	Percent of Cases[a]	Disutility[b] (Toll)	Disability Weight[c]	Duration[a] (Years)
Pulmonary Tuberculosis (with Inpatient Treatment)	40%	0.30	0.28	0.06
Pulmonary Tuberculosis (with Outpatient Treatment)	20%	0.08	0.27	0.16
Latent Tuberculosis (with Treatment)	8%	0.00	0.00	0.00
Extrapulmonary Tuberculosis (with Inpatient Treatment)	22%	0.30	0.29	0.06
Lung Impairment	10%	0.08	0.29	
Vaccine Complications	**Probability per Dose[a]**	**Disutility (Toll)[b]**	**Disability Weight[c]**	**Duration (Years)[a]**
Injection Site Abscess	0.000010	0.05	0.1	0.082100
Lymphadenitis	0.000010	0.05	0.01	0.043000
Severe Local Reaction	0.000050	0.05	0.1	0.008200

[a]Committee's expert opinion.

[b]Guo, N., F. Marra, and C. A. Marra. 2009. Measuring health-related quality of life in tuberculosis: A systematic review. *Health and Quality of Life Outcomes* 7:14.

[c]Mathers, C. D., A. D. Lopez, and C. J. L. Murray. 2006. The burden of disease and mortality by condition: data, methods, and results for 2001. Global Burden of Disease and Risk Factors. Table 3A.6. *Global burden of disease 2004 update: Disability weights for diseases and conditions* 1:45–93.

Costs

Health Care Services	Cost	Disease Morbidity					
		Death	Pulmonary Tuberculosis (Inpatient)	Pulmonary Tuberculosis (Outpatient)	Latent Tuberculosis with Treatment	Extrapulmonary Tuberculosis	Lung Impairment
Direct Observed Therapy (DOT) Drugs[a]	$46	0	0	0	1	0	0
Outpatient Treatment[a]	$250	0	0	1	0	0	0
Inpatient Treatment[a]	$637	0	1	0	0	3	0
Hospitalization[b]	$360	1	0	0	0	0	5

Health Care Services	Cost	Vaccine Complications		
		Injection Site Abscess	Lymphadenitis	Severe Local Reaction
Direct Observed Therapy (DOT) Drugs[a]	$46	0	0	0
Outpatient Treatment[a]	$250	1	1	0
Inpatient Treatment[a]	$637	0	0	1
Hospitalization[b]	$360	0	0	0

[a]Floyd, K., D. Wilkinson, and C. Gilks. 1997. Comparison of cost effectiveness of directly observed treatment (DOT) and conventionally delivered treatment for tuberculosis: Experience from rural South Africa. *British Medical Journal* 315(7120):1407–1411.

Sinanovic, E., and L. Kumaranayake. 2006. Cost effectiveness and resource allocation. *Cost Effectiveness and Resource Allocation* 4:11.

[b]WHO. 2011. Econometric estimation of unit costs. WHO-CHOICE 2011 unit cost estimates for service delivery, http://bit.ly/GWGwF1.

Vaccine Characteristics

Length of immunity[a]	life	years or life
Doses required per person[a]	1	doses
Cost per dose[a]	$25	$
Cost to administer per dose[a]	$50	$
Research costs[a]	$200,000,000	$
Licensure costs[a]	$600,000,000	$
Start-up costs[a]	$10,000,000	$
Time to adoption[a]	5	years

[a]Committee's expert opinion.

C
Stakeholder Speakers

BRUCE GELLIN (*Sponsor*), Deputy Assistant Secretary of Health; Director, National Vaccine Program Office, Department of Health and Human Services

JON ANDRUS, Deputy Director, Pan American Health Organization

NORMAN BAYLOR, Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration

SETH BERKLEY, President and Chief Executive Officer, International AIDS Vaccine Initiative

GUTHRIE BIRKHEAD, Deputy Commissioner, Office of Public Health, New York State Department of Health

DONALD BURKE, Jonas Salk Chair in Global Health and Dean, Graduate School of Public Health, University of Pittsburgh

CARTER DIGGS, Senior Technical Advisor, Malaria Vaccine Development Program, United States Agency for International Development

RENATA ENGLER, Founder and Director, Vaccine Healthcare Centers Network, Walter Reed Army Medical Center

MARK FEINBERG, Vice President, Medical Affairs and Policy, Merck & Co., Inc.

LANCE GORDON, President and Chief Executive Officer, ImmunoBiologics Corporation

CAROLE HEILMAN, Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health

HAYLEY HUGHES, Chief, Safety and Evaluation Division, Military Vaccine Agency

MICHAEL KRUKAR, Director, Military Vaccine Agency
PRASAD KULKARNI, Medical Director, Serum Institute of India Limited
SUSAN LAHR, Deputy Director, Military Vaccine Agency
NICOLE LURIE, Assistant Secretary for Preparedness and Response, Department of Health and Human Services
OSMAN MANSOOR, Senior Advisor, The Expanded Programme on Immunisation (New Vaccines), United Nations Children's Fund (UNICEF)
RICHARD MARTINELLO, Chief Consultant, Clinical Public Health, Veterans Health Administration, Department of Veterans Affairs
KAREN MIDTHUN, Director, Center for Biologics Evaluation and Research, Food and Drug Administration
BARBARA MULACH, Director, Office of Scientific Coordination and Program Operations, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health
LAWRENCE PHILLIPS, Visiting Professor of Decision Sciences and Professorial Research Fellow, London School of Economics
RUBEN PROANO, Assistant Professor of Industrial and Systems Engineering, Rochester Institute of Technology
REGINA RABINOVICH, Director, Infectious Diseases, Global Health Program, The Bill and Melinda Gates Foundation
DAVID SALISBURY, Co-Chair, R&D Working Group of Decade of Vaccines Collaboration; Director of Immunization, UK Department of Health
JULIA SCHMITZ, Technical Officer, Initiative for Vaccine Research, World Health Organization
ANNE SCHUCHAT, Assistant Surgeon General, United States Public Health Service; Director, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention

D

Biographical Information

Committee members

Lonnie King, D.V.M. (*Chair*), is dean of the College of Veterinary Medicine, and executive dean for the Health Science Colleges at the Ohio State University. Earlier, King was the director of the National Center for Zoonotic, Vector-Borne and Enteric Diseases at the Centers for Disease Control and Prevention (CDC). Before serving as director, King was the first chief of the CDC's Office of Strategy and Innovation. King has also served as dean of the Michigan State University College of Veterinary Medicine for 10 years. Prior to this, King was the administrator for the U.S. Department of Agriculture's Animal and Plant Health Inspection Service. He served as the country's chief veterinary officer for 5 years, and worked extensively in global trade agreements within North American Free Trade Agreement and the World Trade Organization. He has served as president of the Association of American Veterinary Medical Colleges and was the vice chair for the National Commission on Veterinary Economic Issues. King received his B.S. and D.V.M. degrees from the Ohio State University, an M.S. in epidemiology from the University of Minnesota, and an M.P.A. from American University. He is a member of the Institute of Medicine.

Paul Citron, M.S.E.E., retired as vice president of technology policy and academic relations from Medtronic, Inc., after a 32-year career there. His previous positions include vice president of science and technology, vice president of ventures technology, and vice president as well as director of applied concepts research. Citron received a B.S. in electrical engineering

from Drexel University and an M.S. in electrical engineering from the University of Minnesota. He has authored many publications, has served on several committees of the National Academies, and holds several medical device pacing-related patents. Citron was elected a founding fellow of the American Institute of Medical and Biological Engineering and has twice won the American College of Cardiology Governor's Award for Excellence and was inducted as a fellow of the Medtronic Bakken Society, the company's highest technical honor. Citron is a member of the National Academy of Engineering.

Rita Colwell, Ph.D., is a distinguished university professor both at the University of Maryland at College Park and at Johns Hopkins University Bloomberg School of Public Health. Her interests are focused on global infectious diseases, water, and health, and she is currently developing an international network to address emerging infectious diseases and water issues, including safe drinking water for both the developed and developing world. Colwell has shown how changes in climate, adverse weather events, shifts in ocean circulation, and other ecological processes can create conditions that allow infectious diseases to spread. In addition to her academic roles, Colwell is senior adviser and chairperson of Canon U.S. Life Sciences, and chairman and president of CosmosID, which is exploring the potential applications of molecular diagnostic technologies to the field of life sciences. Colwell served as the 11th director of the National Science Foundation from 1998 to 2004. Colwell has previously served as chairman of the board of governors of the American Academy of Microbiology and also as president of the American Association for the Advancement of Science, the Washington Academy of Sciences, the American Society for Microbiology, the Sigma Xi National Science Honorary Society, and the International Union of Microbiological Societies. Colwell has also been awarded 54 honorary degrees from institutions of higher education, including her alma mater, Purdue University. Colwell holds a B.S. in bacteriology and an M.S. in genetics, from Purdue University, and a Ph.D. in oceanography from the University of Washington. Colwell is a member of the Royal Swedish Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society. She is the recipient of the Order of the Rising Sun bestowed by the emperor of Japan and the National Medal of Science bestowed by the president of the United States. She is a U.S. science envoy and a member of the National Academy of Sciences.

Kathryn Edwards, M.D., is the Sarah H. Sell Professor of Pediatrics in the Division of Infectious Diseases at Vanderbilt University School of Medi-

cine. As a graduate of the University of Iowa College Of Medicine, Edwards was elected to Alpha Omega Alpha. She completed her pediatric residency and fellowship in infectious diseases at Children's Memorial Hospital, Northwestern University School of Medicine in Chicago, Illinois, and then served as a postdoctoral fellow and instructor in immunology at Rush Medical School, Presbyterian St. Luke's Hospital, also in Chicago. Then she joined the faculty of the Vanderbilt University School of Medicine in Nashville, Tennessee, where she has remained and risen in the ranks to professor and director of the Vanderbilt Vaccine Research Program. Edwards has spent much of her career evaluating the safety and effectiveness of vaccines. As a member of both the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices and the U.S. Food and Drug Administration Vaccines and Related Products Advisory Committee, she has played a critical role in recommending new vaccines for licensure and establishing guidelines for their use. She has also been a frequent advisor to the U.S. National Institutes of Health, where she was a member of the advisory council of the National Institute of Allergy and Infectious Diseases, and to the CDC in improving ways to evaluate vaccines and to ensure their safety. Edwards served on numerous data safety and monitoring boards for national and international trials in high-risk groups such as pregnant women, infants, children, and members of developing nations. She is a member of the Institute of Medicine.

Joshua Epstein, Ph.D., is professor of emergency medicine at Johns Hopkins University (JHU), with joint appointments in the departments of economics, biostatistics, and environmental health sciences. He is director of the JHU Center for Advanced Modeling in the Social, Behavioral, and Health Sciences. He is an external professor at the Santa Fe Institute and member of the New York Academy of Sciences. Earlier, Epstein was senior fellow in economic studies and director of the Center on Social and Economic Dynamics at the Brookings Institution. He is a pioneer in agent-based computational modeling of biomedical and social dynamics. He has authored or co-authored several books including *Growing Artificial Societies: Social Science from the Bottom Up*, with Robert Axtell (MIT Press/Brookings Institution); *Nonlinear Dynamics, Mathematical Biology, and Social Science* (Addison-Wesley); and *Generative Social Science: Studies in Agent-Based Computational Modeling* (Princeton University Press). Epstein holds a B.A. from Amherst College and a Ph.D. from Massachusetts Institute of Technology. He has received a Director's Pioneer Award from the National Institutes of Health and a honorary doctorate from Amherst College.

Dennis Fryback, Ph.D., is professor emeritus of population health sciences and industrial and systems engineering at the University of Wisconsin, Madison. He specializes in methodological issues underpinning medical decision making, cost-effectiveness analysis of health care interventions, and health policy. Fryback was a member of the U.S. Preventive Services Task Force and also of the U.S. Panel on Cost-Effectiveness in Health and Medicine—two working groups that have been influential for national policy on comparative effectiveness research methods in health care. Among other honors he has received the Career Achievement Award of the Society for Medical Decision Making, which he helped to found over 30 years ago. He is a member of the Institute of Medicine.

Patricia Garcia, M.D., Ph.D., M.P.H., is the dean and professor in the School of Public Health and adjunct professor in the School of Sciences at Cayetano Heredia University (UPCH) in Peru. She is also director of the unit of epidemiology, STD and HIV; an affiliate professor in the Department of Global Health, School of Public Health, University of Washington; an affiliate professor in the School of Public Health at Tulane University; and former chief of the Peruvian National Institute of Health. Garcia has also worked at the National STD/AIDS Program in Peru as chief of comprehensive care of patients with HIV/AIDS and STDs and as vice dean of research at UPCH. She was also a member of the senior technical advisory group of the Reproductive Health Department at the World Health Organization; chair of the WHO HPV Vaccine Expert Advisory Group, secretary of research of the Latin American Association for the Control of Sexually Transmitted Infections (STI), and Latin American regional director of the International Union Against STI. Garcia is a member of several international scientific societies and is actively involved in research and training on STIs and HIV, global health and informatics, and training in Peru. She is also a principal investigator for the Frameworks for Global Health in Peru, co–principal investigator for the ICORHTA project (operations research in TB and HIV), and principal investigator for the QUIPU informatics research training center for the Andean region as well as a Bill & Melinda Gates Foundation–funded project for the implementation of rapid syphilis tests for pregnant women in Peru.

Demissie Habte, M.D., is the first president of the Ethiopian Academy of Sciences and is chair of the board of trustees of the International Clinical Epidemiology Network. He completed his undergraduate medical education at the American University of Beirut in Lebanon and his pediatrics training at the New York Hospital–Cornell Medical Center. He spent the

first three decades of his professional life in Ethiopia working as a clinician and as member of the Faculty of Medicine, Addis Ababa University in Ethiopia, where he rose to become professor and chairman of the Department of Pediatrics and Child Health, and later the dean of the faculty. Other positions he has held in the past are executive director of the International Centre for Diarrheal Diseases in Dhaka, Bangladesh; senior health specialist for the African region at the World Bank, Washington, DC; and founding international director of the James P. Grant School of Public Health, BRAC University in Bangladesh. He is a recipient of the Rosen von Rosenstein Medal of the Swedish Pediatric Society. He is a fellow of the African Academy of Sciences and Honorary Fellow of the London School of Hygiene and Tropical Medicine.

Victoria Hale, Ph.D., is founder, former chief executive officer, and chair emeritus of OneWorld Health, the first nonprofit pharmaceutical company in the United States. Under her leadership the organization developed a new cure for visceral leishmaniasis, launched a novel approach to treat dehydrating diarrhea, and developed a platform technology to reduce the cost of malaria drugs by more than ten-fold. Presently, Hale is founder and chief executive officer of Medicines360, a second generation nonprofit pharmaceutical company. Hale established her expertise in all stages of bio- and pharmaceutical drug development at the U.S. Food and Drug Administration and at Genentech, Inc. She earned her Ph.D. from University of California, San Francisco, where she maintains an adjunct associate professorship in biopharmaceutical sciences. Her honors include being named a MacArthur Fellow and receiving the President's Award of Distinction from the American Association of Pharmaceutical Scientists and the *Economist*'s Social and Economic Innovation Award. She is a member of the Institute of Medicine.

Tracy Lieu, M.D., M.P.H., is professor of population medicine and of pediatrics, and director of the Center for Child Health Care Studies at Harvard Medical School and the Harvard Pilgrim Health Care Institute. Lieu has studied vaccine safety, delivery, and economics for almost two decades and has published many papers about the effectiveness and cost-effectiveness of immunization programs. Her research includes the seminal cost-effectiveness analyses of varicella vaccine and pneumococcal conjugate vaccine for children, conducted with collaborators from the Centers for Disease Control and Prevention (CDC) and Northern California Kaiser Permanente. She has served as senior investigator of several related evaluations of the economic impact of pneumococcal conjugate vaccination,

including an economic impact evaluation for PneumoADIP. In addition to research, Lieu serves as the Children's Hospital Boston site director of the Harvard Pediatric Health Services Research Fellowship, teaches in the Harvard School of Public Health, and practices pediatrics part time with Harvard Vanguard Medical Associates. She was a member of CDC's Advisory Committee on Immunization Practices, the expert group that issues authoritative recommendations on vaccine use in the United States.

William Paul, M.D., is a National Institutes of Health (NIH) distinguished investigator and chief of the Laboratory of Immunology at the National Institute of Allergy and Infectious Diseases of the NIH. He received his undergraduate education at Brooklyn College and his M.D. from the State University of New York Downstate Medical Center. After serving a medical internship and residency at the Massachusetts Memorial Hospitals (now Boston Medical Center) in Boston, he began his research career in the Endocrinology Branch of the National Cancer Institute and was then a postdoctoral fellow at the New York University School of Medicine. He joined the Laboratory of Immunology of the National Institute of Allergy and Infectious Diseases as a principal investigator in 1968 and in 1970, took on his present position of chief of the laboratory. Paul also was director of the Office of AIDS Research at NIH and was associate NIH director for AIDS Research. Paul is well known for his discovery of interleukin-4 and for his extensive analysis of the functions, signaling mechanisms, and regulation of the production of this cytokine and for pioneering studies of CD4 T cell differentiation. He has also made important contributions to the field of B cell activation and antigen-recognition by T cells. He received the Founder's Prize of the Texas Instruments Foundation, the 3M Life Sciences Award from the Federation of American Societies for Experimental Biology, the Tovi Comet–Wallerstein Prize of Bar-Ilan University, and the Max Delbruck Medal. He is the recipient of six honorary doctorates. He has been president of the American Society for Clinical Investigation and of the American Association of Immunologists. Paul is a fellow of the American Academy of Arts and Sciences and a member of the National Academy of Sciences and of the Institute of Medicine.

Charles Phelps, Ph.D., is university professor and provost emeritus at the University of Rochester. Phelps began his research career at the RAND Corporation, where he served as senior staff economist and director of the Program on Regulatory Policies and Institutions. At RAND Phelps's research included the economics of health care, U.S. petroleum price regulations, water markets in California, and environmental regulatory policy.

Later Phelps moved to the University of Rochester, where he held appointments in the departments of economics and political science and served as director of the Public Policy Analysis Program and chair of the Department of Community and Preventive Medicine in the School of Medicine and Dentistry. He served as provost of the University of Rochester from 1994 to 2007. Phelps's research cuts across the fields of health economics, health policy, medical decision analysis, cost-effectiveness analysis of various medical interventions, and other related topics. He wrote a leading textbook in the field, *Health Economics* (Addison Wesley, now in its fifth edition), and *Eight Questions You Should Ask About Our Health Care System (Even if the Answers Make You Sick)* (Hoover Institution Press). Phelps has testified before congressional committees on health policy and intellectual property issues. He serves on the board of directors of VirtualScopics, Inc. and as a consultant to Gilead Sciences, Inc. and CardioDx. He is a founding member of the Health Care Task Force of the Hoover Institution at Stanford University. He received his B.A. in mathematics from Pomona College, an M.B.A. in hospital administration, and Ph.D. in business economics from the University of Chicago. Phelps is a fellow of the National Bureau of Economic Research and a member of the Institute of Medicine.

Rino Rappuoli, Ph.D., is global head of vaccines research for Novartis Vaccines. Previously, he was chief scientific officer and vice president, Vaccines Research, Chiron Corporation. Rappuoli joined IRIS, the Chiron S.p.A. Research Institute, in 1992 and obtained various leadership positions in vaccine discovery and research within the company. Prior to that, he was a head of the Laboratory of Bacterial Vaccines at the Scalvo Research Center and a visiting scientist at Harvard Medical School and the Rockefeller Institute. He is the author of more than 300 original papers in peer-reviewed journals and has served as reviewer for numerous scientific publications. Rappuoli obtained his doctoral degree in biological sciences at the University of Siena, delivering his experimental thesis on the use of nuclear magnetic resonance imaging in biological systems. Rappuoli has been awarded the Albert Sabin Gold Medal in recognition of his work in the field of vaccine discoveries and the Gold Medal by the Italian President for contributions to public health care. He is an elected member of the European Molecular Biology Organization and the U.S. National Academy of Sciences.

Arthur Reingold, M.D., is Edward Penhoet Distinguished Professor of Global Health and Infectious Diseases at the School of Public Health, University of California, Berkeley (UCB). He is also professor of epidemiol-

ogy and biostatistics and clinical professor of medicine at the University of California, San Francisco (UCSF). His research interests include emerging and reemerging infections and vaccine-preventable diseases in the United States and developing countries. Reingold serves on the World Health Organization's Strategic Advisory Group of Experts on vaccines and vaccine policy, is director of the California Emerging Infections Program, and is director of the U.S. National Institutes of Health Fogarty AIDS International Training and Research Program at the UCB/UCSF. His recent publications include articles on the impact of the introduction of pneumococcal conjugate vaccine in the United States and related topics. Before joining the faculty at UCB, Reingold worked for 8 years at the Centers for Disease Control and Prevention. He is a member of the Institute of Medicine.

Vinod Sahney, Ph.D., is senior fellow at the Institute for Health Care Improvement. He previously served as senior vice president and chief strategy officer at Blue Cross Blue Shield of Massachusetts. Earlier, he served as senior vice president at Henry Ford Health System for 25 years. He has served on the faculty of Harvard University for more than 35 years and has been a faculty member for Harvard's Executive Program in Health Policy and Management. His current board service includes Radius Ventures, Healthsense, and Dynamic Computer Corporation. His past board service includes the Institute for Healthcare Improvement as a founding member, director, and board chair; St. Joseph Mercy–Macomb Hospital; St. Joseph Mercy–Oakland Hospital; Enterprise Development Fund; Michigan's Children; Group Practice Improvement Network as a founding member and director; Society for Healthcare Strategy and Market Development; founding member and president of the Society for Health Systems; Faculty Practice Plan at Washington University School of Medicine; and Henry Ford OptimEyes. He has received a number of awards, including the Dean Conley Award from the American College of Health Care Executives for the best paper published in health care management; the Best Paper Award and Quality Award from Health Care Information and Management Systems Society of the American Hospital Association; a Distinguished Service Award from the Institute of Industrial Engineers; the Founders Award from the Society of Health Systems; the Distinguished Service Award from the University of Wisconsin, Madison; the Gold Award from the Engineering Society of Detroit; and the Gilbreth Award for Lifetime Achievement from the Institute for Industrial Engineering. Sahney is a member of the Institute of Medicine and the National Academy of Engineering.

Robert Steinglass, M.P.H., is immunization team leader for the Maternal and Child Health Integrated Program at John Snow, Inc. and project director for the Africa Routine Immunization System Essentials at John Snow Research and Training Institute, Inc. Steinglass received his M.P.H. from the Johns Hopkins University School of Hygiene and Public Health and has led immunization projects for John Snow, Inc. since 1990. In this capacity and in partnership with global, regional, and country partners, he has overseen the technical agenda and implementation of a series of projects funded by the U.S. Agency for International Development engaged primarily in strengthening routine immunization program performance, introducing new vaccines, and controlling vaccine-preventable diseases. Steinglass has served in leadership positions on IMMUNIZATIONbasics, BASICS II, BASICS, REACH II, and REACH at John Snow, Inc. Steinglass began his career in smallpox eradication for the World Health Organization (WHO) in Ethiopia and Yemen and served for 10 years as the resident WHO technical officer for the Expanded Program on Immunization in Yemen, Oman, and Nepal. Steinglass' immunization work has taken him to nearly 50 developing and transitional countries. His recent and current involvement at the global level includes work in such areas as the epidemiology of the unimmunized child, the role of gender and sex in immunization, the effect of new vaccine introduction on immunization systems and health systems, and the feasibility of measles eradication. He has worked with the Immunization Practices Advisory Committee, the Vaccine Presentation and Packaging Advisory Group, the Program Advisory Group of Project Optimize, the Cold Chain and Logistics Task Team, and he is advising the Centers for Disease Control and Prevention on its global immunization research agenda.

Staff

Guruprasad Madhavan, Ph.D. (*Study Director*), is a program officer in the Board on Population Health and Public Health Practice at the Institute of Medicine. He is also a program officer for the Committee on Science, Engineering, and Public Policy—a joint unit of the National Academy of Sciences, National Academy of Engineering, and the Institute of Medicine. Madhavan received his M.S. and Ph.D. in biomedical engineering and an M.B.A. from the State University of New York (SUNY). He has worked in the medical device industry as a research scientist developing cardiac surgical catheters for ablation therapy. Madhavan has received the AT&T Leadership Award, the SUNY Chancellor's Promising Inventor Award,

the Rotary International Foundation's Paul Harris Fellowship, the Institution of Engineering and Technology's Mike Sargeant Career Achievement Award, *EE Times*' Student of the Year Award, the American College of Clinical Engineering's Thomas O'Dea Advocacy Award, the American Society of Agricultural and Biological Engineers' Robert Stewart Engineering–Humanities Award, the Association for the Advancement of Medical Instrumentation's AAMI–Becton Dickinson Award for Professional Achievement, the District of Columbia Council on Engineering and Architectural Societies' Young Engineer of the Year Award, and the IEEE–USA Professional Achievement Award. Madhavan was also selected as one among 14 people as the "New Faces of Engineering" in the *USA Today* in 2009. He is an IEEE ambassador and has co-edited three books.

Kinpritma Sangha, M.P.H., is a research associate in the Board on Population Health and Public Health Practice at the Institute of Medicine. She has internship experiences with the National Women's Law Center as well as the Association of State and Territorial Health Officials. She previously served as a research assistant in the University of California, Davis, Medical Center's Pediatric Emergency Care Applied Research Network. She received her B.S. in cellular and molecular biology, and Asian American studies from University of California, Davis, and an M.P.H. in health policy from George Washington University.

Malcolm Biles is a senior program assistant with the Board on Population Health and Public Health Practice at the Institute of Medicine. He previously served as a program assistant for the National Academies Roundtable on Value and Science Driven Health Care. He received his B.A. in broadcast telecommunications and mass media from Temple University.

Rose Marie Martinez, Sc.D., is senior director of the Board on Population Health and Public Health Practice at the Institute of Medicine. Under her leadership, the board has examined such topics as the safety of childhood vaccines, pandemic influenza preparedness, the revival of civilian immunization against smallpox, the health effect of environmental exposures, the capacity of governmental public health to respond to health crises, systems for evaluating and ensuring drug safety post-marketing, the soundness and ethical conduct of clinical trials to reduce maternal to child transmission of HIV/AIDS, and chronic disease prevention, among others. Prior to joining the Institute of Medicine, Martinez was a senior health researcher at Mathematica Policy Research, where she conducted research on the impact of health system change on the public health infrastructure, access to care for

vulnerable populations, managed care, and the health care workforce. Martinez is a former assistant director for health financing and policy with the U.S. General Accounting Office, where she directed evaluations and policy analysis in the area of national and public health issues. Her experience also includes 6 years directing research studies for the Regional Health Ministry of Madrid, Spain. Martinez received her Sc.D. from the Johns Hopkins School of Hygiene and Public Health.

Patrick Kelley, M.D., Dr.P.H., is senior director of the Board on Global Health and the Board on African Science Academy Development at the National Academies. Kelley has overseen a portfolio of Institute of Medicine studies and activities on subjects as wide-ranging as the evaluation of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), the U.S. commitment to global health, sustainable surveillance for zoonotic infections, global violence prevention, and setting priorities to build capacity for food and drug regulation in low- and middle-income countries. Prior to joining the National Academies, Kelley served on active duty in the U.S. Army for more than two decades as a public health physician–epidemiologist focusing on infectious disease surveillance and control and as a preventive medicine residency director and research program manager. In his last position within the U.S. Department of Defense, Kelley founded and directed the Global Emerging Infections Surveillance and Response System. He also served as the specialty editor for the two-volume textbook *Military Preventive Medicine: Mobilization and Deployment*. Kelley obtained his M.D. from the University of Virginia and a Dr.P.H. in infectious disease epidemiology from the Johns Hopkins School of Hygiene and Public Health.

Consultants

Modeling and Software Development

Scott Levin, Ph.D., is an assistant professor in the Department of Emergency Medicine and holds a joint appointment in the Department of Applied Mathematics and Statistics at the Johns Hopkins University School of Medicine. He also works as a member of the Department of Operations Integration to advance operational, quality, and financial improvement initiatives within the Johns Hopkins Health System. Levin's research focuses on the use and development of systems engineering tools to study and improve the effectiveness, safety, and efficiency of health care delivery, including an emphasis on improving quality of care, access to care, and medical decision making. Levin's research has been funded by the National

Science Foundation, the National Institutes of Health, and the Department of Homeland Security. Levin received his Ph.D. in biomedical engineering from Vanderbilt University.

Matthew Toerper is a senior software engineer for the Department of Emergency Medicine at Johns Hopkins University, where he is the principal information technology resource and administrator of databases. Toerper started his career with Harley Davidson, where he helped support over 1,200 workstations and hundreds of applications. Subsequently Toerper worked with Johns Hopkins University's Clinical Practice Association, where he designed and implemented four enterprise-wide applications to automate manually performed data-entry work. He has also served as a software consultant for T. Rowe Price. Following his return to Johns Hopkins University, Toerper worked at the Institute for Computational Medicine in the Whiting School for Engineering, where he contributed to the Cardiovascular Research Grid project. Toerper received a B.S. in information systems from the York College of Pennsylvania.

Panayiotis Karabetis is partner and lead information designer at VIM Interactive, where he focuses on developing software prototypes for web, mobile, and desktop applications. Karabetis received his bachelor's degree in visual design and communication from the University of Maryland, where he graduated at the top of his class with honors.

Michael Kapetanovic is founding partner and project manager at Reef Light Interactive. He has previously served as chief operating officer of Web 2.0 start-up, FriendTones, as vice president of the Uyiosa Corporation, and as a senior consultant at Booz Allen Hamilton. Kapetanovic attended George Mason University, where he graduated magna cum laude with a degree in decision sciences and management information systems.

Concept Evaluation

Jon Andrus, M.D., is the deputy director of the Pan American Health Organization (PAHO). Previously Andrus served as lead technical advisor for PAHO's immunization program, with a focus on the poorest communities of the Americas. He was also professor and director of George Washington University's Global Health M.P.H. Program. He also holds adjunct faculty appointments at the University of California at San Francisco School of Medicine and the Johns Hopkins Bloomberg School of Public Health. Among other posts, he served as a medical epidemiologist at the Global

Immunization Division at the Centers for Disease Control and Prevention (CDC) in Atlanta and, on assignment by the CDC, as regional advisor for polio eradication and chief of vaccines and biologicals for the South-East Asia Regional Office of WHO. He has received the Emil M. Mrak International Award from the University of California, Davis; the Distinguished Service Medal—the highest award of United States Public Health Service—for leadership in polio eradication in South-East Asia; and the Philip R. Horne Award for sustained worldwide leadership in the global and regional immunization initiatives to eradicate polio and eliminate measles and rubella and to control other vaccine-preventable diseases.

Claire Broome, M.D., is an adjunct professor in the Department of Global Health at Emory University's Rollins School of Public Health. Previously she held several positions at the Centers for Disease Control and Prevention, including as deputy director. Broome has served as an advisor for the following institutions: the World Health Organization; the World Bank; the Global Alliance for Vaccines and Immunization; the Bill & Melinda Gates Foundation; the Burroughs Wellcome Fund; the Wellcome Trust; the U.S. Agency for International Development; the U.S. Food and Drug Administration (as a member of the Vaccines and Related Biologicals Advisory Committee); and the National Institutes of Health. Broome's research experience includes developing and implementing research programs in bacterial disease epidemiology, observational epidemiology for vaccine evaluation, and public health surveillance methodology. She also has informatics experience, including leading the development and implementation of the National Electronic Disease Surveillance System. Broome has received numerous honors and awards, including the Infectious Disease Society of America's Squibb Award for Excellence of Achievement in Infectious Diseases, the American Public Health Association Epidemiology Section's John Snow Award, the Public Health Service Distinguished Service Medal, the Surgeon General's Medallion, and the Charles Shepard Award. Broome received her B.A. from Harvard University and her M.D. from Harvard Medical School, and she specialized in internal medicine at the University of California, San Francisco, and completed a fellowship at Massachusetts General Hospital in infectious diseases. Broome is a member of the Institute of Medicine.

Joachim Hombach, Ph.D., M.P.H., is acting head of World Health Organization's Initiative for Vaccine Research (IVR). In his former position at IVR, he was in charge of implementation research and the flavivirus vaccine portfolio, and he has been working in particular on dengue and Japa-

nese encephalitis vaccines. Before joining WHO, Hombach had assignments as director of vaccine policy at GlaxoSmithKline Biologicals S.A. and as a scientific officer with the European Commission. In the latter role he was seminal in setting up the European and Developing Countries Clinical Trials Partnership. He also served as a board member of the European Malaria Vaccine Initiative. Hombach started his career as a researcher in molecular and cellular immunology, working at the University of Zürich in Switzerland and the Max Planck Institute for Immunology in Freiburg, Germany. He holds a Ph.D. from the University of Cologne, Germany, and an M.P.H. from Johns Hopkins University.

Philip Hosbach is vice president of immunization policy and government relations at Sanofi Pasteur. He serves as Sanofi Pasteur's principal liaison with the Centers for Disease Control and Prevention. He coordinated Sanofi Pasteur's global efforts in responding to the emerging H1N1 pandemic. Hosbach joined Sanofi Pasteur (then Connaught Labs) in clinical research and held positions of increasing responsibility, including director of clinical operations. He also served as project manager for the development and licensure of Tripedia, the first diphtheria, tetanus, and acellular pertussis (DTaP) vaccine approved by the U.S. Food and Drug Administration for use in U.S. infants, and he has contributed to the development and licensure of seven vaccines. He is a graduate of Lafayette College and a member of the Institute of Medicine's Forum on Microbial Threats.

Robert Lawrence, M.D., is Center for a Livable Future Professor and a professor of environmental health sciences, health policy, and international health at the John Hopkins Bloomberg School of Public Health as well as a professor of medicine at the Johns Hopkins School of Medicine. Lawrence is a founding member of Physicians for Human Rights and has served as a member of the board of directors. Lawrence graduated from Harvard Medical School, trained in internal medicine at the Massachusetts General Hospital in Boston, and served for 3 years as an epidemic intelligence service officer at the Centers for Disease Control and Prevention. Lawrence has also served as director of health sciences at the Rockefeller Foundation and has been of the faculty of University of North Carolina and Harvard Medical School. Lawrence is a master of the American College of Physicians and a fellow of the American College of Preventive Medicine. He is a member of the Institute of Medicine.

Adel Mahmoud, M.D., Ph.D., is a professor at the Woodrow Wilson School of Public and International Affairs and the Department of Molecular Biol-

ogy at Princeton University. He recently retired as president of Merck Vaccines and was also a member of the management committee of Merck & Company, Inc. At Merck, Mahmoud led the effort to develop four new vaccines, including a combination of measles, mumps, rubella, and varicella; rotavirus; shingles; and human papillomavirus. Previously Mahmoud spent 25 years at Case Western Reserve University and the University Hospital of Cleveland and served as chairman of medicine and physician-in-chief. Mahmoud earned his M.D. from the University of Cairo and received his Ph.D. from the London School of Hygiene and Tropical Medicine. He is a member of the Institute of Medicine.

Gregory Poland, M.D., is Mary Lowell Leary Professor of Medicine and director of the Mayo Vaccine Research Group at the Mayo Clinic and Foundation. Poland is certified by the American Board of Internal Medicine. His research interests include pediatric and adult vaccines, vaccine delivery and public policy, immunogenetic influences on vaccine responsiveness, and vaccines against agents. Poland has received the Secretary of Defense Medal for Outstanding Public Service, a Doctor of Humane Letters from Illinois Wesleyan University, the Dr. Charles Merieux Lifetime Achievement Award in Vaccinology and Immunology from the Foundation Merieux and the National Foundation for Infectious Diseases, and the Secretary of Defense Award for Excellence and was awarded a mastership in the American College of Physicians.

Jaime Sepulveda, M.D., Sc.D., M.P.H., is executive director of University of California, San Francisco, Global Health Sciences. Previously he was senior fellow and director of special initiatives in the Global Health Program at the Bill & Melinda Gates Foundation. Sepulveda served for more than 20 years in a variety of senior health posts in the Mexican government, including as director of the National Institutes of Health of Mexico. He also served for a decade as director general of Mexico's National Institute of Public Health and dean of the National School of Public Health. As Mexico's director general of epidemiology and later vice minister of health, Sepulveda designed Mexico's Universal Vaccination Program, which eliminated polio, measles, and diphtheria by more than doubling childhood immunization coverage in 2 years. He also modernized the national health surveillance system and founded Mexico's National AIDS Council. Sepulveda holds a medical degree from National Autonomous University of Mexico and three advanced degrees from the Harvard School of Public Health. He is a member of the Institute of Medicine.

Edward Shortliffe, M.D., Ph.D., is president and chief executive officer of the American Medical Informatics Association. He is an adjunct professor in the Department of Biomedical Informatics at Columbia University. Previously he has served as a professor at the University of Texas Health Science Center, at Arizona State University, and at the University of Arizona College of Medicine. Before that he was the Rolf A. Scholdager Professor and chair of the Department of Biomedical Informatics at Columbia College of Physicians and Surgeons in New York City and professor of medicine and of computer science at Stanford University. He received his A.B. in applied mathematics from Harvard College, a Ph.D. in medical information sciences, and an M.D. from Stanford University. His research interests include the broad range of issues related to integrated decision-support systems, their effective implementation, and the role of the Internet in health care. He is a master of the American College of Physicians and editor-in-chief of the *Journal of Biomedical Informatics*. Shortliffe is a fellow of the American College of Medical Informatics and the American Association for Artificial Intelligence and an elected member of the American Society for Clinical Investigation and the Association of American Physicians. He is a member of the Institute of Medicine.

Alastair Wood, M.B., Ch.B., is a partner at Symphony Capital LLC, a private equity company in New York. Wood is professor emeritus of both medicine and pharmacology at Vanderbilt University, where he has served as assistant vice chancellor and associate dean. He is currently a professor of medicine and pharmacology at Weill Cornell Medical College. Wood served on the *New England Journal of Medicine* (*NEJM*) editorial board and was the editor of *NEJM Drug Therapy* for many years. He has served as chair of the Nonprescription Drugs Advisory Committee at the U.S. Food and Drug Administration (FDA) and as a member of the FDA's Cardiovascular and Renal Advisory Committee. His research interests have been focused on understanding the mechanisms for inter-individual variability in drug response and toxicity. Wood is a fellow of the American College of Physicians, the American Association of Physicians, and the American Society for Clinical Investigation, and an honorary fellow of the American Gynecological and Obstetrical Society. He is a member of the Institute of Medicine.