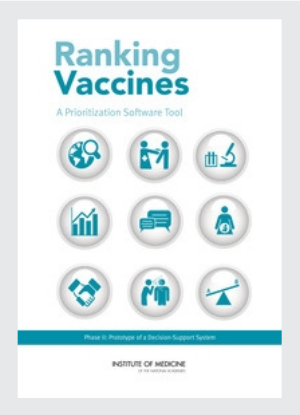

Ranking Vaccines: A Prioritization Software Tool: Phase II: Prototype of a Decision-Support System

DETAILS

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Ranking Vaccines

A Prioritization Software Tool

Phase II: Prototype of a Decision-Support System

Committee on Identifying and Prioritizing
New Preventive Vaccines for Development, Phase II

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

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

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

Gerald Brown, U.S. Naval Postgraduate School
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Alfred Berg,**

University of Washington School of Medicine, and **Stephen Fienberg,** Carnegie Mellon University. Appointed by the Institute of Medicine and the National Research Council, 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

Making choices among investments—whether in research, business, medicine, or daily life—typically involves uncertainties, preferences, and trade-offs. Decision science and modeling provide means to take account of these numerous elements, their interdependencies and interactions, and allow a decision maker to probe and assess each element without losing sight of the whole. This product of the Institute of Medicine, *Ranking Vaccines: A Prioritization Software Tool*, utilizes decision science and modeling to help inform choices among candidates for new vaccine development. This computer-based guide, called SMART Vaccines—Strategic Multi-Attribute Ranking Tool for Vaccines—builds on the blueprint presented in 2012 as *Ranking Vaccines: A Prioritization Framework*.

As a software system, SMART Vaccines provides a customizable tool—with various built-in and user-defined attributes—for a vaccine enterprise that currently has no shared standards to support decision making. As a facilitator of informed discussion and decision making, SMART Vaccines has the potential to engage different users independently or cooperatively when they wish to reduce barriers for new vaccine development and delivery. Unlike many previous recommended priorities, SMART Vaccines does not impose a predetermined value system on decision makers. Instead, users are able to weigh and rank preferences that are relevant to the specific contexts in which they are making decisions.

The usefulness of SMART Vaccines hinges on the availability of reliable data for evaluation. Indeed, by carefully analyzing the variables that go into decisions about new vaccine priorities, the tool exposes those data elements that are especially pertinent to inform choices. Additional work in establishing a data infrastructure—including new partnerships and mechanisms for generating and updating data—will be essential if this tool is to achieve its potential. Over time, users and other experts will be able to con-

tinue to refine this model, as its flexibility and capacity for improvement are key design features.

SMART Vaccines has the potential to contribute to strategic planning in a vaccine enterprise that confronts difficult choices and many constraints. I commend the experts on the committee and the staff who led this pioneering effort at the Institute of Medicine and hope that it will prove useful to policy makers and leaders in the field.

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

Preface

We live in an era of rapid change and frequent disruptions caused by globalization, changing markets, demographics, economies, and innovations in new technology development. These considerations make efforts to prioritize the development and delivery of new vaccines and other health technologies extremely challenging and progressively more complex.

Although the science and engineering underlying vaccine development is progressing in promising new directions, significant barriers remain. Among the key issues that must be addressed are the supply, delivery, safety, and cost of vaccines. Furthermore, despite the significant progress being made toward tackling the threat of infectious diseases, more work remains to be done on improving global public health. In light of these challenges, the development of new vaccines will be even more important in the future, and deciding which vaccines to prioritize will be especially critical. Currently, however, there are no standardized mechanisms in place to support decision making on vaccine prioritization and no systems that effectively involve stakeholders and users in this process.

This study was organized as part of the 2010 National Vaccine Plan and has been conducted in two phases, with separate but closely related sub-studies. In response to the charge provided by the National Vaccine Program Office of the Department of Health and Human Services, an 18-member committee for Phase II was created that included some members from the Phase I committee, who ensured continuity from the first phase, and also new members who greatly expanded the group's expertise.

The Phase II committee extended the proof-of-concept presented in the Phase I report *Ranking Vaccines: A Prioritization Framework*, which was released in 2012. The model developed in Phase I, which was based on multi-attribute utility theory, served as the foundation for the creation of the blueprint for a software tool called SMART Vaccines Beta. The Phase II

committee refined this beta version and created its next iteration, SMART Vaccines 1.0.

This report, *Ranking Vaccines: A Prioritization Software Tool,* discusses the methods underlying the development, validation, and evaluation of SMART Vaccines 1.0. It also discusses how SMART Vaccines should—and, just as importantly, should not—be used. The committee has also offered ideas for future enhancements for SMART Vaccines as well as for ideas for expanded uses and considerations and possibilities for the future. SMART Vaccines will need to secure ongoing feedback and input from potential users so the software can ultimately perform up to its maximum capacity. The committee invites suggestions for further improvements to enhance this software tool.

Our committee was highly diverse with a broad range of experiences and expertise. With a combination of ideas and intellect, the committee greatly enhanced the SMART Vaccines tool. We envision this tool serving as a living guide, one that will gain greater utility over time through continuous learning and improvements.

The creation of SMART Vaccines is unique to the Institute of Medicine (IOM), and it may also be ushering in a new era for the National Academies. There are multiple users and stakeholders who could benefit from SMART Vaccines 1.0 and they include decision makers in all realms of vaccine development and delivery in the public, private, and nongovernmental enterprises. Their involvement and input is necessary to further enhance the utility and functionality of SMART Vaccines. More importantly, the committee believes that the development of a data warehouse to support SMART Vaccines will be crucial for the successful application of this tool.

On behalf of the committee I would like to recognize and thank a number of individuals whose expertise, time, and counsel helped to develop SMART Vaccines and to produce this report. We were indeed fortunate to have a very talented, diligent, and especially hard-working IOM project staff. The committee gratefully acknowledges our study director Guru Madhavan, whose knowledge, organizational skills, and commitment to our work and to this topic were truly outstanding. We also appreciate the exceptional contributions of our research associate Kinpritma Sangha, and we recognize Angela Martin for her administrative support.

We are indebted to Rose Marie Martinez, senior director of the Board on Population Health and Public Health Practice, whose experience, guidance, and intellect proved invaluable. We wish to thank Patrick Kelley, senior director of the Board on Global Health; Clyde Behney, interim executive officer of the IOM; and Marc Gold, the associate general counsel for the National Academy of Sciences for their continued advice to the com-

mittee. For their terrific editorial and other assistance, the committee also thanks Anton Bandy, Katharine Bothner, Patrick Burke, Laura DeStefano, Megan Ellinger, Chelsea Frakes, Dev Mani, Abbey Meltzer, Robert Pool, and Jessica Rasmussen.

We were especially well served by Scott Levin of Johns Hopkins University whose help with modeling was critical to the committee's vision for SMART Vaccines. The committee's software development process was also greatly informed by the feedback of prototype evaluators Jon Andrus, Mark Feinberg, David Heymann, Tyler Martin, Simon Mercer, Paul Radspinner, and John Spika. We also thank the commentators at the committee's public forum and elsewhere as well as the expert reviewers, whose rigorous and thoughtful input helped to improve the committee's products substantially.

A final note of thanks goes to the National Vaccine Program Office of the Department of Health and Human Services for their enthusiastic commitment to this project, for their encouragement, and for their sponsorship.

Lonnie King, *Chair*

Contents

Disclaimer

This report describes SMART Vaccines—Strategic Multi-Attribute Ranking Tool for Vaccines—an early-stage prototype software application based on multi-attribute utility theory. This report does not provide a ranking of vaccine priorities. It describes the committee's modeling strategy and assumptions in order to demonstrate a proof of concept.

The SMART Vaccines software application is intended to serve only as a decision-support tool. Specific decisions about priorities should not be made solely on the basis of SMART Vaccines. The examples that appear in this report are limited to comparing hypothetical vaccines only.

The National Academy of Sciences and the Institute of Medicine do not warrant the completeness of the model, the accuracy of the software in development, or the reliability of any data presented in this report.

September 2013

Summary

Throughout most of the history of vaccines, severe infectious diseases were so common and the benefits of vaccination were so obvious that decisions regarding the development and use of vaccines required little more than common sense. Today the scenario is different and far more complex. Stringent fiscal pressures on health care and research budgets have pushed analysts to take a more careful look at the health benefits and cost-effectiveness that have traditionally driven decisions concerning vaccine development while at the same time a variety of other considerations have also become important in prioritizing the development and use of vaccines. This in turn makes it particularly important to have vaccine prioritization models that allow analysts to take into account the various factors in making decisions on which vaccines to prioritize.

However, the prioritization models available today are incomplete and provide no real standards for comparisons among vaccines, nor do they make it easy for decision makers to collaborate on vaccine prioritization decisions. Furthermore, in today's prioritization models the factors that have influenced a particular recommendation generally remain obscure, which makes it much more difficult for decision makers to use such recommendations to come up with their own decisions for prioritizing vaccines.

As an effort to guide new vaccine development, in 2010 the Department of Health and Human Services released the National Vaccine Plan, which outlined five main goals for the next decade of U.S. vaccine development and utilization. The plan's first goal is to "develop new and improved vaccines," an objective that the National Vaccine Program Office (NVPO) plans to achieve by developing "a catalogue of priority vaccine targets of domestic and global health importance."

As a first step toward achieving this objective, in late 2010 the NVPO commissioned the Institute of Medicine (IOM) to produce a framework for identifying and prioritizing new preventive vaccines for development. The

creation of this framework has so far proceeded in two phases. In Phase I a 15-member committee developed a multi-attribute utility model and an associated software blueprint called SMART Vaccines, an abbreviation for Strategic Multi-Attribute Ranking Tool for Vaccines. The committee evaluated the model using hypothetical vaccine candidates for the prevention of influenza, tuberculosis, and group B streptococcal infection in the United States and South Africa. The methodologies and the software framework are described in the 2012 report *Ranking Vaccines: A Prioritization Framework* (IOM, 2012).

The Phase II study described in this report, *Ranking Vaccines: A Prioritization Software Tool*, is a continuation of the Phase I work. A committee of 18 members further refined the multi-attribute utility model and also enhanced the software, creating a new version—SMART Vaccines 1.0—for public release.

Prioritization Models for New Vaccine Development

The IOM has contributed scholarly work to the subject of vaccine prioritization since the 1980s. In 1985 and 1986 the IOM published two reports under the same title, *New Vaccine Development: Establishing Priorities*, one that focused on vaccine priorities for the United States (IOM, 1985) and another that focused on international priorities (IOM, 1986). These two reports used equivalents of infant lives saved as the sole measure of benefit in prioritizing vaccines. IOM's next prioritization report, *Vaccines for the 21st Century* (IOM, 2000), used an efficiency measure (in the form of a cost-effectiveness ratio) rather than a direct benefit measure such as life-years saved and focused only on U.S. vaccine priorities. The approach used in *Ranking Vaccines: A Prioritization Framework* (IOM, 2012) and in this report has been informed by these previous studies but has significantly expanded the attributes that are relevant for the prioritization and development of new vaccines.

The committee, which gathered feedback from groups and individuals with a broad range of perspectives about the 1985–1986 and the 2000 reports, regularly heard that while those reports were valuable, their focus on life-years saved and cost-effectiveness ratios as outcomes limited their usefulness. The Phase I committee thus chose an approach that provided users and stakeholders with a list of vaccine attributes and allowed them to choose which particular ones they would use in prioritizing vaccines. The committee also developed an intuitive approach to prioritizing vaccines, based on the multi-attribute utility model, which allows users to develop prioritizations based on their assessments of the relative importance of

various attributes. One important advantage to the approach developed by the committee is that while life-years saved, cost-effectiveness ratios, and other traditional measures are still available for selection, SMART Vaccines allows users to evaluate vaccine candidates based on many other important attributes, including, for example, the benefits to vulnerable populations or the potential to improve production platforms or delivery methods.

After Phase I of the project had been completed, the NVPO commissioned the IOM to collect feedback and to continue the development of SMART Vaccines, which the second committee has done, taking into account information obtained from a public workshop and from the presentations of various committee member carried out at the beginning of Phase II. The committee's task, as laid out by the NVPO, also included expanding the vaccine datasets to include at least three more vaccine candidates. In addition to the influenza, tuberculosis, and group B streptococcus vaccines tested in Phase I, the committee included human papillomavirus, pneumococcal infection, and rotavirus as test vaccine candidates for both the United States and South Africa (the same two countries considered in Phase I) in this study. Box S-1 provides the complete charge to the committee for its Phase II work.

BOX S-1
Committee on Identifying and Prioritizing New Preventive Vaccines for Development, Phase II

Institute of Medicine
Statement of Task

Task 1: Engage stakeholders and obtain feedback about the usefulness of the prototype model developed in Phase I for prioritizing new preventive vaccines for development.

Task 2: Make modifications to the prototype model and test three additional pre-determined vaccine candidates of domestic and global importance.

Task 3: Prepare a report containing the enhanced model, test results, and recommendations for strategies toward developing a catalog of vaccine targets.

Design of SMART Vaccines

SMART Vaccines 1.0 is a decision-support tool that is intended to help users carry out more effective discussions and make better decisions about the research and development, manufacturing, implementation, and delivery of vaccines. It provides a scientific basis for decision making in an environment characterized by financial pressures, uncertainty, and a lack of standard information. Decision makers and other users can employ SMART Vaccines to assist them in reaching a consensus decision or simply to guide them in establishing the knowledge base needed in various decision-making scenarios. A particularly useful characteristic of SMART Vaccines is that it offers dynamic capabilities that allow users to examine several scenarios by changing the inputs and seeing the results change instantaneously.

SMART Vaccines has four basic inputs: (1) the demographics of the population to be immunized, (2) the disease burden for that population, (3) the value-relevant attributes of potential vaccines, and (4) the user's ranks and weights relating to the vaccine attributes.

***Demographic Characteristics*:** The user specifies the population of interest (e.g., a nation, a state or province within it, or perhaps a consortium of nations) and then imports life-table data for that country or region from World Health Organization (WHO) databases. The user can also focus on specific populations with special characteristics, such as infants less than one year old or HIV-positive individuals.

***Disease Burden*:** Next, the user specifies the disease and enters data for the associated disease burden. The required data include incidence rates (by age and sex), case-fatality rates (by age and sex), morbidity due to the disease, duration of the condition, how health-related quality of life is affected by the condition, and the estimated costs associated with treatment of the disease. Data from WHO and the Global Burden of Disease project can be used to provide a basic source of information for nations that do not have a reliable disease surveillance system.

***Vaccine Characteristics*:** The user next estimates the economic and functional characteristics—for example, potential efficacy, uptake, and product development costs—of the candidate vaccines. Many of these characteristics will be unknown, especially for new or undeveloped vaccines. Therefore, SMART Vaccines allows the user to explore how sensitive the ultimate rankings are to the various parameter estimates.

TABLE S-1

Choices of Attributes in SMART Vaccines 1.0

Health Considerations	• Premature Deaths Averted per Year • Incident Cases Prevented per Year • QALYs Gained or DALYs Averted
Economic Considerations	• Net Direct Costs (Savings) of Vaccine Use per Year • Workforce Productivity Gained per Year • One-Time Costs • Cost-Effectiveness ($/QALY or $/DALY)
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 • 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	• Interest for National Security, Preparedness, and Response • Advances Nation's Foreign Policy Goals
User-Defined Attributes	• Up to Seven Attributes

NOTE: DALYs = disability-adjusted life years; NGOs = nongovernmental organizations; QALYs = quality-adjusted life years.

***Attributes and Weights*:** This portion of SMART Vaccines is its most novel feature. Users can select from 28 attributes arranged in eight categories. The committee chose to retain the original attribute list following the discussions with various stakeholders during Phase I, with an addition of a ninth category of user-defined attributes, which allows up to seven qualitative attributes defined by the user (see Table S-1). Attributes concerning health and economic considerations are calculated by the computational submodel with the provided data while the remaining attributes are value

preferences selected by the user. In particular, the user-defined attributes are qualitative binary assessments requiring a "yes" or "no" response. Users specify which of the 28-plus attributes will be considered in the multi-attribute utility function and place those attributes in rank order, the first being most important.

SMART Vaccines approximates a set of weights for the rank-ordered selections by using a mathematical process known as the rank-order centroid method. This method calculates averages of all weights and assigns weight to each attribute corresponding with the user's rank order, with the final weights adding up to 100 percent. Most of the weight is placed on the first five to six attributes. In the committee's experience, most applications of multi-attribute utility theory (whether using the rank-order centroid method or not) place only small weights (5 percent or less) on attributes that are ranked below the fifth attribute. The weight of each attribute beyond the seventh one becomes very small (less than 2 percent). Although SMART Vaccines 1.0 allows users to select up to 10 attributes, selection of no more than 7 attributes is suggested in order to allow each weight to sufficiently influence the SMART Score However, should the user wish, the weights applied to each attribute can be adjusted with slider bars, altering the weight positions until the user is satisfied with the final weights applied to each attribute for every vaccine candidate under consideration.

SMART Score

The multi-attribute utility model underlying SMART Vaccines produces a value score—called a SMART Score—which helps users interpret the relative performance and rank of their vaccine candidates. Because each user will have specified his or her own value function, a sample SMART Score of 60 has meaning only when comparing other vaccines within the same user's framework. Comparisons across individual users' scores are meaningful only if the users select the same attributes and use identical endpoints (worst and best level) for each attribute. Otherwise, a score of 60 for one user may mean something very different than a score of 60 for another user.

Multi-attribute utility scales preserve the order of preferences or priorities among vaccines. A vaccine with a higher score is preferred or has higher priority. SMART Scores are always relative to the user's choice of two reference points: a zero (assigned to a vaccine that is the worst possible on all attributes) and a score of 100 (a vaccine that is the best possible on all attributes). Thus, a score of 50 would mean that the vaccine is halfway between the worst and best vaccines. It is also meaningful to interpret

differences between SMART Scores. For example, a difference of, say, 10 points has the same meaning anywhere on a single user's scale, so a difference of 10 points on a SMART Score between 60 and 70 has the same meaning as a difference between 30 and 40. However, it is not correct to think of a vaccine with a score of 40 as being twice as good as a vaccine with a score of 20.

One way to understand this is in analogy with measures of temperature. Some thermometers measure temperature in Celsius, some in Fahrenheit, and some in Kelvin. Only the Kelvin scale begins at absolute zero, so it alone allows statements about the *relative* magnitude of its values—300 K is twice as hot as 150 K, while 20°C is not twice as hot at 10°C. Comparisons of temperatures across these scales lack intrinsic meaning unless each user has a "standard event" he or she can measure. With thermometers, the values for the freezing (32°F and 0°C) and boiling (212°F and 100°C) points of water provide such measures. Knowing these two "standard scores" allows us to also understand that 20°C is the same temperature as 68°F. Final scores from different users cannot be aggregated to obtain a common SMART Score because the users may have chosen a different set of attributes for their valuation; hence each score reflects different priorities based on different preference structures. But, users can help calibrate each others' SMART Scores by ranking two or more vaccines where the population, disease burden, treatment cost, and vaccine attributes are all identical (e.g., comparing vaccine candidates in the United States for influenza and tuberculosis). This comparison is most fruitful within a single population, for instance, comparing influenza and tuberculosis for South Africa is useful whereas comparing a new influenza vaccine for the United States against a new tuberculosis vaccine for South Africa is infeasible. This is because the disease burden and other characteristics in South Africa differ greatly from those in the United States for both influenza and tuberculosis, thus, the comparison across two populations is not a valid one.

Test Vaccine Candidates

Building upon the Phase I work, the Phase II committee chose to add three additional vaccine candidates for use in evaluating the software and to expand the data library for SMART Vaccines. Again, the United States and South Africa were chosen as the populations representing the different perspectives of high- and low-income nations and also to provide an interesting contrast in disease burdens. In addition, these two countries also have different income, health, and demographic profiles, and different social and economic priorities for developing and delivering vaccines.

The previously existing portfolio of diseases consisted of influenza, tuberculosis, and group B streptococcus. The committee chose to add human papillomavirus, pneumococcal, and rotavirus vaccines as the three additional test candidates. Human papillomavirus infects individuals when they become sexually active and may progress to cervical or anal cancer with time. Both rotavirus and pneumococcal infections occur commonly in children and have a greater impact in low-income settings.

Data Needs

SMART Vaccines is only as robust as the data that are available for use in its calculations. However, the data gathered by this committee for the test case vaccines are only estimates, intended to demonstrate the functionality of SMART Vaccines. The data were gathered to provide a starting point for users to edit or change the data or to introduce their own information. And if users wish to compare vaccines other than the ones provided with the software, they can modify the pre-loaded data as necessary.

Many different types of data, including data on demographic factors, disease burden, economic factors, and vaccine characteristics, are available to users from various sources and estimations. Because many vaccines are still hypothetical—which means that data about them do not yet exist—a user who wishes to analyze such a vaccine must provide some estimates of what could be possible (such as cost per dose, the developmental costs for the vaccine), and these estimates may be difficult to determine. Much of the remainder of the information needed to use SMART Vaccines can be obtained from public sources and the published literature, but the data vary in comprehensiveness and accuracy.

The next stage of this study—Phase III—will attempt to provide estimation strategies toward assisting users in thinking about data compilation for SMART Vaccines. In doing so, an Institute of Medicine committee is also expected to collaborate with potential users to determine software use case scenarios.

Accessing and Using SMART Vaccines

An executable file of SMART Vaccines 1.0, currently available for computers running the Windows operating system, can be downloaded from the Institute of Medicine (IOM) website (www.iom.edu/SMARTVaccines) or from the National Academies Press (www.nap.edu/SMARTVaccines). The current version is pre-populated with test data which allow the user to use

the model to evaluate vaccine candidates chosen by the committee for the United States and South Africa. To compare vaccine candidates other than the ones provided in the software, users will need either to import data from other sources or to provide their own data. The software leads users through this process to some extent, generally relying on users to first enter data in spreadsheet format (e.g., using Microsoft Excel). These data can then be imported into SMART Vaccines.

To assist individuals in using SMART Vaccines, spreadsheets containing data for the six vaccine candidates have been made available along with an empty spreadsheet template that is included for data entry purposes, if needed by the user, and that is available on the same websites where the software and this report are available for download.

Next Steps

As has been noted in *Ranking Vaccines: A Prioritization Framework* (IOM, 2012) and re-emphasized in this report, SMART Vaccines should not be thought of as a decision maker. It is a decision-support tool intended to provide insight to users and to facilitate discussions before ultimate decisions are made.

To inform future versions of SMART Vaccines, the committee adopted a guiding principle: **SMART Vaccines will have the greatest potential and value if it is programmed as a dynamic, continuously evolving software application, and made freely available in an open-source environment to all decision makers and developers around the world.**

The committee also believes, as a related strategy, that the benefit will be achieved with the greatest likelihood if the **National Vaccine Program Office of the Department of Health and Human Services identifies a host for SMART Vaccines and its future versions.** Furthermore, no decision-support system, including SMART Vaccines, has any intrinsic value without accurate and relevant data. Consequently, **the committee places highest importance on the creation of a data architecture and expanding data collection for use in SMART Vaccines.**

This last point in turn leads to six related future conditions that the committee believes will enhance the long-term success of SMART Vaccines. These conditions are:

1. SMART Vaccines—and its future versions—is hosted in an open-source setting on a widely trusted website with a distinct identity and is appropriately protected from unwarranted modifications or intrusions.

2. The host organization creates, maintains, funds, and facilitates a community of users to curate and manage further development of SMART Vaccines and supporting data.
3. The community of users includes decision makers involved in research, development, regulation, and implementation of new vaccines as well as developers with expertise in such areas as modeling, epidemiology, demography, software engineering, database management, and visual design.
4. The community of users—independently or in collaboration with the host organization—establishes an advisory group to help plan future versions and the adoption of SMART Vaccines.
5. The community of users, together with the host and sponsors, develops mechanisms to encourage the development and updating of various types of data: on populations at regional, national, and sub-national levels; on the disease burdens they confront; on the costs of preventing and treating those diseases in each distinct environment; and on the productivity losses associated with these disease burdens. Ideally, these data are accessible in a standardized format, shared with other users through the common website that hosts SMART Vaccines, and improved through an editing process agreed upon and overseen by the user community. These processes could ultimately help guide improvements in global communication and coordination of data and initiatives of common interest and shared importance.
6. The community of users studies the application of SMART Vaccines for retrospective analysis, validation, or confirmation of previous decisions relating to new vaccine development. Results would have both an educational and a continuous learning benefit.

Immediate next steps for further development of SMART Vaccines could focus on creating a data warehouse that enables users to create, share, access, and validate data for a broad range of populations, diseases, and vaccine candidates in standardized formats. Without large increases in the availability of structured data, it will not be possible to create prioritization catalogues. A data warehouse of this sort could be seeded with publicly available population data, and it would likely be focused on nation-level statistics, but it could also include global, regional, or state-level data as required by the user base. Others—for example, vaccine manufacturers—may wish to take a more global perspective but with a narrower set of candidate vaccines. Another important next step would be user review of the

software design, coupled with formal usability studies targeted at potential user organizations, in order to develop a flexible software design that will ensure that SMART Vaccines is maximally intuitive for a broad range of end users and easily extensible by the open source community.

Observations

The study described in this report is a wholly novel exercise for the IOM and the National Academies in that a primary output of the committee's work is a software product. Developers and users of any commercial software understand that keeping software current requires continual improvements and upgrades. No software application is flawless in its first version. SMART Vaccines is no different, and, moreover, it has been developed in an academic and policy setting rather than in an industrial software engineering environment. For these reasons the committee has set forth a vision to carry the work of SMART Vaccines forward, both in database development and in software enhancements through usability studies and other strategies.

Unlike previous IOM reports on vaccine prioritization, this study does not provide a "list" of vaccine priorities, nor was the committee tasked with achieving such an outcome. Users of SMART Vaccines will create their own priority lists with their own values and available data. In short, rather than imposing the value system of the committee, SMART Vaccines allows users to specify what is most important to them—thus creating their very own value structures, each of which will result in its own unique list of vaccines.

If appropriately used, SMART Vaccines should help enhance discussions among users about differences in their priority lists and about the explanations for those differences. The committee hopes that SMART Vaccines will allow every voice to be heard in such discussions.

1

Introduction: New Vaccines and SMART Vaccines

Decision making is not always easy, especially under complex circumstances. Deciding which vaccines—or which of any sort of health care products or services—that one should invest in requires a complex assessment of alternatives. And the planning process, which can consume massive amounts of resources, generally must contend with a variety of uncertainties and sometimes also biases and bits of "conventional wisdom" that may actually be incorrect.

New vaccine development is a demanding process. It is long and often arduous, and few appreciate the amount of work and resources that go toward producing and delivering what may seem to many like a trivial matter—say, half a milliliter of fluid contained in a vaccine vial or ampoule. The process typically consumes hundreds of millions of dollars, and its success relies on the co-evolution of scientific understanding, regulatory environment and requirements, production technologies, public health needs, human resource management, and often an understanding of the culture of the intended recipients of vaccination (Rappuoli et al., 2011).

The process for developing new vaccines has changed significantly over the last three decades (see Figure 1-1). In the 1980s the major obstacles for new vaccines were on the discovery side, while development was relatively easy, and the licensing process required only several hundreds of subjects evaluated in clinical trials (Rappuoli and Alderem, 2011).

During the 1990s many new promising technologies, including recombinant DNA, conjugation, and genomics, emerged and aided vaccine discovery (Bagnoli et al., 2011). However, during the same period the timelines and budgets required for the development of vaccines soared

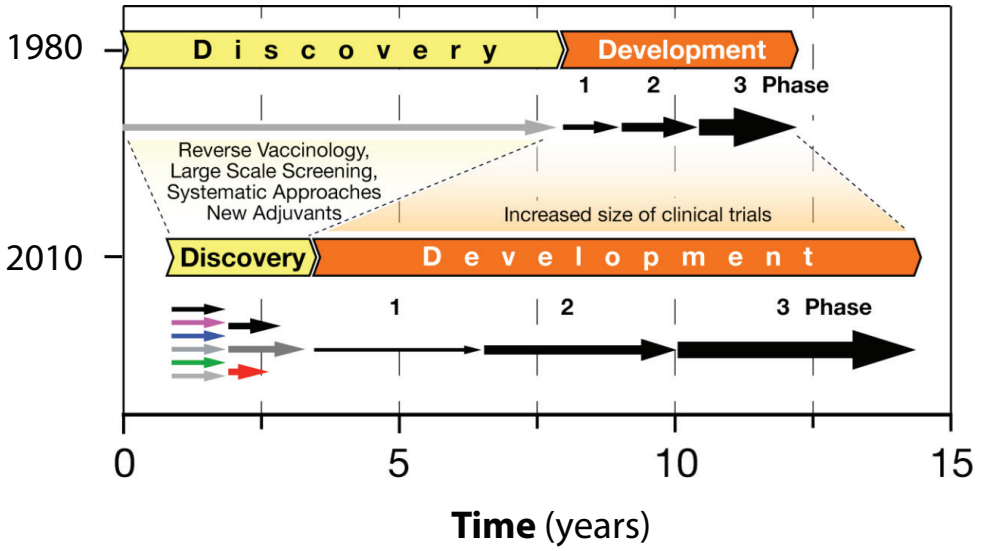

FIGURE 1-1
Change in the time and resources required for vaccine discovery and development from 1980 to 2010. In the 1980s vaccine discovery required a long time, while development periods were relatively short. More recently, the time involved in new vaccine discovery has shortened dramatically due to the availability of various new technologies. However, in the meantime the regulatory requirements have lengthened the development timelines substantially. This results in longer times for vaccine licensure and significant increases in development costs.

SOURCE: Adapted from Rappuoli and Alderem, 2011.

(Milstien and Candries, 2002). The burgeoning research and development budgets coupled with increasing regulatory complexity and the increased time required for the development of a new vaccine made the decision process very challenging and necessitated the use of sophisticated models to predict the returns on the investment.

Moreover, while high-income countries face greatly increased lengths of time and various financial and scientific challenges when developing new vaccines, as illustrated in Figure 1-1, developing vaccines for use only in low-income countries is perhaps even more challenging, as there are fewer mechanisms in place to develop those vaccines (Batson, 2005; Rappuoli and Alderem, 2011). It may take a number of additional years after a vaccine is commercially available in high-income countries to introduce the same vaccine in low-income countries. And even if a vaccine is available in high-income countries, it may be the case that models are unable to justify the investment required for the development of the same vaccine in low-income countries, where they may not be a profitable market; this is a particular challenge with innovative vaccines. An example is a conjugate vaccine against meningococcus A that was developed specifically for

a low-income region of sub-Saharan Africa. The development effort was made possible only through the work of a vaccine manufacturer from a low-income country with the support of the Bill & Melinda Gates Foundation—even though these meningococcal conjugates were already developed and licensed in high-income countries (Bishai et al., 2011). This inequity between high- and low-income countries needs to be captured within decision-support tools in order to emphasize economic and health returns.

Another example that illustrates the need for decision-support tools concerns the introduction of improved vaccines. Older vaccines continue to be used because the business models are not able to justify the investment necessary to improve those products. An example is the pertussis vaccine. Because of reactions associated with the older whole-cell pertussis vaccines developed and licensed in the late 1940s, new vaccine development became a high priority for research funding agencies, regulatory bodies, and industry in the 1980s. New, more highly purified acellular vaccines were developed and licensed in the mid-1990s and were shown to have an excellent safety profile. After that success, interest in the science of pertussis decreased, and little effort was made to improve the vaccine further. The situation has recently changed with the finding that the immunity created by the acellular vaccines appears to be not as long-lasting as the immunity from the whole cell vaccine. Now, with the shortcomings of the pertussis vaccines apparent, funding agencies are being asked to support research in the biology of pertussis, and regulatory agencies are being requested to find innovative ways to license new pertussis vaccines in the absence of efficacy trials. However, private industry has little incentive to invest in this work because a company cannot justify investing in a new full-fledged development program without proof of concept, a clear regulatory strategy, a price point advantage or an authoritative use recommendation that will generate a return on its investment.

Yet another example illustrating the need for a comprehensive prioritization model concerns discounting, which typically puts vaccination at a disadvantage to therapeutic interventions in a company's financial calculations. In most calculations the benefit of an intervention is captured in full for the first year and then discounted in following years. This is not an issue for a therapeutic intervention, where the cost occurs very close to the benefit. However, it is an issue for vaccines because the benefits occur many years after vaccination. Therefore, applying similar discounting methods to both vaccines and therapeutics—which is typical—can have a strong influence on the outcome of models that are based solely on cost-effectiveness and thus can profoundly affect the resulting decisions (Bloom et al., 2005).

Finally, there are some features that are unique to vaccination and

that make impact assessment even more complicated. One of these is the concept of herd immunity, which refers to the fact that vaccines protect not only the vaccinated subjects but also unvaccinated people by reducing the circulation of a pathogen (Drummond et al., 2007). This benefit is realized several years after implementation of the primary intervention and is often not included in most cost-effectiveness models. Furthermore, if herd immunity is included in the model, it is discounted, thus reducing the calculated true value of the intervention. Yet herd immunity can have major benefits. An extreme example is the eradication of the pathogen that causes a disease. For example, smallpox has been eradicated, and polio is on the verge of eradication (Brilliant and Foege, 2013; Tomori, 2011). Thus, it is important that the impact of herd immunity be adequately captured in decision models.

Today, decision-support frameworks provide guidance in planning and prioritizing many of the above-mentioned scenarios. However, those involved in such assessments plan and prioritize development and implementation processes in their own ways, which are sometimes proprietary. Decision making related to the development and implementation of vaccines is complex and involves many stakeholders, including vaccine manufacturers, public and private funding agencies, nongovernmental organizations, regulators, and purchasers. Each of these partners needs tools or mechanisms to compare the relative benefits of different vaccines in their portfolio, of new vaccines that may become available, and of vaccines weighed against other interventions. Decision making involves understanding the existing and emerging landscape of vaccine development, the real benefits that vaccination brings to society, and the limitations of the decision models available today. Sound decision making sometimes also involves persuading others; for example, a minister of health may need to convince the minister of finance about the value of a given vaccine (or a vaccination program) and why it should be prioritized versus other interventions.

Decision makers in different areas look at different factors in making their decisions. Industrial executives, for instance, may need to first evaluate the technical feasibility and the projected efficacy of a new vaccine and then decide whether the investment in a particular vaccine provides better return to the investors than an investment in other options, such as therapeutic drugs, where profit margins are usually higher. Funders of vaccine research, development, and implementation prioritize different vaccines in different countries for different reasons. A tool that facilitates an assessment of the decision-making process of all the diverse, independent, and sometimes conflicting stakeholders would greatly improve the quality of the discussions and decisions related to individual and public health pri-

orities. This is reinforced by the fact that all stakeholders operate under conditions of limited resources and must choose among alternatives.

The need for a better and more comprehensive tool that can support different entities is also underscored by the abundance of varying perspectives within the vaccine enterprise. The stakeholders involved in vaccine development range from government entities to public and private funding organizations, vaccine manufacturers, and vaccine program implementation leaders. It was in order to accommodate the many different scenarios and even more viewpoints that the Institute of Medicine (IOM) Committee on Identifying and Prioritizing New Vaccines for Development designed SMART Vaccines. This software has been developed, keeping various stakeholders in mind, to provide a more consistent method for informing decisions and to offer an analytical base for reaching individual or collective decisions.

Study Context and Scope

A critical development in the realm of vaccine policy was the release of the 2010 National Vaccine Plan by the U.S. Department of Health and Human Services' National Vaccine Program Office (NVPO) (HHS, 2010). The plan's various goals and priorities make it compellingly clear that all strata of the vaccine enterprise must work toward the development of safe, effective vaccines that are important to global public health. The first goal of the plan is to "develop new and improved vaccines," with one of the corresponding implementation priorities relating to the development of a catalogue of vaccine targets that are domestically and globally important (highlighted as bold text in Box 1-1).

In order to achieve the first goal of the National Vaccine Plan 2010, the NVPO requested that the IOM conduct a study to create a framework for prioritizing vaccines. This work has been carried out in two phases, whose places in the overall plan are shown in Figure 1-2, which outlines the tasks required to reach the ultimate vision of creating a catalogue of priority vaccines for both domestic and international importance. The Phase I committee developed a multi-attribute utility framework and a blueprint for software named the Strategic Multi-Attribute Ranking Tool for Vaccines—or SMART Vaccines Beta.

The Phase II committee continued the Phase I committee's work by refining the model underpinning SMART Vaccines Beta. (See Box S-1 for the Statement of Task.) The current enhanced version of the software, SMART Vaccines 1.0, is a product of continuous stakeholder feedback coupled with the committee's deliberations and has been made available for public use.

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.

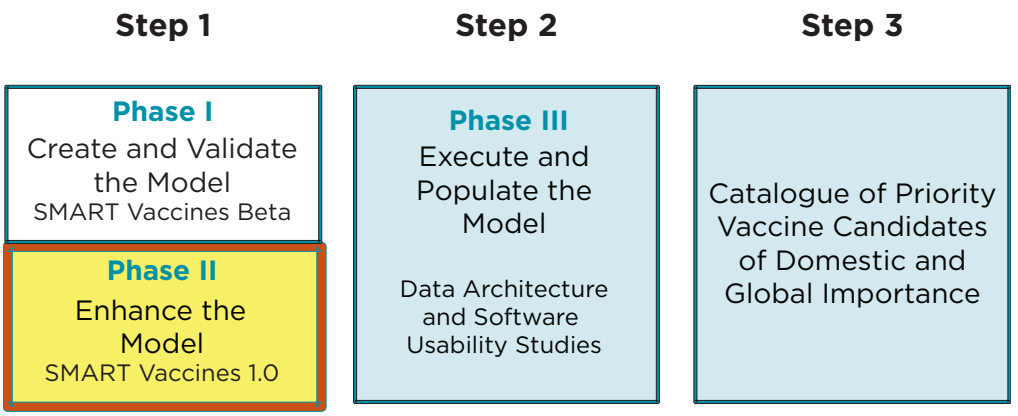

FIGURE 1-2
Steps needed to achieve the first goal of the National Vaccine Plan, according to the National Vaccine Program Office of the Department of Health and Human Services. Phase I in Step 1 resulted in the Institute of Medicine's *Ranking Vaccines: A Prioritization Framework* as well as the blueprint of the software SMART Vaccines Beta (IOM, 2012). Phase II in Step 1 (highlighted in yellow) relates to this report, *Ranking Vaccines: A Prioritization Software Tool,* and SMART Vaccines 1.0. Step 2 (Phase III) involves the data architecture and software usability studies, with Step 3 efforts ultimately resulting in a catalogue of domestically and globally significant vaccine candidates.

The committee has also expanded the datasets available for use with the software and evaluated three additional vaccine candidates for the United States and South Africa. The combined group of vaccine candidates consists of vaccines for influenza, tuberculosis, group B streptococcus, human papillomavirus, pneumococcal infection, and rotavirus.

Study Process and Feedback from Stakeholders

In the summer of 2012, immediately after the release of the Phase I report *Ranking Vaccines: A Prioritization Framework* (IOM, 2012), an 18-member committee was formed that contained some members who had served on the Phase I committee plus some new members. (Appendix F contains the biographical information of the members.) To accomplish its task, the committee held three committee meetings as well as several ad hoc subgroup committee meetings held via teleconference. The committee worked with eight consultants, one of whom assisted with modeling and programming, while the others helped to evaluate an early prototype version of SMART Vaccines 1.0.

As with any software application, the development of SMART Vaccines followed an iterative process. The committee went through multiple versions of the software, each of which took into account feedback and suggested refinements from stakeholders. To gather feedback on the

BOX 1-2
Framing Questions for Stakeholders' Feedback

Usefulness: Do you think SMART Vaccines could be useful to you as you make decisions regarding new vaccine development and prioritization? Please elaborate on how you might use it and for what purposes. How does this approach complement and/or differ from your current decision-making approach?

Usability: Does SMART Vaccines cover the most relevant issues related to vaccine development and prioritization? Is the current software version user-friendly? Please comment on the ease of understanding how to use it and the demands on the user.

Data Library: How should the committee address the intensive needs for data inputs into the model? How should the user groups think about data requirements and resources for data collection and standardization?

Application Development: In what ways can SMART Vaccines be enhanced?

Outreach: What advice can you give regarding how best to engage various user groups and decision makers to use—and further develop—SMART Vaccines?

model, software, and data, the committee organized and conducted several feedback-gathering sessions with interested stakeholders and the public.

As part of the efforts to gather public feedback, the committee members used a variety of formats for demonstrating the concept and utility of SMART Vaccines. Webinars, teleconferences, plenary talks, group discussions, and presentations were offered for a variety of audiences that included representatives from federal advisory groups, professional societies, policy groups, international governmental agencies, private industry, and philanthropic and trade organizations. The committee also organized an international stakeholder workshop to obtain additional feedback for

use in improving the functionality of SMART Vaccines. (See Appendix E for a listing of speakers.)

The questions posed to the speakers fell into five main categories: usefulness, preliminary usability, data needs, application development, and possibilities for outreach (described in Box 1-2). In the course of numerous public presentations about SMART Vaccines (based on the Phase I report), the committee members received many comments and questions. Table 1-1 contains a listing of the most common questions and comments from stakeholders, along with the committee's response and commentary.

The committee took the gathered feedback into account in its deliberations on refining the model, on informing the data collection for additional vaccine candidates, and on redesigning the software interface. Those efforts are detailed in Chapter 2.

TABLE 1-1

Frequently Asked Questions and the Committee's Responses

Stakeholder Question	Committee's Response
Is there not a risk that the multi-attribute utility model underlying SMART Vaccines can be "gamed" so that users get the rankings they wanted in the first place?	Technically yes, but SMART Vaccines makes explicit what has previously remained hidden from view. The committee anticipates and hopes that when various users begin to discuss the rankings they have produced using SMART Vaccines, others will insist that each user make clear the levels of attributes they have assigned to various vaccine candidates (including cost, efficacy, coverage, side effects) and the multi-attribute utility value weights. With these data available for open discussion, various parties can compare their inputs and results and reach an understanding on what drives each user's results.
Should the most important variable in the system be life-years saved? Why bother with anything else?	Previous ranked lists, including the 1985–1986 and 2000 reports from the Institute of Medicine, used a single attribute for vaccine prioritization: The 1985–1986 reports used a metric similar to life-years saved, and the 2000 report used an efficiency measure of cost-effectiveness measured as cost per quality-adjusted life year (IOM, 1985, 1986, 2000). But both studies stated clearly in their reports that many other issues would guide final decision making on vaccine priorities. SMART Vaccines seeks to make explicit exactly how these "other issues" affect the decisions. There will still remain issues and attributes not taken into account by SMART Vaccines, but the committee believes that making these considerations explicit will improve decision making and communication among affected and interested parties.
SMART Vaccines is of limited use without much better data, is it not?	Yes. The committee not only agrees with this, but hopes that the creation of SMART Vaccines will accelerate the production of necessary data. In the absence of such data, decisions continue to be made, and the committee believes that decision making about vaccine priority ranking will improve with the production of better data and the use of a carefully structured model such as SMART Vaccines. This report concludes with some strategic steps that the committee believes will greatly enhance the production of high-quality datasets for use in SMART Vaccines.

TABLE 1-1

Continued

Stakeholder Question	Committee's Response
It is unusual to place "corporate profits" into a social welfare function such as created by SMART Vaccines, is it not?	SMART Vaccines does not create a classic social welfare function. Users *can* do such by choosing attributes in the multi-attribute utility model and weights attached to those attributes that are consistent with traditional economic models of social welfare maximization. But it is not limited to that use. For example, vaccine manufacturers can also use SMART Vaccines to measure value from their own viewpoint (including, presumably, corporate profitability) and also to help them understand the values and resultant rankings of their potential customers.
SMART Vaccines creates a large data burden on users, does it not?	To some extent, yes, but if one carefully assesses the data needed to analyze the related issues intelligently, it becomes apparent that the data needs are driven by the intrinsic issue at hand, not the software. The committee has sought to make the best possible use of extant databases that will help SMART Vaccine users simplify the data burden, including, for example, population data (from the World Health Organization) and other data on burden of disease and related issues.
Would not the rankings from SMART Vaccines become useless if, for example, some new treatment emerges for a disease for which a new vaccine is under development?	Yes, but that remains true whether people have used SMART Vaccines or not. It cannot predict the emergence of disruptive technologies. It can readily re-estimate the priority scores in the presence of new information, and all rankings should be re-calculated when conditions surrounding any vaccine's potential use change.
How can you expect decision makers to deal with the complexity of this software program?	In general, the committee believes that high-level decision makers will not in fact have to deal with many facets of the software's complexity. More likely, specialized assistants to decision makers will create or import relevant data and possibly even carry out preliminary analyses using weights specified by the decision maker. The current version of SMART Vaccines provides entry points into the software at appropriate points for each possible type of user, ranging from technical data specialists to final decision makers.

continued

TABLE 1-1
Continued

Stakeholder Question	Committee's Response
How can I interpret what the scores from SMART Vaccines mean?	Each user's particular set of values and weights helps define the scale for the final priority score, so users cannot compare scores from one user to another unless they use the same attributes and endpoints. This is a standard feature of multi-attribute utility models. Some users have found it useful to think about the priority scores in the same way that we think about reports of temperature. In a Fahrenheit scale the difference between 50°F and 70°F (20 degrees) has the same meaning as the difference between 20°F and 40°F. However, in the Fahrenheit scale 40°F is not twice as hot as 20°F. Similarly, on a Celsius scale the difference between 20°C and 30°C (10 degrees) has the same meaning as the difference between 10°C and 20°C, but 20°C is not twice as hot as 10°C. Furthermore, 20°C and 20°F do not have the same meaning. These differences do not make thermometers useless, but they do require an "anchor" to interpret them. With thermometers, we can use standard reference points to help understand what 20°F and 20°C mean. We know that water freezes at 0°C and boils at 100°C, and similarly that water freezes at 32°F and boils at 212°F. Knowing these two pairs of values allows us to make direct comparisons between Fahrenheit and Celsius values, and we can calculate that they have the same meaning at only one temperature—that is, minus 40°C has the same value as minus 40°F.
Who is expected to use SMART Vaccines and why?	Potential users of SMART Vaccines (individually or collaboratively) include decision makers in a wide range of constituencies: federal and private research groups, funders, vaccine manufacturers, purchasers of vaccines, regulators, and nongovernmental groups. SMART Vaccines offers a new framework that could help provide a new standard for decision making among various stakeholders in many circumstances such as decision making under opacity; prioritizing under constrained resources, complexities associated with globalization, economies, and health. Furthermore, changing realities need decision models to be refreshed, which is what this tool offers—a dynamic, living decision-support framework that can be updated as new data, diseases and potential vaccine candidates emerge.

2

Refinements to the SMART Vaccines Model

SMART Vaccines is based on a multi-attribute utility model. The rationale, the structure, and the mechanistic basis of the computational and value submodels were detailed in *Ranking Vaccines: A Prioritization Framework* (IOM, 2012). A brief review is presented here.

A Brief Review of the Modeling Framework

The multi-attribute utility model underpinning SMART Vaccines is able to blend quantitative and user-based qualitative attributes. Priorities for vaccine candidates are then set according to a weighted average of the attributes chosen by the user (Keeney and Raiffa, 1976).

Some attributes are computed quantities, such as the estimated number of deaths averted due to the presence of the new vaccine under consideration. This particular attribute relies on data and expert estimates concerning known or partly known aspects of the epidemiology of the disease and anticipated characteristics of the hypothetical vaccine (e.g., effectiveness, duration of immunity, and coverage or uptake in the population).

Attributes can also be qualitative, involving a "yes" or "no" indication to, for example, represent whether the vaccine benefits infants and children (e.g., perinatal group B streptococcus infection) or adolescent girls (e.g., human papillomavirus infection). Attributes can also be represented by categorical rating scales to capture, for example, the user's best estimate of the likelihood that a targeted vaccine might be financially profitable for

a manufacturer, with a 5 representing highest likelihood and 1 representing least likelihood.

Using each attribute's measure (X_i for the *i*th attribute), a utility scale, $U_i(x_i)$, is formed so that the least desired (worst) level ($X_i=x_i^0$) is scaled as $U_i(x_i^0)=0$ and the most desired (best) level for that attribute ($X_i=x_i^1$) is scaled as $U_i(x_i^1)=100$. In SMART Vaccines the intermediate levels of X_i are scaled linearly relative to these two endpoints.

Each vaccine to be prioritized, V, may be considered as a vector of attributes, $V=(x_1, x_2, ..., x_n)$, where each component of the vector indicates the expected performance of that vaccine on the measure for the particular attribute. This is rescaled into a vector of single attribute utility scales, $V_j=(U_1(x_{1j}), ..., U_n(x_{nj}))$, to represent the vaccine as input to the multi-attribute utility scoring algorithm.

Finally a set of weights, w_i, i=1...n, is specified to represent the relative value from 0 to 100 for each attribute in relation to the others. The weights are then normalized so that their sum is equal to 100, which allows each weight to be interpreted as a percentage of the total weight. The final scoring function is the weighted sum represented as

$$U(V_j)=\sum_{i=1}^{n} w_i U_i(x_{ij})$$

where $U(V_j)$ is the utility score for the vaccine V_j. By scaling the worst and the best levels of each attribute between 0 and 100 and by normalizing the sum of the w_i's to be 1, this score will also range between 0 and 100. In SMART Vaccines this resulting score is labeled the "SMART Score." Vaccines are ranked in priority according to the rank order of their SMART Scores. Figure 2-1 shows a diagram of the SMART Vaccines framework, slightly revised from the 2012 IOM report. Appendix A details the computational model supporting SMART Vaccines.

In the 2012 report, the committee organized 29 stakeholder-informed attributes into eight categories. Following the Phase II deliberations, the committee slightly revised this listing (see Table S-1). In SMART Vaccines 1.0, a choice of 28 attributes spread across eight categories is available to users, with an option of adding up to seven user-defined attributes in a ninth category.

One attribute, the likelihood of successful licensure within the next 10 years, was removed from the original list and instead incorporated as a vaccine characteristic because this attribute works as a multiplier on the overall SMART Score. In the extreme, if there is no chance of licensure, then it does not matter how good the vaccine scores on other attributes—

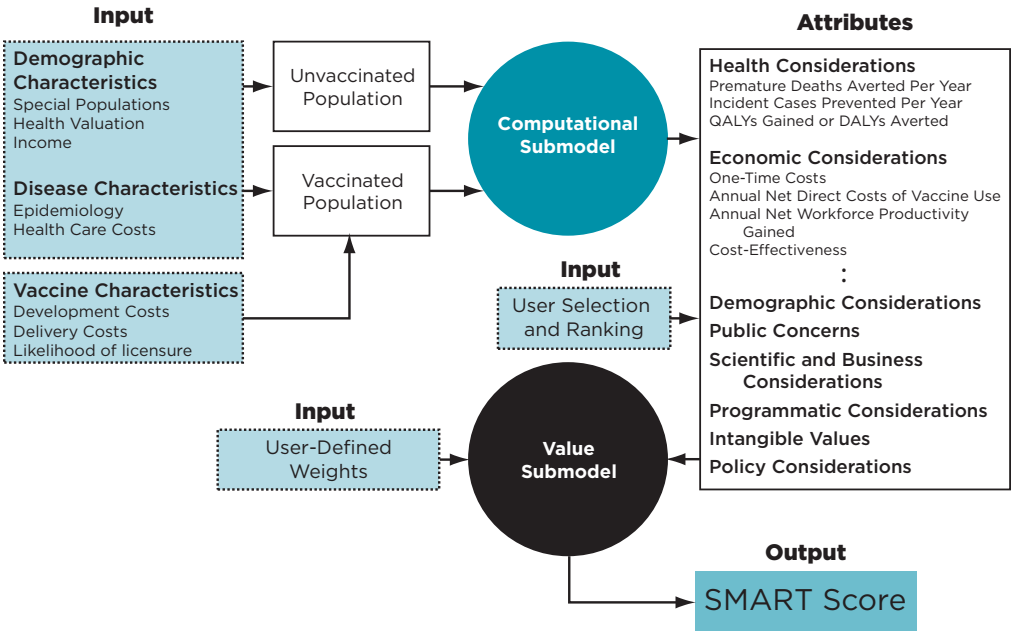

FIGURE 2-1
SMART Vaccines framework showing the computational and value submodels that help produce the SMART Score for various vaccine candidates under consideration.

NOTE: DALYs = disability-adjusted life years; QALYs = quality-adjusted life years.

the overall value should be zero. If there is a 50 percent chance of licensure, then the expected score should be 0.50 times the overall SMART Score. To reflect this multiplicative impact of the licensure attribute, this value is now elicited from the user after the SMART Scores are produced for the vaccines being compared. Thus, if the resulting SMART Score for a specific vaccine candidate is calculated as 70, but the user-defined likelihood of successful licensure of that vaccine over a 10-year period is 50 percent, then the SMART Score is set to 35 to reflect the product of the original score and the probability of licensure. Using this multiplier is optional for the user, but it is helpful for comparative assessment when the probabilities of licensure success differ significantly across vaccine candidates.

SMART Vaccines 1.0 uses the rank-order centroid method (Barron and Barrett, 1996) (detailed in the 2012 report, Chapter 2) to obtain quick initial weights, but the redesigned software interface allows dynamic adjustment of these weights (using slider bars) to obtain a final weighting leading up to the SMART Score. This adjustment process uses the so-called "swing weighting" method, in which the relative effect of an attribute is determined by the effect of changing the attribute level from the worst one to the best one.

Setting Ranges for Attributes: A Heuristic Process

SMART Vaccines is designed for prioritizing a wide but realistic range of vaccine candidates. This led the committee to provide specific design choices of scales for the attributes.

A useful analogy in this context is the task of designing an instrument to measure the weights of a class of objects. To design a useful instrument one needs to know the range of weights that will be measured. A bathroom scale is not useful to weigh the quantities of ingredients normally used for meal recipes in the kitchen, nor is a roadside vehicle scale useful to weigh either these kitchen ingredients or to weigh people. The point is that weight scales are built to accommodate a suitable range of objects.

Similarly, SMART Vaccines has been devised to accommodate the variation expected across a range of different vaccine candidates. For some attributes, two levels—a minimum value at 0 and a maximum value at 100—appear to be sufficient. For others it is difficult to find appropriate reference points. For example, the committee found it challenging to scale the attributes related to health and economic considerations. The reference points described next are a first attempt, which was based on an appraisal of the relevant literature but not on an actual application of SMART Vaccines to the six test vaccine candidates used to assure its current functionality. Future users of SMART Vaccines may wish to revisit the setting of these reference points following cumulative experiences with the software.

Weights and Ranks: Attention to the Ranges of the Attributes

Once the attributes are selected by the user to inform the calculation of SMART Score, they must be weighted. In the 2012 report the committee suggested that the attributes be ranked in order of importance, from most to least important. Then the weights were computed from the user's ordering using the rank order centroid method to approximate ratio scale weights. The process of ranking and weighting has been substantially upgraded in SMART Vaccines 1.0, and it is briefly reviewed in this section.

In the previous section a utility function for the *i*th attribute was scaled between $U_i(x_i^0)=0$ and $U_i(x_i^1)=100$, where x_i^0 and x_i^1 were the worst and best level of attribute *i*, respectively. But the size of the units of these U(x) scales still needs to be set so that the units of one scale, U_i, may be added to those of another scale, U_j. That is, the 100 point on one scale may indicate a much larger distance in units of value from the 0 point on that scale than does the 100 point on another scale.

For example, the English scale of distance uses inches as its unit of distance, while the metric scale uses centimeters. The distance between 0 and 100 inches is not the same as the distance between 0 and 100 centimeters even though they are numerically labeled the same. One inch is approximately 2.54 centimeters, and a scaling factor of 2.54, therefore, must be applied to translate the units from one format to another. In the context of SMART Vaccines, the "distance" measured is not objective, but rather a subjective judgment that reflects the values of the decision maker.

Let us assume, for example, that a user has selected four attributes from among the 28 attributes relating to a U.S. population in SMART Vaccines:

Health Considerations:
Premature deaths averted per year (x^0=0 deaths averted; x^1=14,000 deaths averted)
Economic Considerations:
Cost-effectiveness, $/QALY gained ($x^0$=$203,000/QALY gained; x^1=$0/QALY gained)
Demographic Considerations:
Benefits infants and children (x^0=No; x^1=Yes)
Programmatic Considerations:
Reduces challenges relating to cold-chain requirements (x^0=No—requires refrigeration; x^1=Yes—thermostable)

If all four of these attributes score at level x^0, the vaccine candidate will receive a SMART Score of zero (on a scale of 0 to 100), irrespective of the weights, because all four $U_i(x_i)$ components of the score would be zero. This low-achieving vaccine defines zero on the SMART Score scale. Its opposite, with all four attributes at level x^1—that is, a vaccine that has the potential to avert 14,000 premature deaths per year, has net incremental costs of $0 per QALY gained, is targeted to the primary benefit of infants and children, and is thermostable—would achieve a SMART score of 100 and defines the highest value possible on the SMART Score.

At this stage the user is asked, in essence, "If you currently had a vaccine candidate which had all attributes at the x^0 level, and you could change one and only one attribute to the x^1 level, which attribute would you choose?" This question identifies that attribute for which the most value is achieved by this change, and this attribute is ranked as most important. Suppose the user chooses "Deaths averted per year." This implies that the change from x^0=0 deaths to x^1=14,000 deaths per year is valued most highly by the user among all such changes among the attributes. This attribute is

TABLE 2-1

Attribute Ranking and Weights for a Hypothetical User Scenario

Attribute	Rank	Preliminary Weight from the Rank Order Centroid Method
Premature deaths averted per year	1	52.1%
Benefits infants and children	2	27.1%
Cost-effectiveness ($/QALY)	3	14.6%
Reduces challenges relating to cold-chain requirements	4	6.3%

NOTE: QALY = quality-adjusted life year.

thus ranked as the most important. Correspondingly, when asked for the least important attribute to be changed from x^0 to x^1 level, if the user picks, "Reduces challenges relating to cold-chain requirements," and then this attribute is valued least by the user.

Finally, after having decided on the most important and least important attributes, the user ranks the remaining attributes. If the user ranks "Benefits infants and children" at 2 and "Cost-effectiveness" at 3, then SMART Vaccines assigns preliminary weights to the four attributes using the rank order centroid method as shown in Table 2-1.

The rank order centroid method calculates the geometric average of all possible combinations of weights that are consistent with the rank ordering chosen by the user and normalizing the weights so that they sum to 100 percent (Barron and Barrett, 1996; Edwards and Barron, 1994).

In the Phase I work that produced SMART Vaccines Beta, the rank order centroid approximation resulted in the final weights. In Phase II, however, the user is allowed to use the ranked weights as a starting point and then to adjust the relative weights for the four attributes using slider bars and see the changes reflected in the SMART Score of the vaccine. These adjustments should be done so that the magnitude of the weights reflects the relative importance of changing an attribute from its worst to its best level. In parallel, the graphical changes resulting from slider bar adjustments are a visual representation of the relative distance in value from the x^0 to x^1 levels on the attributes. This feature also permits real-time sensitivity analysis in SMART Vaccines 1.0.

Now suppose that having obtained the rank order centroid outputs, the user chooses to alter the weights using slider bars for the specific attributes under consideration to 60 percent (premature deaths averted per year), 18 percent (benefits infants and children), 18 percent (cost-effectiveness), and 4 percent (reduces challenges relating to cold-chain requirements). Let V be a candidate vaccine whose levels are now $x_1 = 3{,}000$

deaths averted per year, x_2 = primary benefit to infants and children; x_3 = –$30,000/QALY gained; and x_4 = requires refrigeration. The final SMART Score is then numerically calculated as follows:

$$SMART\ Score(V) = 0.6U_1(3000 \text{ deaths averted per year}) + 0.18U_2(\text{benefits infants and children}) + 0.18U_3(-30000\ \$/QALY) + 0.04U_4(\text{requires refrigeration})$$

$$SMART\ Score(V) = 0.6 \cdot \frac{3000-0}{14000-0} \cdot 100 + 0.18 \cdot 100 + 0.18 \cdot \frac{-30000-203000}{0-203000} \cdot 100 + 0.04 \cdot 0$$

$$SMART\ Score(V) = 1.29 + 18 + 20.7 + 0$$

$$SMART\ Score(V) = 40.0$$

The output indicates that the candidate vaccine is approximately 40 percent of the distance "up" from a vaccine that is scored 0 toward a vaccine that is scored 100.

Comparison of SMART Scores

Given the intrinsic variability in SMART Scores from user to user, how can the ranks then be compared in a user group? While some comparisons can be made, nothing guarantees the ability to map user A's scores to those of users B, C, and D. The committee has used the analogy of Fahrenheit and Celsius thermometers to assist users in understanding what the SMART Scores mean (and what they do not mean), but the choices of parameter settings in the software may create further complexity in multi-user group settings.

All multi-attribute utility models—including SMART Vaccines—have the characteristic that a difference of, say, 10 points for user A has the same meaning all along user A's scale, so it is correct to say that the difference between 20 and 10 has the same meaning as the difference between 80 and 70. But one cannot say that "20 is twice as good as 10" any more than one can say that "20°F is twice as warm as 10°F." It is also correct to say that a 10-point difference on user A's scale is not the same as a difference of 10 points on user B's scale, just as with the thermometer analogy: A difference of 10 degrees is not the same in Fahrenheit and Celsius scales.

Unfortunately, the analogy becomes less useful when users A and B have employed a different set of attributes for their valuation. To the extent that they have commonly chosen attributes (e.g., premature deaths averted per year, cost-effectiveness, or potential to improve delivery methods), then the weights they have placed on these attributes lead to predictable changes in each user's SMART Scores. If they have no common attributes in their respective value models, then it is not possible to compare one user's SMART Scores (and hence rankings) to those of another user.

This issue is closely related to Arrow's impossibility theorem—after economist Kenneth Arrow—in the realm of social choice theory (Arrow, 1950, 1963). Arrow sought to understand the conditions under which voting rules could be devised that would translate individual voter's rankings of various alternatives into a global "community" ranking. He famously demonstrated that, subject to certain "fairness conditions," no voting system can transform the ranked preferences of individuals into a society-wide ranking

Similarly, in the context of SMART Vaccines, individual SMART Scores cannot be lumped into a society-wide SMART Score by any voting system. This is not a defect of the SMART Vaccines system per se, but rather it is intrinsic to all ranking systems when people (voters) have different preference structures.

Arrow's impossibility theorem and the mechanism to interpret SMART Scores come from the same basic source: different people value different things differently. The priorities that drive user A to prefer different vaccine attributes may be similar to those of users B, C, and D, or they may be completely different. This does not mean that SMART Vaccines is not effective in establishing ranking lists for new preventive vaccines. Quite to the contrary, SMART Vaccines makes clear what assumptions users have made about vaccine attributes and how they value each candidate vaccine's attributes.

In the following chapter, the approaches taken to expand the test vaccine candidates and evaluate them using SMART Vaccines 1.0 are discussed.

3

Data Synthesis, Software Redesign, and Evaluation

The data collection and the software programming for SMART Vaccines proceeded simultaneously, and both were informed by feedback from various stakeholders. The committee chose to retain the United States and South Africa, the test countries selected for Phase I of the SMART Vaccines development, for use in Phase II. These two countries not only have different income, health, and demographic profiles, but they also have different social and economic priorities for developing and delivering new vaccines. South Africa was chosen, in part, because data were available from that country with which to test the vaccine candidates selected in both Phase I and Phase II. The early part of this chapter is devoted to describing the committee's data synthesis efforts and the latter part toward describing the software prototyping efforts.

Selection of Vaccine Candidates

In Phase I the committee selected influenza, tuberculosis, and group B streptococcus as test vaccine candidates for the United States, and tuberculosis as a test vaccine candidate for South Africa. Supporting data for these candidates are presented in an appendix of the 2012 Institute of Medicine (IOM) report.

The committee was tasked to test three additional vaccine candidates in Phase II. The committee members began with a list of hypothetical vaccine candidates for seven infectious agents: cholera, dengue, human immunodeficiency virus, human papillomavirus, rotavirus, pneumococcal

infection, and malaria. The committee chose human papillomavirus, rotavirus, and pneumococcal infection as the test cases for evaluation; licensed vaccines currently exist for the causative agents of each of these three diseases.

The purpose of including these candidate vaccines in SMART Vaccines was to demonstrate the functionality of the software. Each vaccine candidate offers a scenario that may arise in the process of developing and delivering a new preventive vaccine. These scenarios may include decision points that arise in the development and distribution of a vaccine that is aimed at a particular disease and that has certain intended health and economic benefits.

Because vaccines for human papillomavirus, rotavirus, and pneumococcal infection currently exist, the committee considered their inclusion in the model as providing test examples of the process one goes through in developing improved vaccines by such methods as including adjuvants, increasing effectiveness, or reducing doses. Another reason for the selection of these three particular vaccines is that each targeted disease affects a different population and has different health implications: Human papillomavirus infects sexually active individuals and can lead to anal or cervical cancer over time; rotavirus affects children, and this burden is greater in low-income countries; pneumococcal disease is known to affect young children and the elderly population worldwide.

Disease profiles for these three diseases as well as for the diseases targeted by the vaccine candidates evaluated by the Phase I committee—influenza, tuberculosis, and group B streptococcus—are provided in Appendix B. A snapshot of the data needs for SMART Vaccines is presented in Table 3-1. Due to time constraints in the Phase I study, data for South Africa were collected only for tuberculosis; for the United States, data for influenza, tuberculosis, and group B streptococcus were collected.

In this study, the data for human papillomavirus, pneumococcal infection, and rotavirus were collected for both the United States and South Africa. Thus, a total of six datasets for the United States and four for South Africa are available as downloadable spreadsheets (along with the SMART Vaccines software package) on the Institute of Medicine and the National Academies Press websites. Data sources for the necessary parameters are provided in the spreadsheets along with explanatory notes and references. For ease of use, SMART Vaccines 1.0 contains these datasets pre-populated as defaults.

TABLE 3-1

A Snapshot of Data Required for SMART Vaccines 1.0

Parameter	Data Available in the Public Domain	Data Requiring User Estimation
Demographics	• Life Tables[a] • Standard Life Expectancy[a]	• Health Utility Index 2 • Hourly Wage Rate
Disease Burden	• Incidence • Case Fatality Rate	
Disease Morbidity	• Disutility (Tolls)[b] • Disability Weights[b] • Duration[b]	• Percent of Cases • Costs (Hospital, Outpatient, Medication)[b]
Vaccine Characteristics	• Target Population[a] • Coverage • Effectiveness • Length of Immunity • Doses Required per Person	• Herd Immunity • Time to Adoption • Cost per Dose • Administration Cost • Research and Development Costs • Licensure Costs • One-Time (Start-Up) Costs

[a] Standard data irrespective of the vaccine candidates.

[b] Requires case-by-case judgment and modification for specific vaccine complications or morbidity.

Data Sourcing and Quality

The data gathered by the committee are by no means the best or the most detailed estimates for each disease. They are neither precise projections nor comprehensive analyses. For example, there are data available on the burden of influenza and on the impact of seasonal influenza vaccines in the United States, but because there are no currently licensed vaccines for group B streptococcus, the only data available from the United States for that disease concern the disease burden, with nothing on the impact of a vaccine if it were licensed; thus, the vaccine information for group B streptococcus is largely hypothetical. In fact, much of the information required for SMART Vaccines, especially the information related to the use of the vaccines in low-income countries, was based on the opinions of the committee members.

A significant concern regarding the committee's data analysis was the variability and the lack of standardization in surveillance methods. While data may be widely available for certain parameters, the committee thought it important to use only those data that had been collected using standard, comparable methodologies. To ensure the quality of the data, public sources such as peer-reviewed literature, the World Health Orga-

nization, the Centers for the Disease Control and Prevention, and publications of national health agencies were used as often as possible. Data sourcing and methodology are discussed in Appendix C.

Development of a Test Model to Inform Software Redesign

In Phase II, as part of the model enhancements, the committee developed a spreadsheet prototype to illustrate the possibilities of a dynamic weight-adjustment tool and to show how real-time graphical changes could facilitate the user's prioritization process. Figure 3-1 shows an early prototype interface that allowed the user to rank selected values. This interface served as an evolving "test bench" prototype that the committee used to make changes and to incorporate stakeholder feedback obtained during the public presentations. In short, the spreadsheet in the screenshot is an experimental draft shown in order to illustrate the committee's back-end work as SMART Vaccines 1.0 underwent interface redesign.

This prototype spreadsheet allowed the committee members to select up to 10 attributes, with pop-up boxes featuring quick definitions. In Figure 3-1, for example, nine attributes have been chosen (indicated by check marks in the left-hand column). Those nine attributes are ranked from 1 to 9 (in the second column). The most important attribute is ranked 1, and the least important is ranked 9. The fourth column (in yellow) shows the weights as calculated by the rank order centroid method. The slider bars in the third column (labeled "fine adjustment") allow users to adjust the computed weights. This feature illustrates the committee's early efforts to provide users with an option to carry out intuitive sensitivity analyses without needing to understand the details of the multi-attribute utility model.

The attributes shown in Column 5 are collected into groups, each with a colored heading—purple for "health considerations," maroon for "economic considerations," yellow for "demographic considerations," dark blue for "intangible values," and so on. These same colors appear in the bar graph at the lower right corner of the screen that shows the calculated SMART Scores for five hypothetical candidate vaccines: an influenza vaccine with 1-year efficacy, an influenza vaccine with 10-year efficacy, a group B streptococcus vaccine costing $100 per dose, a group B streptococcus vaccine priced at $50 per dose, and a tuberculosis vaccine that does not achieve any herd immunity. Each vaccine bar is divided into colored sections showing how much each of the nine attribute categories adds to the SMART Score for that vaccine.

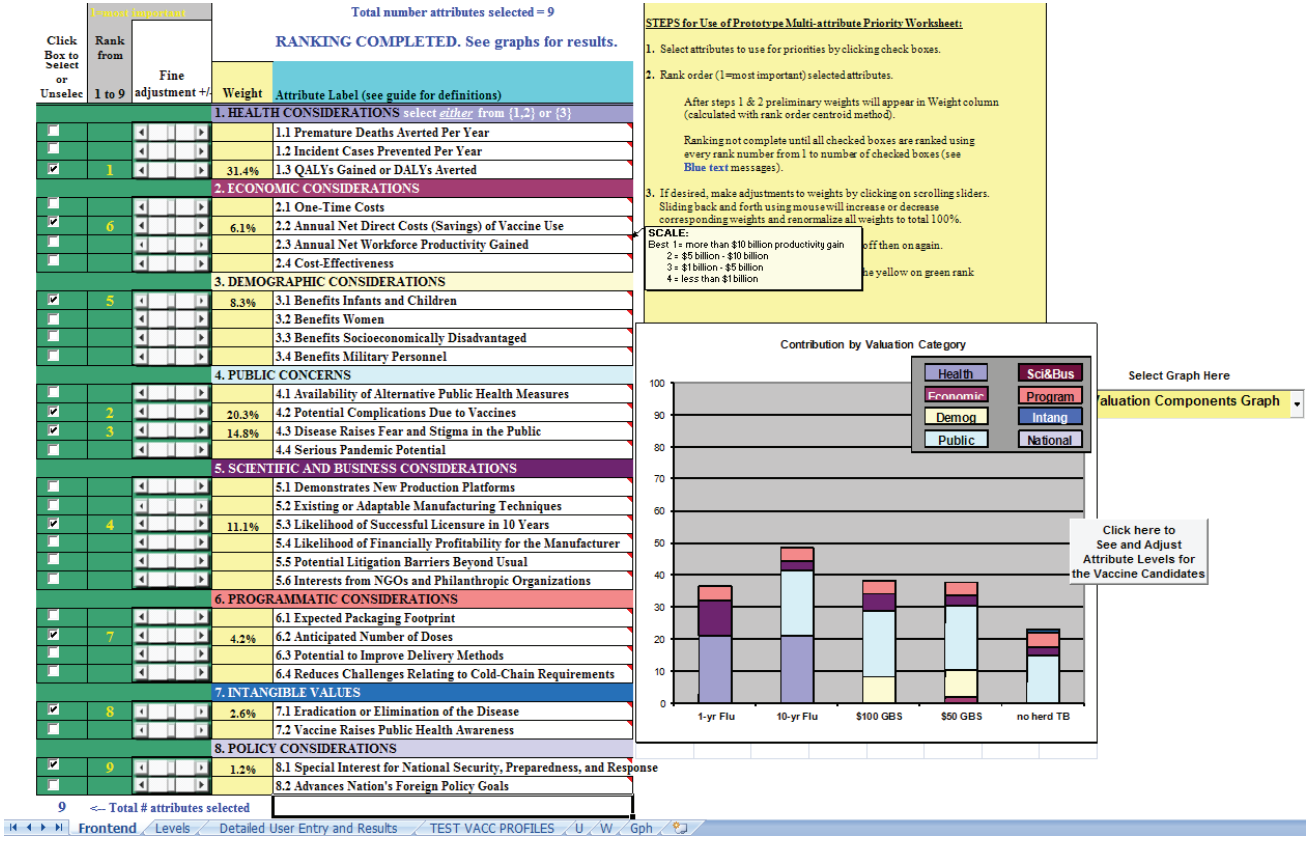

FIGURE 3-1
An early experimental prototype developed for committee use. This prototype was adjusted based on feedback obtained from stakeholders after the public presentations made by committee members. This spreadsheet design informed the subsequent redesign of SMART Vaccines in a MATLAB platform.

As users change the ranking and then fine tune the weights for each chosen attribute, the heights of the bars for each candidate vaccine adjust automatically. Thus, users can interactively see the effect of altering their weights immediately—by making changes to the rank order, or by fine tuning of the weights calculated by the rank order centroid method as part of the sensitivity analysis.

Interface Redesign for SMART Vaccines 1.0

In Phase I the blueprint of SMART Vaccines Beta was developed using three software tools: MATLAB for the algorithm, Java servlets for the middleware, and Axure for visual interface design, with Microsoft SQL Server used for preliminary database management. Stakeholder feedback made it clear that SMART Vaccines needed to be developed in a simpler, platform-independent fashion to aid the end users. Therefore, the committee elected to use MATLAB as the sole programming platform for developing, testing, and producing a downloadable and executable package for SMART Vaccines 1.0. This choice was made easier by enhancements to MATLAB that allowed it to be used both for implementation of the model and for the creation of a dynamic, cross-platform user interface. Data can be directly entered or imported from spreadsheets into SMART Vaccines for application and storage.

To illustrate the current operational features of SMART Vaccines 1.0, this section includes a step-by-step screenshot tour. SMART Vaccines 1.0 is substantially different from the SMART Vaccines Beta presented in the 2012 report (IOM, 2012). The committee appreciated how direct data entry using the previous software interface format could be burdensome to the user, and hence it spent substantial efforts to simplify data entry with the goal of making it more efficient and intuitive.

Figure 3-2 shows the welcome screen of SMART Vaccines 1.0. Here, users are presented with the disclaimer that stresses that SMART Vaccines is a decision-support system and not a decision making tool.

By clicking on the radio buttons (selectable circles) at the top, the user can select what to enter and how to use the program. Relevant screens appear when the user selects any of the "Specify" or "Evaluate" buttons. For instance, by selecting "Attributes" the user is taken to a screen where each vaccine candidate's attributes are chosen; selecting "Weights" takes the user to a screen where attributes are ranked and weighted; and selecting "Priorities" allows the user to observe the priority rankings calculated by SMART Vaccines once all of the relevant data entry has been completed. The user has the option either to proceed linearly through the program

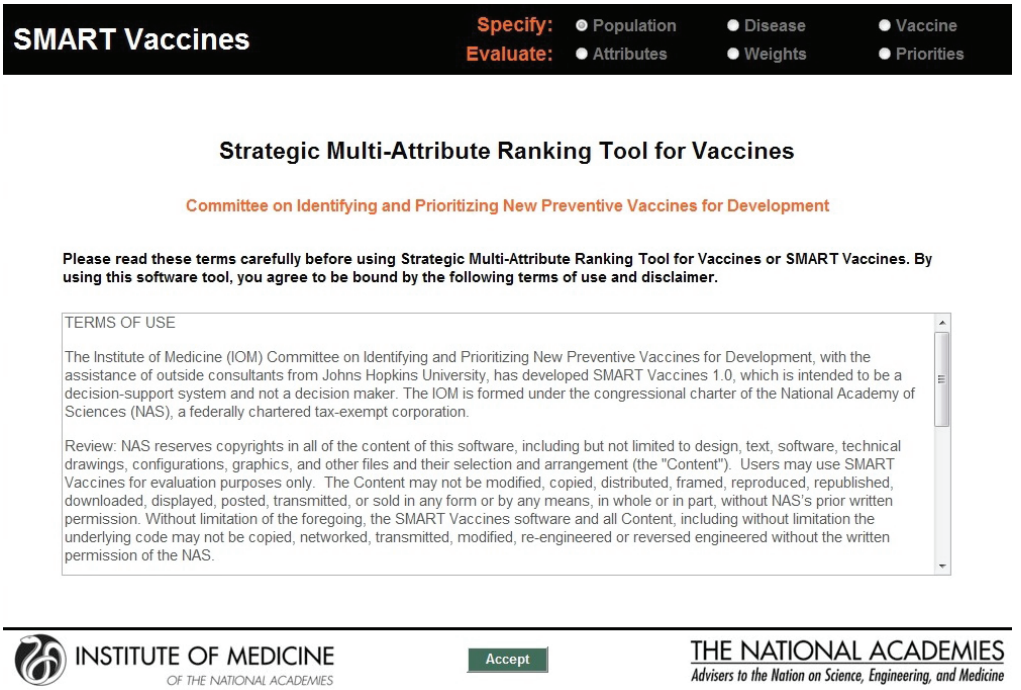

FIGURE 3-2
Welcome page presenting the terms of agreement and disclaimer. SMART Vaccines 1.0 was developed on a MATLAB platform with a redesigned user interface.

using the "Continue" buttons or to skip to certain sections, thereby making possible a division of labor among data collection, attribute selection, and weighting.

The next screenshot (see Figure 3-3) shows a typical data page—in this instance, demographic data for females in the United States that can be specified using a pull-down menu. As noted earlier, the basic population data can normally be taken directly from institutions that maintain various databases, such as the World Health Organization.

For infants, for children from 1 through 4 years of age, and then for each 5-year age group after that (5 through 9, 10 through 14, and so on), SMART Vaccines requires the number of persons in each age group, the number living at the end of the period, the life years that the group members are expected to have, their life expectancy, and a standard life expectancy used in calculating disability-adjusted life years (DALYs).

The health utilities index (HUI2) provides the quality adjustment for a typical person in each age category, which is used in calculating quality-adjusted life years (QALYs). Finally, the hourly wage rate (converted to U.S.

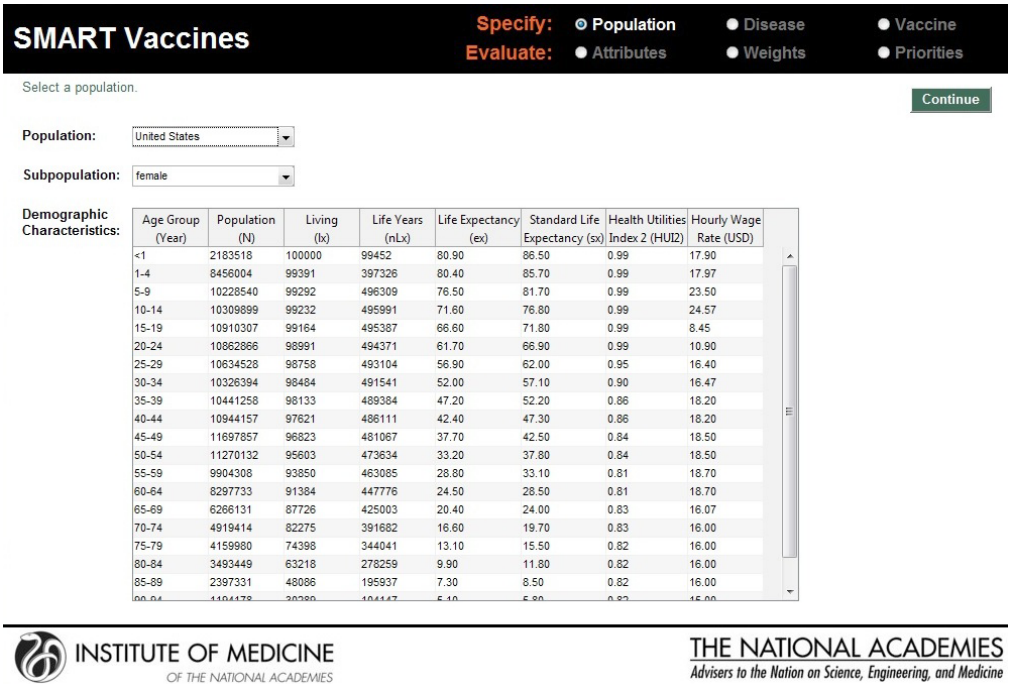

FIGURE 3-3
SMART Vaccines 1.0 screen where the user specifies the population information (by age and sex) to be used for ranking vaccines.

dollars) gives a simple estimate of the value of time lost to illness for this population.

In the screenshot shown in Figure 3-4, the user defines the characteristics of the disease for which candidate vaccines might be targeted. SMART Vaccines treats the disease characteristics separately from vaccine attributes, because the user may wish to consider a number of different vaccines that might apply against the same disease.

In the example shown in Figure 3-4, the first block of data describes the disease impact on the relevant population (in this case, females in the United States), categorized by age group, but in less refined groupings than the actual population data. This approach is intended to reduce user burden in data entry, reflecting the many cases where more refined disease burden data may not be available. The population data include the number of people in each age group (calculated automatically from the population data if entered previously), the annual incidence per 100,000 people, and the case fatality rate (probability of death, conditional upon contracting the disease).

The second block of data on this page shows the disease burden,

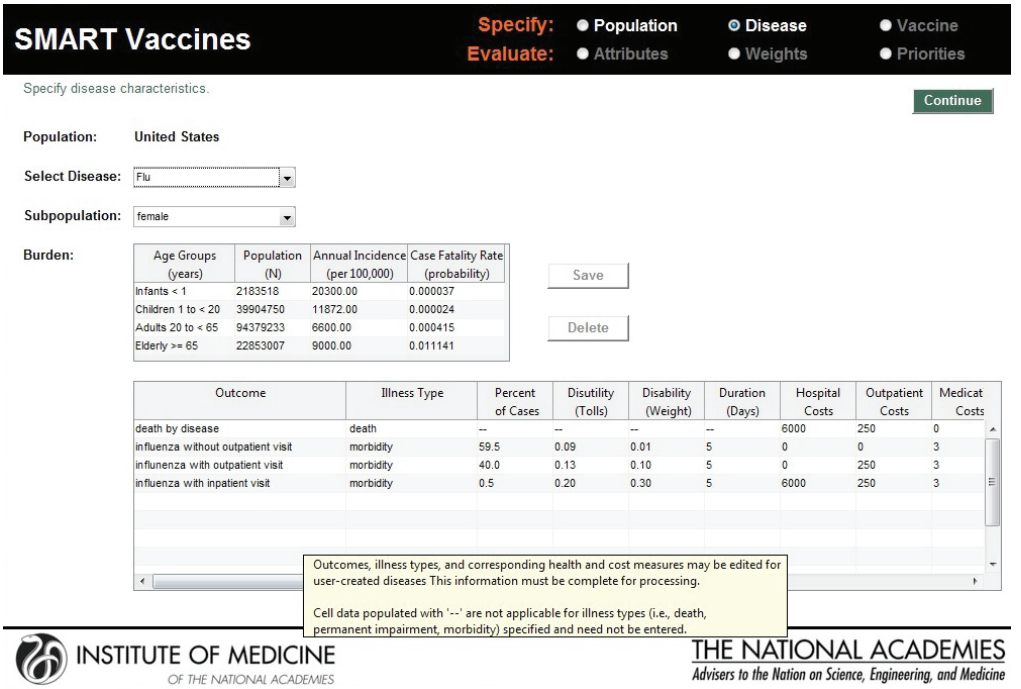

FIGURE 3-4
SMART Vaccines 1.0 screen where the user defines the burden of the selected disease, including morbidity scenarios and quality-of-life scores. Mouse-over pop-ups guide the user with additional information on the parameters.

breaking the cases down into categories of severity, including death, and categories of required treatment (without outpatient treatment, with outpatient treatment, and with inpatient hospital care). For each of these categories the user must enter the costs of providing each type of treatment (hospital costs, outpatient costs, medication costs, and other costs) as well as the disease duration and the disability tolls (for DALYs) or weight (for QALYs).

The user then enters vaccine characteristics—a central component of the priority-setting process—in the screen shown in Figure 3-5. In this example, which involves information concerning an influenza vaccine for the U.S. female population, separated into several age groups, the user specifies (using check marks) which age groups might appropriately receive the vaccine, the percent receiving the vaccination (coverage), and the effectiveness of the vaccine. It also provides the option of making herd immunity present or absent by using a check box.

The second block on this screen requires data about the vaccine candidate itself—the duration of immunity conferred, the time to adop-

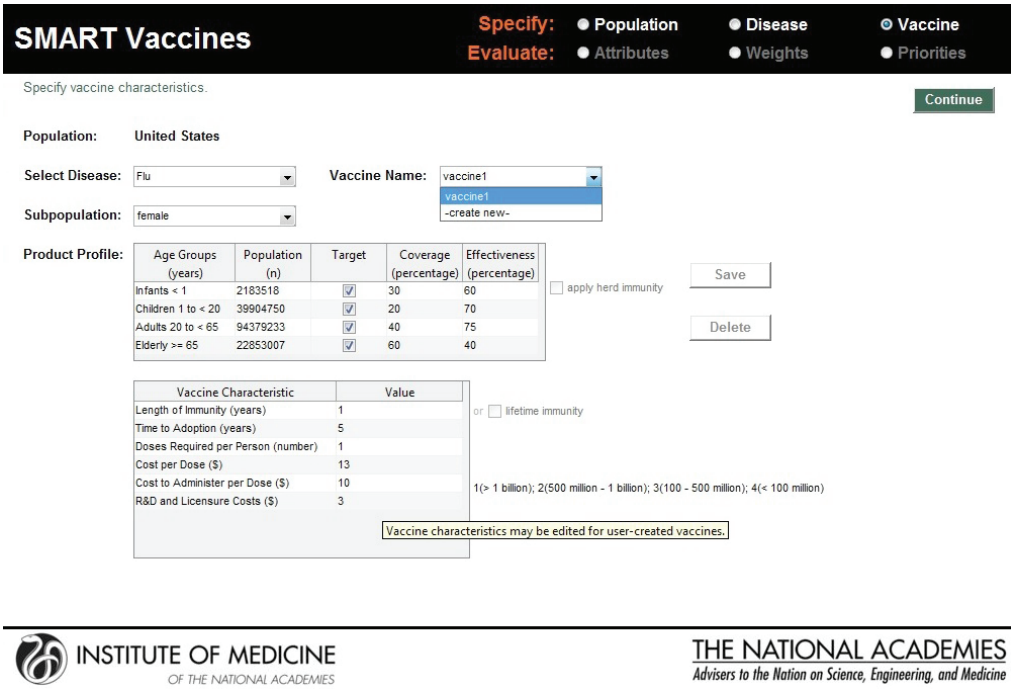

FIGURE 3-5
SMART Vaccines 1.0 screen where the user enters such information as the product profile characteristics and other characteristics related to the vaccines being ranked.

tion, doses required, cost per dose, administration cost, and estimates of research and development cost, licensure cost, and one-time start-up costs.

In the next step, the user selects the vaccine attributes of interest. The attributes selected and the weights attached to them apply to every candidate vaccine (see Figure 3-6). In SMART Vaccines 1.0, the user can click a radio button for any category to bring up the list of attributes within that group. Using a check box, the user can then select the attributes that will be entered into the analysis.

In this screenshot the set of attributes in the category "Health Considerations" is shown, and the user has selected "Incident cases prevented per year" and "Quality-adjusted life years gained." In the subsequent screenshot (see Figure 3-7), the selection of attributes in the category "Scientific and Business Considerations" is shown. The user has selected "Likelihood of financial profitability for the manufacturer," "Demonstrates new production platforms," and "Interest from NGOs and philanthropic organizations." This set of attributes might be chosen by, say, a vaccine manufacturer, whereas a different user might select a completely different set. Figure 3-8 shows the empty fields in which users can enter user-

FIGURE 3-6
SMART Vaccines 1.0 attribute selection page that permits the user to select and subsequently rank the attributes of importance listed in nine categories from health to policy, including up to seven user defined attributes.

defined attributes. Currently, SMART Vaccines 1.0 can only handle binary options for user-defined attributes—that is, any attribute defined by the user is answered with either yes or no.

The next screen (see Figure 3-9) appears in the form of a ranking dashboard and shows the attributes selected by this hypothetical user from all of the categories (note the color coding). The user assigns a rank to each of the seven chosen attributes. The weights calculated by the rank order centroid method appear in the bar chart on the right, with the greatest weight being applied to the attribute with the highest ranking.

As with the prototype discussed earlier, the slider bars allow the user to modify these preliminary weights (calculated by the rank order centroid method) up and down (see Figure 3-10), and SMART Vaccines automatically recalculates the weights on other attributes so that the weights continue to sum to 100 percent (a requirement of the multi-attribute utility model). More radical changes in weights can be accomplished by altering the rankings altogether. In this example, the user has increased the weights placed on "Likelihood of financial profitability for the manufacturer" from 4 percent in Figure 3-9 to 31 percent in Figure 3-10, thus making this the

FIGURE 3-7
SMART Vaccines 1.0 attribute selection page, continued.

attribute with the highest rank. The weight on "Incident cases prevented per year" has been decreased from 37 percent to 20 percent, making it the second highest ranking attribute. Other attributes' weights have been automatically adjusted so that the final sum of the weight's percentages is 100.

This screen also informs the user of the range of outcomes built into the SMART Vaccines. For example, for the attribute "Incident cases prevented per year," the least favorable outcome is 0 (i.e., the vaccine has no effect on preventing the disease incidence), while the most favorable outcome is 100,000.

Furthermore, in SMART Vaccines 1.0 any sensitivity analysis conducted on vaccine attributes, disease burden, and utility-function weights is a one-way sensitivity analysis allowing the user to alter one set of numbers (e.g., the weights). The resulting SMART Scores are conditional on the specific numbers assigned for the vaccine attributes and disease burden (additional information can be found in Appendix D). Similarly, once the weights are set, the user can conduct a sensitivity analysis on the characteristics of a potential vaccine (recalling that the vaccine characteristics are unknown before the vaccine exists), but in this case the sensitivity analysis hinges on the weights assigned to each attribute. Thus, a sensitivity analysis in which the characteristics of a potential new vaccine were altered

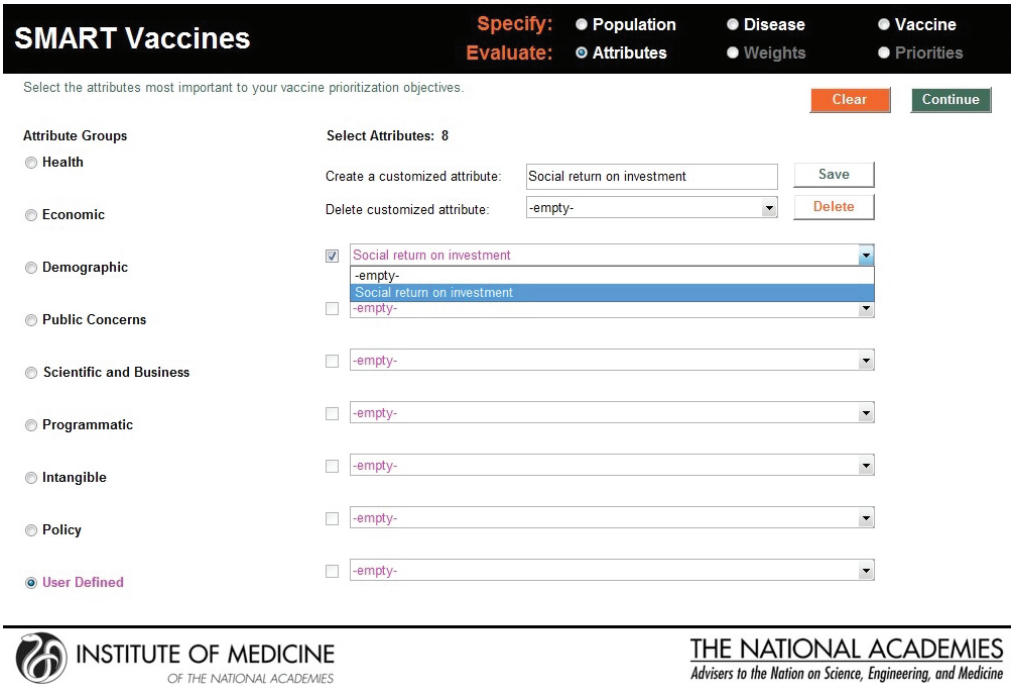

FIGURE 3-8
User-defined attributes permit inclusion of up to seven new qualitative attributes that can be answered with a yes or a no response.

using the utility weights assigned by user A will give different results from an identical sensitivity analysis in which the vaccine characteristics of a potential new vaccine were altered using the utility weights assigned by user B.

In the final output screen (see Figure 3-11), the user-selected attributes are listed on the far left side, with color coding to indicate their attribute category. The user is provided an option to compare multiple vaccine candidates using the horizontal pull-down menus for the population originally selected. The computed values appear automatically for each of the vaccine candidates that are selected, with scoring indicated in parenthesis.

The categorical values that require the user's judgments include pull-down menu options with selections ranging from Yes or No to Level 1 through Level 5. As soon as the selections are made, a bar graphical representation of SMART Scores appears on the right hand side (see Figure 3-12).

In the screen shown in Figure 3-12, a hypothetical influenza vaccine has the highest score (75) in the comparison pool, while the human papillomavirus vaccine has the lowest score (25), based on the user's preference structure. The resulting SMART Scores are color coded to indicate

FIGURE 3-9
SMART Vaccines ranking dashboard showing initial weights produced by the rank order centroid method. The dynamically adjustable rank order centroid weights (presented as graphs) can be adjusted up or down using slider bars. Alteration of weights and ranks are permitted for the user to conduct "What if?" analyses.

the weight of the user-selected attributes on the final output. In this case the health-related attributes (dark blue) received the highest priority from this user, while the attributes related to vaccine's capacity to create new production platforms (violet) received the lowest priority.

The SMART Score is also normalized for the entire population even though the initial population specifications were stratified by sex to reflect the differences in life expectancy, quality of life, and the variation of disease effects in males and females. The computational submodel calculates health and economic measures for both sexes as an aggregate. Thus, the user can interpret and compare the SMART Scores among two or more candidate vaccines for the total population.

The user is allowed to carry out real-time sensitivity analysis by making changes to three key components of the SMART Score that rely on user input—the utility weights, the vaccine characteristics, and the disease burden data. The user can also make changes to the weights that are pre-applied and see instantaneous shifts in the SMART Scores on different screens (see Figures 3-13, 3-14, and 3-15).

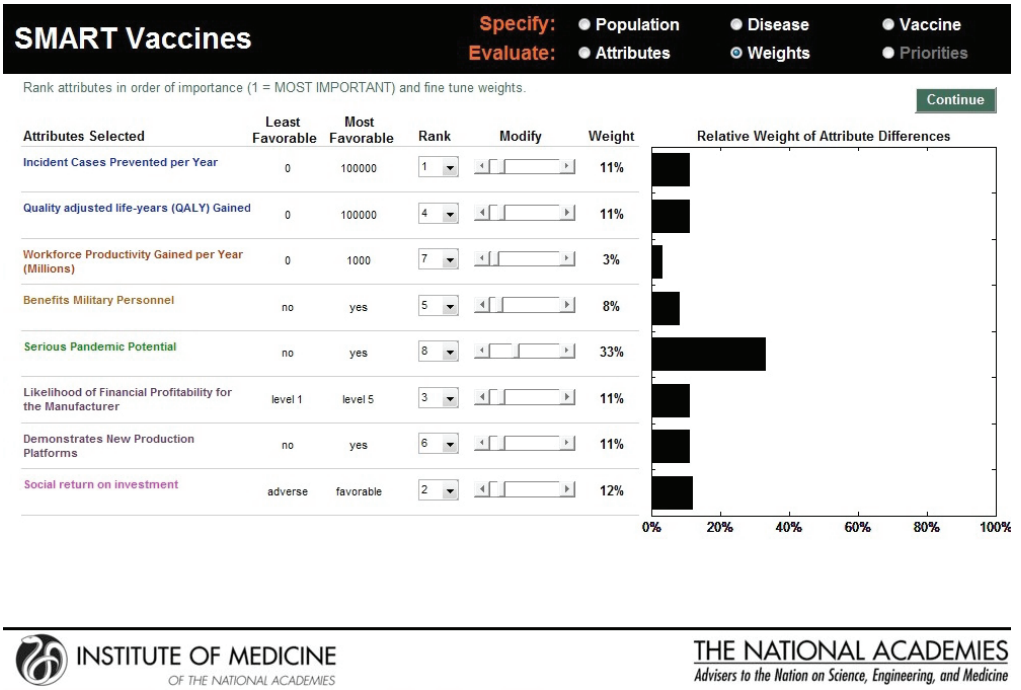

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FIGURE 3-10
SMART Vaccines ranking dashboard showing the dynamically adjustable rank order centroid weights (presented as graphs) using slider bars. The alteration of weights and ranks is permitted for the user to be able to conduct "What if?" analyses.

In SMART Vaccines 1.0, sensitivity analysis is limited to one-way analysis only, but the user can construct two-way or higher analysis by conducting a series of one-way analyses with different values for the second variable under consideration. The output screen for SMART Vaccines 1.0 was significantly redesigned from the version presented in the Phase I report in response to stakeholder feedback.

Representative Use Case Scenarios

The committee then developed hypothetical case scenarios to illustrate the potential use of SMART Vaccines in different settings and from different perspectives. Two such scenarios are discussed in this section, with each scenario involving the perspectives of two users with different attribute and ranking structures. Rank order centroid weights are used in all the scenarios as an illustration, although, as noted earlier, it is possible to adjust the weights with the slider bars in accordance to the user's preferences.

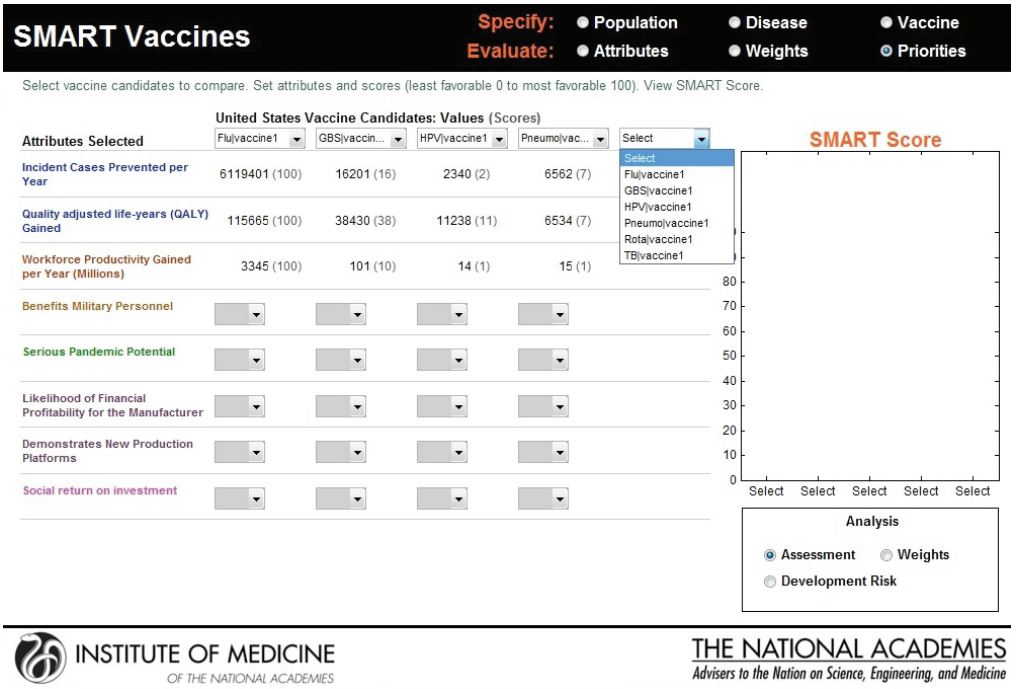

FIGURE 3-11
Output screen for SMART Vaccines. Computational values are instantaneously produced for each of the vaccines under comparison, which can be selected by pull-down menus.

Users with Different Attributes and Different Ranking Systems for Two New Vaccines

Hypothetical user A is a federal agency director in the United States interested in evaluating two new vaccine candidates: a preventive vaccine for human papillomavirus and an influenza vaccine. He sets his value preference with highest ranks for health burden reduction, through the measures of premature deaths averted per year (weighted at 34 percent) and incident cases prevented per year (weighted at 21 percent), followed by economic and other attributes. Figure 3-16 shows the attributes selected, their ranks, and the rank order centroid weights. In Figure 3-17, the selected attributes are combined to produce SMART Scores of 50 for a new human papillomavirus and of 64 for a new influenza vaccine that are based on user A's preference structure.

Hypothetical user B, also from the United States, is a senior executive in a major pharmaceutical firm. She is interested in the prioritization of a new human papillomavirus vaccine versus an influenza vaccine. Figure 3-18 shows that she has ranked the likelihood of financial profitability for her company as her top prioritiy, while the last rank is assigned to

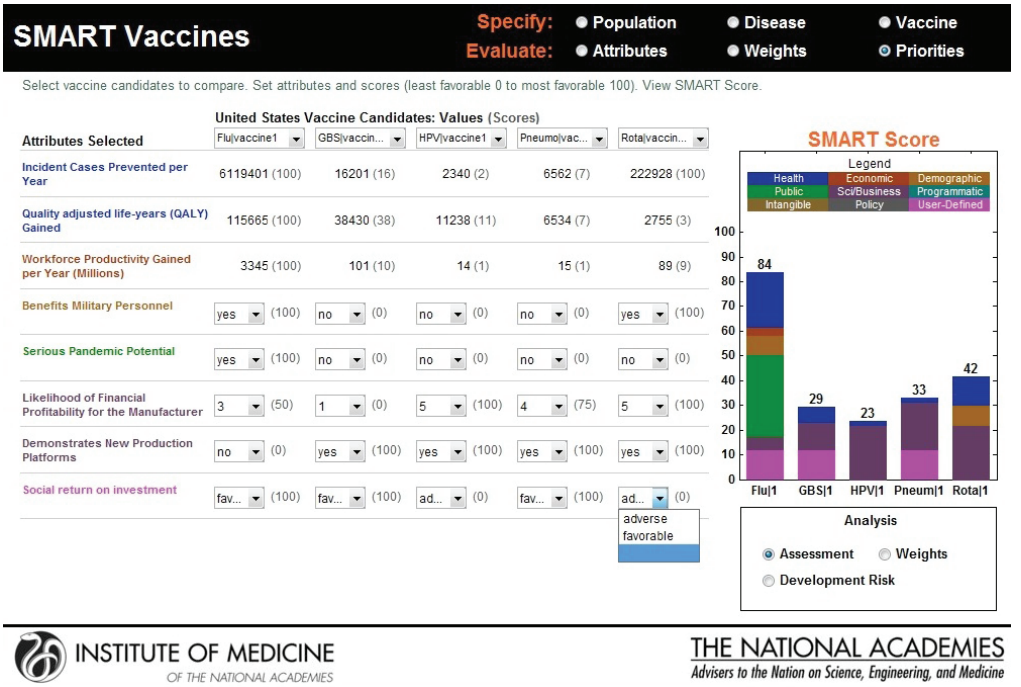

FIGURE 3-12
Output screen for SMART Vaccines. Qualitative values are combined with the computed values to produce a color-coded bar graph showing the SMART Scores for the vaccines under comparison. Real-time sensitivity analysis is possible through the user's adjustment of values, disease and vaccine characteristics, and weights.

reducing challenges relating to cold-chain requirements. Figure 3-19 indicates SMART Scores of 88 for a new human papillomavirus and of 65 for a new influenza vaccine that are based on user B's selected attributes. This scenario demonstrates how user A and user B selected and ranked different attributes in their prioritizations of identical new vaccine candidates and obtained different results. According to user A's attribute and ranking structure, influenza vaccine is a better candidate, while user B's preferences identify human papillomavirus as the best investment option for her company.

Users with Same Attributes But Different Ranking Systems for Two New Vaccines

As an extension to the above scenario, but in a different context—South Africa—suppose that user X (a hypothetical health minister) and user Y (a hypothetical finance and trade minister) are interested in comparing two

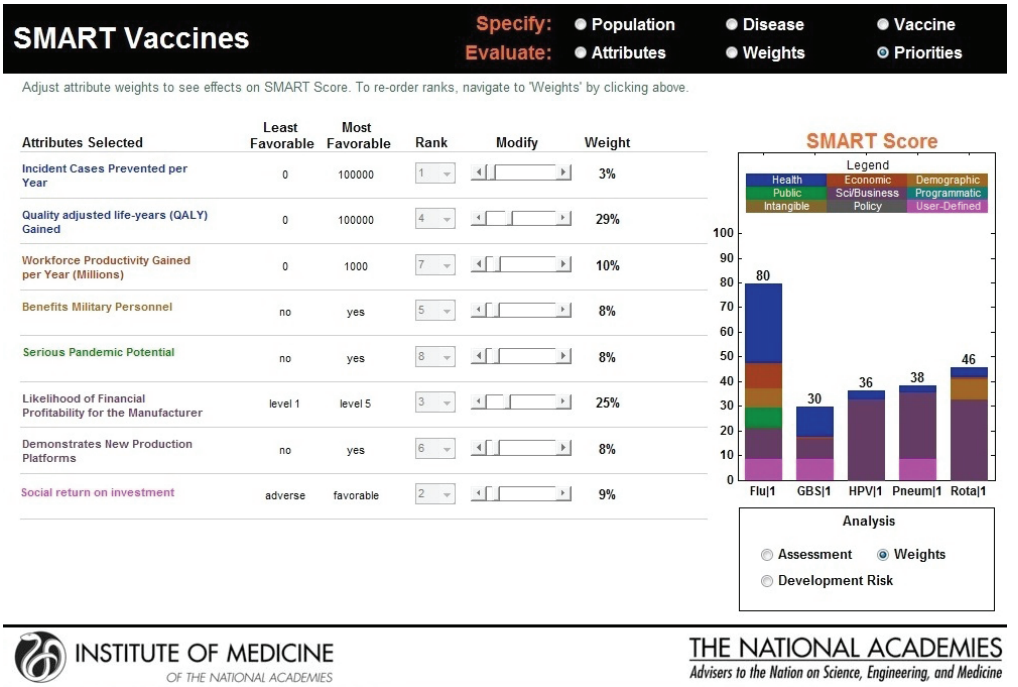

FIGURE 3-13
Output screen for SMART Vaccines permitting sensitivity analysis based on adjustment of weights.

new candidates: a rotavirus and a pneumococcal vaccine. Though the users choose the same attributes—see Figure 3-20 for user X and Figure 3-21 for user Y—their rank orders for the selected attributes are different. User X has ranked incident cases prevented per year as most important, whereas user Y has selected net savings resulting from vaccine use as having the highest priority, with the other ranks also varying according to the different perspectives of the two users.

Figure 3-22 shows user X's comparative scores: a 33 for rotavirus and an 82 for pneumococcal vaccine. User Y's results are shown in Figure 3-23: a SMART Score of 52 for rotavirus and of 77 for pneumococcal vaccine. The users may have arrived at these scores independently, but now their SMART Scores could enable a discussion between them. In this case, the "winner" in both cases is pneumococcal vaccine, albeit with slightly different scores. If user X and user Y had settled on other sets of attributes and value judgments, then their preferences could have led to quite different results, as often happens in real-world scenarios. Regardless of the outcome, however, the SMART Scores can help start a discussion between the users in which they compare their differing values and results.

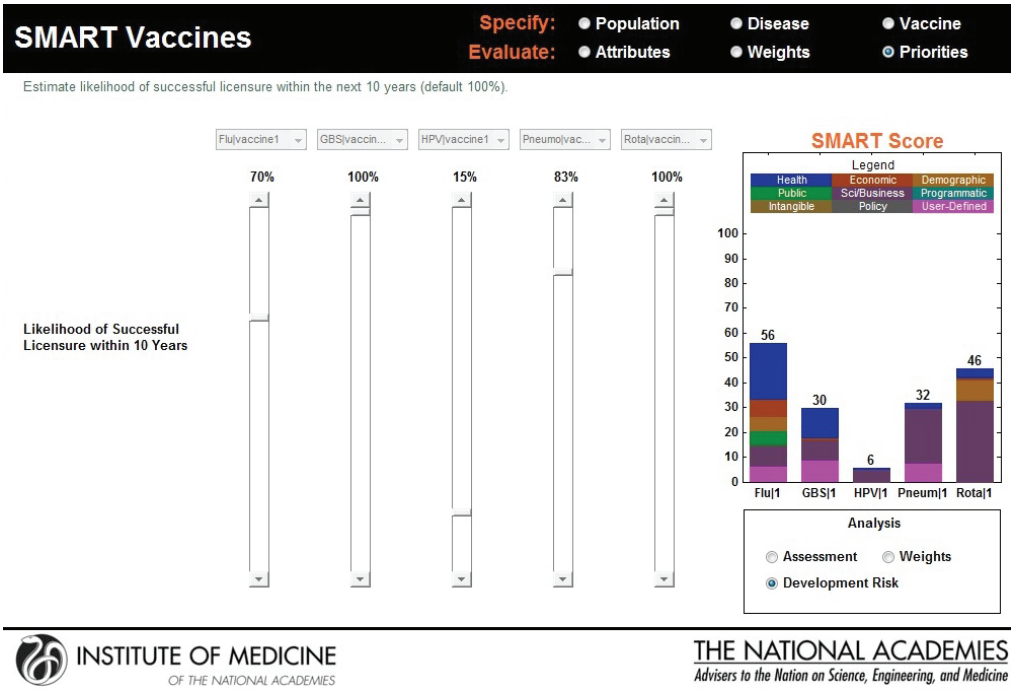

FIGURE 3-14
Output screen for SMART Vaccines permitting sensitivity analysis based on adjustment of development risk.

Users' Evaluation of the Prototype

The committee engaged seven potential users to provide comments on the user interface and functionalities relating to an early prototype of SMART Vaccines 1.0. These consultant evaluators participated in a webinar led by a committee member. Three evaluation sessions were conducted, with two of them lasting 1 hour each (one and two participants, respectively) and a third session lasting about 90 minutes (four participants). These sessions, which were carried out via a remote desktop connection, were intended to illustrate the dynamic capabilities of the software and to engage the evaluators in constructing possible evaluation scenarios. The evaluators were given a set of framing questions (see Box 3-1) in advance of the demonstration sessions as a way of directing the focus of their feedback during those sessions.

The reactions of the evaluators were overall very positive concerning the design and innovation underlying SMART Vaccines. In addition to this positive overall response, the consultants also provided feedback about possible further improvements and explored potential additional applications of SMART Vaccines, which are discussed in Chapter 4. Moreover,

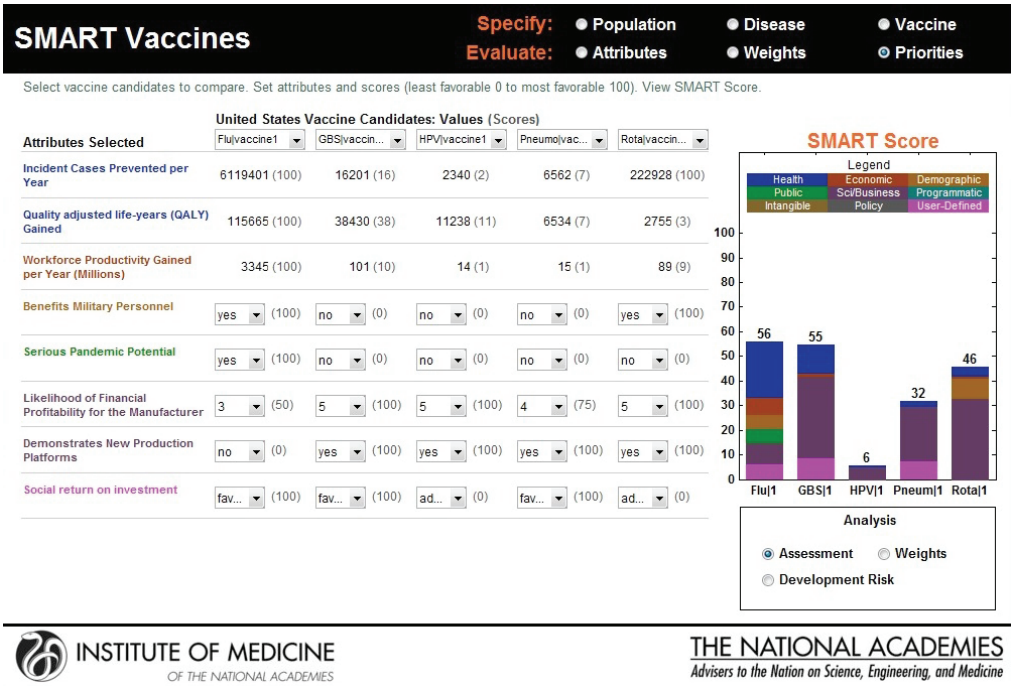

FIGURE 3-15
Output screen for SMART Vaccines permitting adjustment or reassessment of original scores.

during the review process, external reviewers of this report participated in a webinar session containing the software demonstration and offered feedback. Subsequently, the prototype evaluators were re-engaged to allow hands-on interaction with SMART Vaccines and to provide additional feedback prior to the software and report release.

BOX 3-1
Framing Questions for Evaluators of SMART Vaccines 1.0

- Do you foresee using SMART Vaccines in the decision-making process of your organization?
- What additional features would be desirable in SMART Vaccines?
- Could the SMART Score be persuasive in guiding you to a decision?

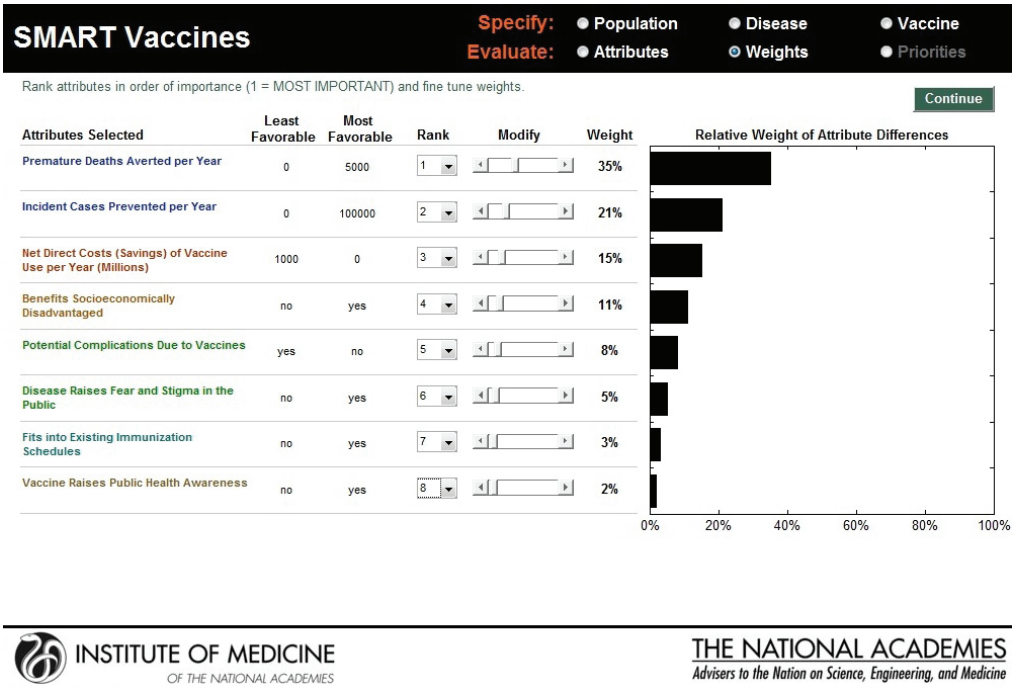

FIGURE 3-16
Attribute structure and ranks created by a hypothetical federal agency director (user A) for evaluating a new human papillomavirus vaccine and a new influenza vaccine.

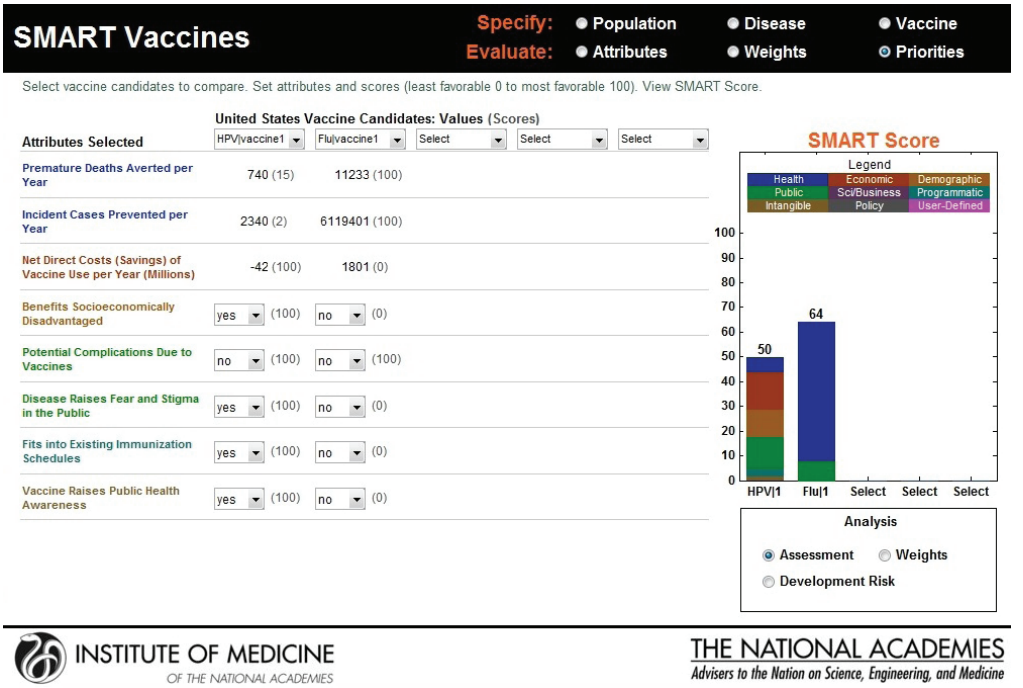

FIGURE 3-17
Comparison of SMART Scores for two hypothetical new vaccines resulting from user A's selected attributes and ranking system.

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FIGURE 3-18
Attribute structure and ranks created by a hypothetical senior executive of a major pharmaceutical company (user B) for prioritizing development between a new human papillomavirus vaccine and a new influenza vaccine.

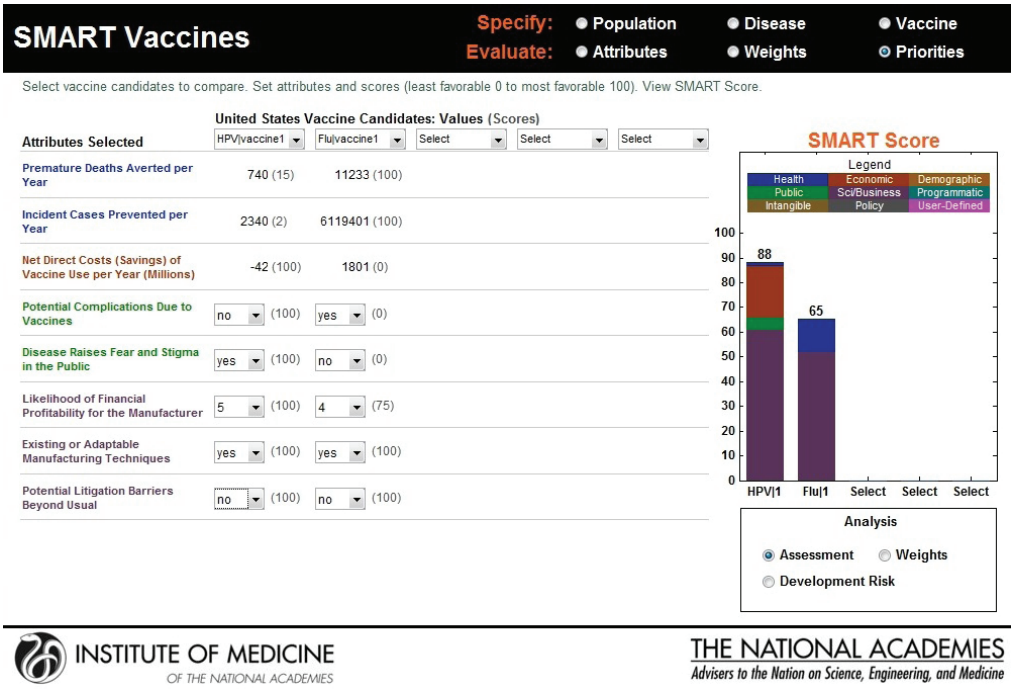

FIGURE 3-19
Comparison of SMART Scores for two hypothetical new vaccines based on user B's selected attribute and ranking structure.

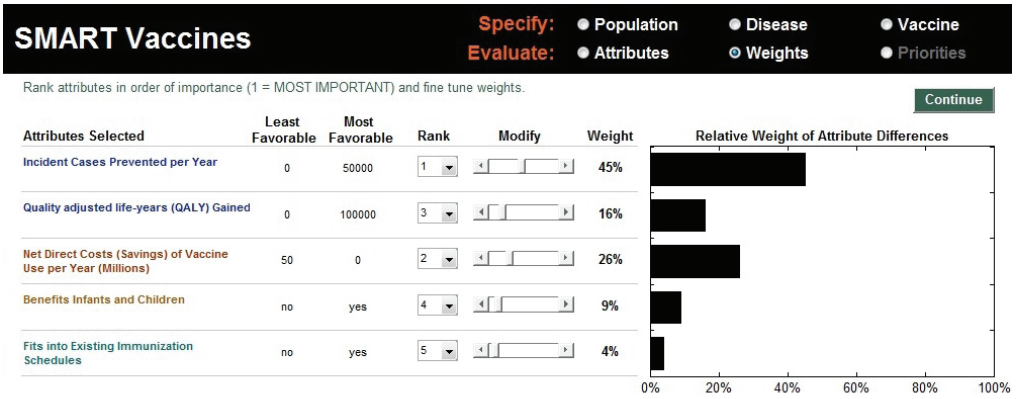

FIGURE 3-20
Attribute and rank structure selected by a hypothetical health minister (user X) in South Africa.

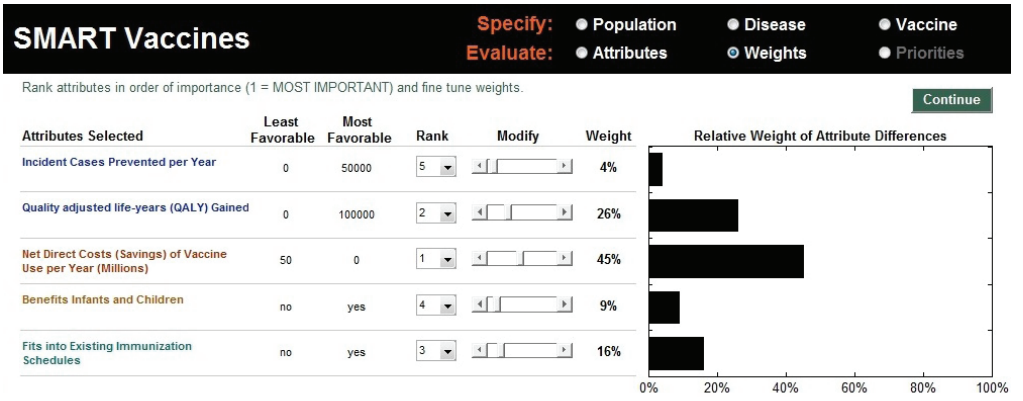

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FIGURE 3-21
Attribute and rank structure selected by a hypothetical finance and trade minister (user Y) in South Africa.

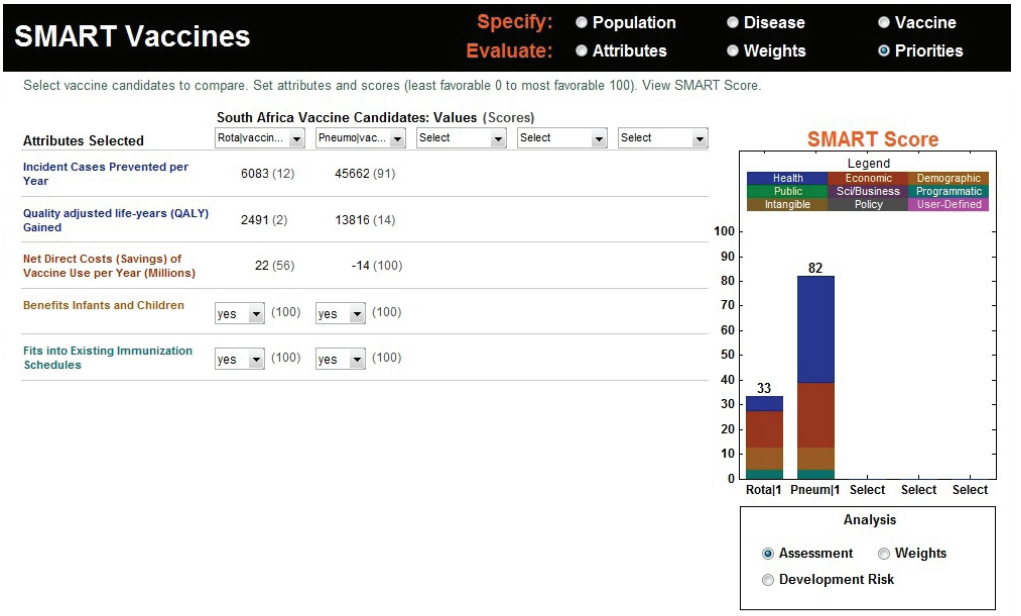

FIGURE 3-22
Comparison of SMART Scores for a new rotavirus vaccine and a new pneumococcal vaccine with user X's rank and value structures.

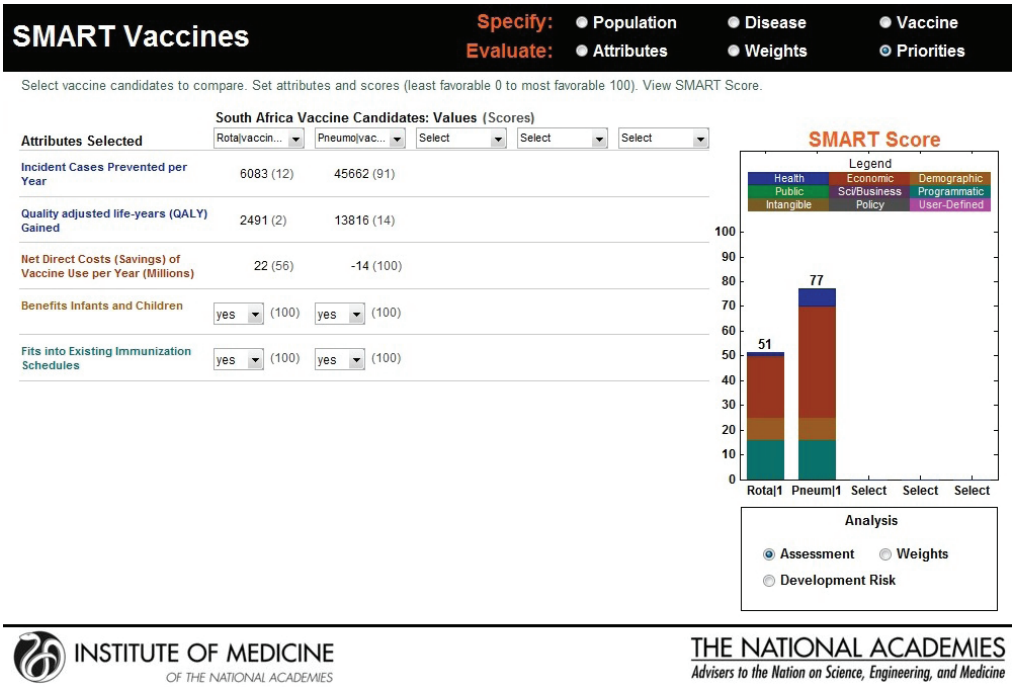

FIGURE 3-23
Comparison of SMART Scores for a new rotavirus and a new pneumococcal vaccine with user Y's rank and value structures.

4

Observations and Looking Forward

Previous efforts in the realm of prioritizing new vaccines have been limited because of the small number of attributes and value preferences those models were able to accommodate. Moving from the traditional single-attribute modeling framework to a multi-attribute modeling framework involved substantial public input and a wide range of expertise in order to develop the computational model and the user interface that support SMART Vaccines.

As noted in the 2012 Institute of Medicine (IOM) report *Ranking Vaccines: A Prioritization Framework* (IOM, 2012) and earlier in this edition, the committee's charge did not include the production of a "list" of vaccines for development. Instead, through this work the committee developed SMART Vaccines as a dynamic, customizable decision-support tool to guide planning for the future development of preventive vaccines. It can also be used to select among existing vaccines for investment in a public health setting or to support other vaccine-related investment and implementation decisions. SMART Vaccines should always be used as a tool to discuss values and preferences across various user groups and not as the ultimate determinant of a decision that needs to be made.

Guiding Principle and Strategy

To inform future efforts in this area, the committee adopted a guiding principle: **SMART Vaccines will have the greatest potential and value if it is programmed as a dynamic, continuously evolving software applica-**

tion and made freely available in an open-source environment to all decision makers and developers around the world.

As a strategy relating to this principle, the committee believes that it would be most beneficial if the **National Vaccine Program Office of the Department of Health and Human Services identifies a host for SMART Vaccines and its future versions.** Moreover, any decision-support system such as SMART Vaccines has no intrinsic value without accurate and relevant data. Consequently, **the committee places the highest importance on creation of a data architecture and expanding data collection for use in SMART Vaccines.**

A Vision for the Future

Consistent with this guiding principle and strategy, the committee believes that SMART Vaccines will achieve optimal value if the following events occur:

1. SMART Vaccines and its future versions are hosted in an open-source setting on a widely trusted website with a distinct identity and appropriately protected from unwarranted modifications or intrusions.
2. The host organization creates, maintains, funds, and facilitates a community of users to curate and manage further development of SMART Vaccines and supporting data.
3. The community of users includes decision makers involved in research, development, regulation, and implementation of new vaccines as well as developers with expertise in such areas as modeling, epidemiology, demography, software engineering, database management, and visual design.
4. The community of users—independently or in collaboration with the host organization—establishes an advisory group to help plan future versions and facilitate the adoption of SMART Vaccines.
5. The community of users, together with the host and sponsors, develops mechanisms to encourage the development and updating of data for populations at regional, national, and sub-national levels; for the disease burdens these populations confront; for the costs of preventing and treating those diseases in each distinct environment; and for the productivity losses associated with these disease burdens. These data are accessible in a standardized format, shared with other users through the common website that

hosts SMART Vaccines, and improved through an editing process agreed upon and overseen by the user community. These processes could ultimately help guide improvements in global communication and coordination of data and initiatives of common interest and shared importance.

6. The community of users studies the application of SMART Vaccines for retrospective analysis, validation, or confirmation of previous decisions relating to new vaccine development. The results would have both an educational and a continuous learning benefit.

Future Steps

No software product remains static—it either evolves or becomes obsolete, as examples from every realm of software development demonstrate. This remains true even when a single software system dominates a market, as in word processing, spreadsheet, graphical presentation, relational database management, or statistical analysis. In light of the continuous cycles of improvement required for SMART Vaccines, the committee developed a set of steps to guide future development, which are listed in priority order here:

Establishing a Data Architecture

If SMART Vaccines is to become a valuable component of decision making in the vaccine enterprise, concerted data collection efforts will need to be initiated and sustained. The most useful first step would be to establish a data warehouse containing the best sources and estimates for various populations. While demographic datasets are widely available and adaptable for SMART Vaccines, data on disease burden, economic factors, and vaccine characteristics are largely unavailable and need to be estimated with expert guidance. Once experts provide such information for settings around the world, then it will be beneficial to develop training and guidance tools regarding common definitions, calculation formulas, estimation principles, and standardized nomenclature because this will enhance comparability among users.

Conducting Usability Studies

The most useful evolution of SMART Vaccines will occur if there is input from early adopters involved in the on-site testing and assessment of Ver-

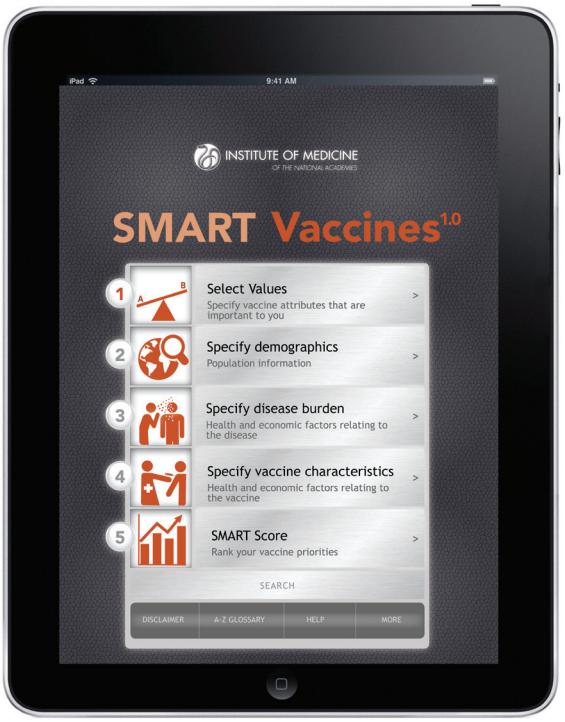

FIGURE 4-1
A rendering of SMART Vaccines imagined as a potential tablet application. Future versions of SMART Vaccines in an open-source setting have the potential to be instantiated in a range of different formats, including different languages, and using different visual design features.

sion 1.0 as a support tool in actual decision making. Such input will help point to additional modifications that can improve SMART Vaccines and will help inform the requirements for multiple or customizable visual interfaces for users from various sectors and countries. The usability testing may also shed light on the value of developing versions of SMART Vaccines in alternate software and visual design platforms and also in various of the official languages of the United Nations besides English—for example, Arabic, Chinese, French, Russian, or Spanish. An artist's rendering of SMART Vaccines in the form of a potential tablet application is shown in Figure 4-1.

Developing Standard Profiles to Enhance Cross-User Comparisons

Multi-attribute value models (including multi-attribute utility theory as used in SMART Vaccines) do not provide a uniform scale of comparison for different users. As has been explained before with the temperature anal-

ogy, each user's value structure creates its own value metric. While some of the vaccine examples employed in this and in the Phase I report allow such a comparison, they are limited to the United States and South Africa. Expanding the availability of such "comparison cases" to many other settings will improve the ability of users to understand their own and others' SMART Scores in various settings. Thus, the committee believes that there will be great value in the further development of a series of "standard" vaccine descriptors for which the disease burdens, prevention and treatment costs, mortality and morbidity, productivity losses, and vaccine effectiveness are well understood and there are no misinterpretations of results.

Refining the Software Platform and Model

No model is perfect, and the modeling work the committee has undertaken will require continuous refinements. Thus, future work will have the greatest impact if the model is enhanced and improved using software languages that are widely accessible and platform-neutral. The current model is programmed in MATLAB, which can be compiled for use on standard operating systems from Microsoft, Apple, and Linux.

SMART Vaccines will work best if it incorporates or allows the use of a variety of commonly used data-management platforms, either commercially developed platforms or other open source spreadsheet programs for data entry and export. The current version allows a Microsoft Excel–based spreadsheet structure for data entry and export, an approach widely used with both Microsoft products and the Open Source Initiative.

Users of SMART Vaccines will find numerous existing databases that provide information about populations, their disease burdens, and the desirable attributes of yet-to-exist vaccines which can form the basis for initial uses of SMART Vaccines. Future enhancements can facilitate the easy introduction and use of such extant data sources and accommodate them as they change structure and content.

Different diseases are best modeled with different population dynamics. Future enhancements can enlarge the number of ways in which population growth is treated. The most complex of these could include, for example, a population with evolving death rates and fertility rates and even a fertility rate that changes in response to alterations in the mortality rate caused by various diseases.

As decision sciences and modeling techniques continue to improve, future versions of the software may incorporate improvements in the multi-attribute utility theory modeling or the ranking approach used by SMART Vaccines 1.0, and they could offer options for alternative value modeling, such as mathematical programming or analytic hierarchy process.

Expanding Outreach and Training

The use of SMART Vaccines will increase as more people become aware of its capabilities, which should in turn increase the breadth, depth, and overall competence and expertise within the community of users. Thus, the committee has considered a variety of outreach platforms and tools, and it believes that outreach through presentations, publications, online guides, tutorials, and academic courses will help expand awareness of the software's capabilities and increase its future potential.

Enhanced Applications of SMART Vaccines

Comparisons of New and Existing Vaccines, Public Health Prevention, and Treatment

This committee was charged with creating a modeling framework that, when fully instantiated, would allow users with different perspectives to create their own rankings of the potential value of new preventive vaccines. While SMART Vaccines was designed to accomplish this specific goal, the committee believes that it can be applied to a broader array of related applications with little or no change in the software structure by assembling the data necessary to describe the particular options being evaluated. Several of these potential applications are described briefly in the following paragraphs.

Choosing Among Existing Vaccines

SMART Vaccines has the potential to help health administrators in various settings compare existing vaccines in order to determine those that best fit their own demographic, economic, and contextual needs. This task is actually easier than ranking new vaccines, because the characteristics of existing vaccines—such as cost, distribution, storage and administration requirements, potential side effects, likely population coverage, and efficacy—are already available and do not have to be estimated.

Alternative Public Health Measures

Although the word "vaccines" appears explicitly in the name "SMART Vaccines," the software need not be limited to comparing vaccines. Consider, for example, methods of reducing the disease burden of malaria. In principle, one could use SMART Vaccines to evaluate a variety of measures for achieving that goal and could thus compare the performance of vari-

ous vaccines with the medical treatment of malaria and with the prevention of malaria through the use of mosquito netting or mosquito abatement programs. While SMART Vaccines cannot incorporate the exact details of such programs, the committee believes that adept users will be able to guide decision making among these types of choices using the existing capabilities of SMART Vaccines. Thus, "clean water" or "mosquito netting" or "improved sewage disposal" can be entered as "new preventive vaccines" with considerable efficacy and so expand the potential uses of the software application.

Veterinary Vaccines

While this report focuses on human diseases and human vaccine prioritization and development, vaccination is also used to protect hundreds of millions of livestock, poultry, aquatic life, and companion animals worldwide. Interestingly, the second disease completely eradicated worldwide, after smallpox, was rinderpest in 2011. This paramyxovirus does not infect humans, but it was nonetheless responsible for countless human deaths that resulted from the losses of millions of head of livestock, which led to famine and disease.

Currently, veterinary vaccines account for approximately 20 percent of the total vaccine market. SMART Vaccines can be modified for use in the world of veterinary medicine. Intuitively, it seems likely that the greatest interest would be in analyzing the economic attributes of animal vaccines; however, the broad area of animal health would benefit from a tool that guides the making of policy and various other decisions that affect animals. Furthermore, healthier food animals lead to safer food, and a number of animal diseases pose risks of transmission to humans. Thus, an investment in animal vaccines will also have a real benefit to human health, which leverages and adds value to the investment in veterinary vaccines. Except for the new and different data demands, there is no difference between comparing human vaccines and comparing vaccines for domesticated animals. And improving vaccines for food animals has the additional advantage that it could help reduce the use of antibiotics, thereby reducing the risk of developing highly resistant organisms in both animal and human populations.

Disease-Resistant Plants

The hybridization and genetic modification of plants to enhance disease resistance is conceptually similar to vaccinating humans or animals against

disease. The multi-attribute model embedded in SMART Vaccines could be used to compare alternative approaches to creating disease resistance in plant; for example, it could be used to compare the potential risks of creating disease immunity in plants by hybridization versus through gene modification.

Facilitating Discussions Among Various User Groups

From discussions with various user groups throughout Phase I and Phase II, the committee has concluded that interest groups often fail to fully communicate with each other concerning values, choices, and impediments to reaching their goals. The resulting shortcomings in understanding can be seen, for example, in questions that arise during the design phase about the best compromises in vaccine attributes or product profiles. What is more valuable to stakeholders: oral administration or thermal stability of the vaccine? Do vaccines fit within the existing immunization schedules and programs? What social customs might enhance or limit population acceptance of certain vaccines? The answers to these questions will differ widely from setting to setting, but the committee believes that these types of trade-offs have not been fully discussed or understood by various user communities. SMART Vaccines allows the formal consideration of these trade-offs at the local level. Thus, the software can allow users to comprehend and communicate their own preferences more clearly.

Vaccine manufacturers face other constraints and may have different objectives. They seek profitable products, because sales revenues are typically the only source for financing research, development, testing, and production. Intellectual property laws provide temporary market protection for recouping research and development costs, but ultimately the risks surrounding scientific research and eventual commercial products drive many corporate decisions about new product development. Knowing which attributes are more or less valuable to potential user communities could enhance vaccine developers' decision-making process and ensure that they better understand the values that users place on various potential vaccines as a way of improving their decision making.

In short, it is the committee's hope that SMART Vaccines will serve as a valuable tool to enhance and clarify discussions among various user communities, which will, over time, lead to improved public health outcomes.

Next Phase

In an immediate follow-up Phase III activity, an Institute of Medicine and National Academy of Engineering committee is expected to evaluate the utility of SMART Vaccines and offer guidance on a data warehouse for the software. Specifically, the committee is expected to produce some use case scenarios in collaboration with actual end users of the software. In doing so, it will also attempt to develop a framework for a data warehouse including estimation strategies to create future datasets for the software.

References

Arrow, K. J. 1950. A difficulty in the concept of social welfare. *Journal of Political Economy* 58(4):328–346.

Arrow, K. J. 1963. *Social choice and individual values*. 2nd ed. New York: John Wiley & Sons.

Bagnoli, F., B. Baudner, R. P. Mishra, E. Bartolini, L. Fiaschi, P. Mariotti, V. Nardi-Dei, P. Boucher, and R. Rappuoli. 2011. Designing the next generation of vaccines for global public health. *OMICS: A Journal of Integrative Biology* 15(9):545–566.

Barron, F. H., and B. Barrett. 1996. The efficacy of SMARTER—Simple multi-attribute rating technique extended to ranking. *Acta Psychologica* 93(1):23–36.

Batson, A. 2005. The problems and promise of vaccine markets in developing countries. *Health Affairs* 24(3):690–693.

Bishai, D. M., C. Champion, M. E. Steele, and L. Thompson. 2011. Product development partnerships hit their stride: Lessons from developing a meningitis vaccine for Africa. *Health Affairs* 30(6):1058–1064.

Bloom, D. E., D. Canning, and M. Weston. 2005. The value of vaccination. *World Economics* 6(3):15–40.

Brilliant, L., and W. Foege. 2013. Lessons from smallpox guide polio endgame. *Scientific American*, April 22. http://blogs.scientificamerican.com/guest-blog/2013/04/22/lessons-from-smallpox-guide-polio-endgame (accessed May 31, 2013).

Drummond, M., C. Chevat, and M. Lothgren. 2007. Do we fully understand the economic value of vaccines? *Vaccine* 25(32):5945–5957.

Edwards, W., and F. H. Barron. 1994. SMARTS and SMARTER: Improved simple methods for multiattribute utility measurement. *Organizational Behavior and Human Decision Processes* 60(3):306–325.

HHS (U.S. Department of Health and Human Services). 2010. *The 2010 National Vaccine Plan, protecting the nation's health through immunization*. http://www.hhs.gov/nvpo/vacc_plan/2010%20Plan/nationalvaccineplan.pdf (accessed May 31, 2013).

IOM (Institute of Medicine). 1985. *New vaccine development: Establishing priorities. Volume I, diseases of importance in the United States*. Washington, DC: National Academy Press.

IOM. 1986. *New vaccine development: Establishing priorities. Volume II, Diseases of importance in developing countries*. Washington, DC: National Academy Press.

IOM. 2000. *Vaccines for the 21st century: A tool for decisionmaking*. Washington, DC: National Academy Press.

IOM. 2012. *Ranking Vaccines: A prioritization framework: Phase I: Demonstration of concept and a software blueprint*. Washington, DC: The National Academies Press.

Keeney, R., and H. Raiffa. 1976. *Decisions with multiple objectives: Preferences and value tradeoffs*. New York: John Wiley & Sons.

Milstien, J., and B. Candries. 2002. *Economics of vaccine development and implementation: Changes over the past 20 years*. Bethesda, MD: U.S. Department of Health and Human Services, National Institute of Health, National Institute of Allergy and Infectious Diseases.

Rappuoli, R., and A. Alderem. 2011. A 2020 vision for vaccines against HIV, tuberculosis and malaria. *Nature* 473(7348):463–469.

Rappuoli, R., S. Black, and P. H. Lambert. 2011. Vaccine discovery and translation of new vaccine technology. *Lancet* 378(9788):360–368.

Tomori, O. 2011. From smallpox eradication to the future of global health: Innovations, application and lessons for future eradication and control initiatives. *Vaccine* 29(Suppl. 4):D145–D148.

A

Computational Modeling for SMART Vaccines

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Estimates for the health and economic measures used to prioritize vaccine candidates in SMART Vaccines 1.0 are produced by a collection of formulas referred to as the computational submodel (see Figure 2-1). The submodel uses as its input data from the following parameters: demographic characteristics, disease burden, and vaccine characteristics (see Table 3-1). This section outlines the formulas and describes the multi-state population process model underlying these estimates. Health measures include premature deaths averted per year, incident cases prevented per year, quality-adjusted life years (QALYs) gained per year, and disability-adjusted life years (DALYs) averted per year. Economic measures include net direct costs (savings) of vaccine use per year, workforce productivity gained per year, one-time costs, and cost-effectiveness in cost per QALY or cost per DALY (see Table S-1).

Central to interpreting each health and economic measure is an understanding of the populations being compared, the time-scale applied, and the estimate formulation. The underlying population process model is described below, followed by a detailed account of the estimation procedures.

The Population Process Model

The mathematical framework underlying SMART Vaccines was developed in Phase I and has been enhanced to result in the present software, a comprehensive explanation about the model is provided in the second and third chapters of the Phase I report, *Ranking Vaccines: A Prioritization Framework* (IOM, 2012). The SMART Vaccine 1.0 population process model uses a cohort component method to project populations forward at yearly intervals (Preston et al., 2001) The yearly aging process is simulated for both a baseline population with no vaccine (i.e., the control) and a test population with either (1) the vaccine in approximated steady state delivery or (2) the vaccine having been newly introduced, and the two populations are compared. Table A-1, provides a comprehensive description of these three population vaccine conditions. It is through comparing a vaccinated population to the baseline that the various health and economic measures are estimated over the appropriate time-scale.

The model assumes a constant number of infants entering the population each year, with the number being given by the number of infants (i.e.,

TABLE A-1

Population Comparison in the SMART Vaccines Process Model

Population	Description
Baseline	The baseline population is the reference for comparison. Vaccines not yet developed and those used in SMART Vaccines 1.0 have a baseline population in which no vaccine has been used. However, in cases where a vaccine does exist, the baseline population may reflect the current vaccination state as reference against which to compare hypothetical newly developed vaccines for the same disease that have different (i.e., more desirable) characteristics.
Vaccine in approximated steady state delivery	In a population in which the vaccine is being administered under the steady state approximation it is assumed that individuals of all ages have had the opportunity (i.e., accounting for coverage) to receive the vaccine. For example, in the case of a vaccine that solely targets infants, individuals of all ages are assumed to have had the opportunity for vaccination. Achieving steady state for an infant vaccination would require many years, unlike the case with a vaccine designed for delivery to all ages.
Vaccine first being introduced	In the case of a vaccine first being introduced into a population it is assumed that the vaccine was delivered solely to the target population (i.e., accounting for coverage) at model initialization. No other members of the population will have had the opportunity to have received the vaccine.

age less than 1) present in the World Health Organization (WHO) population life-table input (WHO, 2013). This is operationalized by assuming that the number of infants (i.e., children under age one) observed at baseline will remain constant in the future. This assumption eventually produces a stationary age distribution, but the total population size eventually reached will be somewhat different from that of a population immediately reaching replacement fertility (Preston et al., 2000). Information on population below age 1 is taken from WHO population life-table input. Individuals may exit the population by death caused by disease or by all other causes. The model does not account for migration of any sort. The committee chose to use this simplified version of the population process in light of the constraints present in the early development phase of SMART Vaccines 1.0. The model minimizes assumptions regarding population dynamics and, consequently, reduces the burden of data entry, making it easier to use. It is expected that this simplified version will serve as a foundation upon which more complex population processes may be constructed as SMART Vaccines advances.

The step-by-step computations of the population process model are as follows. The model is initialized at time zero t_0, which corresponds to the year of the population data that are input into the model (e.g., 2009 for the vaccine candidates). At initialization, linear interpolation is used to produce a population age distribution in 1-year increments from the standard WHO life-table format, which is in 5-year increments. Age-specific probabilities of dying from all causes, ${}_nq_x$, are computed; the subscript x refers to the age at the beginning of the age interval, and the subscript n refers to the length of the interval. The probabilities for dying in a given 1-year time period, ${}_1q_x$, are derived from the number of individuals alive at each age, l_x, along with the probability of survival and the death rate between ages x and $x+n$, written as ${}_np_x$ and ${}_nM_x$, respectively. The following equations are used to estimate yearly ${}_nq_1$ (Preston et al., 2001):

$$ {}_np_x = l_{x+n} / l_x \qquad {}_nM_x = -ln({}_np_x) / n $$
$$ {}_1M_a = {}_nM_x \quad for\ x \le a \le x+n-1 \qquad {}_1q_x = 1-exp(-{}_1M_x) $$

The process model directly computes age-specific population parameters, including population size *N*; population size disease-eligible *NE* (i.e., that part of the population that has not previously been permanently impaired by the disease); and the subset of the population targeted to receive vaccination, *TI* or *TS,* as seen in Table A-2: Population Parameters. At each yearly interval starting with t_0 the population is composed of individuals in mutually exclusive vaccination states. These states are the

TABLE A-2

Population Process Model

Population Parameters	Baseline^0	With Vaccine^1	Impact
Population size (N)	${}_nN_x^0 = {}_nN_{x-1}^0 - {}_nDA_{x-1}^0$	${}_nN_x^1 = {}_nN_{x-1}^1 - {}_nDA_{x-1}^1$	${}_nN_x^1 - {}_nN_x^0$
Population size disease eligible (NE)	${}_nNE_x^0 = {}_nN_{x-1}^0 - {}_nCP_{x-1}^0$	${}_nNE_x^1 = {}_nN_{x-1}^1 - {}_nCP_{x-1}^1$	${}_nNE_x^1 - {}_nNE_x^0$
Target population (TI) Vaccine in Steady State	${}_nTS_x^0 = 0$	${}_nTS_x^1 = {}_nNE_x \times 1$	${}_nTS_x^1$
Target population (TS) Vaccine Introduced	${}_nTI_x^0 = 0$	${}_nTI_x^1 = {}_nNE_x \times {}_nTARG_x$	${}_nTI_x^1$
Vaccination States	**Baseline^0**	**With Vaccine^1**	**Impact**
Vaccinated immune (V)	${}_nV_x^0 = 0$	${}_nV_x^1 = {}_nT_x^1 \times {}_nCOV_x \times {}_nEFF_x$	${}_nV_x^1$
Vaccinated susceptible (VS)	${}_nVS_x^0 = 0$	${}_nVS_x^1 = {}_nT_x^1 \times {}_nCOV_x \times (1 - {}_nEFF_x)$	${}_nVS_x^1$
Unvaccinated immune (B)	${}_nB_x^0 = 0$	If $\sum ({}_nCOV_x \times {}_nN_x0) / \sum_n N_x^0 \geq 80\%$ ${}_nB_x^1 = ({}_nNE_x^1 - {}_nV_x^1 - {}_nVS_x^1) \times {}_nEFF_x$ Else ${}_nB_x^1 = 0$	${}_nB_x^1$
Unvaccinated susceptible (BS)	${}_nBS_x^0 = {}_nN_x0$	${}_nBS_x1 = {}_nNE_x1 - ({}_nV_x1 + {}_nVS_x1 + {}_nB_x1)$	${}_nBS_x^0 - {}_nBS_x^1$
Health Events	**Baseline^0**	**With Vaccine1**	**Impact**
Total cases (C)	${}_nC_x^0 = {}_nNE_x^0 \times {}_nINC_x$	${}_nC_x^1 = ({}_nVS_x^1 + {}_nBS_x^1) \times {}_nINC_x$	${}_nC_x^0 - {}_nC_x^1$
Deaths by disease (D)	${}_nD_x^0 = {}_nC_x^0 \times {}_nCFR_x$	${}_nD_x1 = {}_nC_x1 \times {}_nCFR_x$	${}_nD_x^0 - {}_nD_x^1$
Cases: Impairment (CP)	${}_nCP_x^0 = ({}_nC_x^0 - {}_nD_x^0) \times {}_nIP_x$	${}_nCP_x^1 = ({}_nC_x^1 - {}_nD_x^1) \times {}_nIP_x$	${}_nCP_x^0 - {}_nCP_x^1$
Cases: Morbidity (CM)	${}_nCM_x^0 = {}_nC_x0 - {}_nD_x^0 - {}_nCP_x^0$	${}_nCM_x^1 = {}_nC_x1 - {}_nD_x^1 - {}_nCP_x^1$	${}_nCM_x^0 - {}_nCM_x^1$
All-cause deaths (including deaths caused by disease) (DA)	${}_nDA_x^0 = {}_nNE_x^0 \times {}_nq_x^0$	${}_nDA_x^1 = {}_nNE_x^1 \times {}_nq_x0 - ({}_nD_x0 - {}_nD_x^1)$	${}_nDA_x^0 - {}_nDA_x^1$

NOTE: CFR = annual case fatality risk; COV = coverage; EFF = effectiveness; INC = annual incidence proportion; IP = annual case impairment risk; TARG = target proportion.

vaccinated immune, *V*; the vaccinated susceptible, *VS*; the unvaccinated immune, *B* (i.e., those who may have indirect protection through herd immunity); and the unvaccinated susceptible, *BS* (Table A-2: Vaccination States). No members of the population belong to the vaccinated immune, vaccinated susceptible, or unvaccinated immune states in a baseline population when a vaccine is not in existence. Various "health events" occur each year and are computed based on parameters set by user input (e.g., disease incidence, vaccination effectiveness, etc.). These events include the number of disease cases, *C*; deaths by the disease, *D*; diseases cases leading to permanent impairment, *CP*; disease cases leading to morbidity, *CM* (i.e., complete recovery by year end); and all-cause deaths, *DA*. The mathematical formulas for these measures are displayed in Table A-2. The superscript *0* refers to the simulated baseline population, as opposed to the simulated population with vaccine *1*. Vaccinated populations may be either in the steady state delivery approximation or in the vaccine newly introduced state.

The model described in Table A-2 has several notable characteristics. First, the calculated value for the population size disease-eligible (*NE*) may vary from year to year. The difference from one year to the next is the number of people in the population who were permanently impaired in the intervening year. For example, if a member of the population contracts tuberculosis and, as a result, has permanent lung impairment, that person is not eligible to contract the same disease in subsequent years (i.e., not disease-eligible).

Next, the variable *T* that represents the target population is used to distinguish populations (see Table A-1). For example, no proportion of the baseline population receives the vaccine; therefore the corresponding target multiplier ${}_nTARG_x$ equals zero for all ages. This serves as a proxy for scenarios in which the vaccine does not exist. By contrast, populations assumed to have reached steady state vaccine delivery have an target multiplier of one for all ages. This may be interpreted as an initialization state in which all members of the current population (i.e., all ages) have had the opportunity to receive the vaccination (i.e., coverage rates apply) at t_0. Alternatively, in populations where the vaccine is newly introduced, delivery proceeds only for the age-specific target population specified at input ${}_nTARG_x$. For example, consider the influenza vaccine, for which there is no difference between steady state delivery and the introduction of a new vaccine. The two states are equivalent because the vaccine targets the entire population (i.e., all ages) each year. By contrast, a vaccine candidate for tuberculosis may be designed to target only infants, which will create a major difference between initialization states.

The effect of herd immunity is incorporated into the process model for contagious diseases with human-to-human transmission. In particular, the effect is represented by the presence of an unvaccinated immune population *B* that may receive the benefits of indirect protection (see Table A-2). If the user chooses to apply herd immunity, the overall coverage within the population is calculated. If this coverage is greater than or equal to 80 percent, the entire unvaccinated susceptible population *BS* receives indirect protection. Receiving disease immunity through indirect protection is treated identically to receiving the vaccine and is conferred in accordance with the vaccine's effectiveness. If overall coverage is less than 80 percent, no indirect protection is assumed.

Finally, a connection exists between the baseline and the vaccine comparison process models. The number of all-cause deaths with disease, *DA*, for a vaccinated population is equal to tbe number of all-cause deaths in the baseline population minus the number of deaths prevented by the vaccine in that year. The same age-specific all-cause mortality rates are applied to both populations (i.e., the baseline and the vaccinated), and the prevented deaths, ${}_nD_x^0 - nDx^1$, are subtracted out for the case of the vaccinated population, as can be seen in Table A-2. Thus, the resultant deaths *DA* diverge, and the difference is projected forward each year of the simulation.

Health and Economic Measures

Health and economic estimates are computed using the population process model comparisons as their basis (Table A-2: Impact). However, understanding the populations in comparison and the time scale applied is fundamental to interpreting the meaning of each individual measure. Table A-3 displays this context for each of the nine health and economic measures.

Measures that apply to the steady-state delivery approximation are calculated for the 1-year time period after initialization; each of these measures is distinguished by a "per year" phrasing (see Table A-3). Cost-effectiveness measures such as cost per QALY gained or cost per DALY averted are computed over a 100-year time horizon for those populations first being introduced to the vaccine (see Table A-3). If desired, the user can choose to apply a lesser time horizon through the SMART Vaccines 1.0 interface. The one-time costs measure is designed to capture the estimated total costs for research, development, and licensure of the new vaccine. This is input directly as more than $1 billion, $500 million to $1 billion, $100 million to $500 million, or less than $100 million. One-time costs are interpreted as taking place over the period of time until vaccine adoption, which is provided by user input.

TABLE A-3

Comparator Populations and Time Scale

Vaccine in Steady State Approximation Time Scale: 1-year horizon	Vaccine First Introduced Time Scale: 100 years, or a user-defined horizon less than 100 years
Premature deaths averted per year	Cost-effectiveness in cost per QALY gained
Incident cases prevented per year	Cost-effectiveness in cost per DALY averted
QALYs gained per year	
DALYs averted per year	
Net direct costs of vaccine use per year	
Workforce productivity gained per year	
One-time costs Time scale: Applied over time to adoption (user defined)	

NOTE: DALYs = disability-adjusted life years; QALYs = quality-adjusted life years.

The formulas for each health and economic estimate are shown in Table A-4. The notations correspond to the definitions presented in Table A-2.

Discounting is applied to both the health and the economic measures, with a default annual rate of 3 percent, and the user can modify the annual rate or eliminate the discounting altogether by setting the annual rate to zero. Further aggregate discounting is applied to the cost-effectiveness measures only in order to account for time to adoption (see Table A-3). The duration ($_{n}Duration_{x}$) used to produce the health and economic estimates (see Table A-4) varies by measure. The durations for QALYs and DALYs due to morbidity are input by the user and can be no longer than one year. Individuals with a disease that causes morbidity are assumed to completely recover by year's end. The durations used for QALYs due to death or permanent impairment are given by the age-specific future life expectancy, adjusted and discounted by the health utilities index (HUI2). The durations used for DALYs due to death or permanent impairment similarly use discounted life expectancy but are based on the standard life expectancy and remain unadjusted for HUI2. The durations due to morbidity used for workforce productivity calculations are input by the user and are identical to the time-periods used for QALYs and DALYs. However, workforce productivity loss due to death or permanent impairment is assumed to be six months. This is the average duration over the 1-year projection inter-

TABLE A-4

Health and Economic Formulas

Measure	Formula
Premature deaths averted	$\sum_n D_x^0 - {}_nD_x^1$
Incident cases averted	$\sum {}_nC_x^0 - {}_nC_x^1$
Quality-adjusted life years (QALYs) gained	$\sum_n QALY_x^0(\text{Death + Impairment + Morbidity}) - \sum_n QALY_x 1(\text{Death + Impairment + Morbidity})$ ${}_nQALY_x(\text{Death}) = ({}_nQALY_x 0_D - {}_nQALY_{x\,D}^1) \times {}_n\text{Duration}_x$ ${}_nQALY_x(\text{Impairment}) = ({}_nQALY_{x\,CP}^0 - {}_nQALY_{x\,CP}^1) \times {}_n\text{Toll}_x \times {}_n\text{Duration}_x$ ${}_nQALY_x(\text{Morbidity}) = ({}_nQALY_{x\,CM}^0 - {}_nQALY_{x\,CM}^1) \times {}_n\text{Toll}_x \times {}_n\text{Duration}_x$
Disability-adjusted life years (DALYs) averted (Rushby and Hanson, 2001)	$\sum_n DALY_x^0(\text{Death + Impairment + Morbidity}) - \sum_n DALY_x^1(\text{Death + Impairment + Morbidity})$ DALYs = years of life lost (YLL) + years of life lived with disability (YLD) $\text{YLD or YLL (W=1)} = W\left\{\frac{KFe^{rj}}{(r+G)^2}\left\{e^{-(r+G)(L+j)}\left[-(r+G)(L_j)-1\right]-e^{-(r+G)j}\left[-(r+G)j-1\right]\right\}+\frac{1-K}{r}\left(1-e^{-rL}\right)\right\}$ ${}_nDALY_x(\text{Death}) = ({}_nDALY_{x\,D}^0 - {}_nDALY_{x\,D}^1) \times {}_nYLL_x$ ${}_nDALY_x(\text{Impairment}) = ({}_nDALY_{x\,CP}^0 - {}_nDALY_{x\,CP}^1) \times {}_nYLD_x$ ${}_nDALY_x(\text{Morbidity}) = ({}_nDALY_{x\,CM}^0 - {}_nDALY_{x\,CM}^1) \times {}_nYLD_x$ 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)

Net direct costs (savings) of vaccine use	$\sum_n DeliveryCosts_x - \sum_n HealthcareCosts_x$ $_nDeliveryCosts_x = [(_nV_x^1 + _nVS_x^1) \times doses \times (dose\ cost \times cost\ to\ administer)]/length\ of\ immunity$ $_nHealthcareCosts_{x=n} = _nHealthCare_x^0(Death + Impairment + Morbidity) - _nHealthCare_x1(Death + Impairment + Morbidity)$ $_nHealthcareCosts_x(Death) = (_nD_{x\,D}^0 - _nD_{x\,D}^1) \times \sum_n CostOfServices_x$ $_nHealthcareCosts_x(Impairment) = (_nCP_{x\,D}^0 - _nCP_{x\,D}^1) \times \sum_n CostOfServices_x \times _nDuration_x$ $_nHealthcareCosts_x(Morbidity) = (_nCM_{x\,D}^0 - _nCM_{x\,D}^1) \times \sum_n CostOfServices_x \times _nDuration_x$
Workforce productivity (WP) gained	$\sum_n WP_x^0(Death + Impairment + Morbidity) - _nWP_x^1(Death + Impairment + Morbidity)$ $_nWP_x(Death) = (_nD_{x\,D}^0 - _nD_{x\,D}^1) \times _nHourlyWage_x \times 2000\ hours \times _nDuration_x$ $_nWP_x(Impairment) = (_nCP_{x\,D}^0 - _nCP_{x\,D}^1) \times _nHourlyWage_x \times 2000\ hours \times _nDuration_x$ $_nWP_x(Morbidity) = (_nCM_{x\,D}^0 - _nCM_{x\,D}^1) \times _nHourlyWage_x \times 2000\ hours \times _nDuration_x$
Cost-effectiveness	QALYs / Net Direct Costs (Savings) or DALYs / Net Direct Costs (Savings)

vals. In short, workforce loss calculations are limited to one year and do not account for future years lost for those who experience death or permanent impairment.

Model Limitations and Further Work

The computational model that underpins SMART Vaccines has a few limitations that would benefit from improvements in subsequent versions. First, closing the population process to migration does not allow the model to account for population dynamics that may influence health and economic measures, especially for cost-effectiveness modeled over a 100-year time horizon. However, this basic design does reduce user assumptions and the practical burden of data entry, and it leads to results that can be interpreted as vaccine impacts exclusive to the current population, with minimal confounders.

Second, the steady-state approximation does not account for changes in the population that may occur by the time steady-state vaccine delivery is reached. As the time to steady state increases (e.g., it is longer for tuberculosis than for influenza), so does the potential for inaccurate estimation. Given this limitation, we chose to model an immediate steady-state proxy because the purpose of vaccine intervention is to swiftly achieve steady state and to maximize health benefits. This ultimate purpose was deemed most significant to the prioritization exercise, so we chose to keep this exercise free from the complications that may be inevitable during vaccine ramp-up periods.

Finally, a limitation exists in the level of detail required for the disease and the vaccine characteristics specified as input. Under some circumstances, the input required may appear coarse in order to capture specific details of a disease. In these cases data input may be altered to produce a desired average effect, or the use of pre-defined special populations may be used.

A good understanding of the modeling concepts within SMART Vaccines 1.0 will allow adept users to treat input data appropriately and to capture the complexities of different diseases and vaccines that are not apparent through data input interfaces. Overall, the committee wished to balance the complexity of the modeling and data requirements against the model's capabilities in order to accurately characterize a broad range of diseases and vaccines and software usability. In short, SMART Vaccines 1.0 is designed to serve as a foundation for further work in this area.

References

IOM (Institute of Medicine). 2012. *Ranking Vaccines: A prioritization framework: Phase I: Demonstration of concept and a software blueprint*. Washington, DC: The National Academies Press.

Preston, H., P. Heuveline, and M. Guillot. 2001. *Demography: Measuring and modeling population processes*. Malde, MA: Blackwell.

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.

WHO (World Health Organization). 2013. Life tables. http://tinyurl.com/cd2lpou (accessed May 11, 2013).

B

Candidate Disease Profiles[1]

[1] Boxes B-1 (influenza), B-2 (tuberculosis), and B-3 (group B streptococcus) were previously published in Appendix B of *Ranking Vaccines: A Prioritization Framework*, pp. 128–133, and they are included here with edits. Boxes B-4 (human papillomavirus), B-5 (pneumococcal infection), and B-6 (rotavirus) in this appendix describe the disease profiles for the additional vaccine candidates evaluated in Phase II.

BOX B-1
Influenza Disease Profile

***Infectious Agent*:** Orthomyxoviruses, RNA viruses that infect birds and mammals. Three genera cause influenza: influenza A, which is the most common cause of the 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 have caused an average of approximately 36,000 deaths each year from 1990 to 1999 and 226,000 hospitalizations each year between 1979 and 2001.

The incidence 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 report 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 caused by the H1N1 virus A infected an estimated 11 to 21 percent of those populations in which 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 infection from virus strains that the World Health Organization and the U.S. Food and Drug Administration predict 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 or those individuals who are hospitalized.

***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).

BOX B-2
Tuberculosis Disease Profile

***Infectious Agent*:** Tuberculosis is due to organisms 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.

***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 spreads to blood, bone, brain, 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 those in close contact, such as household members. However, infection in the lung can be contained by the immune system and remain latent; fewer than 10 percent of latently infected individuals subsequently develop reactivation pulmonary tuberculosis, which generally occurs 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. The World Health Organization 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 the increased attention and resources devoted to diagnosing cases and ensuring that patients receive and complete the prescribed treatment regimen.

***Prevention*:** In most wealthy countries with low incidence rates, the prevention of tuberculosis rests primarily on prompt diagnosis, correct multi-drug treatment, and ensuring the completion of treatment among those with pulmonary tuberculosis. Latently infected individuals, especially those at high risk of reactivation tuberculosis, such as HIV-infected individuals, are also treated with drugs. In poor countries with high incidence rates of tuberculosis, infants are given a single dose of the vaccine given shortly after birth. However, effective TB prevention in those cases also depends on prompt diagnosis, correct treatment, and ensuring the completion of treatment.

***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 (e.g., isoniazid), also given for an extended period of time (6 to 12 months).

***Vaccine*:** The Bacille Calmette-Guerin (BCG) vaccine is widely used at birth throughout many countries, including South Africa. BCG is given to all newborns as soon as possible after birth to protect infants from *M. tuberculosis* infections.

BOX B-3
Group B Streptococcus Disease Profile

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

***Routes of Transmission*:** Transmission from mother to infant occurs at the time of vaginal delivery through a colonized birth canal. Exposure to Group B streptococcus in the hospital, at home, or in the community may result in late-onset disease.

***Health Effects*:** Group B streptococcus 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, while 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 is one of the most common causes of these conditions 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 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, intra-partum antibiotics are administered to pregnant women who are infected or who have known risk factors for group B streptococcus. This approach was widely adopted in the United States and many developed countries and resulted in substantial declines in disease in infants younger than seven days. In the United States, culture-based screening is used to identify candidates for chemoprophylaxis, but implementing this strategy has been 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 provided as therapy for infants with signs of severe infection before infection has been confirmed. 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 but is under development.

BOX B-4
Human Papillomavirus Disease Profile

***Infectious Agent*:** Papillomaviruses are non-enveloped DNA viruses. Approximately 100 types of papillomaviruses have been described; types 6 and 11, the most common types of human papillomavirus (HPV), cause genital warts, while types 16, 18, 31, and 45 are associated with the overwhelming majority of cases of cervical dysplasia and cervical cancer.

***Routes of Transmission*:** HPV is primarily transmitted through sexual contact, especially genital contact; mother-to-infant transmission can occur during passage through an infected birth canal.

***Health Effects*:** HPV infection is clinically silent, but after a latent period it is the cause of cervical dysplasia (low- and high-grade squamous intraepithelial lesions) and cervical cancer in women. HPV also causes ano-genital and other types of warts in men and women as well as recurrent respiratory papillomatosis in young children. The virus is also associated with squamous cell cancers of the vagina, vulva, anus, and penis and possibly with squamous cell cancers at other mucosal and skin sites.

***Incidence, Prevalence, and Mortality*:** Genital infection with HPV is very common among sexually active men and women. More than 80 percent of sexually active individuals will acquire genital HPV infection by age 50. The prevalence of genital HPV infection is also very high, exceeding 25 percent in U.S. women of ages 20–24 years. Nearly 6.2 million new HPV genital infections occur each year in the United States among

individuals 14–44 years of age. However, 70 percent of these infections are cleared by the immune system within 12 months, and 90 percent within 24 months. Persistent infection with high-risk HPV types leads first to low-grade and then to high-grade squamous intraepithelial lesions of the cervix in women. In the United States it is estimated that 1,250,000 women develop low-grade squamous intraepithelial lesions and 300,000 women develop high-grade squamous intraepithelial lesions annually. If undetected and untreated, high-grade squamous intraepithelial lesions can progress to cervical cancer, of which there are approximately 11,800 new cases in the United States each year, which lead to 3,700 deaths annually. The incidence and prevalence of HPV infection are similar in most geographic regions of the world, but the incidence of and mortality from cervical cancer vary greatly, depending on the availability and use of pap smear screening for cervical dysplasia.

***Prevention and Treatment*:** There is no treatment for HPV infection itself. Low- and high-grade squamous intraepithelial lesions can be managed using various modalities whose aim is to prevent the development of cervical cancer. Correct and consistent use of male condoms may reduce the incidence of genital HPV infection by about 70 percent.

***Vaccines*:** Two formulations of HPV vaccine are licensed and approved for use in the United States: a bivalent vaccine containing types 16 and 18 and a quadrivalent vaccine containing types 6, 11, 16, and 18. HPV vaccine is recommended for all girls 11–12 years of age in three doses; it can be administered to girls as young as 9 years of age, and "catch-up" vaccination is recommended for girls and women 13–26 years of age if they have not previously been vaccinated or have not completed the full three-dose series. It is also recommended routinely for males.

BOX B-5
Pneumococcal Disease Profile

***Infectious Agent*:** *Streptococcus pneumoniae* organisms are lancet-shaped, gram-positive, facultative anaerobic bacteria. Based on their polysaccharide capsules, more than 90 different pneumococcal serotypes have been identified, although most disease is caused by a limited number of serotypes.

***Routes of Transmission*:** Transmission of *S. pneumoniae* occurs as the result of direct person-to-person contact via respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract. Its spread among family groups is influenced by crowding, the season of the year, and the presence of other upper respiratory infections.

***Health Effects*:** In the United States, *S. pneumoniae* infection is the most common community-acquired bacterial pneumonia, estimated to affect approximately 100 out of every 100,000 adults each year. Pneumonia, febrile bacteraemia, and meningitis are the most common manifestations of invasive pneumococcal disease; bacterial spread within the respiratory tract may result in middle-ear infection, sinusitis, or recurrent bronchitis. Compared with the invasive disease, the manifestations of the non-invasive form, such as acute otitis media, sinusitis, community-acquired pneumonia, empyema, and conjunctivitis, are usually less severe and more common.

***Incidence, Prevalence, and Mortality*:** Although all age groups may be affected, the highest rates of pneumococcal disease occur in young children and in the elderly population. As many as 175,000 adult hospitalizations occur due to *S. pneumoniae* annually in the United States. The case-fatality rate is 5 to 7 percent and may be much higher among elderly persons. According to the World Health Organization, *S. pneumoniae* kills close to 1 million children under 5 years of age worldwide every year, and most of these are in developing countries. Even in economically developed regions, invasive pneumococcal disease carries high mortality; for adults with pneumococcal pneumonia the mortality rate averages 10 to 20 percent, while it may exceed 50 percent in the high-risk groups. The risk for one or more of these manifestations is much higher in infants and elderly people. In addition, persons suffering from a wide range of chronic conditions and immune deficiencies are at increased risk. In developing countries, infants under 3 months of age are at particularly high risk, especially for pneumococcal meningitis.

***Vaccines*:** Currently, there are two general types of pneumococcal vaccines: pneumococcal polysaccharide vaccine and pneumococcal conjugate vaccine. In the United States, the pneumococcal conjugate vaccine PCV13 is currently recommended for all children under 5 years of age. Pneumovax, a 23-valent polysaccharide vaccine, is currently recommended for use in all adults who are older than 65 years of age and for persons who are 2 years and older and at high risk for disease (e.g., sickle cell disease, HIV infection, or other immune-compromising conditions). It is also recommended for use in adults 19 through 64 years of age who smoke cigarettes or who have asthma.

BOX B-6
Rotavirus Disease Profile

***Infectious Agent*:** Rotavirus is a double-stranded RNA virus of the family *Reoviridae*. In the United States from 1966 to 2005, five strains of rotavirus (G1–4, G9) have accounted for 90 percent of isolates from children younger than 5 years, with the G1 strain accounting for more than 75 percent of the isolates.

***Routes of Transmission*:** Transmission is by fecal–oral spread, both through close person-to-person contact and by fomites. Rotaviruses are also probably transmitted by other modes, such as fecally contaminated food and water and respiratory droplets.

***Health Effects*:** Clinical manifestations of infection vary and depend on whether it is the first infection or reinfection. The first infection after 3 months of age is generally the most severe. Infection could result in watery or severely dehydrating diarrhea with fever and vomiting. Up to one-third of infected children have a temperature greater than 102°F (39°C). Gastrointestinal symptoms generally resolve in 3 to 7 days. Clinical features and stool characteristics of rotavirus diarrhea are nonspecific.

***Incidence, Prevalence, and Mortality*:** Rotavirus occurs throughout the world, and prevalence of rotavirus strains varies by geographic area. The disease is less seasonal in tropical climates than in temperate areas.

Incidence of rotavirus is similar in developed and developing countries, suggesting that improved sanitation alone is not sufficient to prevent the infection. In 2008 approximately 453,000 child deaths due to rotavirus gastroenteritis infection occurred worldwide, accounting for about 5 percent of all child deaths.

Rotavirus is highly communicable, with near universal infection of children by age 5. Spread within families, institutions, hospitals, and childcare settings is common. In the pre-vaccine era in the United States, about 3 million rotavirus infections occurred annually, with 95 percent of children experiencing at least one rotavirus infection by 5 years of age. In the United States, rotaviruses are responsible for 5 to 10 percent of all gastroenteritis episodes in children less than 5 years old. Rotavirus accounts for 30 to 50 percent of all hospitalizations for gastroenteritis among U.S. children younger than 5 years of age.

***Prevention and Treatment*:** Rotavirus vaccination is recommended for all national immunization programs. No specific therapy is currently available against rotaviruses. Fluid replacement is required to prevent dehydration. Promotion of early and exclusive breastfeeding, hand washing, improved water supply, and sanitation is part of a comprehensive strategy to control diarrheal disease.

***Vaccines*:** Two live attenuated oral rotavirus vaccines are presently licensed for use in the United States. RV5 (RotaTeq) is given in three doses, while RV1 (Rotarix) is given in two doses. The vaccination series for both vaccines may be started as early as 6 weeks of age. The maximum age for vaccine doses varies by country.

C

Data Sources and Methodology for SMART Vaccines

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SMART Vaccines is a data-intensive tool and compilation of pertinent, high-quality data can be burdensome. At its core, SMART Vaccines relies on three types of data for producing final scores:

Readily available "known-knowns." Some examples of this type of data would include population data for most nations of the world (and sometimes for smaller areas within nations such as states and counties in the United States). These data are available from several sources such as the World Health Organization and provide the lowest level of challenge for future users of SMART Vaccines. In high-income countries, economic and epidemiologic data resources are also available. These types of data include disease burden, typical patterns and cost of treating these diseases, productivity loss arising from these diseases, and similar data needed as inputs into SMART Vaccines. However, these types of data may be available only sporadically or not at all in low-income countries with less investment in data gathering infrastructures.

Theoretically knowable "unknown knowns." Some data that are available readily in high-income countries would be in theory be available in low-income countries as well, but do not exist. In these cases, potential users of SMART Vaccines will have to decide whether to make new investments in data gathering infrastructures or to rely on low-cost approximations for initial priority setting exercises using SMART Vaccines.

In many settings, the most useful way to get sufficient data to begin

the priority setting process is to obtain best expert estimates, often relying on different individuals for different types of estimates. This could be done in a more formalized structure using group consultation techniques such as the Delphi methods or its variations for estimating unknown data.

The sensitivity analysis capabilities of SMART Vaccines provide another way to help users understand the importance of improving the quality of various types of data. If the user finds that within their context—and using their own weights—and across a wide range of possible data levels that the priority rankings do not change, then it is an indication that further investments to improve those data elements is not necessary. Alternatively, if the priority rankings are sensitive to the levels of certain data elements, then it signals the importance of investing resources to improve those data.

Currently unknowable "known unknowns." These are data whose nature is well known but they do not exist, including the vaccines that do not yet exist, and the nature and hence the dangers of diseases that do not yet exist.

Data Categories

Specific data needed for SMART Vaccines can be categorized into four broad categories: population, epidemiology, economics, and vaccine-related characteristics. As mentioned in this report, the data are merely estimates derived from available information in order to offer guidance for further data collection.

The primary sources for SMART Vaccines data were publications reporting primary epidemiologic and economic data or else reporting sufficient information to derive estimates of the primary data. Studies reporting data on a national scale were given precedence over those that analyzed populations on a state, county, or provincial basis. In some instances when national estimates were unavailable, estimates from a smaller subset of a population were extrapolated to the entire population. Indirect estimates from mathematical modeling studies were consulted when firsthand data were unavailable. Specific source references are embedded in the data spreadsheets.

As part of the Phase II data collection efforts, the disease burden and vaccines data for Phase I candidates were revised to closely reflect the population measures of the 2009 U.S. and South African populations as used in the software. Data will naturally differ from year to year as updated sources become available. The examples provided here represent only a subset of all data sources and estimation approaches; they are not representative of

the data from all the surveillance measures that are available to the user. All datasets and specific source references are embedded in the data spreadsheets that are available online with the report and the software.

To ensure best estimates for each disease and associated vaccine, the data inputs were verified and standardized to the 2009 U.S. and South African populations. Disease burden data were verified internally within the model and also against existing estimates. Number of deaths and cases were standardized to the 2009 U.S. and South African populations using estimates for each age group (available from life tables) to obtain the data needed for the model in the following four age groups: less than 1 year old, 1 to less than 20 years old, 20 to less than 65 years old, and 65 years or older.

Next, given the number of cases and deaths within a population, the incidence and case fatality rates were calculated using the following formula: Incidence = (number of cases/total population)*100,000, and Case fatality rate = (number of deaths/number of cases). The calculated incidence and case fatality rates are checked with original number of deaths and cases, followed by verification using existing publications. To the extent possible, costs were also standardized to 2009 U.S. dollars; however, in many instances cost estimates from another year were used.

Standard Data Sources

Centers for Disease Control and Prevention (CDC): CDC is a reliable source of disease- and vaccine-specific information within the United States. Its surveillance systems follow national guidelines within its scope of work to maintain standardized data collection. For instance, two surveillance systems collect information about rotavirus disease and the rotavirus vaccine: the National Respiratory and Enteric Virus Surveillance System and the New Vaccine Surveillance Network. Similarly, there are multiple surveillance systems for influenza, including FLU VIEW (a weekly influenza surveillance report) and International Influenza Surveillance. Information from surveillance systems on mortality and morbidity are available through the *Morbidity and Mortality Weekly Report* (*MMWR*). The *MMWR* series, prepared by the CDC, contains disease burden data from 1990 to present.

World Health Organization (WHO): The WHO Global Health Observatory (GHO) data repository provides epidemiologic and health indicator data for WHO's 194 member states. The GHO data repository contains more than 50 datasets on priority health topics, including the mortality and burden of diseases, immunization, and health systems. Annual summaries of health-related data are also available for member states. WHO Choosing

Interventions that are Cost Effective (WHO-CHOICE) assembles regional databases on the costs, population health impact, and cost-effectiveness of key health interventions. Using WHO-defined regions, WHO-CHOICE developed standard tools and methods to generate regional databases for collecting costs and health data. The costs and effectiveness of a wide range of health interventions are determined with probabilistic uncertainty analysis. Currently there is also a contextualization tool that makes it possible to adapt regional results to the country level. Information about health interventions, demography, epidemiology, and cost effectiveness analyses for certain diseases are also available by WHO regions.

Global Burden of Disease (GBD): GBD (most recent version released in 2012) is an international collaboration that describes the global distribution and causes of a wide array of major diseases, injuries, and health risk factors. GBD provides data on, among other things, age and sex-specific mortality, global and regional mortality from 235 causes of death, disability-adjusted life years for 291 diseases, and healthy life expectancy for 187 countries.

Healthcare Cost and Utilization Project (HCUPnet): HCUPnet is a free online data system that provides access to health statistics and information on U.S. hospital inpatient and emergency department utilization, both at the national and the state level. The Nationwide Inpatient Sample (NIS) is particularly important because it contains information found in a typical hospital discharge or billing record. Using this information, HCUPnet provides data for specific conditions and their associated durations of stay, hospital costs, national costs, percent of patients who died in the hospital, and discharge status. However, the national averages are not suited for regional analyses because of geographic differences among and within states both in health care utilization and in costs.

Custom Data Sources

When high-quality data were unavailable or when data sources varied in quality, accuracy, and comprehensiveness, proxy measures were used to produce estimates. Estimates of vaccine manufacturing costs were largely informed by vaccine industry experts on the committee. When the age-specific disease burden for certain diseases was unavailable in South Africa, epidemiologists based in South Africa were contacted via e-mail or telephone for their assistance in developing estimates. Furthermore, disease burden data from South Africa provinces were used in place of national assessments, and vaccine costs and analyses from other low- and middle-

income countries were used to substitute for costs of vaccines in South Africa.

Data Collection Methodology

Population Characteristics: SMART Vaccines was designed to accommodate demographic differences within a country, a region, or a consortium of countries. The U.S. and South African population data were obtained from the WHO country statistics database, which houses actuarial data for various countries.

Population data for each country are given by sex and are divided into 5-year age intervals, with the exception of children under 5, who are further divided into children up to 1 year in age and children from 1 to 5 years old. The data provided for each age interval are the total population (N), the number of people left alive at age x (lx), person-years lived between ages x and x+n (nLx), and life expectancy at age x (ex). The standard life expectancy (sx) is the life expectancy for Japanese women—the group that is known to have the world's longest life expectancy and so is used in calculations for disability-adjusted life-years. The health utilities index 2 (HUI2) is used to estimate the quality of life for people in the various age intervals in order to calculate quality-adjusted life-years. Because HUI2 data are unavailable for South Africa, U.S. estimates were used.

The hourly wage rate is used in estimating the value of time lost to illness; the hourly wage rate of parents is used for children less than 15 years old. The wage rate for South Africa was approximated in U.S. dollars by using the prevailing currency exchange rate.

Special populations can include groups manifesting specific characteristics that ought to be considered in developing or delivering a vaccine—for instance, immunocompromised individuals with multiple comorbidities, or people in a particular state or province within a country. A population table divided into males and females will need to be filled in for this group as well.

To illustrate this further, let us consider a special population that includes HIV-positive individuals. If nearly 2 percent of a country's total population is living with HIV, then the absolute number of people living with HIV can be obtained by multiplying the total population by 0.02. If we assume, for instance, that the life expectancy of an HIV-positive individual is 10 years less than that of a healthy individual, then it is a straightforward matter to fill in the life table for this special population using the standard life table. Similarly, an HIV-positive individual will likely have a lower quality of life and hence a lower HUI2. However, these assumptions will change

depending on the country in question. In a low-income country, HIV is a debilitating condition physically, economically, and socially, whereas it can be managed with anti-retroviral drugs in the United States.

Similarly, a health official may be interested in focusing on a particular province within a country as a special population. In addition to specifying the total population, there would be another step to define the special population—the total number of people (N) in the province, the number of people left alive at age x (lx), the person-years lived between ages x and x+n, (nLx), and the life expectancy at age x (ex). A major concern in creating subsets of a special population from the total population is double counting.[1] To avoid this error, it is important to subtract the special (province) subset from the total (country) population to represent the different population, disease and vaccine characteristics between the two groups.

When using SMART Vaccines to prioritize several vaccines in a population, the demographic data defining that population remain constant, while parameters specifying disease burden and vaccine-related information vary.

Disease Characteristics: To illustrate the methods used to collect data on disease characteristics, we will use the case of influenza in the United States as an example. The first step in estimating disease burden is to estimate age- and sex-specific incidence and case-fatality rates for the selected population. In this case, contrasting claims for the magnitude of influenza incidence and case-fatality rate must be reconciled in order to capture the appropriate and complete burden of disease. This is done by calculating the number of deaths by age and sex using incidence and case fatality rate, and the figures must sum to the total number of deaths for that age–sex group estimated via the standard data sources described above.

Because vaccine-preventable diseases affect sex and age groups differently, it is important to make the distinction between, for example, the disease burden caused in infants and the disease burden in the elderly. This is an important consideration for decision makers thinking about investment in pediatric vaccines versus adult vaccines. Thus, disease burden is specified by sex and in the following age intervals: infants (less than 1 year), children (1 to <20 years), adults (20 to <65 years), and elderly (65 years or older).These age intervals are selected to reflect the availability of data because most disease burden is measured in aggregated age groups of infants, children, adults and elderly. These categories also relieve user

[1] A discussion on potential double counting can be found in Phase I report, pp. 63–65 (IOM, 2012).

burden because the software imports the previously specified age-specific population data to create the aggregated age intervals for the disease burden profile.

Despite the difference in disease burden due to age, influenza affects both sexes equally, thus the incidence and case fatality rate are assumed to be the same for both males and females. However, conditions affecting certain ages or sexes disproportionately will generally have higher mortality for certain groups; for instance, human papillomavirus has higher mortality rates in women because of cervical cancer, while rotavirus causes high mortality in children in low-income countries.

For influenza, the epidemiologic information was obtained from a CDC-based publication examining disease burden and costs associated with seasonal influenza in the United States (Molinari et al., 2007). To estimate age and sex-specific deaths for influenza, consider influenza in female infants (less than 1 year old) in 2009 in the United States: The incidence is 20,300 cases per 100,000 people, there are 2,183,518 female infants (less than 1 year old) and the case fatality rate (the proportion of deaths within those affected with the disease cases) is 0.000040. This information is then used by the software to calculate the number of deaths due to influenza in female infants in the United States by using the following formula: incidence*the population (N) in the age group*case fatality rate = [(20,300/100,000)*2,183,518*0.000040] = 17.73 female infant deaths.

Because disease burden includes both mortality and morbidity, SMART Vaccines allows the user to specify morbidities associated with the disease in question. Morbidities are any conditions causing health and economic burden due to the disease and can be specified simply by stating the consequent condition with its severity, such as mild (influenza without outpatient visit), moderate (influenza without outpatient visit), and severe (influenza with inpatient visit).

Morbidities can also include other complications that are a consequence of the principal condition, such as meningitis, sinusitis, and otitis media due to pneumococcal infection or fever and abdominal pain due to rotavirus. Morbidities are obtained from the disease burden publications relevant for each condition and vaccine (Molinari et al., 2007; O'Brien et al., 2009; Payne et al., 2008).

Health Utility Index 2 and Disability Weights: A reduction in the health-related quality of life for the amount of time an individual is sick is represented using the HUI2. For instance, if a healthy individual with an average HUI2 score of 0.99 is home sick with the influenza for 3 days, his or her quality of life may drop down to, say, 0.90 or perhaps even 0.80 in severe

cases. To account for this reduction in quality of life due to morbidity, disutility tolls are calculated. Disutility tolls represent the difference between the HUI2 of the healthy state prior to illness (0.99) and the state during sickness (0.90), or an overall toll of 0.09.

HUI2 values were used because these are available for the general U.S. population and for the disease and vaccine disutility tolls. The disutility tolls were taken from articles in the refereed literature that directly measured disutilities related to the target conditions. In the absence of such data either reported directly or else indirectly supported in the literature (e.g., used in a cost-effectiveness analysis with substantiated disutility estimates), estimates were obtained using nearest analogy health states to segment the data (Fryback, 2009; Fryback et al., 2007). Individuals' answers to the quality of well-being scale were used to identify relevant health states. The HUI2 values were regressed on an indicator for the health condition and age, the regression coefficient for the indicator being a rough estimate of the toll. The disutility tolls are also rough estimates.

There are several other health utility measures that are available, such as HUI2, HUI3, and EQ-5D, and information from them can be used as well. The only caveat is that users should be consistent throughout the model because the health utility and disutility information is used to calculate QALYs, which will not be appropriately computed if different indexes are used. For example, if HUI3 data are used for the population tables, it is best to also use HUI3-related disutility tolls for the disease and vaccine morbidities, as listed in the disease morbidity and vaccine complications in the Phase I report, *Ranking Vaccines: A Prioritization Framework* (IOM, 2012).

To estimate HUI2 tolls for influenza, individuals' answers on the quality of well-being scale were used to identify relevant health states—e.g., a day with influenza was equated to a positive answer to Question 2(w), which asks respondents which of the past 3 days they have had fever, chills, or sweats. The HUI2 was regressed on an indicator for the health condition and age, and the regression coefficient for the indicator served as a rough estimate of the toll.

To estimate disability weights, datasets from the GBD were used (Salomon et al., 2012). The GBD provides disability weights by categories, such as communicable diseases, cancers, and chronic diseases. For this report, proxies for DALY weights were identified from the GBD 2012 list of conditions that were sufficiently similar to the morbidities in question. Specifically, the proxies were estimated based on the severity of the disease. For instance, GBD 2012 lists the following for infectious diseases: (1) acute episode, mild = 0.005, (2) acute episode, moderate = 0.053, and (3)

acute episode, severe = 0.210. Using these estimates as well as the judgment of clinicians, the DALY weight for influenza was derived based on the severity of the condition—mild, moderate, and acute.

Economic Characteristics: The economic burden of each disease was estimated at the population level. Both payer and societal perspectives were used to calculate direct medical costs, vaccine delivery costs, and workforce productivity costs. Costs were estimated for four outcomes: (1) death due to the disease, (2) outpatient visit due to the disease, (3) hospitalization (with the disease as primary diagnosis), and (4) medication costs (including over-the-counter drugs).

For deaths that occurred in the hospital, the cost for an inpatient admission that resulted in a fatality was obtained using the 2010 HCUPnet. Cost per case was averaged using the disease-associated diagnostic categories, such as the International Classification of Diseases, Ninth Revision (ICD-9) codes for primary diagnosis in the United States (AHRQ, 2012). Hospital costs for a death that occurred due to influenza were estimated to be $6,000.

For hospitalization, the cost for an inpatient admission that resulted in a discharge was also obtained using information from the 2010 HCUPnet. Again, cost per case was averaged using the disease-associated diagnostic categories, such as the ICD-9 codes for primary diagnosis in the United States as listed in HCUPnet (AHRQ, 2012) In the case of influenza, hospitalization costs were not included in the analysis.

Outpatient visits include costs for visits to the physician that did not include hospital admission. Direct medical expenses for outpatient visits included physician costs and outpatient and pharmaceutical needs, such as lab tests, imaging tests, and consults. The outpatient visit costs for influenza were estimated at $250. For cases in which the patient did not seek medical attention, the direct costs were assumed for over-the-counter medications. For example, the average over-the-counter influenza medications cost $3 in the United States (Molinari et al., 2007).

Vaccine Characteristics: If the vaccine under consideration currently exists, data for coverage costs were obtained from CDC and WHO for the United States and South Africa. Vaccine effectiveness and length-of-immunity information were derived from published literature in vaccine randomized control trials. Because effectiveness and length of immunity depend on the location of the population as well as age, sex, and environment, these estimates are specific to regions and demographics. SMART Vaccines also allows the option to "turn on" herd immunity; if herd immunity is applied,

indirect protection is conferred when vaccine coverage is greater than or equal to 80 percent of the target population. Once vaccine coverage reaches the threshold of 80 percent, there are no additional benefits from increasing vaccination coverage because those who are unvaccinated receive protection (according to vaccine effectiveness) from those who have been vaccinated.

Data for cost per dose, doses required per person, and cost to administer per dose were purely hypothetical and based upon proxy vaccines. Cost per dose is generally the price paid by the government to purchase wholesale vaccines from manufacturers. Cost to administer a dose are the costs involved in provision of the vaccine. Because SMART Vaccines considers new preventive vaccines for which these data do not exist, those vaccines that are judged to be sufficiently similar to the one under consideration are used to derive this information. Estimates from industry experts on the committee provided estimates for research and development costs, time to adoption, licensure costs, and one-time start-up costs.

Vaccine safety is not quantified in the current version of SMART Vaccines, it is only included in the qualitative attributes because vaccines considered within the software are hypothetical and may not have this information readily available.

References

AHRQ (Agency for Healthcare Research and Quality). 2012. HCUPnet, healthcare cost and utilization project. http://hcupnet.ahrq.gov.

Fryback, D. G. 2009. United States national health measurement study, 2005–2006. http://www.icpsr.umich.edu/cocoon/NACDA/STUDY/23263 xml: Inter-university Consortium for Political and Social Research (ICPSR) [distributor].

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.

IOM (Institute of Medicine). 2012. *Ranking Vaccines: A prioritization framework: Phase I: Demonstration of concept and a software blueprint*. Washington, DC: The National Academies Press.

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

O'Brien, K. L., L. J. Wolfson, J. P. Watt, E. Henkle, M. Deloria-Knoll, N. McCall, E. Lee, K. Mulholland, O. S. Levine, and T. Cherian. 2009. Burden of disease caused by streptococcus pneumoniae in children younger than 5 years: Global estimates. *Lancet* 374(9693):893–902.

Payne, D. C., M. A. Staat, K. M. Edwards, P. G. Szilagyi, J. R. Gentsch, L. J. Stockman, A. T. Curns, M. Griffin, G. A. Weinberg, C. B. Hall, G. Fairbrother, J. Alexander, and U. D. Parashar. 2008. Active, population-based surveillance for severe rotavirus gastroenteritis in children in the United States. *Pediatrics* 122(6):1235–1243.

Salomon, J. A., T. Vos, D. R. Hogan, et al. 2012. Common values in assessing health outcomes from disease and injury: Disability weights measurement study for the global burden of disease study 2010. *Lancet* 380(9859):2129–2143.

D

Verification and Analyses of the SMART Vaccines Computational Model

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Institute of Medicine

The SMART Vaccines' computational submodel has been used to evaluate ten different scenarios for the following vaccine candidates: influenza, group B streptococcus, human papillomavirus, rotavirus, tuberculosis, and pneumococcal infection for the 2009 U.S. population, and human papillomavirus, rotavirus, tuberculosis and pneumococcal infection for the 2009 South African population.

These baseline scenarios were developed to demonstrate application of the SMART Vaccines computational submodel and determine face validity for health and economic measures output. Sensitivity analysis is performed on two vaccine candidates (influenza in the United States and tuberculosis in South Africa) to verify model calculations and display how variability in inputs affects health and economic measures output. A by-product of these analyses is to provide users a more in-depth understanding of the computational model and highlight the function of population, disease, and candidate vaccine characteristics within the model. These analyses are limited to the computational submodel housed within the SMART Vaccines platform.

The overall SMART Scores rely on a combination of data input by the user including the selected attributes and their weights that define the multi-attribute utility model portion of SMART Vaccines, and the population, disease, and vaccine candidate input parameters that specify the computational submodel. SMART Scores are inherently sensitive to the

selected attributes and weighting input by each user. Therefore, the model evaluation and sensitivity analyses are designed to isolate computational submodel results independent of user preferences. As such, this appendix describes sensitivity analysis scenarios exclusively for attributes of health and economic considerations.

Table D-1 presents the calculated health and economic measures for six vaccine candidates in the United States using data available as accompanying datasets. All attributes included in the health and economic measures are calculated within the model using this baseline input data. The calculated health measures specify the following attributes: premature deaths averted per year, incident cases prevented per year, quality-adjusted life years (QALYs) gained per year, and disability-adjusted life years (DALYs) averted per year. The economic measures are the net direct costs (savings) of vaccine use per year, workforce productivity gained per year, one-time costs, cost-effectiveness in costs per QALY, and cost-effectiveness in costs per DALY.

The computational submodel calculates the health and economic burden due to a disease. Among the six vaccine candidates tested for the United States, influenza vaccine had the highest health impact. Compared to other hypothetical vaccine candidates, a seasonal influenza vaccine candidate with 1-year immunity was shown to potentially avert 11,233 deaths, prevent the incidence in 6,119,401 cases, and produce a gain of 115,665 QALYs per year. Because of its annual administration costs, the net direct costs for the influenza vaccine were considerably higher than the costs of a two- or three-dose vaccine conferring lifetime immunity, such as a human papillomavirus (HPV) vaccine. The model found that a vaccine candidate for HPV was most cost-effective of all the evaluated vaccines because preventing this infection in young women provides them with improved health for the remainder of their lifetimes. In particular, the calculation indicated a gain of 11,238 QALYs per year with minimal costs for administration. Consequently, in this example, vaccine for HPV is a beneficial investment in the long run because its effects are long lasting unlike a seasonal influenza vaccine that only confers health benefits for a year. For some women, the HPV vaccine can result in health gains for as long as their lifetimes, which has an added economic benefit of reduction in the amount of health services otherwise used to treat HPV-associated disease.

Similarly, the computational submodel was also tested for vaccine candidates in the context of South Africa. Table D-2 presents four vaccine candidates with calculated health and economic measures for human papillomavirus, rotavirus, tuberculosis, and pneumococcal vaccine candidates in the South African population using data available online. The

TABLE D-1

Computational Submodel Evaluation for U.S. Vaccine Candidates (2009)

Health Measures	Group B Streptococcus	Human Papillomavirus	Influenza	Pneumococcal Infection	Rotavirus	Tuberculosis
Premature deaths averted per year	1,302	740	11,233	621	102	231
Incident cases prevented per year	16,201	2,340	6,119,401	6,562	237,800	6,580
QALYs gained per year	38,430	11,238	115,665	6,534	2,950	6,017
DALYs averted per year	45,960	12,998	100,145	6,323	3,771	6,871
Economic Measures						
Net direct costs (savings) of vaccine use per year (millions)	390	–42	1,801	–8	118	256
Workforce productivity gained per year (millions)	101	14	3,345	15	95	31
One-time costs	>1 billion	>1 billion	100–500 million	<100 million	<100 million	>1 billion
Cost-effectiveness in costs per QALY	22,103	–3,903	12,821	–1,222	53,857	134,992
Cost-effectiveness in costs per DALY	16,766	–3,475	15,363	–1,333	42,665	105,990

TABLE D-2

Computational Submodel Evaluation for South Africa (2009) Vaccine Candidates

Health Measures	Human Papillomavirus	Pneumococcal Infection	Rotavirus	Tuberculosis
Premature deaths averted per year	1,337	1,212	109	4,935
Incident cases prevented per year	2,531	45,662	6,083	33,575
QALYs gained per year	16,858	13,816	2,491	91,529
DALYs averted per year	26,197	19,628	3,888	151,336
Economic Measures				
Net direct costs (savings) of vaccine use per year (millions)	6	–14	22	–10
Workforce productivity gained per year (millions)	6	7	1	54
One-time costs	<100 million	>1 billion	>1 billion	<100 million
Cost-effectiveness in costs per QALY	2,435	2,659	11,329	–734
Cost-effectiveness in costs per DALY	1,463	1,737	7,413	–440

model shows that a new tuberculosis vaccine would result in about 4,935 premature deaths averted per year, and a pneumococcal vaccine candidate would prevent 45,662 incident cases per year. A tuberculosis vaccine, by preventing new incident cases, could provide the greatest benefit—151,336 DALYs averted per year—and would also be the most cost-effective among the four vaccine candidates.

Sensitivity Analysis

Sensitivity analysis was conducted using a hypothetical influenza vaccine for the United States and a hypothetical tuberculosis vaccine in South Africa, both using 2009 population data. Health and economic attributes were evaluated for each scenario. The health output measures examined include: premature deaths averted per year, incident cases prevented per year, QALYs gained per year and DALYs averted per year. The economic output measures examined include cost per QALY gained, cost per DALY averted, net direct costs of vaccine use per year and workforce productivity gained.

The specific input parameters tested include incidence of the disease, case fatality rate, coverage for a vaccine, vaccine effectiveness, administration costs per dose, health care costs and workforce costs. Each parameter is changed in 25 percent increments from the baseline scenario to observe the resulting trend in attribute under consideration. A –75% to +100% from baseline range was created to encompass the high variation in disease and vaccine characteristics that may be input for each scenario. This testing range also allows for full evaluation of the direction, magnitude, and functional relationship (e.g., linear versus non-linear) between inputs and health and economic measure outputs. That is, trends in economic and health attributes were obtained while altering associated parameters from the baseline scenarios. Lines for each input parameter analysis are purposefully offset such that the trends are clearly visible. Each tested example scenario and the sensitivity analyses tests are described in following sections.

A New Influenza Vaccine for the United States

Using seasonal flu vaccine as the baseline scenario, health considerations were examined for the following attributes: premature deaths averted per year, incident cases prevented per year, QALYs gained per year, and DALYs averted per year. Specific parameters that were tested for sensitivity were incidence of the disease, case fatality rate, coverage for a vaccine, vaccine

effectiveness, administration costs per dose, health care costs, and workforce costs. Each parameter is changed in 25 percent increments from the baseline in order to observe the directional sensitivity of the resulting trend among the attribute under consideration. Results relating to the health-related attributes are presented in Figure D-1.

Figure D-1(a) shows the test results for premature deaths averted per year. As incidence, case fatality rate, coverage, and effectiveness increase, so do the premature deaths prevented per year. An increase in the potential number of cases or an increase in the deadliness of the strain of influenza each provides greater opportunity for a vaccine to produce positive effects, while having a greater percentage of the population covered or having a more effective vaccine each improves the vaccine's ability to take advan-

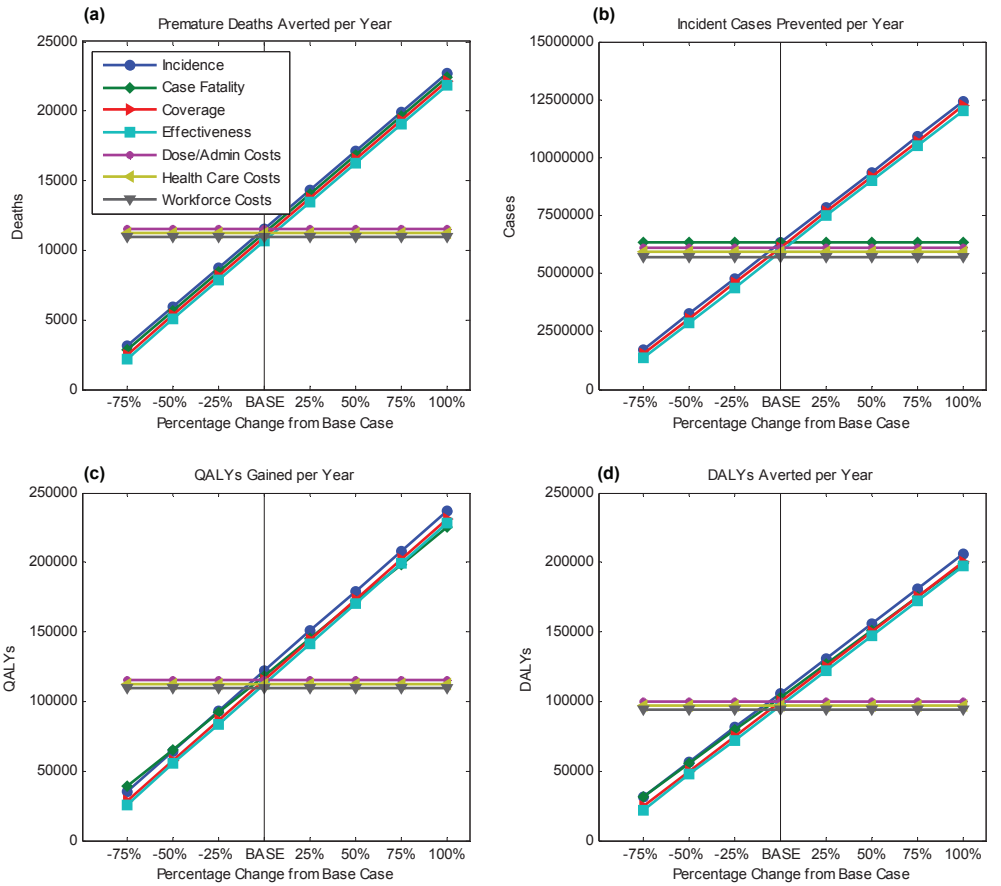

FIGURE D-1
Sensitivity analysis of the health-related attributes for a new influenza vaccine for the United States. The baseline scenarios from 2009 data were used to study the changes in 25 percent increments (–75% to 100%) for (a) premature deaths averted per year, (b) incident cases prevented per year, (c) QALYs gained per year, and (d) DALYs averted per year.

tage of that opportunity. The cost parameters do not influence the health parameters, that is, disease incidence, case fatality, coverage, and effectiveness are independent of the vaccine administration costs, health care costs, and workforce costs.

With regards to incident cases prevented per year, the resultant trend, illustrated in Figure D-1(b), shows that as vaccine coverage and effectiveness increase, there is an increase in the number of incident cases prevented per year. Case fatality rates do not affect incident cases. Although the number of deaths will decrease if the case fatality rate is reduced, the number of incident cases prevented appears to remain the same. Again, cost parameters are independent of the health parameters.

Figure D-1(c) and D-1(d) use 115,665 QALYs gained per year and 100,145 DALYs averted per year, respectively, as baselines, and they show that an increase in disease incidence, case fatality, vaccine coverage, and effectiveness leads to an increase in QALYs gained per year and also DALYs averted per year. A deadly strain of influenza causing a large number of disease cases and deaths for which an effective vaccine with high coverage can be attained, will result in greater gains in health in terms of QALYs gained and DALYs averted.

Further, Figures D-1(c) and D-1(d) show that the case fatality rate line has a slightly different slope than the other plotted parameters. This is because QALYs are comprised of life years lost from death, impairment, and morbidity. When case fatality rate (number of deaths caused by the disease/number of cases due to the disease) is increased, it implies that more cases that would have resulted in impairment or morbidity due to the disease now lead to death. The lines (QALYs and DALYs) have a different slope in panels D-1(c) and D-1(d) because the case fatality rate alters these outcomes only through reducing life-years lost for some of the people who acquire the disease, whereas changing the disease rate (either through changing the coverage or effectiveness of the vaccine) changes QALYs and DALYs in addition by improving the quality of life of all survivors.

Economic considerations were tested for sensitivity using cost-effectiveness and annual costs as measures. In regards to cost-effectiveness, using $12,821 per QALY gained, as shown in Figure D-2(a), and $15,363 per DALY averted as the baseline, as in Figure D-2(b), all parameters were changed in 25 percent increments from the base case in order to observe the resultant trend. The graphs show that an increase in disease incidence and case fatality rate improves the cost-effectiveness of a vaccine. A higher case fatality rate is associated with more deaths and higher health care costs, but net direct costs (delivery costs–health care costs) are shown to decrease because delivery costs are expected to be minimal. Because net

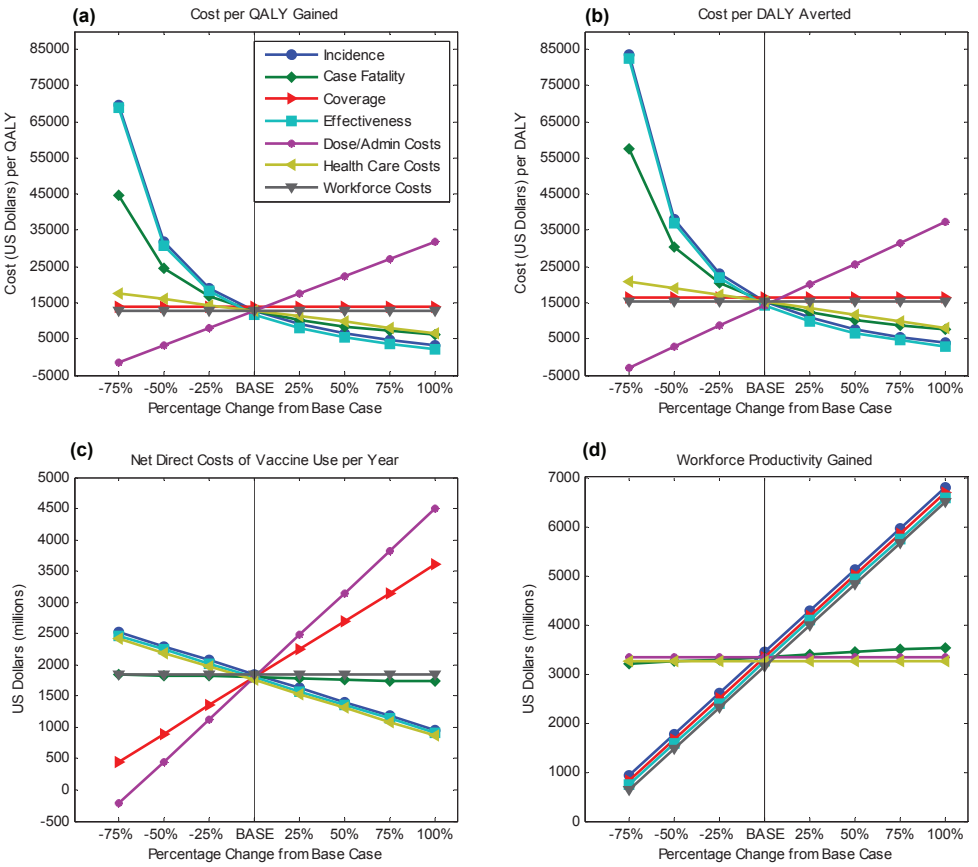

FIGURE D-2
Sensitivity analysis of the economic attributes for a new influenza vaccine for the United States. The baseline scenarios from 2009 data were used to study the changes in 25 percent increments (–75% to 100%) for cost-effectiveness using (a) QALYs and (b) DALYs, and for (c) annual net direct costs associated with the vaccine use and (d) workforce productivity gained per year.

direct costs are calculated by subtracting health care costs from delivery costs, low delivery costs and high health care costs would lead to negative net direct costs. As observed in Table D-1, both HPV and pneumococcal vaccines have negative net direct costs whereas a new influenza vaccine appears to have positive net direct costs that indicate higher delivery costs associated with a seasonal flu vaccine. The output also suggests that as the effectiveness of a vaccine increases, cost-effectiveness ratio for the hypothetical vaccine decreases because a more effective vaccine leads to higher gains in health for the same costs. Anticipated coverage does not seem to affect cost-effectiveness. As administration costs per dose increase, it costs more to produce the same improvement in quality of health; another way to say this is that the cost-effectiveness ratio ($/QALY, $/DALY)—the ratio of

the incremental costs of the vaccine divided by the incremental benefits of the vaccine—increases. Workforce productivity does not affect cost-effectiveness because it is not included in these calculations. As administration costs (i.e., numerator) increase, the cost effectiveness increases.

For evaluating the net direct costs of vaccine use per year, shown in Figure D-2(c), $1,801 is used as a baseline. The graph shows that an increase in incidence, vaccine effectiveness, or health care costs will each result in a decrease in the net direct costs, whereas an increase in coverage or administration costs per dose increases the net direct costs of vaccine use per year. Workforce costs have no effect because they are not included in this calculation. An increase in the case fatality rate will lead to a reduction in net direct costs because a higher case fatality rate will result in more deaths and higher health care costs. Finally, because the net direct costs are calculated by subtracting health care costs from delivery costs, low delivery costs for a vaccine will lead to a decrease in net direct costs.

Next, the net direct costs of vaccine use per year and administration costs (a component of net direct costs) per vaccine dose were examined in relation to the length of immunity for a new influenza vaccine (see Figure D-3). The baseline scenario is represented by the points corresponding to a 1-year immunity. Length of immunity only influences the economic measure of net direct costs—as the length of immunity increases, the net direct costs of vaccine use per year decrease because of the reduction in

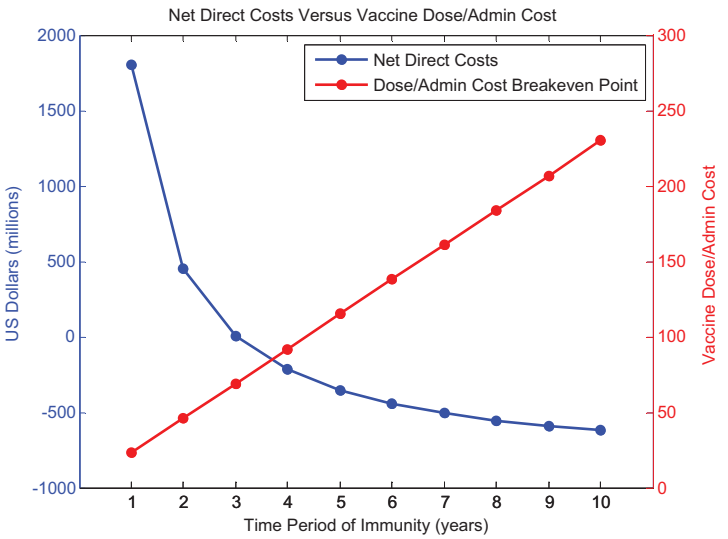

FIGURE D-3
Sensitivity analysis of the net direct costs and administration costs per dose of a vaccine with a given length of immunity for a new influenza vaccine for the United States.

vaccine delivery costs every year. This is because the model assumes that if the length of immunity is 5 years, one-fifth of the target population receives the vaccination each year so as to maintain constant rates of coverage and effectiveness. As a result, the breakeven cost of vaccine dosage and administration of a 5-year vaccine would be five times that of the 1-year baseline vaccine scenario.

A New Tuberculosis Vaccine for South Africa

Using a tuberculosis vaccine in South Africa as the baseline scenario, the health and economic attributes within the computational submodel were evaluated. Health-related attributes include premature deaths averted per year, incident cases prevented per year, QALYs gained per year, and DALYs averted per year. Specific parameters that were tested for sensitivity are the following: incidence of the disease, case fatality rate, coverage for a vaccine, vaccine effectiveness, administration costs per dose, health care costs and workforce costs. Each parameter is changed in 25 percent increments from the baseline in order to observe the resulting trend in attribute under consideration. Results on the health-related attributes are presented in Figure D-4.

Figure D-4(a) shows the test results for premature deaths averted per year. As incidence, case fatality rate, coverage, and effectiveness increase, there is a corresponding increase in premature deaths prevented per year. For the South African population, a new tuberculosis vaccine with high effectiveness and coverage, has the potential to avert more deaths per year.

Next, Figure D-4(b) shows the results of the sensitivity test on the number of incident cases prevented per year. The resultant trend shows that as vaccine coverage and effectiveness increase, the number of incident cases prevented per year increases as well. The case fatality rate does not affect the number of incident cases, although it is directly related to the number of deaths caused by tuberculosis.

Figures D-4(c) and D-4(d) use 91,529 QALYs gained per year and 151,336 DALYs averted per year, respectively, as baselines. It can be seen from the figures that the QALYs gained per year and DALYs averted per year are directly proportional to the disease incidence, case fatality rate, vaccine coverage, and effectiveness. Stated differently, an increase in the number of potential cases of tuberculosis, an increase in the deadliness of the disease, and an increase in the effectiveness or the coverage of the vaccine all result in greater vaccine-produced gains in health, measured either in terms of QALYs gained or in terms of DALYs averted.

To study the economic effects of the vaccine, sensitivity analysis was

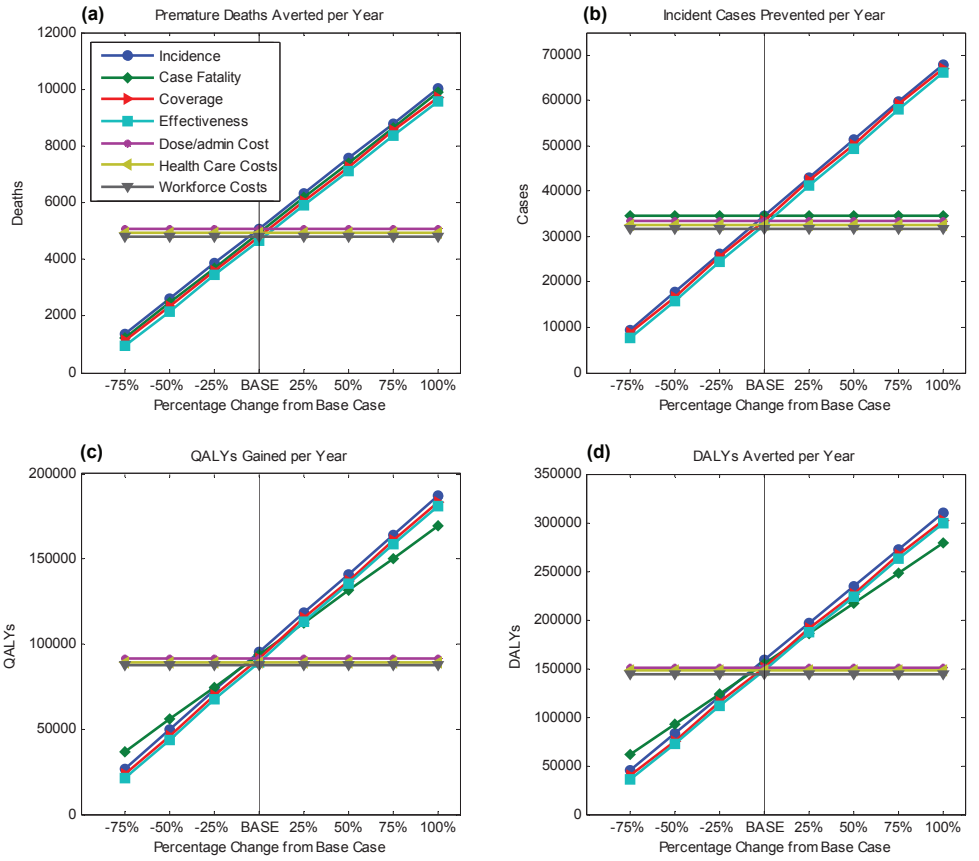

FIGURE D-4
Sensitivity analysis of the health-related attributes for a new tuberculosis vaccine for South Africa. The baseline scenarios from 2009 data were used to study the changes in 25 percent increments (–75% to 100%) for (a) premature deaths averted per year, (b) incident cases prevented per year, (c) QALYs gained per year, and (d) DALYs averted per year.

conducted using cost-effectiveness and annual costs as measures. Using –$734 per QALY gained (see Figure D-5[a]) and –$440 per DALY averted as the baseline (see Figure D-5[b]), all parameters were changed in 25 percent increments from the base case. As can be seen in the figure, as disease incidence increases, the cost-effectiveness ratio for a new tuberculosis vaccine decreases (that is, the value of the vaccine improves). However, an increase in the case fatality rate results in a higher cost-effectiveness ratio because the treatment for tuberculosis and anti-retroviral drug therapies are costly and those alive with long-term morbidities are more expensive to treat than those dying from tuberculosis. In calculating the cost-effectiveness ratio, one compares the overall health care costs with the vaccine (includ-

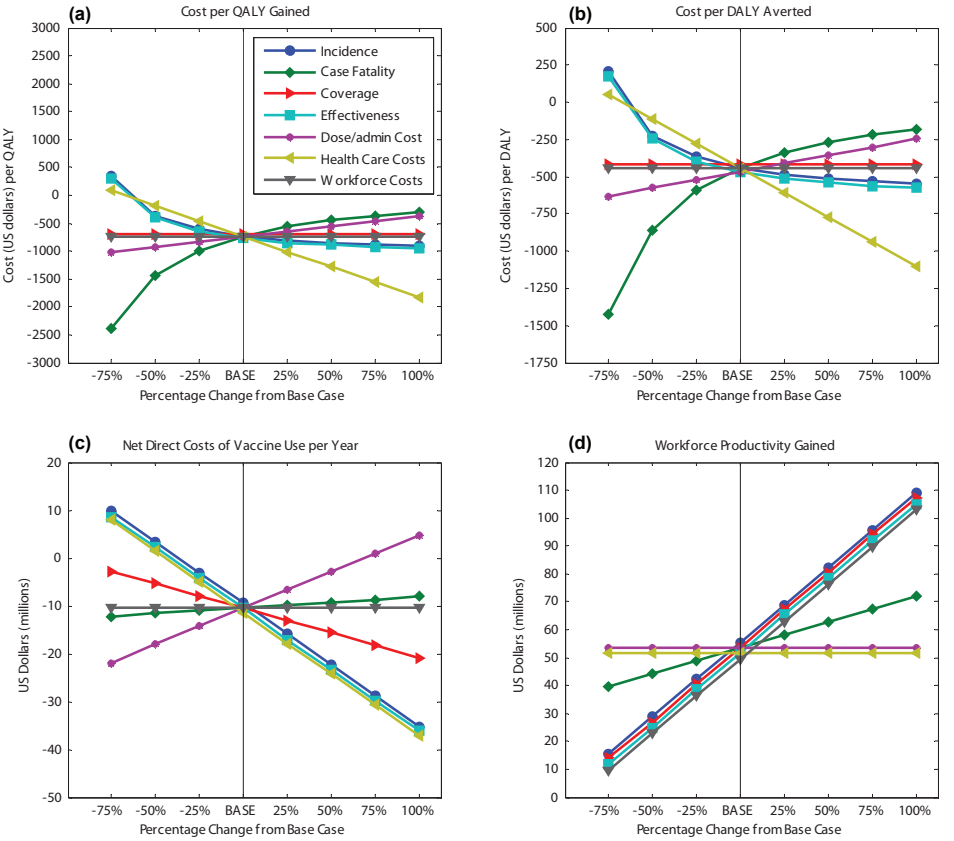

FIGURE D-5
Sensitivity analysis of the economic attributes for a new tuberculosis vaccine for South Africa. The baseline scenarios from 2009 data were used to study the changes in 25 percent increments (–75% to 100%) for cost-effectiveness using (a) QALYs and (b) DALYs, and for (c) annual net direct costs associated with the vaccine use and (d) workforce productivity gained per year.

ing the costs of vaccination) versus the health care costs without the vaccine, and when the case fatality rate is higher, the health care costs without the vaccine are lower, so that the difference between the cost with vaccine and cost without vaccine is greater, leading to a higher cost-effectiveness. That is the numerator of the cost-effectiveness ratio. The denominator—the increase in QALYs or DALYs resulting from the vaccine—will also increase with an increase in case-fatality rates, but not as quickly as the denominator increases. Thus, for a situation in which survivors of a disease impose a great long-term cost on the health care system, the cost-effectiveness ratio of the vaccine will increase when the case fatality rate is higher.

Conversely, the cost-effectiveness ratio decreases as the vaccine

effectiveness increases. Coverage does not affect cost-effectiveness. Nor do workforce costs because they are not included in this calculation.

For evaluating net direct costs of vaccine use per year (see Figure D-5[c]), –$10 is used as the baseline. One can see from the figure that an increase in incidence, vaccine effectiveness, or health care costs will result in a decrease in net direct costs. However, as the case fatality rate increases, the annual net direct costs of vaccine use also increase. The net direct costs (delivery costs–health care costs) rise because of the reduction in health care costs caused by people dying young. This is because a higher case fatality rate results not only in more deaths but also in a reduction in health care costs because, unlike the case in the United States, in South Africa the costs associated with death from tuberculosis are less than the health care costs for treatment of living tuberculosis patients.

This evaluation exercise revealed interesting insights. Calculated health attributes of cases and deaths prevented per year appear to be influenced predominantly by the incidence and case fatality rate caused by the disease, both of which are also included in computing QALYs and DALYs. Anticipated vaccine coverage and effectiveness affect the potential health impact of a vaccine, altering either or both of these parameters can provide users an insight into the ideal range for effectiveness and coverage necessary to achieve the desired health effects.

The sensitivity analysis shows that the health and economic impact of a vaccine is influenced by the anticipated effectiveness and coverage desired from the vaccine as well as the initial health and economic disease burden that can be averted by the candidate vaccine. Therefore, a hypothetical tuberculosis vaccine in South Africa capable of averting 4,935 premature deaths per year (see Table D-2) alludes to the high mortality caused by the TB virus. A potential new tuberculosis vaccine can also lead to a reduction in net direct costs of 10 million per year, this is so because hypothetically the TB vaccine would confer lifelong immunity thus reducing the number of people requiring a vaccine every year. Consequently, yearly vaccine delivery costs would dwindle while the vaccine would remain cost effective, the $/DALY ratio of –440 suggests a potential greater improvement in health (by averting DALYs) for lower costs.

The computational submodel performed as expected—absent user preferences (i.e. the value submodel), a vaccine is most desirable if it produces a large health gain for the least financial investment. A hypothetical human papillomavirus vaccine in the United States is most cost-effective with $/QALY ratio of –3,903 (see Table D-1), assuming an increase in QALYs, a negative number indicates lower costs in the long run. A potential new influenza vaccine has considerable direct costs, $1,801 million,

because the vaccine only confers immunity for one season, i.e. it needs to be administered every year (high delivery costs) and has high morbidity associated with the disease (high health care costs). However, despite the high direct costs, the hypothetical influenza vaccine can lead to large workforce productivity gains, $3,345 million, due to the large number of flu cases prevented each year.

Ideally, a vaccine candidate would reflect the least amount of net direct costs per year, which are calculated as delivery costs–health care costs. Correspondingly, in an ideal situation, the delivery costs for the vaccine would be low because the long length of conferred immunity would preclude many from receiving the vaccine each year while the health care costs associated with the targeted disease would decrease as the vaccine would reduce mortality and morbidity initially caused by the disease. Such a vaccine would also have a low cost effectiveness rate with larger gains in health (i.e., QALYs) and lower costs.

Lastly, because health and economic measures of a vaccine are quantifiable and are generally the important elements in decision making, users interested in these aspects of a vaccine will rank health and economic attributes highly, thus weighing health and economic measures highly within their SMART Score output. Hence, a detailed understanding of the quantifiable attributes will inform the user in selecting, ranking, and weighing attributes.

E

Stakeholder Speakers

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

PHYLLIS ARTHUR, Senior Director, Vaccines, Immunotherapeutics and Diagnostics Policy, Biotechnology Industry Organization

JOHN BOSLEGO, Director, Vaccine Development Program, PATH

CARTER DIGGS, Senior Technical Advisor, Malaria Vaccine Development Program, U.S. Agency for International Development

PHILIP ECKHOFF, Research Scientist and Principal Investigator, Disease Modeling Team, Intellectual Ventures

IRENE ECKSTRAND, Scientific Officer, Models of Infectious Disease Agent Study, National Institute of General Medical Sciences, National Institutes of Health

RAINER ENGELHARDT, Assistant Deputy Minister, Infectious Disease Prevention and Control Branch, Public Health Agency of Canada

ALEXANDER GARZA, Assistant Secretary for Health Affairs and Chief Medical Officer, Department of Homeland Security

ANN GINSBERG, Vice President, Scientific Affairs, Aeras

MARION GRUBER, Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration

DAVID HAMMER, Product Manager, Joint Vaccine Acquisition Program, Chemical Biological Medical Systems, Department of Defense

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

SETH HETHERINGTON, Chief Medical Officer, Genocea Biosciences; Member, National Vaccine Advisory Committee

JOACHIM HOMBACH, Senior Adviser, Department of Immunisation, Vaccines and Biologicals, World Health Organization

PETER HOTEZ, President, Albert Sabin Vaccine Institute, and Dean, National School of Tropical Medicine, Baylor College of Medicine

ROBERT KOLODNER, Chief Health Informatics Officer and Acting Executive Officer, Open Health Tools

PRASAD KULKARNI, Medical Director, The Serum Institute of India Limited

DIANA LANCHONEY, Executive Director, Vaccine Ventures and New Products, Merck & Company

TIMOTHY LANT, Director, Analytic Decision Support, Biomedical Advanced Research and Development Authority, Department of Health and Human Services

OSMAN MANSOOR, Senior Health Advisor, New Vaccines, United Nations Children's Fund

RICHARD MARTINELLO, Chief Consultant, Clinical Public Health, Department of Veterans Affairs

GENEVIEVE MEIER, Health Economics Manager, North America Vaccines Division, GlaxoSmithKline Vaccines

CHRISTOPHER MURRAY, Director, Institute for Health Metrics and Evaluation, University of Washington School of Medicine

ALEX PALACIOS, Special Representative, GAVI Alliance

PATRICIA QUINLISK, Medical Director, Iowa Department of Health

ROBIN ROBINSON, Director, Biomedical Advanced Research and Development Authority, Department of Health and Human Services

JEFFREY STURCHIO, Senior Partner, Rabin Martin

MELINDA WHARTON, Deputy Director, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention

F
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 the 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 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.

Jonathan Carlson, Ph.D., is a researcher in the eScience group at Microsoft Research, where he studies viral evolution, immunology, and vaccine design through statistical modeling. His models of viral escape have achieved broad recognition in the HIV community, where they have led to the discovery of novel viral–host interactions, insights into mechanisms of

natural immune control, and the identification of vaccine candidates that are slated for clinical trials. He has served on advisory panels for the Bill & Melinda Gates Foundation and the Center for HIV/AIDS Vaccine Immunology. Carlson received his B.A. from Dartmouth, where he was awarded the top senior thesis prizes in both biology and computer science, and his Ph.D. in computer science from the University of Washington, where he was awarded the university's distinguished dissertation award and was a finalist for the U.S. Council of Graduate Schools' dissertation award for his work on HIV adaptation.

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 there included vice president of science and technology, vice president of ventures technology, and both vice president and director of applied concepts research. He is currently a senior fellow at the William J. von Liebig Center for Entrepreneurism and Technology and an adjunct professor in the Department of Bioengineering at the University of California, San Diego. 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. He 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 emeritus 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 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, the American Institute of Biological Sciences, and the International Union of Microbiological Societies. Colwell has been awarded 56 honorary degrees from institutions of higher education, including her alma mater, Purdue University. Colwell holds a B.S. in bacteriology, 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, the Royal Society of Canada, the Royal Irish Academy, and the American Philosophical Society. She is the recipient of the Order of the Rising Sun bestowed by the emperor of Japan, the Stockholm Water Prize awarded by the king of Sweden, 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 Medicine. 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. She next 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's 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.

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 more than 30 years ago. He is a member of the Institute of Medicine.

Glenda Gray, M.B.B.Ch., is executive director of the Perinatal HIV Research Unit and associate professor of pediatrics at University of the Witwatersrand, South Africa. She is based at the Chris Hani Baragwanath Hospital, where she is the principal investigator of the Soweto Clinical Trials Unit. She has expertise in the field of mother-to-child transmission of HIV, adolescent HIV prevention and treatment, and HIV vaccine and microbicide research. She has received the *Femina* "Woman of the Nineties" award, Nelson Mandela Health and Human Rights award, and International Association of Physicians Against AIDS's "Hero of Medicine" award for her research contributions. Gray received her medical degree from the University of Witwatersrand and was a fellow of College of Physicians of South Africa in pediatrics. She was awarded a Fogarty Training Fellowship at Columbia University and completed an intensive program in clinical epidemiology at Cornell University. She is a member of the Academy of Science in South Africa and a member of the Institute of Medicine.

Michel Guillot, Ph.D., is an associate professor of sociology at the University of Pennsylvania and a research associate at its Population Studies Center. He is a demographer specializing in the areas of formal demography and population health. Initially trained in France, Guillot obtained a Ph.D. in demography and sociology from the University of Pennsylvania in 2000. After a postdoctoral fellowship at the Harvard Center for Population and Development, he joined the Department of Sociology at the University of Wisconsin and subsequently returned to the University of Pennsylvania as a faculty member. In the area of formal demography, Guillot's research

deals with designing new approaches for measuring population health and understanding population dynamics.

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 and developed a platform technology to reduce the cost of malaria drugs by more than tenfold. Presently Hale is founder and chief executive officer of Medicines360, a second-generation nonprofit pharmaceutical company. Their first product is a hormonal interuterine device, currently in Phase 3 clinical trials in the United States. Hale established her expertise in all stages of biopharmaceutical drug development at the U.S. Food and Drug Administration and at Genentech, Inc. She earned her Ph.D. from the University of California, San Francisco, where she maintains an adjunct associate professorship in biomedical engineering and therapeutic 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.

Joseph Jasinski, Ph.D., is an IBM Distinguished Engineer and the Global Industry Executive for Smarter Healthcare and Life Sciences at IBM Research. In this role he is responsible for developing strategies and coordinating research efforts across IBM's Research Division in areas ranging from the use of information technology in payer/provider health care to computational studies in molecular biology. Prior to his current position, Jasinski was worldwide operations manager for IBM Life Sciences, where he was responsible for day-to-day operations and strategy for one of IBM's fastest growing new businesses. He has also served as the senior manager of the Computational Biology Center at IBM Research and managed and carried out research in nanotechnology, materials chemistry, and chemical kinetics in his career with IBM. Jasinski graduated from Dartmouth College with an A.B. in mathematics and chemistry and received a Ph.D. in chemistry from Stanford University, where he held a National Science Foundation pre-doctoral fellowship. Following postdoctoral work at the University of California, Berkeley, he joined the IBM Thomas J. Watson Research Center as a research staff member in 1982. Jasinski is a fellow of the American Physical Society and the American Association for the Advancement of Science.

Tracy Lieu, M.D., M.P.H., is director of the Division of Research at Kaiser Permanente Northern California. She was previously a 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 Kaiser Permanente Northern California. 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 carrying out 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. She is a member of the Institute of Medicine.

Charles Phelps, Ph.D., is a 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. In 1984 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 and an M.B.A. in hospital administration and a 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 of vaccines research at Chiron Corporation. Rino joined IRIS, the Chiron S.p.A. Research Institute, in 1992 and attained 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 Sclavo Research Center and a visiting scientist at Harvard Medical School and the Rockefeller Institute. He is the author of more than 500 original papers in peer-reviewed journals and has served as a 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 Paul Ehrlich and Ludwig Darmstaedter Prize, the Gold Medal by the president of Italy for contributions to public health, the Albert B. Sabin Gold Medal, the Lifetime Achievement Award from the Institute of Human Virology, and the Excellence Award from the European Society of Clinical Microbiology and Infectious Diseases. He is a member of the 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 a professor of epidemiology and biostatistics and a 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 as vice-chair of the World Health Organization's Strategic Advisory Group of Experts on vaccines and vaccine policy. He is also director of the California Emerging Infections Program and of the U.S. National Institutes of Health Fogarty AIDS International Training and Research Program at 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.

Edward Shortliffe, M.D., Ph.D., is a professor at Arizona State University, adjunct professor of biomedical informatics at Columbia University, and a scholar in residence at the New York Academy of Medicine. Previously, he served as president and chief executive officer of the American Medical Informatics Association. He has also served on the faculty of the University of Texas Health Science Center and 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 University College of Physicians and Surgeons and professor of medicine and of computer science at Stanford University. He received his A.B. in applied mathematics from Harvard College and 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.

Robert Steinglass, M.P.H., is an immunization team leader for the Maternal and Child Health Integrated Program at John Snow, Inc., and the 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 that are 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's 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 is a member of WHO's Immunization Practices Advisory Committee, the Vaccine Presentation and Packaging Advisory Group, the Program Advisory Group of Project Optimize, and the Cold Chain and Logistics Task Team. He recently led one of the delivery working groups for the Decade of Vaccines and advised both the Centers for Disease Control and Prevention and WHO on their global immunization implementation research agenda.

Oyewale Tomori, D.V.M., Ph.D., is vice-chancellor emeritus and professor at Redeemer's University in Nigeria. Tomori received his D.V.M. from the Ahmadu Bello University, Zaria, and his Ph.D. in virology from the University of Ibadan. Tomori's research interests include a wide range of human viruses as well as zoonotic and veterinary viruses, including the yellow fever virus, the Lassa fever virus, the poliomyelitis virus, the measles virus, the Ebola virus, and a hitherto unknown virus, the Orungo virus, which he elucidated the properties of and registered with the International Committee of Virus Taxonomy. He served as head of the department of virology at the University of Ibadan, and he was later appointed as the regional virologist for the World Health Organization (WHO) Africa Region. During his 10-year tenure with WHO, he set up the African Regional Polio Laboratory Network, consisting of 16 laboratories, which provides diagnostic support to the global polio eradication initiative. In addition, Tomori has served on several WHO advisory committees and expert groups. He received the Nigerian National Order of Merit, the country's highest award for academic and intellectual attainment and national development, and the Nigeria National Ministry of Science and Technology Merit Award for excellence in medical research. Tomori is a fellow of the Academy of Science of Nigeria, a fellow of the College of Veterinary Surgeons of Nigeria, and a fellow of the Royal College of Pathologists of the United Kingdom. He is president of the Nigerian Academy of Sciences.

Detlof von Winterfeldt, Ph.D., is a professor of industrial and systems engineering at the Viterbi School of Engineering at the University of Southern California (USC). He also holds appointments as professor of public policy at the USC Sol Price School of Public Policy. He served as director of the International Institute for Applied Systems Analysis in Austria and cofounded and directed the National Center for Risk and Economic Analysis of Terrorism Events, the first university-based Center of Excellence funded by the U.S. Department of Homeland Security. His research interests are in the foundation and practice of decision and risk analysis as applied to

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Staff

Guruprasad Madhavan, Ph.D. (*Study Director*), is a senior program officer with the Board on Population Health and Public Health Practice at the Institute of Medicine. He is also a senior 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 a number of awards, including the AT&T Leadership Award, the SUNY Chancellor's Promising Inventor Award, the Institution of Engineering and Technology's Mike Sargeant Career Achievement 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 is a founding member of the Global Young Academy, and has co-edited four books. He has also been named as one of the "New Faces of Engineering" in *USA Today*, and as a distinguished young scientist by the World Economic Forum.

Kinpritma Sangha, M.P.H., is a research associate with the Board on Population Health and Public Health Practice at the Institute of Medicine. She has worked at 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

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Angela Martin, B.S., is a senior program assistant with the Board on Population Health and Public Health Practice at the Institute of Medicine. She previously worked with the Board on Army Science and Technology at the National Research Council. She received a B.S. degree in psychology with a minor in English from the University of Maryland University College. She received an honorable discharge from the U.S. Navy after serving 6 years on active duty and is currently an inactive member of the U.S. Air Force Reserves, where she serves as a flight attendant on distinguished visitor airlifts.

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 postmarketing, the soundness and ethical conduct of clinical trials to reduce mother-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, and the Cecil Award, the highest distinction for a staff member of the Institute of Medicine.

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, 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 received 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

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, 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 the World Health Organization. He has received the Emil M. Mrak International Award from the University of California, Davis; the Distinguished Service Medal—the highest award of U.S. Public Health Service—for leadership in polio eradication in Southeast 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.

Mark Feinberg, M.D., Ph.D., is vice president and chief public health and science officer for Merck Vaccines at Merck & Co., Inc. Prior to joining Merck, Feinberg worked for more than 20 years in both academia and government, where he was actively engaged in basic and clinical research, patient care, and health care policy with a primary focus on HIV/AIDS pathogenesis, treatment, and prevention research. Feinberg has also served

as a member of several committees of the Institute of Medicine and the National Academy of Sciences, on the National Vaccine Advisory Committee, and numerous other advisory boards. He is a recipient of an Elizabeth Glaser Scientist Award from the Pediatric AIDS Foundation and an Innovation in Clinical Research Award from the Doris Duke Charitable Foundation. Feinberg is a fellow of the American College of Physicians and a member of the Association of American Physicians and the Council on Foreign Relations.

David Heymann, M.D., is chairman of the U.K. Health Protection Agency. He is also the head of the Centre on Global Health Security at Chatham House and a professor of infectious disease epidemiology at the London School of Hygiene and Tropical Medicine. Previously he was the World Health Organization's (WHO's) assistant director-general for health security and environment and the representative of the director-general for polio eradication. Earlier, he was executive director of the WHO Communicable Diseases Cluster, director of the WHO Programme on Emerging and Other Communicable Diseases, and the chief of research activities in the WHO Global Programme on AIDS. Before joining WHO, Heymann worked as a medical epidemiologist in sub-Saharan Africa on assignment from the U.S. Centers for Disease Control and Prevention. Prior to that, he worked in India for 2 years as a medical epidemiologist in the WHO Smallpox Eradication Programme. Heymann has been awarded the American Public Health Association's Award for Excellence, the Donald Mackay Award from the American Society for Tropical Medicine and Hygiene, and the Heinz Award on the Human Condition. He has been appointed an honorary Commander of the Most Excellent Order of the British Empire for his services to global public health. Heymann is an elected member of the U.K. Academy of Medical Sciences and the Institute of Medicine.

Scott Levin, Ph.D., is an associate 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 the 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.

Tyler Martin, M.D., served as the president, chief medical officer, and a director on the board of Dynavax Technologies. Martin has almost 20 years of drug development experience. Before joining Dynavax, Martin was president of Humabs, LLC. Previously Martin worked at Chiron as the vice president in charge of development and as the director of clinical research. In his 7 years at Chiron, Martin led the team responsible for the development of the novel vaccine adjuvant MF59, the first vaccine adjuvant licensed by regulatory agencies since alum, which was approved as part of the FLUAD influenza vaccine in Europe. He has also held senior development and research positions at Sangamo, Inc.; Valentis, Inc.; and SyStemix/GTI. Martin received a B.S. in chemistry and an M.D. from the University of Nebraska. He completed his fellowship in pediatric infectious diseases and molecular microbiology at Washington University in St. Louis.

Simon Mercer, D.Phil., is director of health and well-being at Microsoft Research Connections. He leads the creation of a global strategic portfolio of collaborations between Microsoft researchers and academics. Before joining Microsoft, Mercer was director of software engineering at Gene Codes Corporation, a company specializing in the sequencing and analysis of DNA. Prior to this, Mercer worked in a variety of jobs related to the application of computing to challenges in the life sciences, including at the UK Medical Research Council to establish the Human Chromosome Abnormality Database, a health care resource subsequently adopted by the UK National Health Service. He then moved to the Max Planck Institute for Molecular Genetics in Berlin, where he helped to create the primary database of the German human genome project. Mercer also led research and development initiatives at Sanger Institute in Cambridge and later became a director in the National Research Council of Canada, where he managed the Canadian Bioinformatics Resource, a pioneer in nationally distributed bioinformatics services and grid technology. Mercer holds a B.Sc. from London University and a doctorate from Oxford. He has also completed training as an ORACLE database administrator and holds several patents in the area of computational biology and health care.

Paul Radspinner, M.B.A., is president and chief executive officer of FluGen, Inc., an influenza vaccine and vaccine-delivery company. After completing his M.B.A. at Northwestern University's Kellogg Graduate School of Management, he spent more than 15 years in management roles oversee-

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John Spika, M.D., is director general of the Centre for Immunization and Respiratory Infectious Diseases at the Public Health Agency of Canada. He also serves as the health portfolio task force leader for pandemic (H1N1) influenza preparations and response. Spika is a specialist in pediatric infectious diseases and has worked in public health for more than 25 years, including time at the U.S. Centers for Disease Control and Prevention (CDC), Health Canada/Public Health Agency of Canada, and the World Health Organization Regional Office for Europe. He is a graduate of the CDC Epidemic Intelligence Service program. He is widely published on subjects related to immunization, host defense, and foodborne and respiratory diseases.