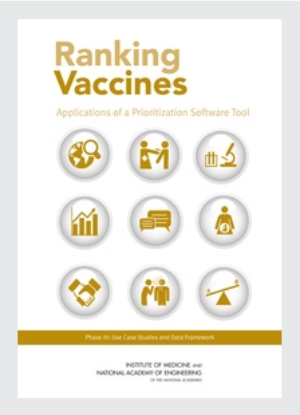

Ranking Vaccines: Applications of a Prioritization Software Tool: Phase III: Use Case Studies and Data Framework

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AUTHORS

Guruprasad Madhavan, Charles Phelps, Rino Rappuoli, Rose Marie Martinez, and Lonnie King, Editors; Committee on Identifying and Prioritizing New Preventive Vaccines for Development, Phase III; Board on Population Health and Public Health Practice; Board on Global Health; Institute of Medicine; National Research Council

Ranking Vaccines

Applications of a Prioritization Software Tool

Phase III: Use Case Studies and Data Framework

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

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

Guruprasad Madhavan, Charles Phelps, Rino Rappuoli,
Rose Marie Martinez, and Lonnie King, *Editors*

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Software Link: SMART Vaccines 1.1 can be downloaded from **www.nap.edu/smartvaccines.**

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

LONNIE KING (*Chair*), Dean, College of Veterinary Medicine, and Executive Dean, Health Sciences College, Ohio State University

PAUL CITRON, Retired Vice President, Medtronic, Inc.; Senior Fellow, William J. von Liebig Center for Entrepreneurism and Technology; and Adjunct Professor of Bioengineering, University of California, San Diego

RITA COLWELL, Chair Emeritus, Canon U.S. Life Sciences, Inc.; Distinguished Professor, University of Maryland, College Park, and Johns Hopkins Bloomberg School of Public Health; and Former Director, National Science Foundation

SIMON MERCER, Director, Health and Wellbeing, Microsoft Research Connections

CHARLES PHELPS, University Professor and Provost Emeritus, University of Rochester

RINO RAPPUOLI, Global Head, Vaccines Research, Novartis Vaccines, Italy

EDWARD SHORTLIFFE, Professor, Arizona State University; Adjunct Professor of Biomedical Informatics, Columbia University; and Scholar in Residence, New York Academy of Medicine

PETER SPEYER, Chief Data and Technology Officer, Institute for Health Metrics and Evaluation, University of Washington

GUY STEELE, Software Architect, Oracle Labs

Staff

GURUPRASAD MADHAVAN, Project Director

KINPRITMA SANGHA, Associate Program Officer (until July 2014)

ANGELA MARTIN, Senior Program Assistant

HOPE HARE, Administrative Assistant

DORIS ROMERO, Financial Associate

ROSE MARIE MARTINEZ, Senior Director, Board on Population Health and Public Health Practice

PATRICK KELLEY, Senior Director, Board on Global Health

PROCTOR REID, Director, Program Office, National Academy of Engineering

Consultants

LORI ADAKILTY, Principal Program Manager, Microsoft Research Connections

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

PRASAD KULKARNI, Medical Director, Serum Institute of India Limited

SCOTT LEVIN, Associate Professor of Emergency Medicine, Johns Hopkins University

EDUARDO GUZMÁN MORALES, Technical Advisor to the Undersecretary of Prevention and Health Promotion, Ministry of Health, Mexico

ESTEFANÍA DE LA PAZ NICOLAU, Advisor to the Undersecretary of Prevention and Health Promotion, Ministry of Health, Mexico

PATRICIA SATJAPOT, Associate Director, Johns Hopkins Medical International

SAULEH SIDDIQUI, Assistant Professor of Civil Engineering and Applied Mathematics & Statistics

JOHN SPIKA, Director General, Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada

Reviewers

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:

Rafi Ahmed, Emory Vaccine Center and Emory University School of Medicine
David Banta, Consultant on Health Technology Assessment
Diane Griffin, Johns Hopkins Bloomberg School of Public Health
Demissie Habte, Ethiopian Academy of Sciences
Joseph Jasinski, IBM Research
Gary Nabel, Sanofi
Sachiko Ozawa, Johns Hopkins Bloomberg School of Public Health
Patricia Quinlisk, Iowa Department of Public Health
Laura Snyder Rosema, Global Good
Oyewale Tomori, Nigerian Academy of Sciences
Christopher Wilson, The Bill & Melinda Gates Foundation

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 **Harold Sox** from Dartmouth Institute for Health Policy and Clinical Practice, and Patient-Centered Outcomes Research Institute, and **Lawrence Brown** from the

University of Pennsylvania. Appointed by the National Research Council and the Institute of Medicine they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

One of the greatest accomplishments in global public health has been the development and use of vaccines. However, making decisions about vaccine development and their utility are becoming progressively more complex and based on a wide variety of factors. Further, these factors may vary greatly across different settings, which may ultimately result in different priorities for vaccine development and delivery.

To help facilitate improved decision making and to provide a common language across various stakeholders, the Institute of Medicine (IOM) in collaboration with the National Academy of Engineering has enhanced Strategic Multi-Attribute Ranking Tool for Vaccines—SMART Vaccines—a groundbreaking software product from the National Academies. The enhancements to the software and its use by three early stage users are discussed in this report that follows the earlier publications *Ranking Vaccines*: *A Prioritization Framework* (Phase I, 2012) and *Ranking Vaccines*: *A Prioritization Software Tool* (Phase II, 2013). These reports and the enhanced software version are available for free download at www.nap.edu/smartvaccines.

In this phase, the committee has demonstrated the practical applications of SMART Vaccines through use case scenarios in partnership with the Public Health Agency of Canada, New York State Department of Health, and the Serum Institute of India. The committee has also explored a novel application of SMART Vaccines in determining new vaccine product profiles and has offered practical strategies for data synthesis and estimation to encourage the broader use of the software.

Just as any software product, enhancements to SMART Vaccines will rely on critical user evaluations and their commitment to cycles of continuous learning and improvement. The committee envisions the use and adoption of this software by a range of stakeholders in the vaccine and the broader public health communities. In addition, SMART Vaccines could

serve as a unique tool for interdisciplinary academic programs across health sciences, engineering, and business management. Finding a reliable host for SMART Vaccines is especially critical to ensure that the tool undergoes further improvements and serves as a focal point for collaborative discussions among different users.

On behalf of the committee, I would like to thank and acknowledge a group of individuals who diligently and adroitly helped to develop the latest iteration of SMART Vaccines and produce this report. The committee is appreciative of, and indebted to, the extremely talented IOM staff, including our project director Guru Madhavan and data manager Kinpritma Sangha. Both of them have superbly contributed to this project series and have been especially recognized by the IOM for their innovative work on SMART Vaccines.

The committee has immensely benefitted from the guidance of Harvey Fineberg, former president of the IOM, Rose Marie Martinez, senior director of the IOM Board on Population Health and Public Health Practice, Patrick Kelley, senior director of the IOM Board on Global Health, Marc Gold, associate general counsel of the National Academy of Sciences, and Proctor Reid, director of programs at the National Academy of Engineering.

The committee appreciates the support of Chelsea Frakes, Greta Gorman, and Angela Martin for their superb assistance during various stages of this project. We wish to acknowledge the excellent technical work of Scott Levin, Patricia Satjapot, and Sauleh Siddiqui of Johns Hopkins University, and the terrific editorial support of Robert Pool.

A special thanks and recognition is also in order for Lori Adakilty, who added great value to our work in guiding our usability studies with the Public Health Agency of Canada, New York State Department of Health, and the Serum Institute of India. At these three organizations, we are appreciative of John Spika, Guthrie Birkhead, and Prasad Kulkarni, and their colleagues Ping Yan, Ken Eng, Gina Charos, Debra Blog, Lynn Berger, and S. Vinayak among others. Likewise, we are indebted to an exceptional group of reviewers whose insights greatly enhanced our products.

Final thanks go to the National Vaccine Program Office, the Fogarty International Center of the National Institutes of Health, and the National Academies' Presidents Committee for their sponsorship, commitment, and support of this project.

Lonnie King, *Chair*

Contents

Disclaimer

This report describes SMART Vaccines—Strategic Multi-Attribute Ranking Tool for Vaccines—an early stage software application intended to serve only as a decision-support tool. Specific decisions about vaccine 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, the National Academy of Engineering, 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.

December 2014

Summary

In 1892 Ralph Waldo Emerson famously wrote in *The Conduct of Life* that "the first wealth is health." Vaccines not only have profoundly improved health and conferred economic benefits to our societies but also have provided a range of other, broader advantages that are hard to capture. Thus, if one wishes to evaluate and prioritize vaccines, either those vaccines in use or those under development, then it is necessary to use a much broader framework than one based purely on health or cost-effectiveness indicators.

The Foundational Work on SMART Vaccines

At the request of the National Vaccine Program Office of the U.S. Department of Health and Human Services, the Institute of Medicine (IOM) initiated a sequence of projects in early 2011 to help provide guidance in prioritizing new vaccines for development. This effort has proceeded in three phases, each building on the key objective of the U.S. National Vaccine Plan: "Develop a catalogue of priority vaccine targets of domestic and global health importance" (HHS, 2011).

The Phase I report, *Ranking Vaccines: A Prioritization Framework* (IOM, 2012), introduced an analytical model that employed multi-attribute utility theory, a specific version of the general class of multi-criteria decision-analysis tools. The decision to use multi-attribute utility modeling represents an important change from the previous IOM approaches to prioritizing vaccines for development. A pair of reports from the mid-1980s selected a single attribute for ranking vaccines—infant mortality equivalents, or what would now be considered "life-years saved" (IOM, 1985, 1986). A subsequent report chose an entirely different metric—cost-effectiveness ratio—as the sole criterion for ranking vaccine candidates for development (IOM, 2000). Thus, the 1985–1986 studies used a direct

health benefit measure, and the 2000 study used an efficiency measure to produce lists of rank-ordered priorities.

The Phase I committee's decision to use a multi-attribute approach was driven in large part by stakeholder feedback indicating that the narrow focus of the earlier studies limited the value of these tools to the many decision makers in the global vaccine community. The Phase I report discussed the testing of the multi-attribute utility model[1] using data for hypothetical vaccines to prevent influenza, group B streptococcus, and tuberculosis in the United States and South Africa. The committee also presented the blueprint of a software system called Strategic Multi-Attribute Ranking Tool for Vaccines, or SMART Vaccines Beta. The multi-attribute utility model embedded in SMART Vaccines allows users to specify which attributes are of highest importance to them and also allows users to specify the amount of weight given to each selected attribute. This was a novel approach in an enterprise that had traditionally relied on priority lists.

The Phase II committee enhanced the model and conducted extensive testing using additional data for hypothetical vaccines for the prevention of pneumococcal infection, human papillomavirus, and rotavirus. A broad range of attributes intended to address a variety of stakeholder interests—28 attributes in total, plus 7 user-defined entries (see Table S-1)—were embedded in SMART Vaccines. This software version, which was programmed in a Matlab environment that was operational only with the Windows operating system, was released for public use in fall 2013. The Phase II committee issued specific guiding principles for the future development of SMART Vaccines in its report *Ranking Vaccines: A Prioritization Software Tool* (IOM, 2013).

Potential Applications of SMART Vaccines

SMART Vaccines is expected to be of use to a variety of decision makers in the public, private, nongovernmental, and other sectors of the vaccine enterprise. Specifically, those users could include ministries and departments of health involved in research, development, delivery, and preparedness efforts relating to new or existing vaccines; industrial manufacturers

[1] The multi-attribute utility model embedded in SMART Vaccines consists of a computational submodel and a value submodel. Background information on these submodels, the overall modeling strategy, mathematical functions, and the associated assumptions (e.g., with costs and time horizon) are explained in *Ranking Vaccines: A Prioritization Framework* (IOM, 2012). Information about the model refinements and testing are included in *Ranking Vaccines: A Prioritization Software Tool* (IOM, 2013). This information is not repeated in this report.

TABLE S-1

Choices of Attributes in SMART Vaccines 1.1

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.

interested in product profile improvements, among other aspects of vaccines and pharmaceuticals; and donor foundations and global and regional vaccine initiatives involved in or supporting vaccine-implementation programs.

This committee emphasizes a point that the Phase I and Phase II committees have already stressed: *SMART Vaccines is only a decision-support system and not intended to be used as a decision maker*. The Phase I committee recognized in its report that "a major use of SMART Vaccines

will be to facilitate discussions about attributes and values among diverse users, helping them to converge upon mutually beneficial priorities and collaborations" (IOM, 2012, p. 8).

Furthermore, this committee recapitulates the Phase I committee's starting vision:

> [V]arious organizations could use SMART Vaccines independently to guide their efforts in vaccine development and implementation. This might begin at the basic science level in organizations conducting and funding research to break through bottlenecks in vaccine development. Other potential users, such as manufacturers, might be involved directly in the development and eventual production of vaccines and thus may wish to emphasize an entirely different set of vaccine attributes (e.g., profitability, development and regulatory risks) compared to a basic research organization. Still some users or user consortia might use SMART Vaccines to enhance market stability (say, through pre-purchase agreements) and hence the likelihood of successful vaccine development. (IOM, 2012, p. 8)

Additionally, as the Phase I report noted:

> SMART Vaccines can help diverse users understand *how* and *why* their rankings differ. Variations in rankings due to differing data inputs can be discussed among users to discover common data sources. When the model produces different results as a consequence of differing values, it can motivate discussions relating to individual or inter-institutional priorities among users. SMART Vaccines may also help inform users of the value of strengthening vaccine delivery methods (e.g., by augmenting the cold-chain capacity) and alternative methods of disease control (e.g., clean water supply, mosquito netting, food safety measures, or health-related education). A further expected benefit of using SMART Vaccines is that it will enable users to identify data needs to ultimately improve their vaccine prioritization process. Future data collection activities, surveillance activities, and resource allocation may be informed and planned by use of SMART Vaccines. (IOM, 2012, p. 8)

Enhancement of SMART Vaccines

This report, *Ranking Vaccines: Applications of a Prioritization Software Tool*, describes the Phase III work of the committee, which was established by the Institute of Medicine and the National Academy of Engineering to enhance SMART Vaccines 1.0 for prioritizing new preventive vaccines. In

particular, this project, which was commissioned by the U.S. Department of Health and Human Services' National Vaccine Program Office in collaboration with the National Institutes of Health's Fogarty International Center, focused on three tasks: (1) the evaluation of the software in four user-based applications, (2) the development of a general data framework for the software, and (3) the definition of next steps that would increase the use and value of SMART Vaccines. The tasks are described more fully in Box S-1. As a deliverable of this work, in addition to this report, the committee has released SMART Vaccines 1.1, software that contains several enhancements informed by use case scenarios and other stakeholder feedback. The same set of attributes used in SMART Vaccines 1.0 has been integrated in SMART Vaccines 1.1 (see Table S-1). The updated software is available for free download at www.nap.edu/smartvaccines.

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

Institute of Medicine
National Academy of Engineering
Statement of Task

Task 1: Evaluate the utility of and support for the vaccine prioritization software in the stakeholder community through four use case scenarios with four potential users of the software. The potential users will be identified in collaboration with the sponsors.

Task 2: Based on the use case scenarios, compile one new dataset for each of the two vaccine candidates to be compared per user. Develop a framework for a data warehouse and data estimation strategy to support the software.

Task 3: Release the datasets and a report containing recommendations for further development, maintenance, and dissemination of the software and the data warehouse.

User Groups and Use Case Scenarios

The committee shortlisted and finalized three user groups to explore three use case scenarios for Phase III. Each user group provided the committee its data for two diseases that it had chosen to evaluate. These datasets compiled by the user groups in conjunction with the committee are available upon request through the Public Access Records Office accessible from the Current Projects System page of the National Academies website.

A software usability expert from Microsoft Corporation conducted the use case studies with the user groups to report on their experiences and feedback for enhancing SMART Vaccines. The user groups were

1. **The Public Health Agency of Canada,** which had a country-level goal of prioritizing new vaccine research and development. It focused its initial efforts in the use of SMART Vaccines on chlamydia and tuberculosis.
2. **The New York State Department of Public Health,** which had a goal not of prioritizing new vaccine development, but of refining the advice it provides to health care providers concerning which of multiple vaccines already available was best suited to use in various populations of New York State. Specifically, the department analyzed two existing vaccines available for vaccinating infants against rotavirus.
3. **The Serum Institute of India,** which had a manufacturing focus on dengue and respiratory syncytial virus vaccines. As a provider of low-cost vaccines for use in many countries besides India, the Serum Institute sought to use the software also to enhance its understanding of potential vaccine markets beyond India.

In addition to these user groups, the committee also worked with two officials from **Mexico's Ministry of Health** who served as advisory consultants in exploring the use of an early version of SMART Vaccines 1.1 to compare the value of two existing influenza vaccines from a policy perspective.

For the fourth use case scenario, with the sponsors' encouragement, the committee tested the use of SMART Vaccines as a mechanism to determine new target product profiles. As a specific case, the committee started with initial SMART Scores and worked backward to understand the impact of different formulations on the desired objective of a hypothetical user. The committee describes this scenario using the case of three pneumococcal vaccine candidates for South Africa. The data for this evaluation were previously synthesized by the Phase II committee members and were available as preloaded information in SMART Vaccines. The use of SMART

Vaccines as a tool to reverse-engineer new vaccine formulations, including, for example, changes in cost, coverage, effectiveness, and the required number of doses is explored in this report.

Lessons from the User Group Studies

The three user groups, and the officials from the Mexican Ministry of Health who served as advisory consultants, fully understood that they were using a preliminary and evolving version of SMART Vaccines and that their feedback was to be applied toward improving the product. As a consequence, none of them attempted to use the software for actual decision making, but rather used the occasion to explore the software, both for their potential future use and to assist in the IOM's unique product development effort.

In none of the use case scenarios did the users actually develop their official sets of attributes to be used in vaccine evaluation or the formal weights to be attached to those attributes. Moreover, the committee found areas where the data from the user groups were either incomplete or inaccurate, further emphasizing that the results were not real decision support but rather familiarization with the SMART Vaccines tool and its potential uses.

In this report, the committee has summarized key lessons learned beginning with the broadest policy issues and then shifting to more narrow issues in application of SMART Vaccines.[2] The committee was highly encouraged by the general positive feedback concerning SMART Vaccines and was especially reassured about the user groups' imagination to potentially expand the tool for broader use scenarios.

Data Framework

The committee was charged with developing a framework for a data warehouse and for a data estimation strategy to support the software. The committee's response to this task comes in three parts.

The committee had addressed this charge in several ways. First, the committee has discussed extensively the importance of a permanent home for SMART Vaccines and the roles of an active network of users and developers supporting the software. One of the key roles of such a group would be the development, curation, and improvement of data to use in SMART Vaccines and its future versions.

[2] The key insights are summarized in Table 3-1 in Chapter 3 of this report.

Second, the committee has presented three ways in which data could be developed: (1) on a user-by-user basis, (2) with large-scale external funding to develop the data in bulk, and (3) by crowdsourcing the data development, particularly with the intent of engaging students in course work relating to public health strategic planning. Students could both use SMART Vaccines in the course work and develop new data that could be entered into a data warehouse supported by the community of users.

Third, the committee has discussed sources for the most complex data, including discussing the sources used for national and state populations integrated in SMART Vaccines 1.1. The committee has also explored sources for the important category of health outcomes data, identifying and discussing sources from the World Health Organization, the World Bank, and the Institute for Health Metrics and Evaluation. One specific enhancement the committee made was to revise the process by which health care cost data will be entered into SMART Vaccines; the new process provides several different pathways to obtain such data and enter them into the system.

Overall, the committee believes that the community of users will be best served by having the host organization manage a central data warehouse, organized through a data quality control mechanism and a well-supported relational database management system. This system would allow input from users and data creators through a standard spreadsheet format and would also create output reports that feed directly into SMART Vaccines to add new data—demographics, disease burden, treatment cost, and vaccine characteristics.

Guiding Principles for Enhancing the Value of SMART Vaccines

With the interest of guiding further efforts in the enhancement of SMART Vaccines, the committee began with a guiding principle established in the Phase II report: **"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."**

As Phase III comes to a close, it has become all the more apparent to the committee that **a transition strategy to a permanent home for SMART Vaccines is necessary for the ongoing use, enhancement, and even the survival of the software as a tool for strategic planning.** Correspondingly, the committee believes that **the National Vaccine Program Office and the Fogarty International Center of the National**

Institutes of Health will be best served if they promptly create a process to facilitate the transition of SMART Vaccines to a permanent home. They could do this by convening a group of relevant stakeholders in vaccine research, development, deployment, funding, and policy to establish a process for soliciting applications for the permanent host—an individual organization or a consortium—and a method for evaluating and choosing among the candidates.

The Phase II report indicated—and this committee strongly agrees—that **the ultimate future applications and benefits of SMART Vaccines depend on the strengths of the organization or consortium that becomes the permanent host.** Based on the committee's analyses of possibilities, it emphasizes **the importance of a host organization that is both neutral among many users' competing viewpoints—and clearly viewed as such—and is well equipped with organizational and technological capabilities.** The committee believes that **the best hosting organization will not only have a significant international presence and reputation, but also best serve the user community if it is a—or partners with a—research-intensive institution of higher education.**

The committee believes that research universities, especially those with a global public health focus, can bring assets to the forefront, including the ready availability of professional expertise pertinent to the endeavor such as the ability to create training modules involving the use of SMART Vaccines at multiple levels and the ability to involve health science and policy students in the production of new or updated datasets for use with SMART Vaccines in a crowdsourcing approach to a broader, globally useful data warehouse development.

In addition to stressing the importance of promptly creating a major outreach and educational effort to expand the awareness and use of SMART Vaccines—hence expanding the user community in parallel—the committee also identifies a set of desirable research activities and a suite of potential extensions of the capabilities of the software into a wider array of decision making.

Furthermore, in terms of data requirements for SMART Vaccines, the committee observes that to carry out any vaccine prioritization task sensibly, decision makers would necessarily have to have these same data in hand, with or without the software tool. Without these basic data, the decisions cannot be made as carefully. **The data requirements may seem to loom large in the eyes of potential users, but the software itself does not create the data burden—it merely brings it to the forefront**. **Once the data are assembled, SMART Vaccines provides a useful tool to enhance decision making that has a significant data-driven basis.**

The committee emphasizes the importance of ultimately creating a successor version of SMART Vaccines that is fully Internet-based, rather than relying on the Matlab approach used in its development of the software prototypes. A Web-based program, linked to a centrally maintained data repository, would avoid the challenges associated with the installation of SMART Vaccines in some environments and would make it platform-neutral, rather than limiting its use to those with the Windows operating system, as the current version requires.

A Sense of Focus and Urgency

Over the years, new vaccine development efforts have become extremely expensive compared with earlier vaccine development successes. In times of financial duress, governmental and corporate priorities often shift their approaches toward those that yield greater returns. Because the impacts of vaccines are multi-generational and thus very hard to capture analytically, vaccines are often compared against other lucrative products, for example, in the realm of therapeutics. Unfortunately, standard analytic tools have trouble dealing with some important aspects of vaccines.

Thus, the need has never been greater for systematic evaluations of potential vaccine targets to help guide the discussion among users, purchasers, and developers of vaccines concerning where best to focus new development efforts. Yet the plethora of approaches available to prioritize vaccine development—many of which are quite opaque—creates its own risk: Something new is not always welcome and, even if it is welcome, often not embraced and nurtured. SMART Vaccines offers a first-of-its-kind platform—a decision-support tool and a discussion facilitator that uses a range of attributes that were previously unavailable for analyses in a single tool and for a wide range of decision makers.

The initial user group evaluations and the positive feedback that the software has generated offer great confidence to the committee about the potential applications and extensions of SMART Vaccines for global public health. The committee understands the challenges and opportunities in the pathway of data development for SMART Vaccines—and for vaccine prioritization in general. The promise of SMART Vaccines depends on the commitment of its past and future sponsors, and of a network of users, developers, and advisors. The committee encourages these stakeholders to have a sense of focus and urgency.

1

Introduction: SMART Vaccines and Smart Priorities

Health is wealth. The public health benefits of vaccines extend over multiple generations—an effect that could be considered as powerful as the value of the spread of education in our society. These health gains continue over generations to have a direct bearing on workforce productivity gains and the economic progress of nations. Moreover, scaling up of vaccination has been acknowledged as one of the most important mechanisms to help reduce the health achievement gaps between the developed and developing countries by 2035—a goal referred to as the "grand convergence" (Jamison et al., 2013).

Previous reports have noted that the impact of infectious diseases has shrunk from accounting for one-third of all deaths in 1990 to just one-quarter of all deaths in 2010 (Lozano et al., 2012). One recent modeling estimate found that "among children born during 1994–2013, vaccination will prevent an estimated 322 million illnesses, 21 million hospitalizations, and 732,000 deaths over the course of their lifetimes, at a net savings of $295 billion in direct costs and $1.38 trillion in total societal costs" (Whitney et al., 2014, p. 352).

While these numbers and those reported by others (Rousch et al., 2007; Hinman et al., 2011; van Panhuis et al., 2013) do not account for other important benefits of vaccines and thus must certainly underestimate the broader value conferred by vaccines on society (Bloom et al., 2005), they do serve to point out an important aspect in improving the health and economic status of nations: the need to invest in the development of new and improved vaccines to tackle a range of unmet, neglected, or emerging needs in infectious and non-infectious disease prevention (Nabel, 2013; Dye, 2014; Greenwood, 2014; Rappuoli et al., 2014).

Progress in science, engineering, and policy systems has dramatically transformed the landscape of vaccine development (De Gregorio and Rappuoli, 2014). Since the development of the first vaccine by Edward Jenner in the late 1700s, vaccine development has been pursued "empirically" by the isolation and inactivation of disease-causing microorganisms. But after nearly two centuries, starting in the 1980s, more "modern approaches" to vaccine development began to emerge to tackle diseases that could not be addressed with the empirical approach. Many of those approaches have the same conceptual basis as the traditional approaches, but they have more often capitalized on technologic advancements such as genome-level targeting or have capitalized on the structural understanding of the strains. An illustrated history is shown in Figure 1-1.

Vaccine development has become progressively more expensive. Decision makers and investors often focus on understanding the monetary and other returns on the investments—when they are making decisions about which vaccines to use as well as about which vaccines to develop. Yet at the same time, there remains considerable doubt as to which vaccines are most desirable to produce, and there are no commonly used methods for reaching consensus on priorities.

The typical valuation measures have centered purely on health metrics or else on a combination of health and economic metrics such as cost-effectiveness or cost versus benefit when prioritizing new vaccine development. These approaches, while functional, are quite narrow and limited (Bloom et al., 2005). Given this situation, not having a comprehensive measure often leads to vaccines being undervalued against other investment priorities, such as therapeutics or the construction of infrastructure.

Project Context and Scope

Against this background, the path that led to the current work began with the National Vaccine Plan (HHS, 2011) developed by the U.S. Department of Health and Human Services' National Vaccine Program Office (NVPO). One of the top priorities set forth in that plan was the development of new and improved vaccines.

At the request of NVPO, the Institute of Medicine (IOM) launched a Phase I effort in late 2010 to help create an empirical foundation for a vaccine prioritization model based on multi-attribute utility theory (IOM, 2012). Multi-attribute utility theory offers a strong axiomatic base for evaluating vaccines beyond a single criterion such as the standard infant mortality equivalents (or in modern terms, life-years saved) or cost-effectiveness—both of which were previously used by the IOM to produce

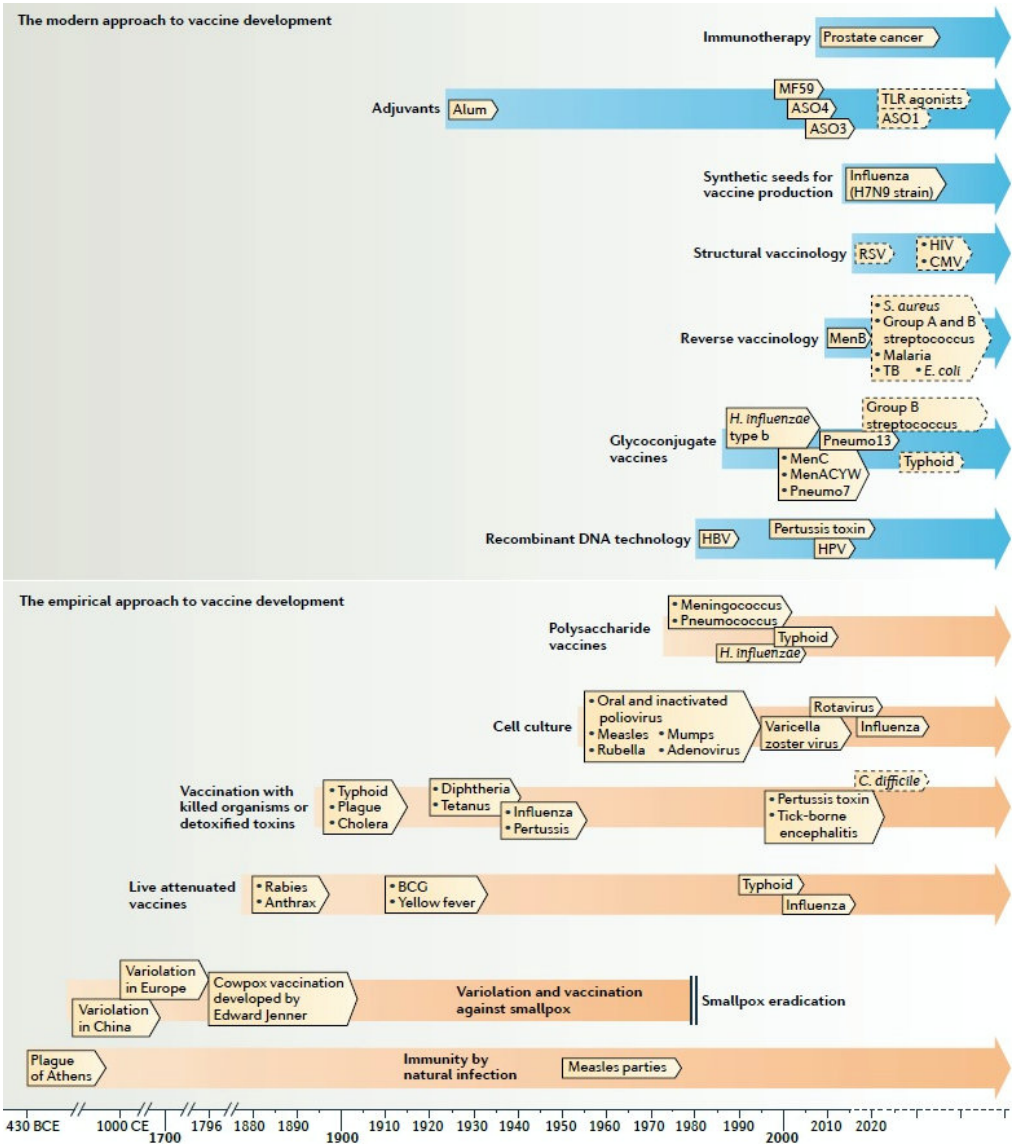


FIGURE 1-1

A timeline of the history of vaccines showing the technologies that have enabled their development. Vaccine research can be divided into two main periods, with the first being the empirical approach, which was based on isolating, inactivating, and injecting the microorganisms that cause disease. The second, modern approach began in the 1980s, when new technologies enabled advances in vaccine development that would not have been possible using the empirical approach.

NOTE: Closed boxes indicate licensed vaccines or vaccination practices that are already used. Boxes with a dashed border indicate vaccines that are still in development. BCG = Bacille Calmette–Guérin; *C. difficile* = *Clostridium difficile*; CMV = cytomegalovirus; *E. coli* = *Escherichia coli*; *H. influenza* = *Haemophilus influenzae*; HBV = hepatitis B virus; HPV= human papilloma virus; MenACYW = meningococcus serogroups A, C, Y, and W; Pneumo7 = 7valent pneumococcus vaccine; Pneumo13 = 13valent pneumococcus vaccine; RSV = respiratory syncytial virus; *S. aureus* = *Staphylococcus aureus*; TB = tuberculosis; TLR = Toll-like receptor.

SOURCE: De Gregorio and Rappuoli, 2014. Reprinted with permission from Macmillan Publishers Ltd.

rank-ordered priority lists (IOM, 1985, 1986, 2000). The Phase I report, *Ranking Vaccines: A Prioritization Framework* (IOM, 2012), that resulted from the IOM's more recent work on vaccine prioritization introduced and validated a multi-attribute approach using 29 attributes, which was thought to offer a significant advance to the thought process of stakeholders. The Phase I committee tested the model[1] using three hypothetical vaccine candidates for three diseases—influenza, tuberculosis, and group B streptococcus—for use in both the United States and in South Africa. The Phase I deliverable also included a blueprint of a software instantiation of the model, which was named Strategic Multi-Attribute Ranking Tool for Vaccines—or SMART Vaccines Beta.

A Phase II committee moved the development of this work forward by updating the model and the attributes in the model—28 of them plus another 7 user-defined entries (see Table S-1). In its report *Ranking Vaccines: A Prioritization Software Tool* (IOM, 2013; also see commentary in Phelps et al., 2014), the Phase II committee described the extensive testing it performed on the model using three additional vaccine candidates—for human papillomavirus, rotavirus, and pneumococcal infections—as it pursued the development of a functional prototype SMART Vaccines 1.0 in a Matlab environment that is executable in a Windows environment.

Project Process and Stakeholders' Feedback

In fall 2013, following the release of the Phase II products, a nine-member committee was appointed by the Institute of Medicine and the National Academy of Engineering to carry out the Phase III project. Some of members had served previously on Phase I and Phase II committees, and some were new. Appendix D contains the biographical information of the members.

In addition to two committee meetings, the Phase III committee members met as subgroups in numerous teleconferences. Three technical consultants offered assistance to the committee on software enhancements and data synthesis. An additional consultant helped conduct usability studies with user groups in collaboration with the committee.

[1] The multi-attribute utility model embedded in SMART Vaccines consists of a computational submodel and a value submodel. Background information on these submodels, the overall modeling strategy, mathematical functions, and the associated assumptions (e.g., with costs and time horizon) are explained in *Ranking Vaccines: A Prioritization Framework* (IOM, 2012). Information about the model refinements and testing are included in *Ranking Vaccines: A Prioritization Software Tool* (IOM, 2013). This information is not repeated in this report.

BOX 1-1
Framing Questions for Stakeholders' Feedback

Uses and Applications: Please describe your experience in using SMART Vaccines 1.0. What aspects of the software are beneficial? What functionalities or features can be enhanced or modified? Where does the software fit within your decision-making process?

Data Needs and Structure: What advice can you provide in terms of using available resources and databases toward creating a data framework for SMART Vaccines? What type of data estimation strategies and standardization tools would be useful for your decision making with the use of SMART Vaccines?

Host: What would be your expectations from the potential host of SMART Vaccines?

As part of their sustained outreach efforts, the committee members demonstrated SMART Vaccines 1.0 (the Phase II product) to a wide range of stakeholders at various meetings of major professional societies, federal advisory committees, and vaccine manufacturers and their consortiums. Additionally, the committee organized a public meeting to gather feedback from other stakeholder leaders for use in refining SMART Vaccines. The meeting's speakers are listed in Appendix C, and the questions posed to them are given in Box 1-1.

Use Case Scenarios and Data Synthesis

To evaluate the utility of and support for SMART Vaccines in the stakeholder community (see Box S-1), the committee, in collaboration with the project sponsors—the U.S. Department of Health and Human Services' National Vaccine Program Office and the Fogarty International Center of the National Institutes of Health—decided on three user groups to serve as early evaluators of SMART Vaccines.

The three user groups were the Public Health Agency of Canada, the New York State Department of Health, and the Serum Institute of India (see Box 1-2). Each user group had different interests in employing SMART

BOX 1-2
Profiles of User Groups

The Public Health Agency of Canada (PHAC) is the main agency responsible for public health in Canada. PHAC is one of seven departments and agencies that make up the Canadian government's health portfolio, and it reports to parliament through the minister of health. PHAC works in close collaboration with all levels of government (provincial, territorial, and municipal) and also with nongovernment organizations, including civil society and business organizations, and with other countries and international organizations, such as the World Health Organization, to share knowledge, expertise, and experiences.

The New York State Department of Health (NYSDOH) bureau of immunization is responsible for the control and prevention of vaccine-preventable diseases. NYSDOH educates providers and the public about vaccines and vaccine-preventable diseases, conducts surveillance and outbreak control activities, and distributes vaccines to ensure their availability to vulnerable populations and populations with limited ability to pay for vaccines. NYSDOH bases routine immunization activities on the recommended immunization schedules, updated annually by the Advisory Committee for Immunization Practices. NYSDOH provides outreach to ensure optimal compliance with those vaccine recommendations.

The Serum Institute of India Limited manufactures life-saving immunobiologicals at affordable prices for India and other countries. It is the world's largest producer of measles and diphtheria-tetanus-pertussis (DTP) group of vaccines and many of its products. In addition to its product portfolio, the Serum Institute of India also works toward bringing down the prices of newer vaccines, including the hepatitis-B vaccine, the rabies vaccine, and other combination vaccines besides DTP.

Vaccines to inform their respective vaccine development or policy planning efforts. Their backgrounds, test cases, and suggestions for enhancing SMART Vaccines are discussed in Chapter 3. A consultant to the committee from Microsoft Corporation led the usability studies with these three user groups and prepared an independent report containing suggestions for improving SMART Vaccines (see Appendix A).

A fourth use case scenario was carried out by the committee as a simulation to demonstrate a different application for SMART Vaccines: to show how the software might be used to reverse engineer vaccine product characteristics. In addition to these four formal use case scenarios, the committee also worked with the Mexican Ministry of Health to gain additional input for enhancing the software.

Each user group worked closely with the committee, which provided various data needed for the software evaluation. The interactions with the user groups informed the committee's thinking on the data framework development described in Chapter 2.

2

Data Synthesis and Framework

SMART Vaccines requires information about the population affected by the vaccine-preventable disease, the disease burden—including the costs of treating diseases of different levels of severity—and the characteristics of potential vaccines. Upon entering these data, the user chooses a set of attributes that, when combined with the user's weights, determine the vaccine priorities. A detailed explanation of the data needs is presented in the Phase II report *Ranking Vaccines: A Prioritization Software Tool* (IOM, 2013; see Appendix C). The following sections summarize the data requirements and present additional considerations especially for those variables requiring estimations.

Data Requirements

The data for SMART Vaccines typically come from different sources. SMART Vaccines has basic population and wage data already loaded for the 34 Organisation for Economic Co-operation and Development (OECD) member countries in addition to India and New York State, data for which were provided by the user groups (see Table 2-1). Analyses for subpopulations such as provinces or states require inputting additional data.

Disease burden data are typically more difficult to obtain, especially for populations with a limited public health infrastructure. SMART Vaccines requires data both on mortality and on disease incidence. Data on the costs of treating various diseases will typically be the most difficult to obtain. In the United States, many data sources provide insight into these treatment cost patterns, but the data from these sources typically pertain to specialized populations (e.g., Medicare databases deal mainly with those

TABLE 2-1

National Population Data in SMART Vaccines 1.1

Australia	India	Portugal
Austria	Ireland	Slovak Republic
Belgium	Israel	Slovenia
Canada	Italy	South Africa
Chile	Japan	Spain
Czech Republic	Korea	Sweden
Denmark	Luxembourg	Switzerland
Estonia	Mexico	Turkey
Finland	Netherlands	United Kingdom
Greece	New Zealand	United States (and, individually, New York State)
Hungary	Norway	
Iceland	Poland	

over age 65, Medicaid databases pertain to low-income populations and commercial insurance databases). In other nations with more centralized health care systems, treatment cost data may be more readily available.

SMART Vaccines 1.1 takes a summary measure of the costs of treatment as a single variable. In the previous version 1.0, users had to fill out a detailed data input table to complete the treatment costs data section. The revised format allows users to calculate their treatment costs completely offline (e.g., in a spreadsheet analysis) and enter the resulting computed total cost in SMART Vaccines. This approach provides more flexibility, including allowing the use of approximations when more precise data are not available.

Details concerning the population, disease burden, and vaccine data requirements are provided in Tables 2-2, 2-3, and 2-4.

Once the data entry is complete, SMART Vaccines prompts the user to choose from a list of attributes. SMART Vaccines includes 28 pre-defined attributes and allows users to add up to 7 more. From these, users can select up to 10 attributes to use in the analyses. A user-defined attribute needs to be a binary question with a yes or a no answer. The chosen attributes are then ranked and weighted by the user.

The limit of 10 attributes represents a software design decision from Phase II. Both the Phase I and Phase II reports (IOM, 2012, 2013) emphasized that the selection of a large number of attributes usually does not lead to meaningful amounts of utility-weight entering the calculation for the attributes as the bottom end of the priority list. Furthermore, aesthetically speaking, the "real estate" in the software screen presenting results becomes overly cluttered if more than 10 attributes are allowed.

TABLE 2-2

Demographic Data Needs for SMART Vaccines 1.1

Demographic Information[a]	Description	Notes and Specific Considerations
1. Total population (N)	Total number of people in a population by sex and 5-year age groups for a selected country.	Data available in spreadsheet format from the United Nations World Population Prospects (2012 version).
2. Number of people alive at age x (lx)	These three variables are standard population life-table attributes, and each country's life table includes lx, nLx, and ex for both sexes, by age groups.	Data extracted from the life tables by country from the country statistics division of the World Health Organization's Global Health Observatory.
3. Person-years lived between ages x and x + n (nLx)		
4. Life expectancy (ex)		
5. Standard life expectancy (sx)	Life expectancy for the Japanese population is used as the standard.	Used for calculations related to DALYs. Japan's life table contains life expectancy for both sexes and age groups.
6. Hourly wage rate (USD)	Hourly wage rate for a population is calculated by dividing average income by total hours worked per year.	As applicable, this value can be converted to U.S. dollars using the prevailing exchange rate to arrive at approximate data for the selected country's subpopulation and their age groups.

[a] SMART Vaccines 1.0 required user input on values from Health Utilities Index 2 (HUI2)—in particular, data providing an estimate of the quality of life that were used to calculate QALYs—but SMART Vaccines 1.1 has this information built in and does not require it as a separate entry, thus reducing the user burden.

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

Attributes and Boundary Setting

In the multi-attribute utility theory model[1] that underpins the SMART Score, users choose attributes as part of the ranking method used to prioritize vaccines. The attributes are based on either quantitative or qualitative measures. The qualitative attributes are simple binary—yes or no—measures or else are based on a Likert scale with 1 being the lowest grade and 5 being the highest grade.

The quantitative attributes are calculated numbers and must be given some boundary values that make appropriate contextual sense. Set-

[1] The details of the multi-attribute utility model and its constituent computational submodel—with its mathematical functions and testing results—are explained in the appendices of the Phase I (IOM, 2012) and Phase II (IOM, 2013) reports.

TABLE 2-3

Disease Burden Data Needs for SMART Vaccines 1.1

Disease Burden Information	Description	Notes and Specific Considerations
1. Incidence (per 100,000)	New cases of a specified disease during a given time period divided by the number of persons in a stated population in which the cases occurred.	Disease burden includes incidence, which can be available from national disease databases and peer-reviewed literature. Incidence of the disease for both sexes and age groups: infants (<1 year old), children (1 to <20 years), adults (20 to <65), and elderly (65 years or older).
2. Case fatality rate (probability)	Probability of death, conditional on the disease being present. Thus, the number of expected deaths equals the annual incidence rate times the case fatality rate.	Disease burden includes case fatality rate, which can be available from national disease databases, the World Health Organization (WHO), and peer-reviewed literature. Case fatality rate for a disease for both sexes and age groups: infants (<1 year old), children (1 to <20 years), adults (20 to <65), and elderly (65 years or older).
3. Death (i) Costs (USD)[a]	Costs per case diagnosed with a disease resulting in death; includes medication and outpatient and inpatient costs.	Data available from the Healthcare Cost and Utilization Project (HCUP net) in the United States. WHO-CHOICE (CHOosing Interventions that are Cost-Effective) publishes health service delivery costs for inpatient and outpatient visits by country.

TABLE 2-3

Continued

Disease Burden Information	Description	Notes and Specific Considerations
4. Permanent impairment (i) Percentage of cases (ii) Disutility (iii) Disability weight (iv) Duration (days) (v) Costs	(i) Out of all disease cases, what percentage result in permanent impairment? (ii) Disutility tolls represent the difference between HUI2 of the healthy state prior to illness (0.99) and the state during sickness. (iii) Disability weights quantify health losses for non-fatal consequences of diseases. (iv) Duration of permanent impairment. (v) Costs per case diagnosed with a disease resulting in permanent impairment; includes medication and outpatient and inpatient costs.	Select and specify a permanent impairment caused by the disease—for instance, permanent loss of hearing due to an infectious disease. (i) Percentage of cases are obtained from disease burden estimates. (ii) and (iii) Disutility tolls and disability weights are used to calculate QALYs and DALYs, respectively. Select one of the two to enter the information. Disability weights are available from the Global Burden of Disease Study (2010). (iv) Duration depends on the intensity of disease. (v) Costs are estimated from national hospital and health services delivery databases.
5. Morbidity (i) Percentage of cases (ii) Disutility (iii) Disability weight (iv) Duration (v) Costs	(i) Out of all disease cases, what percentage result in morbidity? (ii) and (iii) Disutility tolls and disability weights quantify health losses for non-fatal consequences of diseases. (iv) Duration of morbidity. (v) Costs per case diagnosed with a disease resulting in morbidity; includes medication and outpatient and inpatient costs.	Select and specify morbidity caused by the disease—for instance, morbidity due to an infectious disease. (i) Percentage of cases is obtained from disease burden estimates. (ii) and (iii) Disutility tolls and disability weights are used to calculate QALYs and DALYs, respectively. Select one of the two to enter the information. Disability weights are available from the Global Burden of Disease Study (2010). (iv) Duration depends on the intensity of disease within the chosen population. (v) Costs are estimated from national hospital and health services delivery databases.

[a] SMART Vaccines 1.1 takes a summary measure of the costs of treatment as a single variable and does not require more refined data as SMART Vaccines 1.0 did. The committee decided on this approach to reduce user burden.

TABLE 2-4

Vaccine Product Profile Information for SMART Vaccines 1.1

Vaccine Product Profile Information	Description	Notes and Specific Considerations
1. **Coverage** (percentage)	Anticipated coverage rate for the new the vaccine.	Because new vaccines do not yet exist, coverage rates can only be conjectured. Changing the inputs allows a sensitivity analysis for "what if" scenarios in which parameters are varied to observe what changes result in other aspects of the vaccine.
2. **Effectiveness** (percentage)	Anticipated effectiveness for the new vaccine.	For a vaccine that does not yet exist, these inputs are derived from clinical trials conducted for the potential candidates or estimated in advance of such data using the history of similar vaccines.
3. **Length of immunity** (years)	Anticipated length of immunity from the new vaccine.	Effects of a vaccine vary widely depending on the population characteristics—age, sex, environment, etc. For a vaccine that does not yet exist, these inputs are derived from clinical trials conducted for the potential candidates or estimated in advance using data from similar vaccines.
4. **Doses required per person** (number)	Anticipated doses required per person.	Changing this value allows a sensitivity analysis for "what if" scenarios. How does changing the number of doses affect cost or coverage?
5. **Cost per dose** (USD)	Expected costs per vaccine dose.	These costs represent a dose of vaccine.
6. **Cost to administer per dose** (USD)	Expected costs to administer a dose.	These costs can include health care workforce costs, costs to maintain the vaccine potency, etc.
7. **R&D and licensure costs** (USD)	Anticipated costs for a vaccine manufacturer to develop and license a vaccine.	Select from one of the four provided options. (i) >$1 billion (ii) $500 million–$1 billion (iii) $100–$500 million (iv) <$100 million

ting the boundaries for quantitative attributes that hinge on characteristics such as population size, disease burden, or hourly income can be a complicated issue. Preliminary boundaries have been suggested in SMART Vaccines along with strategies for improvement and advice on how to change them, as necessary. As the committee notes in Chapter 4, it would be useful if future software enhancements could be made to augment the program's ability to modify boundaries, particularly when new population data (e.g., data for subpopulations) are used.

As explained in Edwards and Barron (1994), defining attribute boundaries makes it possible to score all attributes on a scale from 0 to 100, even if the attributes have innately different ways of being measured. As a simple example, one might use three attributes with which to compare automobiles: miles per gallon fuel usage (mpg), stopping distance from 60 miles per hour (mph), and the maximum number of passengers. In the miles-per-gallon category, one might set a lower bound (worst case) of 0 and an upper bound (best case) of 50, but almost every car on the road actually achieves at least 15 mpg, so a tighter range would be 10 to 50. Similarly, the stopping distance for real cars will usually fall somewhere between 100 feet (for sports cars) and 150 feet (for heavy sport-utility vehicles, for example). The number of passengers will generally vary between two (sports car) and eight (minivan).

A typical multi-attribute utility weighting would convert the values for each of these factors to fall on a range from 0 to 100—called the "swing distance." In the automobile example this would result in the following metrics: The 40-mpg range would converted to a linear 100-point scale, with 50 mpg being the best (score of 100) and 10 mpg being the worst (score of 0). Similarly, for the stopping distance, the 50-foot range is converted to a 100-point scale, with the shortest distance (100 feet) being the best and the longest distance (150 feet) the worst. Likewise, for the number of passengers the six-passenger range would be converted to a 100-point scale, with two passengers receiving the lowest score of 0 and eight passengers receiving a score of 100.

Having converted all attributes to a common 100-point range using weights provided by the user, the multi-attribute utility model then provides a measure of how well a car performs based on the user's definition of what is desirable. An overall score of 100 is achieved for a car that carries eight passengers, stops in 100 feet, and gets 50 mpg. An overall score of 0 is achieved for a car that carries two passengers, stops in 150 feet, and gets only 10 mpg. Scores in between depend on the weights established by the user on each attribute (mpg, stopping distance, and passenger count) and where each car falls on the three 0-to-100 scales.

To see how this works, suppose a car gets 35 mpg, carries five passengers, and stops from 60 mph in 120 feet. Its attribute scores would be mpg = 62.5 (62.5 percent of the way from worst to best), passengers = 50 (halfway between worst of 2 and best of 8), and stopping distance = 60 (60 percent of the way from 150 feet to 100 feet). If this user had put weights on the attributes of mpg = 0.6, passengers = 0.3, and stopping distance = 0.1, this car would get a score of 58.5 (0.6 × 62.5 + 0.3 × 50 + 0.1 × 60) out of a possible 100.

It is also straightforward to deal with situations in which one or more of the attribute values lie outside the boundaries. Suppose, for example, that a car got 55 mpg on the miles-per-gallon attribute (which is 5 mpg outside the range of 10 to 50 mpg used to determine the 100-point scale) and that it, like the previous car, carries five passengers and stops from 60 mph in 120 feet. Now the miles-per-gallon attribute measure is 112.5, because the additional 5 mpg is 12.5 percent of the 40-mpg range, and adding 12.5 to the upper boundary score of 100 gives 112.5. The total utility score is now 88.5 (0.6 × 112.5 + 0.3 × 50 + 0.1 × 60), which is perfectly legitimate. The score of 88.5 can be compared directly to the previous score of 58.5—it is 30 points better.

In extreme cases the attribute score of an outlier may rise sharply above the upper boundary or fall below the lower boundary. This can create a visualization problem if the display for the utility score only runs from 0 to 100, but the meaning of the score can still be interpreted without a problem. In particular, the new score is still interpreted in comparison to other scores. A car able to achieve 75 mpg instead of 55 mpg would have an attribute score of 162.5, and its overall utility score would be 120.5. This interpretation of this is that the new 75-mpg car is 60 utility points better than the original 35-mpg car, and 30 utility points better than the 55-mpg car.

Such situations where scores fall outside the 0-to-100 range can be avoided by setting the boundaries low and high enough that no conceivable candidate can have attribute scores beyond the boundaries, but setting boundaries too wide can make it difficult or impossible for any scenario to attain the highest score (i.e., 100). For example, if the best stopping distance boundary was set at 0—a convenient but unrealistic scenario—no car would get a decent score on the new scale, which now runs from 150 feet to zero. A car that can stop from 60 mph within 100 feet—and thus achieved a score of 100 on the previous scale—would now get a score of only 33.33, while a car with a 150-foot stopping distance would still get a score of 0. The result is that the possible attribute scores for realistic cars get compressed from the 0-to-100 range into a 0-to-33.33 range, making it impossible for cars to demonstrate their full potential. In short, a too-wide boundary does not allow a scenario to attain the best case because it is not realistic.

Conversely, if the boundaries are set far too narrowly on an attribute, so that, for example, some vaccine candidates are able to achieve a value of 10 times the boundary value, then the model's calculations can mislead the user. In this case, a single attribute would dominate the calculated SMART Scores, effectively making SMART Vaccines something near to a single-attribute weighting system.

Current Algorithms for Setting Boundaries

SMART Vaccines calculates nine variables that need to have boundary values set: deaths averted, incident cases averted, workforce productivity saved, net costs, one-time costs, quality-adjusted life years (QALYs) disability-adjusted life years (DALYs), cost ($)/QALYs, and cost ($)/DALYs. The following section discusses how SMART Vaccines 1.1 sets boundaries for the preloaded national and state population data.

1. *Deaths averted*. This depends on the size of the population, the incidence, and the case fatality rate for the relevant infectious diseases. In SMART Vaccines, the best possible score is taken as 50 percent of the annual deaths in each population that come from the worst death-causing disease. The lower bound is set at 0. Thus, to score 100 on the deaths-averted attribute, a vaccine would have to eliminate half of the deaths caused by the disease that causes the most deaths annually in the population.
2. *Incident cases averted*. Like deaths, incident cases depend on the population size and the disease burden in each country. The current version of SMART Vaccines includes estimated values for the upper boundary with the best case being a 50 percent reduction in the number of incident cases caused by the highest-incidence disease in each country, the incidence data being estimated as a multiple of mortality boundary data. The choice of 50 percent is an arbitrary value, designed so that complete elimination of the worst disease would not become the upper boundary for incident cases averted.
3. *Workforce productivity improvements*. Workforce productivity losses come from a combination of disease incidence, value of time, and duration of illness. The upper boundary for workforce productivity is set by using 50 percent of the highest-incidence disease rates multiplied by the average disease duration multiplied by the average daily wage rate (hourly wage × 16, allowing for 16 hours of productive uses of time under different conditions—

whether working in the market, at home, or enjoying leisure activities—and 8 hours of sleeping). While this approach may overstate the pure financial consequences of disease prevention modestly, it provides a simple and straightforward way of approximating these data without attempting to adjust for specific labor market conditions or taxation.

4. *Net costs saved*. The lower boundary for net costs in all cases is 0—no medical costs saved, which is the case, for example, if the disease causes mild fatigue that requires no medical intervention. The upper boundary is set using a ratio that begins with country-level data where there are extensive data on disease-specific treatment costs, and those costs are then rescaled to other nations. To set the initial SMART Score boundaries for medical costs saved, the committee relied on U.S. data containing precise estimates of costs on many diseases from multiple sources.

   From there the transformation to other population settings was carried out. This transformation is carried out as follows: Let C_j be the U.S. treatment costs for disease j and T_{US} be the total per capita medical spending in the United States. Then using World Health Organization (WHO) data, determine the U.S. dollar–equivalent total spending in country n, T_n. The upper bound on medical costs saved is set as $C_{US} \times (T_n/T_{US})$. Thus, if population n spends $400 per capita (in U.S. dollars) in medical care per year, and on average the United States spends $8,000 per capita, then the ratio $T_n/T_{US} = 0.05$, and the upper bound for treatment costs saved would be 0.05 times the U.S. costs for treating that disease.

5. *One-time costs*. The boundaries for one-time costs—relating to research, development, and licensure—are set by the user by selecting the options available on the page where vaccine characteristics are specified. The boundaries range from 0 dollars (lower bound; if the user scenario, e.g., was the distribution of already existing vaccines) to greater than $1 billion (upper bound).

6. *QALYs, DALYs, $/QALY, and $/DALY*. The upper boundary or best-case scenario for cost per DALYs or cost per QALYs is 0—which occurs in a situation in which the vaccine saves as much in medical costs as the vaccine program itself costs. While a few early vaccines actually reduce the total cost of care, most modern vaccines may have significantly higher $/QALY or $/DALY. The lower boundary is taken from the WHO guidelines for "acceptable" cost-effectiveness ratios, which is set at a value of 15 times

the country's per capita gross domestic product (GDP). Thus, for example, with a per capita GDP in the United States of $51,755 in 2012, the worst-case boundary for $/QALY or $/DALY would be $155,265. In South Africa, the per capita GDP in 2012 was $7,314, so the worst-case boundary would be $21,942.

Considerations for Modifying Boundaries

As noted previously, multi-attribute utility models (and hence SMART Vaccines) rely on the boundary values set by the user. The boundaries suggested in SMART Vaccines are informed by current data, but over time these may become outdated or inapplicable. Furthermore, because no gold standard method exists for setting boundaries, the boundaries suggested by SMART Vaccines are simply suggested ways to create the best and worst scenarios for quantitative attributes.

Changing boundary values mid-course may render all previous calculations useless in terms of comparison with new values created after boundaries shift. Thus, the boundary setting should be done once, thoughtfully, at the beginning of the analysis for a given population. If the boundaries change, then all previous calculations should be redone. SMART Vaccines 1.1 currently does not permit users to alter the boundaries, but future versions of the sotware may offer this function.

Data Framework

Data for SMART Vaccines will accrue through time from various sources. In Chapter 4 the committee discusses the importance of having a host organization and active user community—one function of which would be to manage a central data warehouse, providing widespread user access to demographic data, disease burden data, and illness-treatment cost data for various populations and subpopulations that have been assembled for use in SMART Vaccines. The following discussions of the data framework presume the existence of a host organization (or its equivalent) that will manage the data infrastructure and accept data inputs from outside entities including individual users, contracted providers, and crowdsourced data creators.

No matter how these new data arrive at the data warehouse, the best mechanisms for receiving, validating, storing, and reporting data to users will likely involve a database structure that allows for flexible approaches to the data from many perspectives without a need to reorganize the data-

base tables. In short, the data warehouse will require a relational database management system.

User contributions to the data warehouse will best serve the user community if individual users or data creators can directly enter data into organized spreadsheet formats (e.g., Excel and the many proprietary and open-source equivalents), which then can be imported into the relational database warehouse. Future program modifications for SMART Vaccines could allow data importation either through the central data warehouse—built and maintained by the host organization and supervised by user-group committees—or directly by individual users who wish to use data without going through the central warehouse facility.

A blank spreadsheet template for data assembly was prepared in Phase II and is available for download at www.nap.edu/smartvaccines.

3

Use Case Scenarios and Design Enhancements

The committee worked with three user groups to obtain evaluations of SMART Vaccines from various perspectives. The groups were the Public Health Agency of Canada, New York State Department of Health, and the Serum Institute of India. Profiles of these three user groups are presented in Box 1-2.

User Group Scenarios

Users were asked to choose a test case that was useful and applicable to their organization and that required a comparison of at least two vaccines. The committee offered the following initial guidance to the user groups concerning how they should apply SMART Vaccines to a real challenge they had faced, were facing, or expected to face:

1. Identify a policy question or challenging decision for which you require a comparative analysis of two or more vaccines.
2. Select the population in which you wish to analyze the impact of the vaccines and provide the necessary life-tables information.
3. Specify the burden of the diseases being targeted by the vaccines of interest.
4. Choose two or more vaccine candidates to evaluate. These can be single vaccines for each chosen disease or multiple candidate vaccines for a single disease (i.e., determining the ranking for vaccines with different bundles of attributes) or some combination thereof.

A template spreadsheet developed by the Phase II committee was provided to the three user groups to guide their data compilation. Additional guidance was provided to the user groups to support their data collection, with the specific guidance varying according to the details of the particular test case and the resources available to the user group. Some user groups needed minimal assistance, while others lacked the necessary expertise for gathering population-specific disease burden and vaccine data.

The Public Health Agency of Canada (PHAC) chose to use SMART Vaccines to prioritize vaccines for research and development. The agency chose chlamydia and tuberculosis within the Canadian population as its test case. Although Canada represents only a small fraction (1 to 2 percent) of the world market for vaccines, the PHAC believes that it can influence vaccine development by working with vaccine developers to use Canada as a test bed for early use of vaccines; in this way the PHAC can play a significant role in prioritization despite Canada's relatively small portion of the world market.

The New York State Department of Health (NYSDOH) decided to use SMART Vaccines to compare two existing rotavirus vaccines, Rotateq and Rotarix, for use within New York. The department also used SMART Vaccines to help determine which of four existing influenza vaccines might best serve the population of New York, where vaccine delivery takes place through a variety of private providers as well as some public health clinics.

The Serum Institute of India used SMART Vaccines to prioritize between two vaccines, a vaccine for dengue and a vaccine for respiratory syncytial virus, for use in India. Currently no vaccines exist for either disease.

After the user groups collected the data relevant to their scenarios, they provided the data to the committee, which then sent each group an updated version of the SMART Vaccines that had been preloaded with the data that group had provided. Then each user group tested SMART Vaccines for its chosen scenario. The PHAC team consisted of staff experts in disease spread modeling, policy research, and health economics; the combination allowed the team members to efficiently gather and test data for its use cases. The NYSDOH team included a group of health officials, an epidemiologist, a computer scientist, and immunization officers who supported the effort to compile disease burden and vaccine data. The use case scenario of the Serum Institute of India was spearheaded by its corporate medical director, who was supported by a project assistant.

The users provided feedback about their experience to help the committee understand how each group used the software to analyze its

scenario, the usefulness of various aspects of SMART Vaccines such as sensitivity analysis, and the groups' preferences regarding the software interface. This study was led by an independent consultant to the committee from Microsoft Corporation. The groups' feedback is summarized by the consultant in Appendix A, and the committee's corresponding responses or actions are provided in Appendix B.

The fourth use case scenario—which will be discussed later in this chapter—focused on using SMART Vaccines as a reverse engineering tool to determine the SMART Scores of potential vaccines for a single disease and thus offer guidance to vaccine developers concerning the most desirable bundles of attributes for potential vaccines. In some sense, this scenario expands upon the typical target product profile discussions already common in the world of vaccine discovery and production.

Data Sourcing Guidance to the User Groups

Over a 5-month period, the committee partnered with the user groups to provide general and specific advice for data collection and to answer queries regarding software requirements, data needs, and other user or interface concerns.

The users were provided with general sources for finding relevant data; however, each user group also required sources of specific information concerning its identified population. To help the user groups find such information, the committee provided specific research help for the different users. For instance, NYSDOH required state-specific data on disease burden. To compare the two rotavirus vaccines, highly granular data were needed for Rotateq and Rotarix vaccines within New York, and the committee offered customized help concerning such data. All of the datasets compiled by the user groups in conjunction with the committee are available upon request through the Public Access Records Office accessible from the Current Projects System page of the National Academies website.

Updated Features in SMART Vaccines 1.1

The committee found the usability studies with the three user groups to be very useful and productive. As a result of those studies, several updates and enhancements to SMART Vaccines were made. These updates and enhancements are illustrated with various screenshots in this section.

Terms of Use

The opening page of SMART Vaccines 1.1 presents the terms of use and a disclaimer from the National Academy of Sciences (see Figure 3-1). Once users click the "Accept" button, they enter the program. From this point forward, navigation occurs by using the "Continue" button at the upper right corner of the screen. Subsequent screenshots from the SMART Vaccines 1.1 demonstrate the functions of each page. The functions are grouped into two sections: Specify and Evaluate.

Specifications

The Specify group contains three separate pages for the choice and entry of data that are used in subsequent analyses. The categories of data include Population, Disease, and Vaccine.

SMART Vaccines 1.1 has built-in population data and estimated wage rate data for the 34 countries in the Organisation for Economic Co-operation and Development (OECD) as well as for India, New York State, and South Africa. To navigate to a specific nation's population page, users need to click and select from the drop-down list that gives access to specific country-level populations (see Figure 3-2).[1]

Just as in version 1.0, SMART Vaccines 1.1 provides detailed population data, including life-table information and average hourly wage rates, all of which are used in subsequent calculations for determining the effects of various vaccines (see Figure 3-3).[2]

On the page requesting information on disease burden (see Figure 3-4), users enter population-specific information about the burden of various diseases of interest. Vaccines targeting these diseases will be available for later comparison and evaluation. For each disease of interest, users must enter two types of information: disease burden data and illness descriptors.

The disease burden data require standard epidemiologic estimates of annual incidence and case-fatality rates for diseases in four age groups: infants, children between 1 and 19 years of age, adults between the ages of 20 and 65, and the elderly, that is, those of age 65 and above. Once a dis-

[1] SMART Vaccines 1.1 currently does not have the capability for users to define their own subpopulation—for example, a state or a province—or to do a collective analysis of a vaccine's impact on a group of nations, although future versions could accommodate this feature.

[2] SMART Vaccines 1.1 eliminates a column that SMART Vaccines 1.0 contained where information was requested on Health Utilities Index 2 for age-specific determination of quality-adjusted life years (QALYs). That variable, used only in one attribute's calculations, is not available except for few national populations (e.g., the British Commonwealth nations, Canada, and the United States).

FIGURE 3-1
Opening page containing the software's terms of use. SMART Vaccines 1.1 is currently functional only on the Windows platform.

ease is specified (e.g., pneumococcal infection) and the relevant data are entered, users can save the data for subsequent use. Users can define as many diseases as they desire, and they can define multiple potential vaccines targeting each specific disease.[3]

On the disease page, users must also identify for each disease specified the types of illness outcomes that the disease might cause. These might simply be different degrees of severity (e.g., mild or severe), or they might be distinct diseases (such as, in the pneumococcal infection example in Figure 3-4, meningitis, sinusitis, or otitis media). Users specify the mix of these outcomes (percentage of cases, which must add up to 100 percent), and for each disease state users specify the disutility associated with the condition (e.g., 0.02 for meningitis), the disability weight, the duration (in days) of the condition or its treatment, and the annual costs of treating that disease. The duration measure is used in the calculation of

[3] SMART Vaccines 1.1 cannot analyze vaccines that affect multiple diseases, for example, combination vaccines that protect against diphtheria, tetanus, and pertussis (DTP).

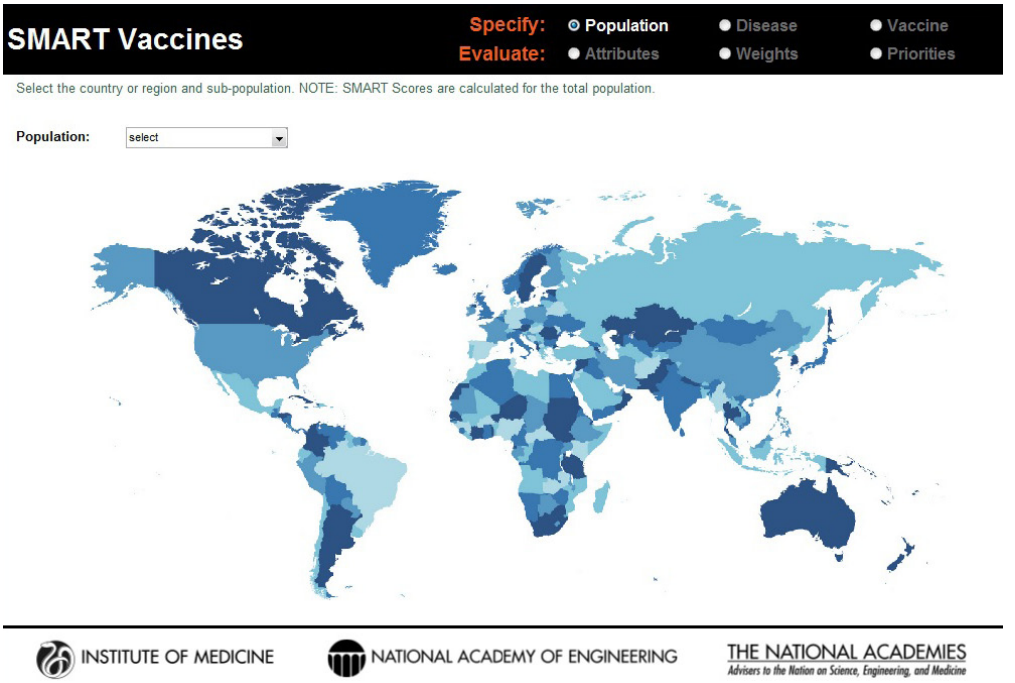
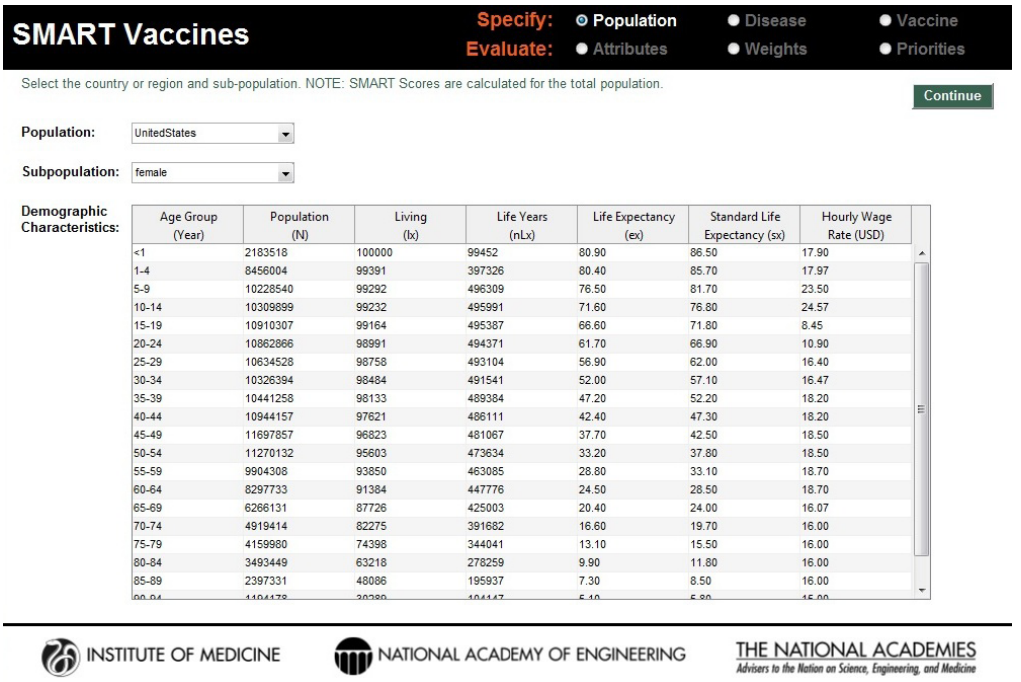


FIGURE 3-2
SMART Vaccines 1.1 population selection map.

quality-adjusted life years (QALYs, which also use the disutility toll) and of disability-adjusted life years (DALYs, which also use the disability weight).

Users are also asked to specify a single value for the annual costs of treating each disease condition. SMART Vaccines 1.0 sought highly detailed data with which to calculate the annual costs. User feedback indicated to the committee that the format was overly restrictive, and the committee responded by replacing that detailed matrix for data entry with a single value (total cost) in SMART Vaccines 1.1. Users need to estimate that total cost offline by using the best data and the best analytic approach that their local resources permit (which may range from an informed expert's best estimate to richly supported true cost data). Users are also asked to specify the costs of a death occurring due to the disease, such as the $4,453 shown in Figure 3-3 as the cost of a death from pneumococcal infection.

Once they have finished entering all of these data for each relevant disease, users hit the "Continue" button at the upper right corner of the page, which takes them to the next page, where vaccine characteristics are defined.



Age Group (Year)	Population (N)	Living (lx)	Life Years (nLx)	Life Expectancy (ex)	Standard Life Expectancy (sx)	Hourly Wage Rate (USD)
<1	2183518	100000	99452	80.90	86.50	17.90
1-4	8456004	99391	397326	80.40	85.70	17.97
5-9	10228540	99292	496309	76.50	81.70	23.50
10-14	10309899	99232	495991	71.60	76.80	24.57
15-19	10910307	99164	495387	66.60	71.80	8.45
20-24	10862866	98991	494371	61.70	66.90	10.90
25-29	10634528	98758	493104	56.90	62.00	16.40
30-34	10326394	98484	491541	52.00	57.10	16.47
35-39	10441258	98133	489384	47.20	52.20	18.20
40-44	10944157	97621	486111	42.40	47.30	18.20
45-49	11697857	96823	481067	37.70	42.50	18.50
50-54	11270132	95603	473634	33.20	37.80	18.50
55-59	9904308	93850	463085	28.80	33.10	18.70
60-64	8297733	91384	447776	24.50	28.50	18.70
65-69	6266131	87726	425003	20.40	24.00	16.07
70-74	4919414	82275	391682	16.60	19.70	16.00
75-79	4159980	74398	344041	13.10	15.50	16.00
80-84	3493449	63218	278259	9.90	11.80	16.00
85-89	2397331	48086	195937	7.30	8.50	16.00

FIGURE 3-3
Population specification screen in SMART Vaccines 1.1. For user convenience, demographic characteristics—population data, life-table information, and wage data—have been preloaded for 34 OECD countries as well as for India, New York State, and South Africa.

Vaccines

Having defined their disease or diseases of interest, users next specify the attributes of a single vaccine or multiple vaccines with different design features that would protect against each disease. When using SMART Vaccines to set priorities for new vaccine development, these attributes are necessarily hypothetical. For some other uses (e.g., selecting among existing vaccines, as one of the user groups chose to do), the vaccine attributes are known with much greater certainty.

Using the same four age brackets as used for the disease burden data, the Vaccines page asks users to indicate with a check box whether or not the vaccine targets each age group and to specify the percentage of each age-group expected to receive the vaccination ("coverage") and the percentage of those vaccinated persons who will gain immunity ("effectiveness"). The number of individuals in the age-specific population groups is brought directly from the previously chosen population profiles (see Figure 3-5).

For each vaccine, users are asked to specify with a check box whether "herd immunity" applies to this vaccine-disease combination. In SMART

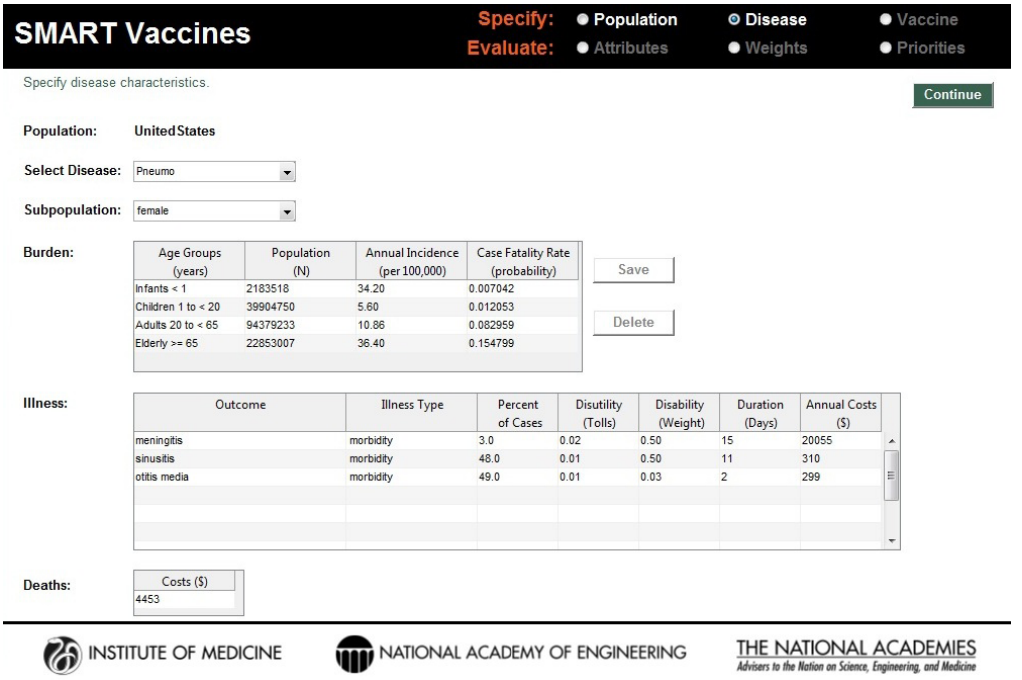


FIGURE 3-4
Disease specification screen in SMART Vaccines 1.1. Having been streamlined since SMART Vaccines 1.0, this page requires user single entry for costs associated with the treating the disease burden.

Vaccines 1.1 (as well as in version 1.0), the herd immunity feature specifies that if greater than 80 percent of the total population receives effective immunity—that is, if the product of the coverage and the effectiveness percentages is greater than 80 percent—then it is assumed that the entire population is protected. Later enhancements of SMART Vaccines may wish to provide more disease-specific models of herd immunity, but currently this simple approach is used.

Users can specify more than one vaccine for each disease. This provides a ready mechanism to determine the value (as measured by the SMART Score) of vaccines with different design profiles. This approach can illuminate desirable features in vaccine design in the development stage, or, as one user group did, the approach can be used to assist in choosing among a set of existing vaccines available on the market. Users can also combine the two, determining which combinations of new (improved) attributes for a vaccine would make it worthwhile to encourage the development of a new vaccine in those cases where existing vaccines provide at least partial protection against a disease. The committee's fourth use

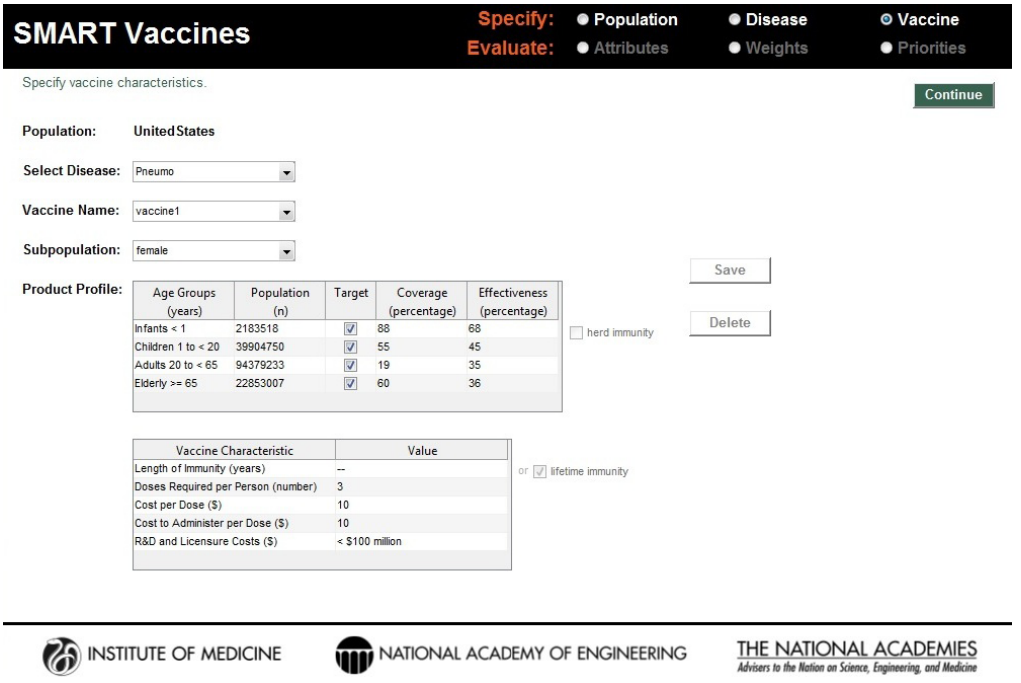


FIGURE 3-5
SMART Vaccines 1.1 screen for defining characteristics of the vaccine candidates considered for prioritization.

case scenario (described later in this chapter) took this approach to reverse engineer the desirable set of attributes of vaccines in pneumococcal vaccines for South Africa.

Upon completing data entry to specify vaccines, users use the "Continue" button to proceed to the Evaluation section of the program.

Evaluation

SMART Vaccines offers a choice among 28 attributes in eight categories as well as allowing for 7 user-defined attributes. Turning on any of the radio buttons (e.g., the economic attributes in Figure 3-6) takes the user to a set of attributes from which the user may choose one or more for a subsequent evaluation of the vaccine candidates. Because of the high similarity between DALYs and QALYs in the "health" group, users may not select both, and choosing one causes the option for the other to be grayed out. Furthermore, if a user selects, say, QALYs as a health outcome, then the user is only allowed to choose the economic variable of $/QALY—and not $/DALY—in the "economic" group.

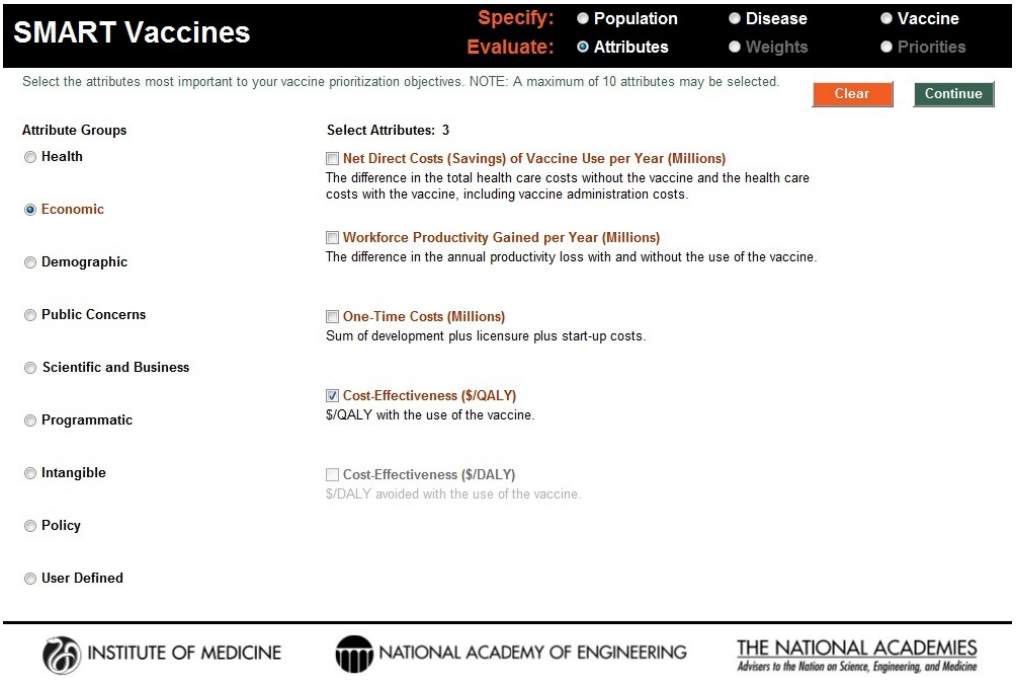


FIGURE 3-6
Attribute selection page in SMART Vaccines 1.1. Options from nine attribute groups can be selected by the user for comparing vaccine candidates, including up to seven user-defined custom attributes.

Reports from earlier phases of this project emphasized the importance of careful judgment in selecting attributes. There are several reasons for this. First, if many attributes are chosen, then the weights assigned to those at the bottom of the priority list will have little meaningful effect on the rankings of candidate vaccines. Second, even with the elimination of double counting with DALYs and QALYs, users can still select sets of attributes that could create additional double counting. For example, in the "Health" section, selecting "life years saved" and either DALYs or QALYs could lead to double counting. Both because many of the attributes on long lists of attributes will inevitably be essentially irrelevant and because of "real estate" issues in screen display, SMART Vaccines limits users to selecting no more than 10 attributes.

The "user-defined" category allows users to specify their own attributes. Figure 3-7 shows the creation of a user-defined attribute evaluating the impact of a vaccine on public education. When the user completes selection of attributes, hitting the "Continue" button at the upper right corner of the screen takes the user to the next step in the Evaluate section—the determination of weights to be used in the SMART Score calculation.

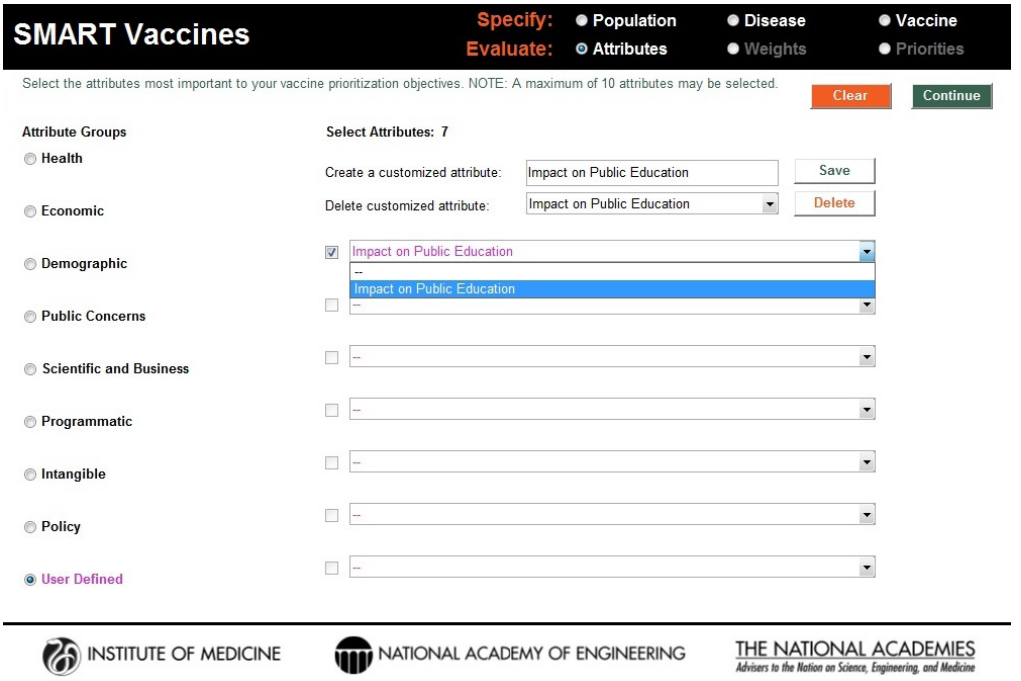


FIGURE 3-7
Creation and inclusion of a user-defined attribute. These entries are answered with a yes or a no response in SMART Vaccines 1.1.

The first step in the Weights section asks the user to rank the selected attributes by order of importance. Figure 3-8 shows a set of attributes that a hypothetical decision maker has selected. The standard approach in using this sort of ranking has the user specify first the most important attribute—number 1—using the pull-down box associated with each attribute. The user should then select the least important attribute (number 7 among 7 attributes selected previously). Next the user selects the most important of the remaining attributes (number 2), and then the least important of the remaining attributes (number 6), and so on, proceeding in this way until all attributes have been ranked.

SMART Vaccines uses these ranks to provide an initial estimate of the weights the user might wish to assign to each attribute, with the weights summing to 100 percent. The weights are calculated using the rank-order centroid process, which is described in detail in the Phase I report (IOM, 2012). Essentially, the rank-order centroid process calculates the average of all possible combinations of weights that are consistent with the original rank ordering specified by the user, and then that set of weights is assigned

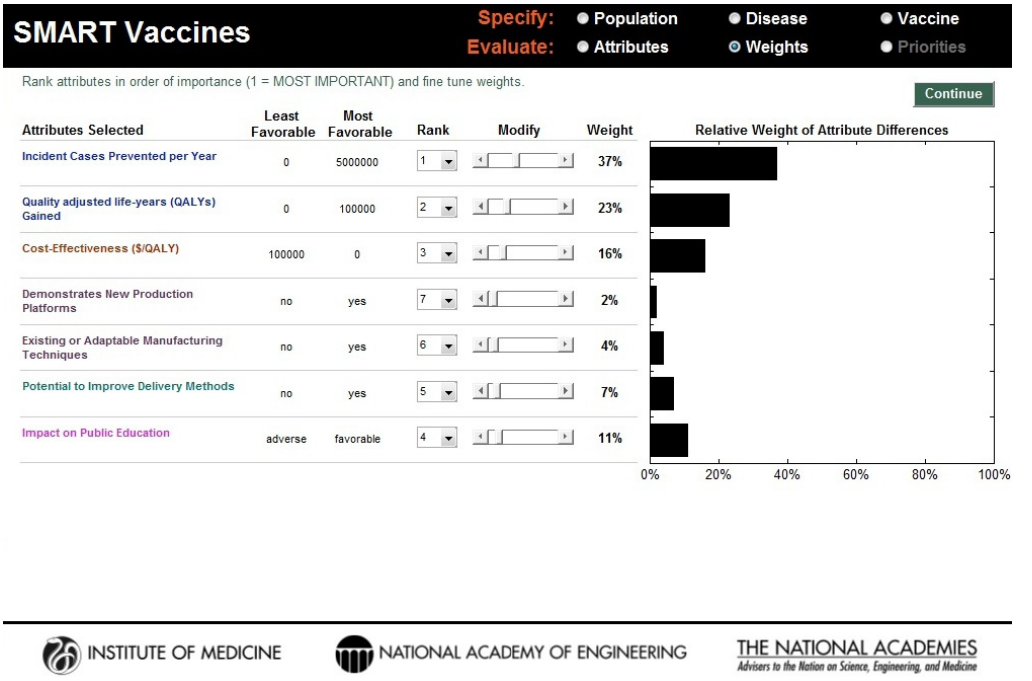


FIGURE 3-8
SMART Vaccines 1.1 screen for ranking and weighting attributes. Initial weights are produced by the software using the rank order centroid method, but they can be modified easily by the users with the provided slider bars.

to the attributes. This set of initial weights appears automatically once the user has completed the ranking process (see Figure 3-8).

Users can then freely adjust the weights attached to each attribute by using the slider bars for each attribute (the Modify option), after which the determination of the weights is complete (see Figure 3-9). For example, the hypothetical user chose to reduce the 37 percent weight applied to "incident cases prevented per year" in Figure 3-8 to 25 percent and increase the weight on "impact on public education" in Figure 3-9 to 15 percent. The other weights are automatically adjusted so that they all add to 100 percent. At this point, using the "Continue" button will take the user to the page where SMART Scores are calculated.

On the Priorities page the user can select up to five vaccine candidates for simultaneous comparison. The limit of five candidates is determined by screen real estate, but users can always calculate SMART Scores for a set of five candidates, save the results using the Print button at the lower right corner of the page, and then proceed to define another set of

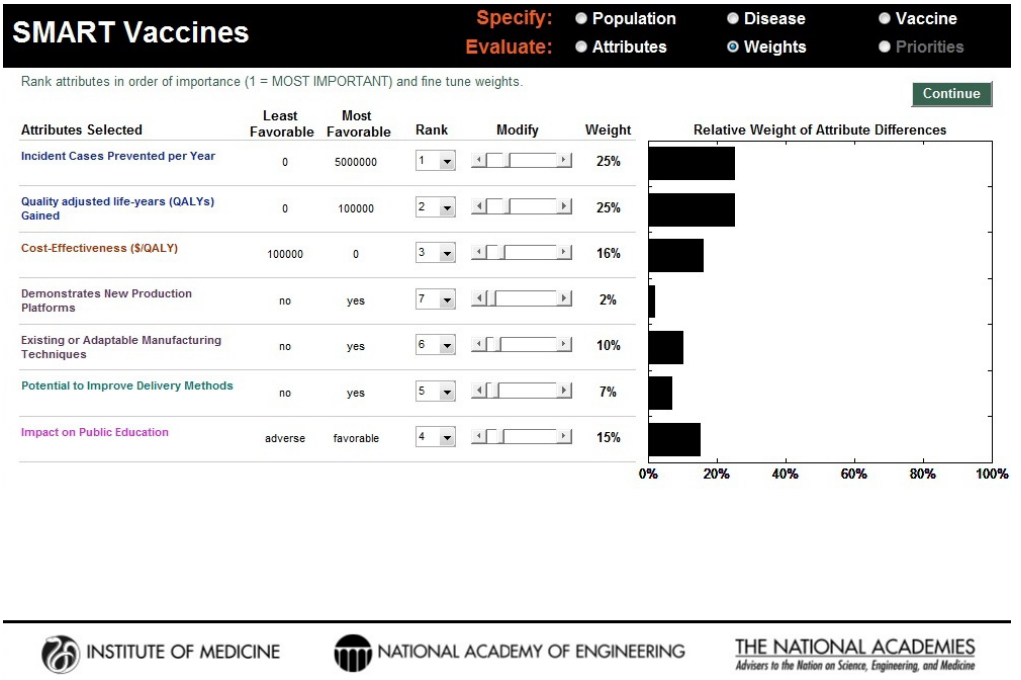


FIGURE 3-9
SMART Vaccines 1.1 screen showing the alteration of the weights based on the user's preference.

five candidates. The calculated SMART Scores will be the same as if all 10 candidates had been analyzed simultaneously.[4]

For each candidate vaccine selected, users must fill in the appropriate value for all of the selected attributes that are not calculated by SMART Vaccines.[5] As Figure 3-10 shows, some of these attributes have values calculated from previously entered data—in particular, the health and economic attributes. Other attributes must be defined by the user.

As the attribute values are completed for a candidate vaccine, a SMART Score appears in the display box on the right side of this screen. In this hypothetical example, the user's selection of vaccine candidates for pneumococcal infection, human papillomavirus, and rotavirus results in

[4] This is possible because multi-attribute utility models are independent of irrelevant alternatives (IIA), meaning that the scores are independent of the actual comparison set. As the Phase 1 report discussed in more detail, other multi-criteria decision analysis models (including the Analytic Hierarchy Process) do not possess this desirable feature.
[5] The reader is referred to the discussion in Chapter 2 regarding boundary setting for the software-defined attributes.

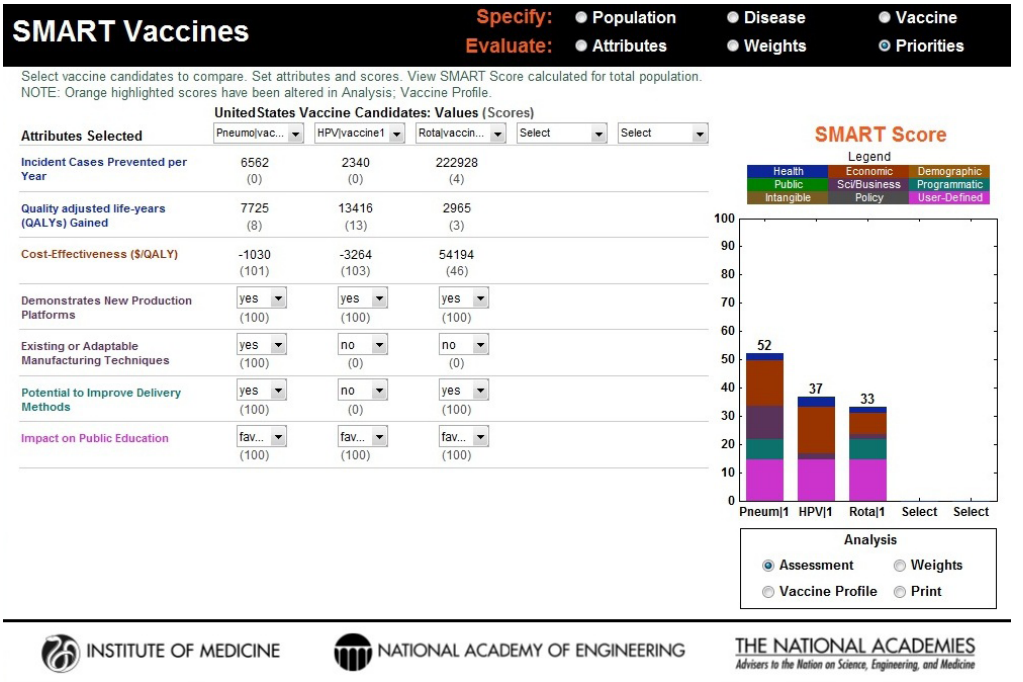


FIGURE 3-10
SMART Score output screen showing vaccines being compared, their computed or selected attribute values, and the color-coded final SMART Scores, a composite of quantitative and qualitative values, highlighting the relative differences between the candidates.

the scores of 52, 37, and 33, respectively. The bar graphs not only provide the total score but also show how much each domain of attributes (e.g., health, economic, demographic, and other categories) contributes to the total score by dividing the bar into color-coded sections.

It is important to keep in mind that the SMART Scores do not provide relative values. A score of 90 is not twice as good as a score of 45, for example, although it is 45 points higher. In other words, the differences in scores have meaning, but their relative sizes do not. Both the Phase I and the Phase II reports discuss this feature in detail (IOM, 2012, 2013). For a simple but useful analogy, users should think of these scores as temperatures that can be given using either the Fahrenheit or the Celsius scale. In neither of these scales is 20 degrees twice as warm as 10 degrees, and 20°F is not the same as 20°C, but the concept of "a difference of 20 degrees" (in either Fahrenheit or Celsius) does have a consistent meaning. Similarly, the SMART Scores of one user do not correspond to those of another, but it still makes sense to speak of differences in the SMART Scores in a single user's analysis.

A small box in the lower right corner of the screen allows the user to select different ways of conducting a sensitivity analysis (the Analysis option). If the user selects the Weight button, then the user simultaneously has the ability to adjust the weights on each attribute and see the effect on SMART Scores. Users should set the weights before conducting the analysis and generally should not modify those weights once they are established. One could, however, use this capability legitimately to explore the scores of a person or entity with a differing viewpoint (e.g., a health minister versus a vaccine developer), which is why this capability is made available.

At any point during the process, the user can capture the state of the program along with a time stamp by using the Print button, enter notes on that analysis for future reference, and save it as a portable document file (PDF). In this screen the upper box shows the weights attached to each attribute and the values each vaccine creates along that attribute's dimension, the lower box describes the vaccine product profile as specified for each vaccine, and the box on the right shows the SMART Score of each candidate (see Figure 3-11).

Two Aspects of SMART Scores

Users should be aware of two features in the display of SMART Scores. First—consistent with the way that multi-attribute utility models generally work—the SMART Scores can go above 100 or below 0. A score above 100 occurs if a candidate vaccine has an attribute outcome (e.g., cases averted) that substantially exceeds the "best-case" outcome boundary established for the population, coupled with a significant weight placed by the user on that attribute. For example, if a candidate vaccine achieves a score of 300 on a single attribute and the user has placed a weight of 40 percent on that attribute, then the multi-attribute utility algorithm adds 120 points to the SMART Score, and the total score will include that 120 value plus contributions from other attributes. The vertical axis on the SMART Score range dynamically adjusts to accommodate scores outside the 0 to 100 range.

Attribute values—and hence also SMART Scores—can also fall below 0 if an attribute value is worse than the "worst-case" outcome established for that attribute. For example, the worst case for a $/QALY cost-effectiveness ratio is set at 15 times the per capita income in the population of interest (e.g., in the United States, at $150,000). If the $/QALY for a candidate vaccine was actually $250,000, then it would have an attribute value of $100,000 more than the worst-case boundary, and hence receive an attribute score of –67, because the boundary values of 0 and $150,000 pro-

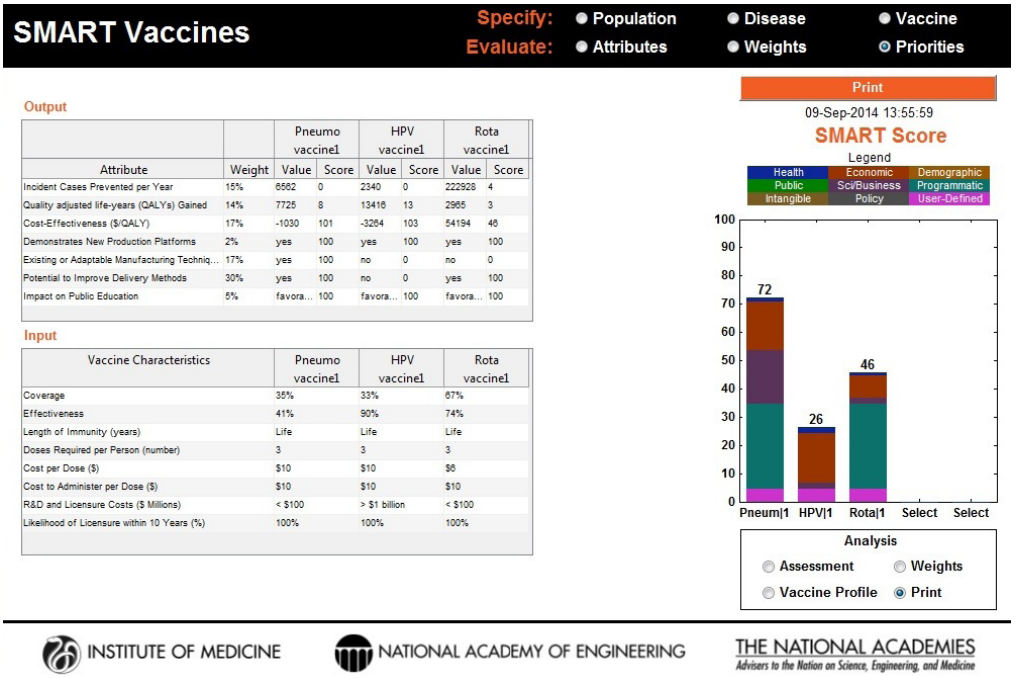


FIGURE 3-11
A new feature in SMART Vaccines 1.1, a Print command, summarizes the input (vaccine characteristics) and output information used in the analysis along with a time stamp for record.

vide a range of 150,000 and the actual value is two-thirds higher (worse). And if sufficient weight is placed on an attribute with such an outcome, the SMART Score can fall below 0. Again, the vertical axis of the graphical display dynamically adjusts to accommodate such a score.

A related case occurs when the SMART Score remains positive but has both positive and negative components. In this case, the graph shows the total score including both the positive and negative components in the sum. This is perfectly legitimate within multi-attribute utility theory, but to alert the user that such a case exists, the SMART Score graph for that candidate vaccine will show hatched bars rather than the standard solid color bars. In this situation, users should carefully attend to the actual values shown—both positive and negative contributions to the SMART Score—rather than just using the bar graph representation of the SMART Score to inform their decision making. Figure 3-12 shows a composite version of hypothetical vaccine candidates scoring above 100, scoring below 0, and having both positive and negative components in the SMART Score.

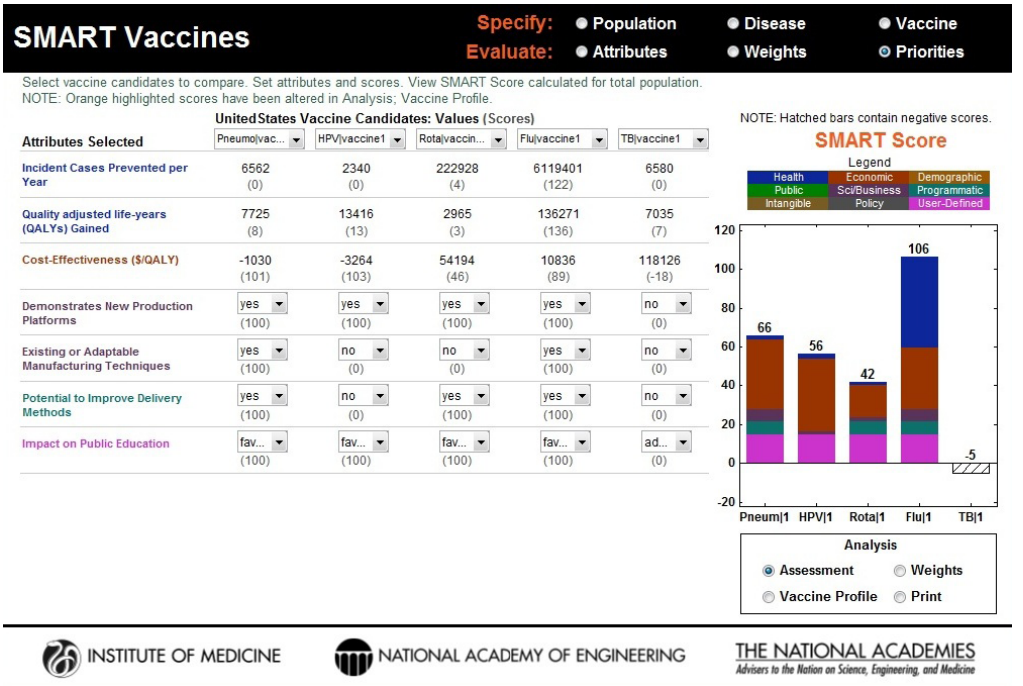


FIGURE 3-12
A hypothetical case comparison of four vaccine candidates where an influenza vaccine candidate scores 106 and a tuberculosis vaccine scores –5 based on the weights and impact of the attributes. Furthermore, the tuberculosis vaccine is represented by a hatched bar instead of solid colors to indicate that both positive and negative components have contributed to its SMART Score.

Key Insights from the User Groups

In this section, the committee summarizes key lessons learned beginning with the broadest policy issues and then shifting to more narrow issues in application of SMART Vaccines to the settings of the three user groups, and the officials from the Mexican Ministry of Health who served as advisory consultants.

All of these users fully understood that they were using a preliminary and evolving version of SMART Vaccines and that their feedback was to be applied toward improving the product. As a consequence, none of them attempted to use the software for actual decision making, but rather used the occasion to explore the software, both for their potential future use and to assist in the Institute of Medicine's (IOM's) unique product development effort.

In none of the use case scenarios did the users actually develop their official sets of attributes to be used in vaccine evaluation or the formal

weights to be attached to those attributes. In general, technical support staff selected a set of attributes as a starting point for discussion within their respective units, with the choices of attributes and their weights often being modified during presentation to support the discussions with higher level decision makers who would eventually make actual policy decisions.

Similarly, as the committee explored the software applications with various users, it found areas where their data were either incomplete or inaccurate, further emphasizing that the results were not real decision support but rather familiarization with the SMART Vaccines tool and its potential uses.

In Table 3-1, the committee has summarized the key things it has learned in these interactions with early users of SMART Vaccines and how this information informed the changes built into SMART Vaccines 1.1. These lessons are categorized by the software's functional aspects.

Fourth Use Case Scenario: Product Profile Design

SMART Vaccines can be used to explore the desirability of potential vaccines with different sets of attributes. This can be done by vaccine developers using their best approximation of the attributes and weights that the public health community might use, by the public health community directly, or perhaps through a collaboration between vaccine developers and other stakeholders.

To illustrate this approach to using SMART Vaccines 1.1—including new features not previously available in SMART Vaccines 1.0—the committee came up with three hypothetical vaccines for pneumococcal infection and used data from South Africa for the test case. The vaccines in this illustration are similar but not identical to actual vaccines, and the example considers their uses in populations where vaccination against pneumococcal disease is not necessarily recommended.[6]

The first hypothetical vaccine under consideration, named PS23, was a polysaccharide vaccine with purified polysaccharides from 23 serotypes of bacteria, which was similar but not identical to a commercially available 23-serotype vaccine. According to the Centers for Disease Control and Prevention, a commercially available 23-valent pneumococcal vaccine has shown effectiveness of 50 to 85 percent. This information was used as baseline information for the hypothetical vaccine under consideration,

[6] These comparisons by the committee are for purposes of demonstrating the vaccine sensitivity analysis feature in SMART Vaccines and should not be considered as contemplating actual vaccines or their uses.

TABLE 3-1

Insights from User Groups and the Committee's Notes

Software Aspects	General Summary and Notes
Specify Demographics, Diseases, Vaccines	• Special population data may be important, but even in a sophisticated setting, difficult to find. For Canada, northern populations matter for several reasons, including climatic and geographic considerations, extremely low population density, difficulty of transportation, and ethnic differences between the native populations and the larger "standard" populations across the country. But even in a data-rich environment such as Canada, users found that obtaining reliable data on these special populations was difficult. • The process of entering illness burden and vaccine attributes separately for males and females seemed redundant to users when both populations would be treated identically. SMART Vaccines was created to allow differential disease burden and vaccine programmatic targeting not only for different age groups but also separately for males and females, as would be appropriate, for example, for an HPV vaccine or potential vaccines against breast cancer or prostate cancer if such were to arise. • The process of entering data for health care treatment costs in SMART Vaccines 1.0 seemed overly cumbersome to many users, forcing them to find and enter highly detailed sub-categories of health care use (e.g., office visits, clinic visits, emergency room visits, hospitalizations) that were not necessarily appropriate for their setting. SMART Vaccines 1.1 therefore uses a much more streamlined process for acquiring treatment costs data, the details of which users can organize offline in their own useful spreadsheet formats and then enter the results in a much more simplified way. • SMART Vaccines was originally created to assist in the prioritization of development of new vaccines. Nevertheless, two users (New York State Department of Health and Mexico's Ministry of Health) had the sole goal of exploring the desirability of deploying existing vaccines in their population, and most prominently a focus on selecting among competing vaccines for the same disease (e.g., influenza). From these experiences and other discussions that committee members and staff have had with industry experts, the committee believes that this application will attract considerable attention among future users, particularly those in lower-resource regions where they do not envision having a major impact on vaccine development priorities.

continued

TABLE 3-1

Continued

Software Aspects	General Summary and Notes
Specify Demographics, Diseases, Vaccines (*continued*)	Some of these applications focused not on the comparison of two or more different vaccines but on an even narrower question—given their chosen attributes and weights, which subsets of their population provided the best potential vaccination targets? For example, such questions might consider whether vaccination should focus more on infants and children, the elderly, or the working adult populations. The committee's experience with these test scenarios suggests that for an expanded use of the future versions of SMART Vaccines it would be better to allow more finely granulated age groups to characterize disease burden of the population at hand and to define (with the same fine granularity) the target populations for a vaccine program's introduction or expansion.
Evaluate Attributes, Weights, Priorities	• The variety of attributes was perceived by the users to be an issue potentially creating the risk of double counting. For example, the "benefits women and children" attribute could be double counted if the disease burden data focused directly on women and children. Thus, they preferred to include the women and children attribute if there was special attention beyond that created by the patterns of disease burden. Because SMART Vaccines calculates costs and benefits by summing across the entire affected population, it does not add any special emphasis for a vaccine that prevents—as an example—only a childhood disease such as chicken pox. The software adds up benefits only across the childhood population in such an instance and may appear to have relatively low benefit in such attributes as "reduction of incident cases" because the childhood population is a relatively small proportion of the total population. This would pertain, for example, with a disease that affected all ages such as influenza. To account for this, users may wish to specify a particular attention paid to children by including that attribute in their evaluation set and placing sufficient weight upon it to counter the effect of the particular vaccine helping only a fraction of the population (children, in this example). The risk of double counting may emerge with other measures as well. Because they are so similar, SMART Vaccines does not permit the use of both QALYs and DALYs. Because life-years are included in the calculations of both QALYs and DALYs, including QALYs (or DALYs) as well as "premature deaths averted" as attributes may create double counting.

TABLE 3-1

Continued

Software Aspects	General Summary and Notes
Evaluate Attributes, Weights, Priorities (*continued*)	• The committee learned that the users preferred to have the capability to modify assumptions about vaccine options dynamically during the evaluation phase, rather than having to go back to the Specify section that defined vaccines originally to alter presumed attributes of various vaccines. They preferred to see the changes in SMART Scores immediately in the Evaluate section of the software. SMART Vaccines 1.1 provides this capability. This version also moves the adjustment feature for the "likelihood of licensure within 10 years" (from what was a separate page in SMART Vaccines 1.0) to the same page where all other vaccine attributes are defined. This capability now appears as a separate radio button on the Evaluate page and opens up a dialog box where the user can directly modify vaccine attributes without repeating intermediate steps (e.g., selecting attributes to be used in the evaluation and assigning weights thereto).
Usability and Usefulness	• Even within their established settings, the user groups had not yet developed a process to achieve a group-level consensus about the attributes and the weights to be attached to these. • The boundary values in SMART Vaccines matter in two ways. First, if they are too narrow, then the SMART Scores can go above 100, and the display in SMART Vaccines 1.0 did not accommodate this. SMART Vaccines 1.1 corrects this and allows SMART Scores to go above 100 or below 0. Second, when boundaries are too narrow (or too wide), the importance of an attribute is over (or under) emphasized. This arises because the multi-attribute utility model expects all attribute scores to have values between 0 and 100, and sets the weights accordingly. Within a reasonable range, allowing SMART Scores to go outside the 0 to 100 range deals with this issue, but there remains a more subtle issue if the boundaries are set so widely or narrowly that individual attribute have values that diverge too far from the 0 to 100 range anticipated by the multi-attribute utility model.

continued

TABLE 3-1

Continued

Software Aspects	General Summary and Notes
Usability and Usefulness (*continued*)	For example, if a boundary range is too wide by a factor of 10, then the component attribute scores for all candidate vaccines will shrink by a factor of 10 (compared with their scoring if the scores all fell into a 0 to 100 range). A user who intended to give that attribute 20 percent of the weight will in effect have assigned only 2 percent of the total weight to that attribute when the boundary range is too large by a factor of 10. The same thing occurs in reverse if the boundary values are set too narrowly. Consider again the effect of a 10-fold error in boundary setting. Some (or all) candidate vaccines will have attribute scores far in excess of 100, and that attribute will be over-represented in the final SMART Score by a factor of 10. In the extreme, it will swamp other attributes, even if assigned a very small weight (e.g., 1 or 2 percent). The committee has attended to this boundary setting problem in SMART Vaccines 1.1 as best it could with available data, but users are cautioned that these boundary value issues in general remain. At this stage of software development, boundary value recalibration must take place through recompilation of SMART Vaccines. Any time boundary values are recalibrated, all analyses must be repeated, because SMART Scores before and after the recalibration will not be commensurate. • Users groups—and other stakeholders—requested a method to save evaluation results at any point in the process. SMART Vaccines 1.1 includes a "print" button that shows both key states of the program (e.g., all vaccine attributes, the choices of the user for attributes to be used in the evaluation and the weights attached thereto, and the resulting SMART Scores for each vaccine candidate). These results are saved in PDF format (as named by the user) with a specific time and date stamp automatically supplied.
Decision Process	• In no case did the users have access to (or were aware of) other software or decision aids that could carry out the types of analyses available in SMART Vaccines. In some cases, technical experts within the user groups' organizations had written (or found access to) software that carried out sophisticated cost-effectiveness analysis on a single vaccine, but in no case did they know of or use software that allowed comparison across multiple vaccine targets, or that allowed specific inclusion of multiple programmatic attributes in the decision-support modeling. The multi-attribute capabilities of SMART Vaccines were (to the user groups' perspective) unique. One user group described SMART Vaccines as "an amazing tool" to help support decision making.

TABLE 3-1
Continued

Software Aspects	General Summary and Notes
Decision Process (*continued*)	• One of the user groups with significant technical expertise independently checked and verified outputs of calculations in SMART Vaccines, including cost-effectiveness ratios. In every case, their calculations matched those of the computer model. This gave them (and the committee) great confidence that the variables calculated within SMART Vaccines perform correctly. The committee has also carried out the same sort of calculation checks throughout the course of programming and testing of the software. However, no software program is devoid of bugs, and only repeated use and feedback to enhance the software system can deal with such issues over time. • In none of our use case scenarios did the user organization actually develop a set of attributes (and their weights) that would represent the group's official metric for evaluation. Several of the user groups noted that they did not have an established process to carry this out. The committee believes that further research to study available methods to support the decision process would be desirable.

which was targeted for a population excluding infants. The hypothesized coverage and effectiveness rates, cost per dose, costs of administration, and developmental cost for this vaccine can be seen in Figure 3-13.

A second polysaccharide vaccine covering 30 serotypes—named PS30—was imagined with increased effectiveness rates but the same coverage rates as PS23 (see Figure 3-14). Because of the presumed additional complexity of creating a 30-serotype vaccine, the cost per dose was set higher than that for PS23, and the presumed developmental costs were set at the highest category—$1 billion or more. As with PS23, PS30 was also treated as a single-dose vaccine.

A third invented vaccine was a new conjugate vaccine that requires three doses to achieve the stated effectiveness, but with the potential to be deployed in all age groups. The assigned coverage and effectiveness rates can be seen in Figure 3-15.

Four attributes were selected for this demonstration to reflect a generic "public health" point of view: deaths averted, QALYs gained, direct cost savings, and cost-effectiveness ($/QALY). To minimize confounding changes, only these four attributes were used for the demonstration, and the

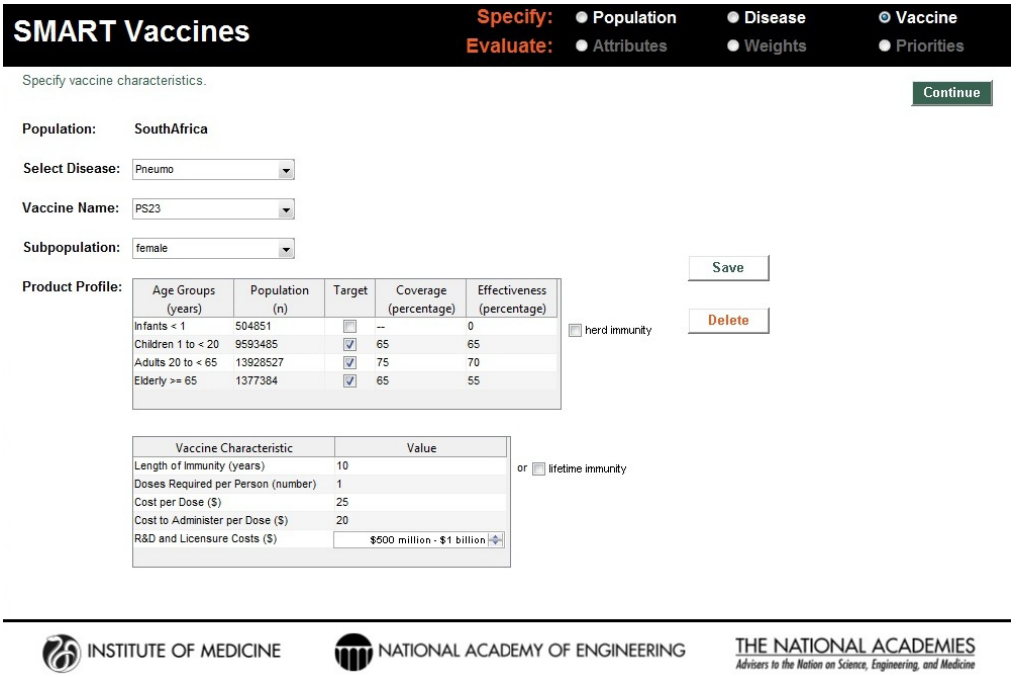


FIGURE 3-13
Characteristics of a hypothetical single dose 23-serotype vaccine (PS23) for pneumococcal infection in the South African population excluding infants.

ranks generated from the software's rank-order centroid process were used without modification (see Figure 3-16). For all of these three candidates, the probability of licensure within 10 years was assumed to be 100 percent.

In the base case results, PS23 and PS30 polysaccharide vaccines scored 31 and 28, respectively, but the scores and the rank order would shift with small changes in any of the pertinent attributes (coverage, effectiveness, or costs). The PC conjugate vaccine invented for use by all ages had a SMART Score of –27. Figure 3-17 shows negative attribute values for net direct costs saved (i.e., it actually increases the total cost, including the vaccine program's costs) and $/QALY, primarily because of the multiple-dose program and the costs per dose assumed in this scenario. Because of the positive attribute values for premature deaths averted per year and QALYs, the SMART Score for the PC vaccine is represented in a hatched bar.

To demonstrate the target product profile concept more fully, some of the key attributes were varied and the resulting changes in the scores of the hypothetical conjugate vaccine were observed. First, the expected coverage of the vaccine was increased to 80 percent. This is an external

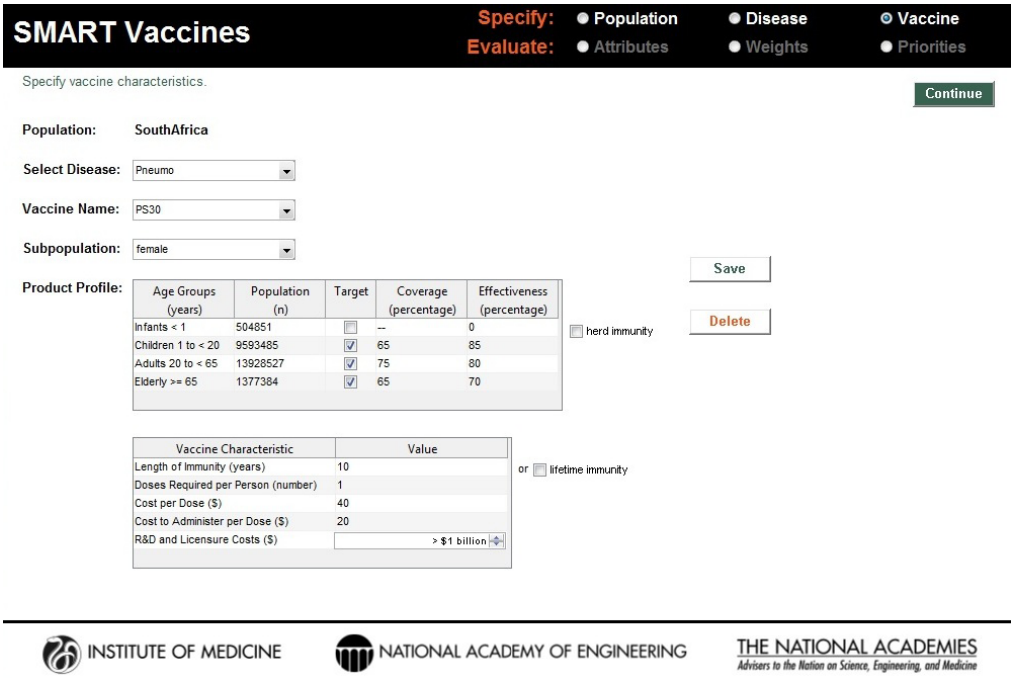


FIGURE 3-14
Characteristics of a hypothetical single dose 30-serotype vaccine (PS30) for pneumococcal infection in the South African population excluding infants. The effectiveness of the vaccine, costs per dose, and the overall research and development and licensure costs are set to be substantially higher than those of the PS23 candidate.

factor beyond the core features of the product profile design, but it is still an important contributor to the vaccine characteristics. Holding everything else constant, this single change in the vaccine's attributes shifted the SMART Score from –27 to –28 (see Figure 3-18). This decrease likely occurred because of the high cost per user associated with the triple-dosed vaccine.

In a second demonstration, increasing the potential length of immunity from 10 to 15 years while holding everything else constant produced a dramatic change in SMART Scores: from –27 to +4 (see Figure 3-19). This demonstrates that the length of immunity plays an integral role in a vaccine's product profile design.

Further, by dropping the number of doses from three to two while maintaining the coverage (set at 80 percent), effectiveness (set at 80 percent), and length of immunity (set at 15 years), the cost per dose was reduced from $30 to $20. This brought the SMART Score for the conjugate vaccine to 35, surpassing the scores of the PS23 and PS30 polysaccharide vaccines (see Figure 3-20).

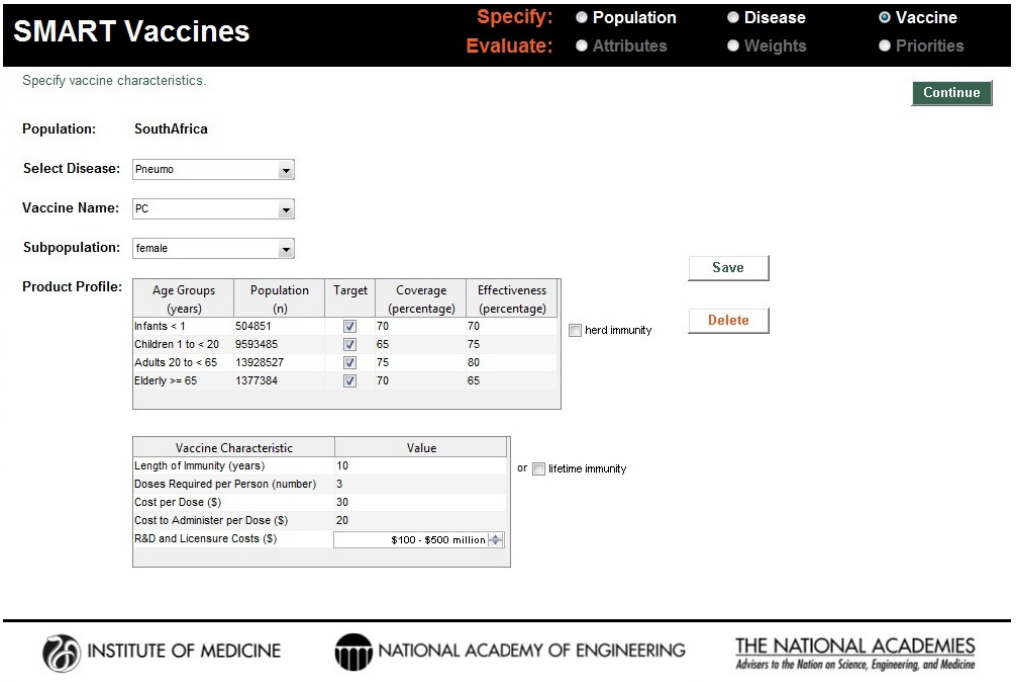


FIGURE 3-15
Characteristics of a hypothetical three-dose pneumococcal conjugate (PC) vaccine for use across all age groups in the South African population.

From a hypothetical South African decision maker's perspective, this simulation demonstrated the following:

- Although the PS30 vaccine has greater effectiveness than PS23—because it covers more serotypes of bacteria—the added costs offset those health gains, making the two nearly identical in the eyes of the hypothetical decision maker involved in this exercise.
- The PC conjugate vaccine—in its original specification—does not provide as much value as either of the polysaccharide vaccines and would not be the vaccine of choice. But if the conjugate vaccine could be developed so that two doses provided the effectiveness originally presumed for the three dose vaccine, and if the cost per dose could be brought down to near $20 per dose, then PC becomes a stronger candidate for development compared with PS23 and PS30.

For additional analysis, one could further alter the product profile attributes of these vaccine candidates, making even greater use of the sen-

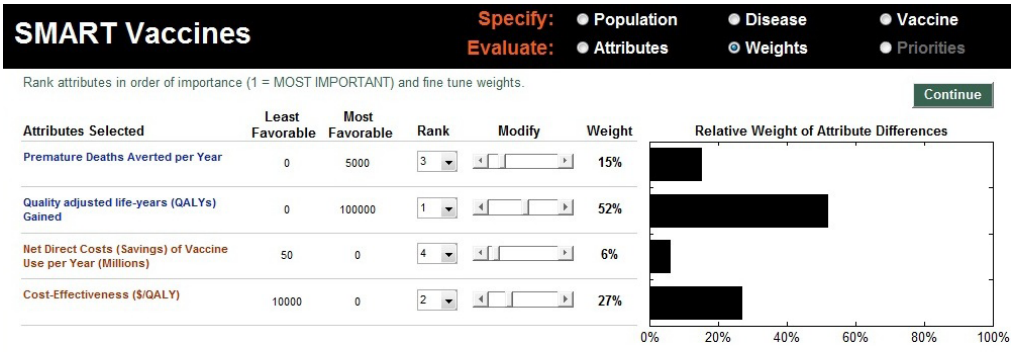


FIGURE 3-16
Attributes and weights selected using a traditional public health perspective (health and economic attributes alone) for comparing the hypothetical PS23, PS30, and PC vaccine candidates for pneumococcal infection in South Africa.

sitivity analysis capabilities in SMART Vaccines 1.1. The reader should keep in mind that the results depend on the choice of attributes and the weights assigned to them and that different preference settings could lead to completely different results. This sensitivity highlights the importance, when using SMART Vaccines, of agreeing on attributes and their weights at the beginning of any evaluation process rather than modifying those weights to achieve some preconceived result.

Just as in version 1.0, SMART Vaccines 1.1 provides detailed population data, including life-table information and average hourly wage rates, all of which are used in subsequent calculations for determining the effects of various vaccines (see Figure 3-3).[7]

[7] SMART Vaccines 1.1 eliminates a column that SMART Vaccines 1.0 contained where information was requested on Health Utilities Index 2 for age-specific determination of QALYs. That variable, used only in one attribute's calculations, is not available except for few national populations (e.g., the British Commonwealth nations, Canada, and the United States).

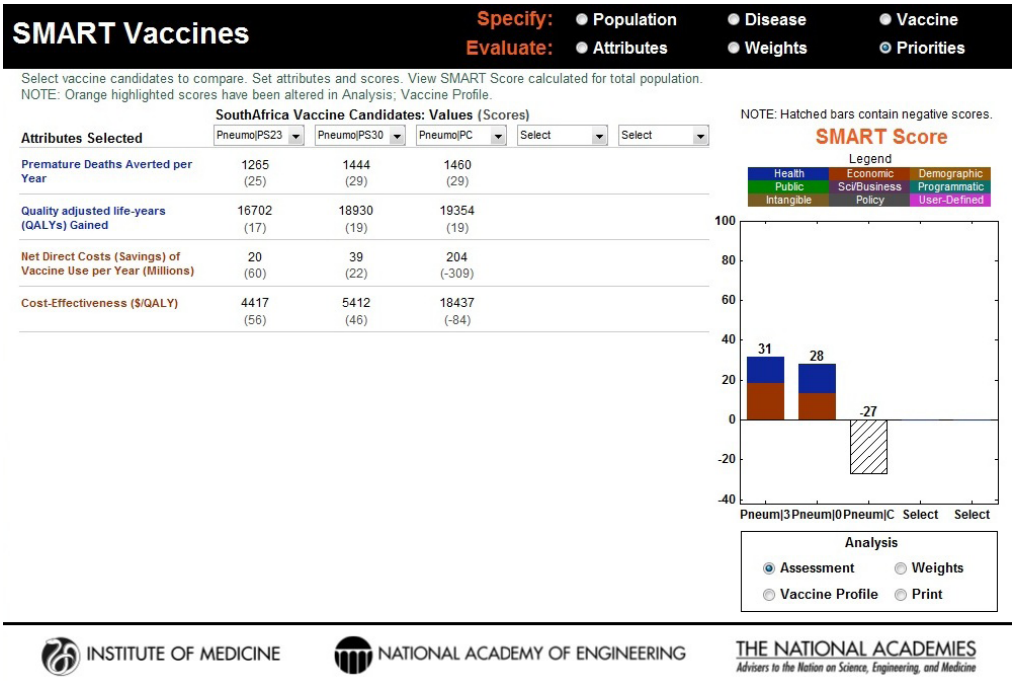


FIGURE 3-17
Computed values and initial SMART Scores for the hypothetical PS23, PS30, and PC vaccine candidates. PS23 and PS30 scored 31 and 28, respectively, and the specific contributions of health (blue) and economic attributes (red) are displayed inside the bars. The PC vaccine scored –27, and the hatched bar indicates the influence of both positive (health) and negative (economic) values on the final score.

On the page requesting information on disease burden (see Figure 3-4), users enter population-specific information about the burden of various diseases of interest. Vaccines targeting these diseases will be available for later comparison and evaluation. For each disease of interest, users must enter two types of information: disease burden data and illness descriptors.

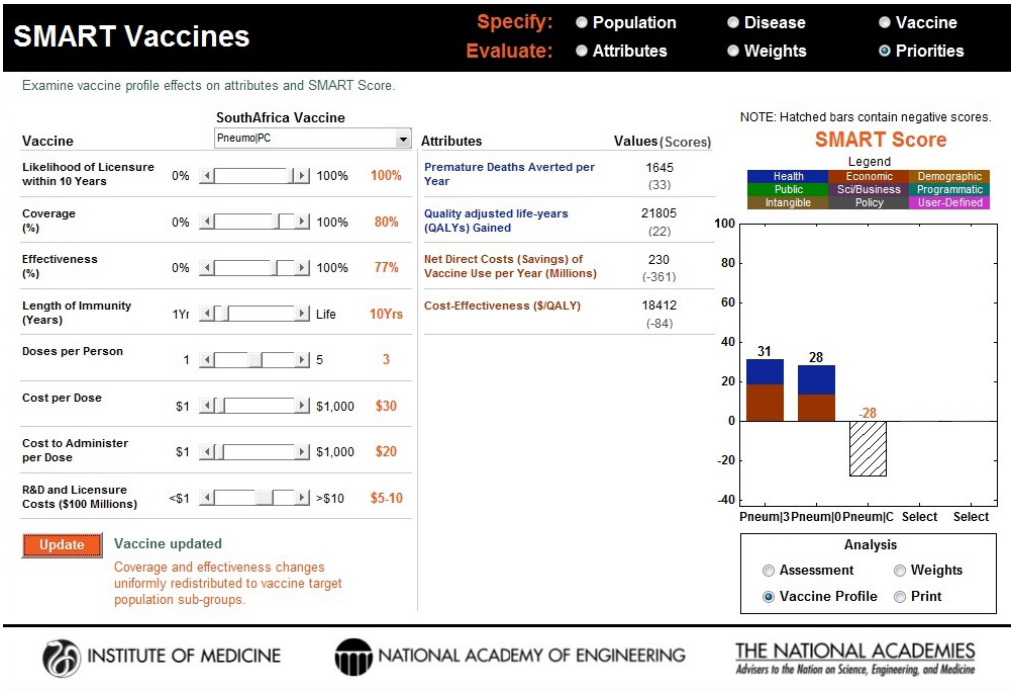


FIGURE 3-18
Changes to the SMART Score of the PC vaccine with an increase in coverage (a factor external to the product profile feature). The initial score of –27 dropped to –28, indicating that the additional costs associated with increasing the coverage outweighed the benefits for this vaccine.

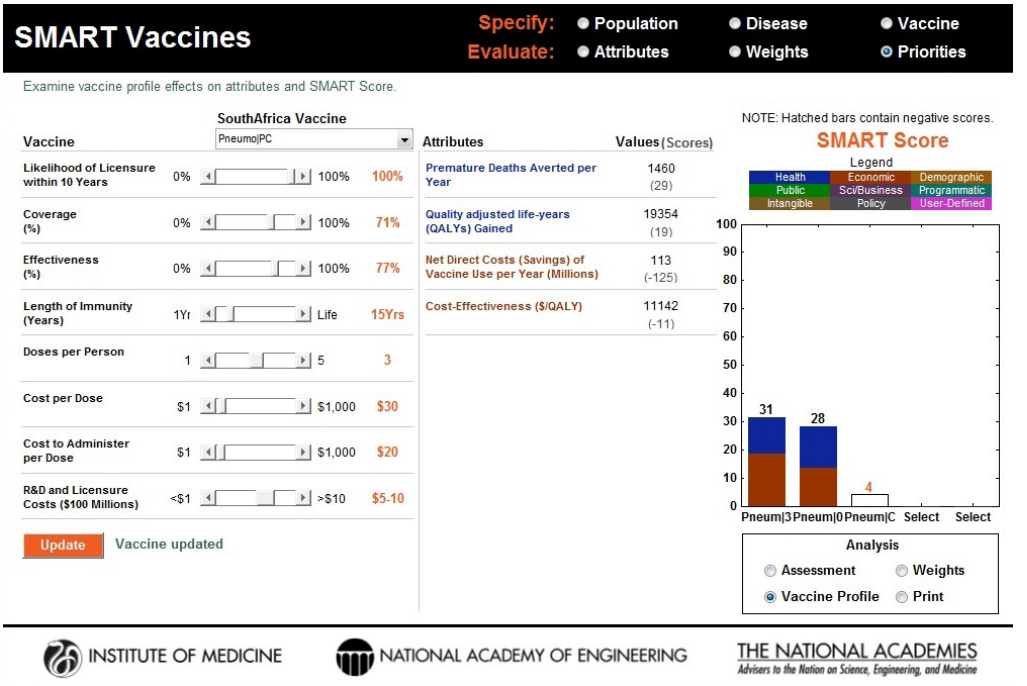


FIGURE 3-19
Changes to the SMART Score of the PC vaccine caused by an increase in the length of immunity from 10 years to 15 years. The vaccine profile (sensitivity analysis) feature shows that this one product design improvement was able to elevate the score from –27 to +4.

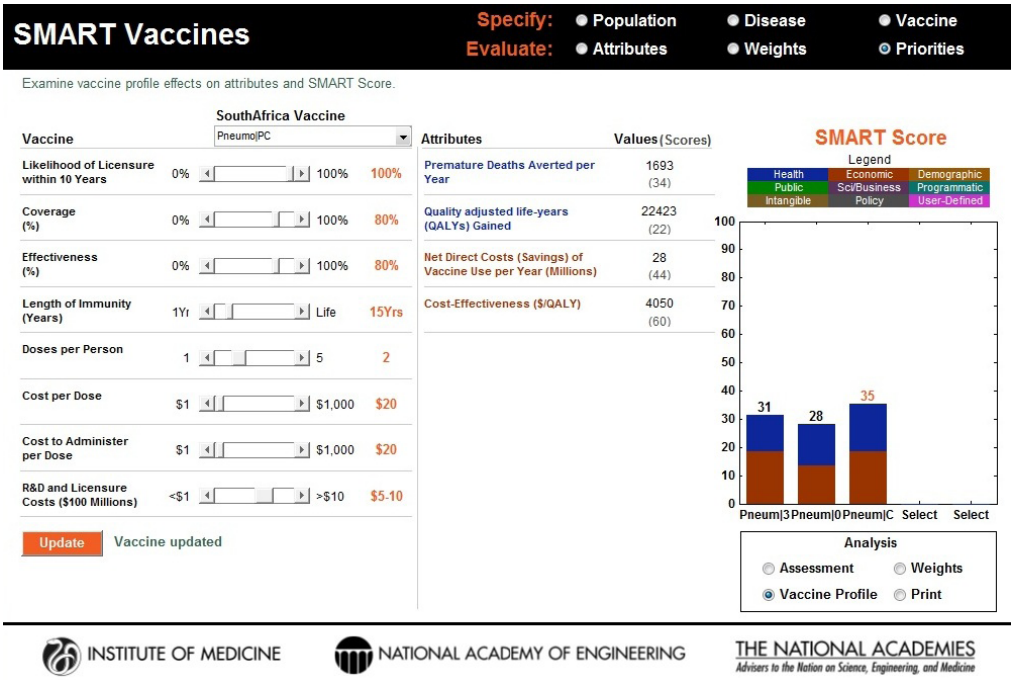


FIGURE 3-20
Changes to the coverage (increased to 80 percent), effectiveness (increased to 80 percent), length of immunity (increased to 15 years), cost per dose (decreased to $20), and the number of doses (decreased from 3 to 2) dramatically increased the SMART Score of the PC vaccine candidate from an initial score of –27 to +35, thus surpassing the scores of PS23 (31) and PS30 (28) motivating the need for product profile changes. In this way the vaccine sensitivity analysis feature in SMART Vaccines permits the reverse engineering of product attributes for gaining comparative advantage.

4

Reflections and Looking Forward

The Phase II report *Ranking Vaccines: A Prioritization Software Tool* (IOM, 2013, p. 9), specified a guiding principle that formed the foundation for the Phase III committee's thinking: **"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 Phase II report also stressed the importance of the National Vaccine Program Office identifying a future home for SMART Vaccines and of creating a data architecture to enhance the creation of useful data for SMART Vaccines users. The report then listed a sequence of events that the Phase II committee believed would increase the long-term value of SMART Vaccines. Those events are summarized here:

1. SMART Vaccines is hosted in an open-source setting in a widely trusted website with a distinct identity, protected from unwarranted modification or intrusion.
2. The host organization creates, maintains, and funds a user community to create and manage data and to facilitate further software and data development.
3. Ideally, the user community includes decision makers from a wide spectrum of the vaccine community and includes expertise in such relevant areas as epidemiology, demographic sciences, software engineering, database management, and visual design.

4. The community of users establishes an advisory group to help plan future improvements and enhancements of SMART Vaccines.
5. The community of users and the host organization facilitate the development and updating of data, which would optimally be accessible in standardized format for users around the world.
6. The community of users retrospectively studies previous choices made about vaccine development as part of a continuous learning and improvement process.

The Phase III committee endorses these concepts and elaborates upon them in the following sections.

Transition Paths

Phase I of this project involved developing the SMART Vaccines concept, and Phase II saw the robust testing of version 1.0 of the software. In Phase III this committee provided an enhanced user interface in version 1.1 and tested the software in actual use cases in collaboration with three user groups based in the Canada, India, and the United States. The committee also added population data for 34 Organisation for Economic Co-operation and Development (OECD) member countries in addition to data from India, New York State, and South Africa, and it provided initial boundary estimates for attributes with values calculated within the software so as to reduce the start-up barrier to its further use.

As Phase III comes to a close, it has become all the more apparent to the committee that **a transition strategy to a permanent home for SMART Vaccines is necessary for the ongoing use, enhancement, and even the survival of the software as a tool for strategic planning.** The committees of the various phases that worked on SMART Vaccines have consistently understood the importance of a permanent home and the need for an active user community working to improve the software and the data library to support it.

There are many examples of existing user consortia involved with software applications—for improving university operations, for enhancing the quality of life for the elderly, for improving ocean ecology, for using and improving statistical analysis and other business software, and more—and these examples suggest that the formation of a similar group devoted to the use and enhancement of SMART Vaccines would neither be difficult to achieve nor complicated to maintain.

The permanent home for SMART Vaccines could be a single institution such as a private foundation or a research university, or it could be

a partnership involving combinations of foundation and university participation. It might even involve a broader public–private partnership that includes for-profit vaccine manufacturers. This committee's task did not include identifying the permanent host, but it did include a discussion of issues that will enhance "further development, maintenance, and dissemination of the software and the data warehouse." With that in mind, we turn next to a discussion of a process that could to a permanent host and a discussion of the key attributes that a desirable permanent home would possess.

A Process Leading to a Permanent Home

The committee believes that **the National Vaccine Program Office and the Fogarty International Center of the National Institutes of Health—the federal sponsors of the Phase III project—will be best served if they promptly create a process to facilitate the transition of SMART Vaccines to a permanent home.**[1] They could do this by convening a group of relevant stakeholders with the goal of having this group recommend a process for selecting the permanent home. This approach might involve, among other things, a process for receiving proposals and a strategic mechanism for determining which of these groups—individually or as a consortium—would be suited to become a permanent home for SMART Vaccines. The relevant stakeholder groups would include public health groups that focus on vaccine research, development, and policy—both domestic and international—as well as representation from producers and suppliers of vaccines, higher educational institutions with a prominent focus on global public health, international governmental and nongovernmental health organizations, and philanthropic donors with strong interests in public health and vaccine policy.

Ensuring the Growth and Value of SMART Vaccines

The Phase II report indicated—and this committee strongly agrees—that **the ultimate future applications and benefits of SMART Vaccines depend on the strengths of the organization or consortium that**

[1] The committee believes that the existing operational structure of the National Academies does not make it a plausible permanent home for a product such as SMART Vaccines that must necessarily evolve through time, a characteristic that would require a qualified host organization to support and oversee software modification, enhancement, and data curation and to facilitate an active community of users.

becomes the permanent host. The committee's discussion of these issues contains seven main elements, many of which are interrelated. We describe these issues here to help illuminate any future discussions that take place leading to the choice of a permanent home.

The Host Organization

SMART Vaccines offers a unique ability for individual users to specify what matters to them—and by how much—rather than limiting the user to a single metric, such as has been the case with previous vaccine-ranking tools from the Institute of Medicine and elsewhere. Because of the inherent flexibility in the viewpoints able to be expressed in SMART Vaccines analyses, a host organization with a particular point of view might lead others with a different point of view to avoid participation in a community of users, and this might also run the risk that SMART Vaccines would become identified with a particular viewpoint.

Thus, **the committee emphasizes the importance of choosing a host organization that both is neutral among many users' competing viewpoints—and is clearly viewed as such—and is well equipped with organizational and technological capabilities**. **The committee believes not only that the best hosting organization will have a significant international presence and reputation, but also that the hosting organization will best serve the user community if it is—or partners with—a research-intensive institution of higher education.**

The Importance of a Higher Education Presence in the Host Organization

The committee believes that a higher education presence in the permanent host for SMART Vaccines could provide important benefits to the user community around the world. In particular, the hosting arrangement should include a major research university or a consortium of universities with a significant global public health focus. Many other government and private-sector organizations possess some of these traits, and consortium arrangements between such organizations could likely provide a similar set of strengths, but they would require an agreement among stakeholders on the management and governance structure.

In addition to important strengths in public health, a major research university presence would bring access to many other important knowledge domains, including vaccinology, immunology, epidemiology, public policy analysis and modeling, demography, health care systems engineer-

ing, health economics, business management, information management, and computer sciences. Many universities around the world also serve as World Health Organization collaborating centers. Some research universities also have partnerships with or have access to technology parks with strengths in new product incubation whose models may inform the development of the successive versions of SMART Vaccines.

Research universities generally possess the requisite independence and neutrality that is desirable in the permanent SMART Vaccines hosting site. One exception to this characterization of research universities would arise if the host university had a major presence in vaccine development, particularly if it was closely linked to the development and testing of the vaccines of one or a small number of vaccine manufacturers. In such a situation, a consortium of universities could reduce the actual and apparent conflicts of interest that might arise otherwise.

Research universities bring another important attribute to the table: They have standing educational programs that could mesh well with the presence of SMART Vaccines. One can easily envision, for example, graduate-level courses on strategic planning in public health or health policy that involve SMART Vaccines and the concepts therein (e.g., multi-criteria decision analysis, multi-attribute utility theory, and systems analysis) in a fundamental way, which would serve as a valuable complement to the cost-effectiveness and cost-benefit analyses traditionally found in such courses.

In addition, a university's undergraduate and graduate students, either through formal course-work or hired on an hourly basis, offer an attractive option for data development. With proper guidance, training, and templates, students could provide a ready mechanism to crowdsource the development of data libraries. Furthermore, SMART Vaccines would offer an almost endless set of opportunities for graduate dissertation material in a wide array of fields.

An Active User Network

From Phase I onward, the committees helping to develop SMART Vaccines have emphasized the importance of developing a network of users. **The committee urges that a community of users, developers, and decision makers be created, fostered, and supported (most likely by the host of SMART Vaccines) to facilitate further use of the tool, data development and curation, and to guide additional software improvements and enhancements.** User consortia such as the one the committee envi-

sions for SMART Vaccines have numerous functions. They include the following:

Manage Product Development and Enhancements

No software system is immune from bugs, and the best way to find them is to use the software extensively. Thus, one of the essential functions of any software user community is to find, report, and fix bugs, and the SMART Vaccines user community will be no different. Furthermore, the Phase II report discussed the option of a user community establishing an oversight group to manage and guide the further development and extension of SMART Vaccines. This committee reaffirms the desirability and importance of such a guiding group.

Practical Contributions from Users

Some software tools are built from the ground up to allow users to develop and share enhancements that run as programs or subroutines within the larger software environment. Even early programming languages such as FORTRAN relied on subroutine libraries that were developed, tested, curated, and made available by various organizations (sometimes competing with one another). The underlying philosophy of the Linux operating system is to base Linux on the contributions of a community of users. Many other software-based systems similarly benefit from user-provided contributions, some of which eventually are embedded into the primary source code of the software, while other contributions remain independent programs that operate within the overall software environment.

Exchange of Ideas and Training

Most software consortia have newsletters, blogs, discussion forums, and social media platforms to allow users to share ideas and help each other solve problems. Ideally the host institution or consortium for SMART Vaccines would provide and maintain the mechanisms for doing that for this software.

Depending on the ultimate size and global spread of the SMART Vaccines user community, it may become useful to create formal training tools to provide instruction both in using the software and in carrying out the data development necessary to expand the populations and the diseases that can be used in SMART Vaccines. This training could be carried out via workshops, webinars, tutorial videos, or formal courses either within higher education settings or affiliated with relevant professional meetings in public health, medical decision analysis, or public policy.

In larger user communities, conferences and seminars are organized on a regular basis, sometimes being hosted by the sponsoring organization or independent groups. Even with SMART Vaccines, it seems likely that at some point in the future it will be desirable to have regular workshops where the user community can share best practices and new ideas.

Data Development, Curation, and Sharing

Another way the user community could help increase the usefulness of SMART Vaccines would be to expand, refresh, and, curate data for different populations around the world, including data on demographics, disease burden, and costs of care. As part of this function, the user community could also verify the quality of datasets submitted by individual users or students using SMART Vaccines in order to provide a sense of the accuracy and trustworthiness of datasets developed around the world.

The data curation for SMART Vaccines—which, as noted earlier, will include such functions as quality control, storage, and access—will likely involve an integrated data warehouse. Such a warehouse will likely include a relational database management system to provide summary analytics and to allow specialized data outputs on all desired dimensions, including reports specific to a given population and reports summarizing disease burden data across all populations represented in the database.

Outreach and Awareness Enhancement

The committee places a strong emphasis on the importance of additional outreach and communication efforts to achieve the best use of SMART Vaccines. Based on previous outreach activities for SMART Vaccines in the form of seminars, workshops, conference symposia, and other ad hoc presentations, the committee knows that people in the vaccine community are eager to learn more about the possible uses of SMART Vaccines and in many cases to pursue further exposure to and use of the system. Those presentations have led many in the vaccine community, both in the United States and internationally, to express interest in contributing to the further development of SMART Vaccines and its potential applications. In addition, the committee has been encouraged by the interest of academic communities which have appreciated the teaching and learning value of SMART Vaccines for students interested in public health, health policy, business, engineering, and biomedicine. These communities could help refine the tool, and suggest further uses.

Early Partners and Value Demonstration

In most endeavors like SMART Vaccines, outreach activities lead to some organizations becoming early adopters (or pioneers) of new software systems. These early users commonly have an important role in determining the eventual success of software systems. They lead the discussion on the software value, which in turn attracts other users. They demonstrate ways in which value creation overcomes the initial barriers to entry that exist when one is starting to use a new system. In the case of SMART Vaccines, the main initial hurdle is developing data to characterize not only the demography of the relevant populations, but also the disease burdens and the costs of treating those diseases. Thus, finding and encouraging a set of early partners is one of the key goals of the initial seminars, workshops, symposia, and other communication modes in the outreach efforts for SMART Vaccines.

Data Development: An Opportunity Awaiting

As daunting as the data requirements for SMART Vaccines might seem, the committee believes that to carry out any vaccine prioritization task sensibly, decision makers will necessarily need to have these same data in hand. Without these basic data, decisions cannot be made as carefully or with an empirical basis.

The data requirements that may seem to loom large in the eyes of potential users are not created by the software itself—it merely brings them to the forefront. One cannot make intelligent, data-informed decisions about vaccine priorities without these data. Once the data are assembled, SMART Vaccines provides a useful tool, which has a significant, data-driven basis, for managing the data and for enhancing decision making. Earlier in this report, a discussion appeared concerning the desirable approaches to providing a data warehouse that allows for the introduction of new data, quality validation, and access to the data from various perspectives (e.g., by country or by disease). All of the data development suggestions that follow will benefit from a carefully constructed and well managed data warehouse capability.

The Phase III committee sought to reduce the data input burden on users by pre-loading the software with the population data for 34 member countries of the OECD as well as India, South Africa, and New York State. The committee also sought to provide users with various resources to simplify finding and entering data in other categories. Ultimately, **the com-**

mittee finds the data warehouses developed by the World Bank,[2] the Global Burden of Disease project of the Institute for Health Metrics and Evaluation,[3] and the International Labour Organization[4] to be desirable templates for informing data synthesis, tutorials, and visualization to support vaccine priority-setting efforts in general.

To further expand the data library for SMART Vaccines at a strategic level, rather than at the tactical level discussed in Chapter 2, the committee envisions three basic approaches to data development, which can be carried out singly or in various combinations. These approaches are

1. *Each user develops the population-specific data required.* This is basically how the three use-case groups described earlier in this report assembled their data—with some assistance from the committee.
2. *Centralized data development with external funding.* One way to fill out the databases for use in SMART Vaccines would be the use of centralized data development. This would require significant external funding to contract for the data development, either globally or region by region. Such funding might come from governments, private-sector resources, or philanthropy. Separate organizations might fund different parts of the data development, e.g., data development in Europe, Central and South America, the Middle East, and various regions of Asia. The committee observes that the use of centralized funding to create the data under contract would be a viable option.
3. *Crowdsourcing.* A crowdsourcing approach would rely on volunteer providers of data, with smaller collections of data sent to a central repository. The benefits and weaknesses of this approach versus the first two are obvious. Crowdsourcing would likely occur at lower cost, but it would also likely occur more sporadically and almost certainly with lower data quality than centralized or user-specific approaches might provide. Crowdsourcing is more likely to succeed in the presence of the following three things:

   (a) Tutorials, videos, and training tools.

   (b) A higher education connection. Students taking classes that use SMART Vaccines provide a natural base for crowd-

[2] See www.data.worldbank.org.

[3] See www.healthdata.org/gbd. See, for example, Murray et al. (2012).

[4] ILOSTAT at www.ilo.org.

sourcing data. Academic courses using SMART Vaccines could (and preferably would) have as a learning component the development of a new data segment. Thus, for example, a course offered in a given country might focus specifically on data development concerning the burden of diseases and costs of treatment in that country. Many U.S. research universities have international partners that would be natural for U.S. students to work with in order to develop data for other populations.

(c) An active user group that can provide guidance and training for participants involved in crowdsourcing with the ability to analyze and rate the quality of newly developed data for other users.

A Web-Based Platform

Based on the feedback from the three user groups' and on numerous presentations made by the committee concerning SMART Vaccines, both in the United States and abroad, the committee observes that the current Matlab-compiled software implementation is an impediment to users. **The committee believes that a fully Web-based version is an essential next step in the development of SMART Vaccines.**

Three features of the current software environment underpin this observation. First, SMART Vaccines is currently platform-dependent—it runs only in a Windows environment, which precludes its use in Apple, Linux, or other operating systems.

Second, the current version requires the downloading of a Matlab compiler, which then creates the operational version of SMART Vaccines on the user's computer. This is time consuming, particularly in environments with less-robust Internet connectivity, and it adds a layer of extra effort and complexity that a Web-based system would avoid.

This in turn leads to the third issue, which the committee has repeatedly experienced in user testing and in other public demonstrations of SMART Vaccines. Particularly in governmental office buildings, firewalls, and other intranet security systems prohibit the downloading or installation of outside software and, in some cases, even the simple act of connecting an externally provided computer to the system. A Web-based version of SMART Vaccines would avoid these difficulties because it would ideally operate through the Web browser on any user's computer with Internet connectivity.

Intellectual Property Considerations

Just as did the Phase I and II committees, the Phase III committee has emphasized the benefits of a consortium of users dedicated to enhancing SMART Vaccines software and data systems. To develop such a consortium properly, the intellectual property associated with SMART Vaccines must have proper licensing terms and conditions both to assure that it is available to the community of users in ways that enhance its use and also to prevent unauthorized uses or modifications of the software and its potential derivative products.

Specifically, the committee envisions a future software environment that allows for open use of SMART Vaccines and its associated data library, but with control over the official versions of the source code and the data governed by appropriate licensing terms and conditions. This type of arrangement is in wide use for open source software, with dozens of various specific models of licenses existing, each with modestly different arrangements.[5]

The Linux operating system software, for example, uses the GNU model, where users around the world are free to use and modify the original code, and can apply to the group that owns the Linux copyright and trademark. The APACHE Software Foundation[6] has a similar license and arrangements, but without the single-person control over dispute resolution (e.g., deciding whether or not to alter the official version of the software code) that is embedded in Linux and other software systems.

This committee does not have the expertise or charge within its task to prescribe the precise legal structure for management, support and improvement of the SMART Vaccines software and its associated data libraries, but it emphasizes the need for appropriate legal protection without curtailing the broad use and refinement of the software within a user-driven consortium.

[5] See www.opensource.org/licenses.

[6] The APACHE Software Foundation is a "U.S. 501(c)(3) non-profit corporation [that] provides organizational, legal, and financial support for a broad range of over 140 open source software projects. The Foundation provides an established framework for intellectual property and financial contributions that simultaneously limits potential legal exposure for our project committers. Through a collaborative and meritocratic development process known as The Apache Way, Apache™ projects deliver enterprise-grade, freely available software products that attract large communities of users. The pragmatic Apache License makes it easy for all users, commercial and individual, to deploy Apache products." See www.apache.org.

Future Improvements and Research

The committee suggests several areas for additional research and development to improve SMART Vaccines.

Setting Boundaries

In the multi-attribute utility model used in SMART Vaccines—which is described fully in the Phase I report *Ranking Vaccines: A Prioritization Framework* (IOM, 2012)—a number of attributes have numerical values that can take on a wide range, depending on the populations of interest. The multi-attribute utility theory process works best when the potential boundaries of each attribute are clearly defined for each population of interest. The upper boundary should represent a best-case scenario (spectacular success) in a vaccine, and the lower boundary should represent the worst-case scenario (failure or no effect).

As a specific example, consider the attribute "premature deaths averted," which depends sensitively not only on the size of the population, but also on the intrinsic disease burden faced in each population. A lower bound on deaths averted would be zero (the vaccine has no effect), but the upper bound would depend on the disease burden confronting the population. In the United States, with a population of 310 million (2010 estimates), we know that the largest number of vaccine-preventable deaths currently arises from lower respiratory infections (at a rate of 18.5 per 100,000 or 57,300 deaths annually). In SMART Vaccines 1.1, we would specify half of that amount—28,650 deaths averted—as an upper bound representing the best-case scenario. This target for success would apply to all vaccines, and they would all be rated on how much of that potential "target" they could achieve.

Consider, by contrast, the deaths from infectious diseases in Bangladesh, which has a population of approximately 155 million. Lower respiratory infections are also the leading killer in Bangladesh, with 65.5 deaths per 100,000, for a total annual death rate of 101,525. Half of that—about 50,000 deaths—would be the upper-bound target in the Bangladesh. Australia, with a population of 24 million, also has more annual infectious disease deaths from lower respiratory infections than any other type of infection, but it has an annual rate of only 14.4 per 100,000 and for a total of 3,456 deaths, so half of that—1,728—would become its upper bound.

Thus, each population therefore requires a different upper bound simply because of its overall size, but also because of overall death rates from the disease that causes the most fatalities (which, in most cases in the World Health Organization database comes from lower respiratory infections). The death rates from lower respiratory infections exceed 200

per 100,000 in numerous African nations as well as some others such as Afghanistan. At the lower end, these rates drop into the single digits per 100,000 in some highly industrialized nations as well as in some less highly industrialized nations such as the Bahamas, Bahrain, and Costa Rica.

Clearly, boundary setting must have a population-specific focus. As discussed in Chapter 2, if the boundaries are set much too wide, the effect of that attribute on the SMART Score is blunted, and if the boundaries are set too narrow, the reverse occurs. Thus, the committee sees significant value in additional research to establish the best ways to set these boundaries within SMART Vaccines for all attributes with population-sensitive values and, hence, population-sensitive boundaries.

Granularity of User-Defined Attributes

Those attributes that do not depend on population values are assigned levels of success by the user. In the current version of SMART Vaccines, some of these attributes have simple Yes/No options (e.g., whether the vaccine "fits within existing immunization schedules" or "benefits military populations"). Some others are graded on a five-point Likert scale (e.g., "likelihood of financial profitability for the manufacturer"). These choices were made by Phase I and Phase II committee members working to develop the initial versions of SMART Vaccines. Further analysis could help determine the best granularity options on each of the user-defined attributes.

Age Granularity for Disease Burden and Costs of Care

For some priority-setting exercises, particularly in selecting among a number of existing vaccines that are all aimed at the same disease, the available options within SMART Vaccines do not perfectly accommodate the desired granularity of illness burden or treatment costs according to the age of affected people. Earlier committees made choices on these dimensions to balance user friendliness against data burden. Research can help clarify the best choices, which may differ from setting to setting.

Display Design

Using human factors engineering and cognitive psychology, one can study whether the current ways of presenting data and the SMART Scores visually in SMART Vaccines are the best options for users. Should there be additional development to look for alternative graphical methods for presenting these values? Further research can illuminate this question.

Indirect Benefits of Immunization

Vaccination programs can produce many benefits that standard cost-effectiveness or cost-benefit analysis cannot readily capture. SMART Vaccines captures some of these with user-defined attributes—such as the potential of the vaccine to target a disease that raises fear and stigma in the public, the possibility of completely eradicating a disease, or the ability to raise public health awareness—yet other indirect benefits remain unmeasured and could apply to some, if not all vaccines, particularly those affecting children. The current analytical model captures the direct economic benefits arising from the elimination of lost work days, for example, but it does not introduce the benefits of reduced illness burden (particularly chronic illnesses) on children's abilities to advance further along their educational paths and thus enjoy such benefits as increased lifetime earnings and greater general productivity. These benefits in turn will provide positive spillovers to subsequent generations. Another possible effect of vaccines is the way that declining infant mortality may affect fertility rates. Extensive research has also shown strong empirical links between the two, but the causality can go in either direction, and research on this issue remains unsettled (NRC, 1998). Further research will help elucidate the best ways to measure these broader benefits in subsequent versions of SMART Vaccines.

Moving from SMART Scores to a Priority List

Unlike previous IOM reports (IOM, 1985, 1986, 2000), SMART Vaccines does not create a priority list, but rather it provides a tool that can be used to create many lists from different perspectives using multiple criteria. This does not mean, however, that SMART Vaccines could not be used to create a priority list if a group or organization chose to do so. This would require the stakeholder group or organization to determine a set of attributes to use in ranking vaccines and also determine the weights attached to each of those attributes. Given such a set of attributes and weights, SMART Vaccines would then readily create a list of vaccine priorities that bore the stamp of the sponsoring organization. The complexity comes in how the group goes about creating the desired set of attributes and their weights.

Mechanisms to convert individual preferences to group preferences have multiple complications associated with them. Numerous approaches have been devised to aggregate individual rank-order preferences into a group rank-order preference system. Systems for doing this always have some defect or another. Economist Kenneth Arrow demonstrated that it was impossible to create a system that unambiguously aggregates individual

preferences into societal preferences, unless the system either contained a dictator or the choice set was limited to only two options (Arrow, 1950). Subsequently, Gibbard (1973) and Satterthwaite (1975) showed that any system seeking to combine individual preferences into social preferences is subject to manipulation—unless, as with Arrow's analysis, there exists a dictator. Subsequent analysis (Reny, 2001) has demonstrated the strong ties between these two obviously related understandings of the problems in creating societal preference rankings.

To move from individual preferences (e.g., those of members of some committee) to a group preference (i.e., the preferences of the committee itself) in the most useful way will require further specific research to understand the strengths and weaknesses of various approaches. Further research and stakeholder input can help illuminate not only the best mechanisms to assemble individual preference ranks into group preferences, but also the question of what group should be polled. Should it be a committee of experts or a population sample survey? Studying such issues should help enhance the value of SMART Vaccines in the future.

Expanded Uses of SMART Vaccines

Beyond the current sole purpose of SMART Vaccines—to prioritize new preventive vaccines for development—the committee believes that it would be fruitful to identify desirable expansions of the software, each of which would have the potential to widen the community of users, data development, and potential philanthropic and other support. The real benefit would come from increasing the scope and scale of the improved decision making made possible with SMART Vaccines.

Choosing Among Existing Vaccines

One alternative use, identified in the Phase II report, emerged as the primary use in one of the user groups: the New York State Department of Health. The team used SMART Vaccines to choose among competing vaccines that accomplish the same goal, i.e., the vaccination of infants against rotavirus or, in a second case, vaccinating against influenza. In the case of influenza, several vaccines exist in the market, many with important differences in their product profiles. The New York team sought to provide better advice to health providers in New York State about which of these vaccines to choose in various settings. In the rotavirus case, the key difference between the two existing vaccines was the number of doses required (two or three), but there were also differences in cost, coverage potential,

and vaccine efficacy. The team's interest was choosing among competing existing vaccines that help prevent the same disease.

Comparing Vaccines with Other Public Health Interventions

Many diseases with a potential for prevention through vaccination programs can also be addressed through other approaches to reducing or eliminating the disease burden. While these other, non-vaccine approaches can be accommodated to some extent with the current version of SMART Vaccines, some software enhancements would make this task easier and more fruitful.

Examples of these situations abound. The example of malaria is often cited in public health. One can reduce malaria infections by reducing mosquito populations (through insecticide sprays, for instance) or by the use of window screens and mosquito netting. And in the many cases of infectious diseases that are waterborne, providing clean water supplies or methods of removing infection vectors from drinking water may offer alternatives to vaccination programs.

Resurrecting Shelved Vaccines

One application that the committee has contemplated—which was suggested during a stakeholder feedback session—is to bring together vaccine manufacturers from around the world to discuss the possibility of resurrecting vaccines that were previously aborted from the development process. The approach could very well be valuable because (a) most vaccine manufacturers have a set of vaccines in a partial development state that were not moved forward for reasons other than potential efficacy, (b) the manufacturers may know a lot more now about the science of these vaccines and the potential for success, and (c) they also may have updated knowledge about the underlying disease burdens and potential markets for these vaccines. Thus, it may be useful to apply SMART Vaccines to a set of aborted vaccines to see which of these is most likely to merit further development.

Animal Health and Veterinary Vaccines

In 2013, the global veterinary vaccine market was valued at $5.8 billion, with an expected growth rate of 8.1 percent over the following 5 years. Decisions about the development of new preventive vaccines are important for animal health and must, as with human vaccines, be based on multiple attributes. A subset of attributes already included in SMART Vaccines

could offer a helpful template and tool for improved decision making in the rapidly developing global animal health markets. The software would need to be revised in various ways, such as moving from human "workforce productivity loss" to economic issues associated instead with raising domesticated animals. It would also probably be important to take into account the spillover effects on human health of animal vaccines, because numerous public health concerns arise because of infections present in the animal food supply chain of humans around the world (or in other domesticated animal populations such as camels, which were implicated in the recent MERS outbreak).

From SMART Vaccines to SMART Health

The SMART Vaccines approach could, if desired, be applied to much broader prioritization questions in the area of public health. If, for example, one was considering investment either in research and development or provision of services through health care systems, then the SMART Vaccines approach—using multi-attribute utility theory to help clarify tradeoffs, benefits, costs, and risks from various health care interventions—could assist decision making across a wide spectrum of organizations. Doing this would require a significant expansion of the current software, and the committee lists this option only for completeness, with no implication that the current version could fulfill this role. But if a group of interested parties desired to do so, then it would be quite natural to extend the SMART Vaccines model to a broader SMART Health.

Overcoming Barriers to Change

With SMART Vaccines, interested entities can make a substantial change to how they approach decision making. This software product is a significant and novel creation from the National Academies, which has not produced software from scratch in any of its previous studies. As a multi-stakeholder decision-support system, the software has the potential to change the practices of many parties in the vaccine enterprise—suppliers, users, and supporters of vaccine deployment, both domestically and internationally. Many of these organizations already have processes in place to help prioritize their decisions about the development and deployment of vaccines. Thus, embracing SMART Vaccines as a tool to assist in these processes would require an investment of both time and other resources that these organizations may see as potentially unnecessary. For those organizations without formal decision models to assist in their prioritization efforts, sim-

ilar resource investments will be required, but they would not be viewed as duplicating existing tools and processes.

Having studied the work of Harvard Business School's John Kotter, a specialist in understanding organizational change (Kotter, 1995), the committee recognizes that successful change requires multiple steps, taken in the proper sequence. These steps include (1) creating a sense of urgency; (2) forming a powerful guiding coalition; (3) creating a vision, explaining it to others, and empowering people to act upon it; (4) creating some short-term "wins" that others can see and emulate; and (5) embedding the changes in the culture of the institution.

The sense of urgency must ultimately come from within the various stakeholder organizations, but the committee believes that this sense of urgency can be helped along by the observation that the various organizations—supply, demand, and facilitation of vaccine development and deployment—all use different approaches to prioritization, each of which involves different metrics and tools. Thus, these organizations have no common language to speak, no common data to share and discuss, and limited ways of bridging the gaps (perhaps even chasms) in their collective understanding about the best pathways forward in vaccine development and deployment. SMART Vaccines can serve as the basis for narrowing or removing these gaps. It need not replace the tools and approaches used by the many stakeholder organizations, but it can serve as a way to help them understand each other's goals, aspirations, and constraints. Finally, the economic challenges and profound changes seen in today's health care system should also create a sense of urgency to improve disease prevention strategies—which this committee believes will help move SMART Vaccines into widespread use.

Finding a permanent home supported by a user group with a formalized leadership structure for advancing SMART Vaccines would at least begin to fulfill the second step identified by Kotter—creating a powerful guiding coalition. As to the "vision" issues, the committee members believe that the proposed future pathway for SMART Vaccines—a software system maintained, enhanced, and improved by an active user community—provides the basis for a shared vision of how to reach an improved future. The proposed user community could also help create the necessary "wins" and share them with other users, an essential feature of successful change as understood by Kotter and others. The process for embedding the changes into the institutional practices of the many stakeholder organizations will necessarily remain the task of those organizations themselves as they continue to manage and lead change through our dynamic and challenging times.

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Use Case Scenarios Report for SMART Vaccines

Lori Ada Kilty
Microsoft Research

Introduction

The primary reason to carry out usability studies is to improve the design of products through observation of, and conversation with, real users. Real users can describe what they think or feel and demonstrate how they use the product or application. It is often best to start such usability studies early, before a product is fully designed or even when it is still in the idea stage, and then continue the studies throughout the development process. This is not always possible, however. In the case of SMART Vaccines, the contracts for Phases I and II did not commission the Institute of Medicine to conduct early-stage usability studies along with the product development effort.

Although many define usability and usefulness separately, I consider usefulness the first principle of usability. In my view, it does not matter how easy it is to use a product if it is not useful. Early site visits help to ensure the usefulness of the eventual design. For SMART Vaccines specifically, the usefulness was already established before the Phase III project began. Thus, the purpose of these site visits at this stage was to formally understand the usability of SMART Vaccines from real decision makers.

The typical metrics used in the software industry for usability studies—such as completion rate, errors, assists, task time, and mean time on task—

are primarily concerned with effectiveness and efficiency. The Phase III user group studies did not involve testing participants to this degree, but it is still useful to have these metrics in mind, even in the early stages and going forward—especially when thinking through what the expected target range should be.

Methodology

The usability study was conducted with three user groups: the Public Health Agency of Canada, New York State Department of Health (NYSDOH), and the Serum Institute of India. Two site visits (which involved interviews and direct observation) were undertaken at the Public Health Agency of Canada and NYSDOH. The Serum Institute of India provided feedback electronically.

The two visits took place in a conference room, not the users' typical work environment. This made it easier to have in-depth discussions with multiple participants who were able to explain their intended use scenarios. However, these visits did not allow for direct observation of how the tool was employed in the users' routine decision-making process.

User Scenarios and Key Interest Areas

The three user groups were interested in using SMART Vaccines in the following scenarios:

1. Identifying new vaccine candidates and influencing their development using an analytical system, which included the following features:
    - Transparency
    - The ability to facilitate discussions among provincial and other organizational leaders
    - The potential to shorten the time to new product licensing
    - A better understanding of the value of lifelong immunizations
    - A lifelong reduction of disease burden
    - Reduce the current "piecemeal" approaches among stakeholders and help improve coordination among them

2. Prioritizing existing vaccines for introduction, focusing on different disease variations, including
    - Comparing the effects of a vaccine on the whole population of interest versus the effects on a targeted population
    - Determining whether the packaging of vaccines (e.g., 1-dose syringe versus 10-dose vial) has an impact on desired public health goals
    - Examining differences in cost, efficacy, and other factors between oral and injected vaccines
    - Comparing the impact of vaccines requiring multiple doses with the impact of single-dose vaccines
    - Determining whether certain ingredients will cause issues with uptake (thimerosal, for example)

Key Observations and Suggestions

The following observations concern only the user studies conducted with the Public Health Agency of Canada, NYSDOH, and the Serum Institute of India. Each group had different scenarios, and it should be made clear that many of the uses they were interested in were extensions of the original application of SMART Vaccines, which was to prioritize new preventive vaccines. The observations represent a composite of feedback provided by the three user groups, and some of the observations reflect feedback from one or two of the groups, rather than from all of them.

Although there were issues that came up during the usability studies that concern data presentation in SMART Vaccines, these issues are not included in this appendix because they are addressed by the committee elsewhere in the report as part of the data framework.

Table A-1 lists some user-reported bugs along with my suggestions to fix them. No critical bugs in SMART Vaccines were reported by the users, but the other, non-critical bugs are summarized in the table with regard to their major and minor impacts. Table A-2 contains additional use case observations with suggestions for enhancements. Table A-3 summarizes the positive attributes discussed by the users.

TABLE A-1

User-Reported Bugs and Suggestions to Fix Them

Observation	Notes	Severity of the Bug	Suggestion
1. Unable to save progress consistently.	This bug was fixed prior to the site visit, but the results were inconsistent and did not consistently work for one user group member. The committee has not been able to reproduce this error, and it is likely that it is particular to the test subject's individual computer configuration.	Major	The committee should continue to investigate this due to the high level of frustration this can create and should provide the ability to save progress consistently, throughout the software.
2. Disease burden percentages appear to add up to 100 percent, but the tool still does not accept them consistently.	Specifically, the problem occurred when one or more decimal places were in use, even if the percentages clearly added up to 100 percent. However, there were cases when one decimal place was accepted, and this behavior is inconsistent and confusing.	Minor	The tool should either allow one or more decimal places consistently or specify the decimal place limit for percentages or better inform the user about the data entry needs.
3. The total attribute acceptance limit is not clear, and the software run does not complete if the limit is exceeded.		Minor	The tool should either inform the user on the limit of 10 attributes or increase the limit, or do both of the above.
4. "Death" as an outcome is required even for diseases with no morbidities.		Minor	The tool should either inform the user that "Death" is a required outcome or allow the user to set criteria in advance so that the tool only requires data for criteria specified.

TABLE A-2

Additional Use Case Observations and Suggestions for Enhancements

Observation	Notes	Suggestion
1. Age refinements are limited.	Age groupings are too broad. Each morbidity entry should correspond with an appropriate age group, similar to the case with gender. Age groups available under disease burden today are not sufficiently granular for two of the user groups. The ability to compare different regions would be useful as well, according to one user group's preference.	Create more granular age groups and allow these groups to be combined as necessary. Suggest using the World Health Organization age group dataset.
2. Subpopulation choices are confusing.	It is not clear that selecting the subpopulation (female or male or special) applies only to disease and vaccine information and that the SMART Scores are calculated on the basis of the whole population. A whole population choice in the tool would be useful if subpopulation is not desired.	The tool should clearly inform the user that the subpopulation data pertain only to the specific disease and vaccine candidates under consideration. The final results are based on the whole population. The committee should consider adding a full population option for analysis.
3. Attributes not required for a scenario are required by the tool, which can adversely impact results.	There are criteria that need to be specified even if they are not applicable to the scenario that the tool is being used for (e.g., time to adoption, research and development costs). If this tool is going to support the prioritization of already developed vaccines and not only new vaccine development, then there will be cases when some attributes do not need to be required.	There should be an option of "zero" or "NA" for attributes that are not required for all scenarios.
4. Data exist to calculate "total cost" offline and must be entered into the tool manually.	"Total cost calculated" is currently calculated by the tool, but all the data are already in another file and need to be hand entered into the tool, which is tedious.	Allow the import of spreadsheet files or requests for a "total cost" calculated offline in order to simplify data entry. To eliminate confusion, this value needs to be clearly defined. It would be better to ask for the "total cost" (assuming the user knows how to calculate this figure) and eliminate duplicate data entry or separate file upload.

continued

TABLE A-2

Continued

Observation	Notes	Suggestion
5. The field highlight and the cursor color are both blue, and this is confusing.		Changing the color of either the cursor or the highlight would eliminate the confusion and should be an easy fix.
6. Attributes, Weights, and Priorities need to be reentered whenever a change is made.	Only weights can be adjusted without having to be reentered. If a user-defined attribute is added, then everything else will need to be reentered.	Allow an option for Attributes, Weights, and Priorities to be adjusted without reentering all the choices.
7. Must select "Continue" when on a previously completed screen instead of navigating from the top.	It was unexpected behavior that when going back to an earlier screen, instead of selecting at the top of the screen to navigate, the user needed to select "Continue" and the data had already been entered and saved.	Eliminate the need to select "Continue" when going back to a screen that is already complete.
8. Change Attributes with Yes/No to Likert scale to allow for more granularity.	The last three attribute groups (programmatic considerations, intangible values, and policy considerations) in the tool are not granular enough and offer only Yes/No as options. A Likert-scale gradation would be useful here. On the plus side, user-defined attributes can be added, and these do offer a Likert scale.	Change Attributes with Yes/No inputs to a Likert scale to allow for more granularity. Provide guidance on adding user-defined attributes.
9. Vaccine-related complications should be a quantitative entity instead of an attribute.	Vaccine-related complications were originally a quantitative entity (in Phase I), but they were changed to an attribute (in Phase II) because they were not a priority for the developing-new-vaccines scenario. However, it would be much more beneficial to have this as a quantitative entity rather than an attribute for prioritizing existing vaccines. It could be useful for new vaccine development as well because users may want to set the tolerance level.	Consider changing vaccine-related complications to be a quantitative entity again instead of an attribute.

TABLE A-2

Continued

Observation	Notes	Suggestion
10. Multi-disease vaccine comparisons are difficult.	When it was pointed out that the tool treats multi-disease vaccines as separate diseases and does not handle this scenario well, one of the user group members came up with a work-around by defining a second disease separately for analysis.	The tool should eventually consider allowing multi-disease vaccines to be compared without treating composite diseases separately.
11. Additional clarity required on data entry needs.	It is not clear how the data on direct costs of vaccine use per year or incident cases prevented per year, for example, are being used in the software.	The committee should consider offering additional information through notes or tool tips so the user understands how these data entries work.
12. Results or output cannot be saved.	After all the effort to set criteria and create a run, it would be hugely beneficial if there was an ability to save the results, especially if users are unable to save their progress consistently.	Provide the ability to save the output results.

TABLE A-3

User Reported Positive Features

Observation	Notes
1. The calculations are accurate.	The numbers calculated were confirmed accurate by a user group member (subject-matter expert in this field) who independently validated the calculations on the side, noting that most users would not be able to easily do that. In summary, the fundamentals are solid.
2. The screen layout and color scheme are pleasant.	Another user group member emphasized that the software layout and colors were appealing.
3. The final results are easy to comprehend.	Because the tool provides comparative SMART Scores with color coding for vaccines, the final results are easy to comprehend.

Conclusion

The studies with the three user groups were productive and contributed to a deeper understanding of core issues and usability. Some of the more challenging issues concern data quality and the ability to properly segment populations. The committee should review alternate scenarios, such as prioritizing existing vaccines, and study the user requirements to determine whether SMART Vaccines can be appropriately adjusted to effectively meet this task.

Most of the remaining usability issues can be addressed with tool tips and call-outs to help the users understand what they are doing. Many users of this tool will be casual users, so help within the interface would be invaluable for ensuring a more positive interaction with SMART Vaccines. The ability to save progress and upload data using spreadsheets would go a long way to easing some user frustrations.

B

Committee's Response to the Use Case Scenarios Report

TABLE B-1

Consultant's Feedback on Bugs and the Committee's Action or Response

Consultant's Feedback (from Table A-1)		Committee's Action or Response
Observation	**Suggestion**	
1. Unable to save progress consistently.	The committee should continue to investigate this due to the high level of frustration this can create and should provide the ability to save progress consistently throughout the software.	The software has been modified to allow users to print results showing all key parameters at any stage of the analysis. The addition of the print option helps provide a log of the user preferences.
2. Disease burden percentages appear to add up to 100 percent, but the tool still does not accept them consistently.	The tool should either allow one or more decimal places consistently or should specify the decimal place limit for percentages or better inform the user about the data entry needs.	As part of the redesigned disease data entry page, the calculations adding to 100 percent have been corrected to remove this bug.
3. The total attribute acceptance limit is not clear, and the software run does not complete if the limit is exceeded.	The tool should either inform the user on the limit of 10 attributes or increase the limit, or do both of the above.	When a user tries to enter more than 10 attributes, that limit is now specified, and the "Continue" button is disabled to prevent this action.
4. "Death" as an outcome is required even for diseases with no morbidities.	The tool should either inform users that "Death" is a required outcome or allow users to set their criteria in advance so that the tool only requires data for the criteria that are specified.	As part of the disease page redesign, the user has been given the option of entering costs relating to "Death" as a separate entry, distinct from what information is needed for illness due to the disease.

TABLE B-2

Consultant's Feedback on Additional Use Case Observation and the Committee's Action or Response

Consultant's Feedback (from Table A-2)		Committee's Action or Response
Observation	**Suggestion**	
1. Age refinements are limited.	Create more granular age groups and allow these groups to be combined as necessary. Suggest using World Health Organization age group dataset.	The committee has suggested the idea of making more refined age groups in future modifications. The original coarsely grained age groups were a choice of the Phase II committee (influenced by the approach taken by the Phase I committee) when balancing precision with likely data availability. The situations where more refined age groups arose came from uses of the software that go beyond the original intent. In particular, this issue arose when users were attempting to select among existing vaccines where highly age-specific recommendations for use were made by the vaccine developers. Because this extended use created the primary concern, the committee decided to focus on other software improvement priorities for SMART Vaccines 1.1.
2. Subpopulation choices are confusing.	The tool should inform users clearly that the subpopulation data pertain only to the specific disease and vaccine candidates under consideration. The final results are based on the whole population. The committee should consider adding a full population option for analysis.	The relevant pages in SMART Vaccines displays now inform the reader that the results pertain to the entire population. As with the previous issue, this comment emerged from an extended use wherein the software was used to select among existing vaccines for deployment. The final SMART Scores are normalized to the entire population. This has been emphasized in a note inside the software.

TABLE B-2

Continued

Consultant's Feedback (from Table A-2)		Committee's Action or Response
Observation	**Suggestion**	
3. Attributes not required for a scenario are required by the tool, which can adversely impact results.	There should be an option of "zero" or "NA" for attributes that are not required for all scenarios.	Because of the basic structure of SMART Vaccines, users are led through the specification of populations, diseases, and vaccines (the Specify section) before they are asked to consider the Evaluate steps. Indeed, the committee envisions that the Specify steps will likely be undertaken by a technical support person and then a decision maker will enter the scene to participate in the Evaluate phase. Although the current structure does impose a data entry burden on users who can anticipate in advance the precise set of attributes that will enter the model, modifying the structure would create a programming task that exceeds the committee's resources at this point. Thus, the committee chose to leave this issue for consideration in future versions of the program.
4. Data exist to calculate "total cost" offline and must be entered into the tool manually.	Allow import of spreadsheet files or request "total cost" calculated offline to simplify data entry. To eliminate confusion, this value needs to be clearly defined. It would be better to ask for the "total cost" (assuming the user knows how to calculate this figure) and eliminate duplicate data entry or separate file upload.	The software has been simplified to show exactly what this suggestion calls for. The discussion in Chapter 2 of the report provides guidance to users for several ways to estimate treatment costs.
5. The field highlight and the cursor color are both blue, and this is confusing.	Changing the color of either the cursor or the highlight would eliminate the confusion and should be an easy fix.	This issue—which the committee believes was specific only to certain operating systems and browsers—has been fixed.

continued

TABLE B-2

Continued

Consultant's Feedback (from Table A-2)		Committee's Action or Response
Observation	**Suggestion**	
6. Attributes, Weights, and Priorities need to be reentered whenever a change is made.	Allow an option for Attributes, Weights, and Priorities to be adjusted without reentering all the choices.	While future versions of SMART Vaccines could offer this option, the committee believes that the current structure is optimal for now, because it requires users to verify that the selection of attributes and weights is correct after other data changes have occurred.
7. Must select "Continue" when on a previously completed screen instead of navigating from the top.	Eliminate the need to select "Continue" when going back to a screen that is already complete.	The committee believes, as with the previous question, that requiring use of the "Continue" button ensures that users do not inadvertently skip past choices that are no longer valid after other data changes have occurred.
8. Change Attributes with Yes/No to Likert scale to allow for more granularity.	Change Attributes with Yes/No inputs to a Likert scale to allow for more granularity. Provide guidance on adding user-defined attributes.	The committee has concluded that there is a need for further research to address the question of granularity in Likert scales for user-defined attributes.
9. Vaccine-related complications should be a quantitative entity instead of an attribute.	Consider changing vaccine-related complications to be a quantitative entity again instead of an attribute.	This issue, as with others discussed before, arose in a creative extended use of SMART Vaccines where the analysis focused on the deployment of existing vaccines. With existing vaccines, the details of vaccine complications are reasonably well known, which would make this feature improvement relevant. For to-be-developed vaccines (the originally intended focus of the program), the Phase II committee chose the current Yes/No description with the belief that the nature and extent of complications could not be known with any meaningful certainty. Thus, the current version retains the Yes/No descriptor. Future enhancements could provide a richer alternative.

TABLE B-2

Continued

Consultant's Feedback (from Table A-2)		Committee's Action or Response
Observation	**Suggestion**	
10. Multi-disease vaccine comparisons are difficult.	Consideration should be given to eventually modifying the tool to allow multi-disease vaccines to be compared without treating composite diseases separately.	The committee suggests that future enhancements to SMART Vaccines incorporate this change.
11. Additional clarity is required on data entry needs.	The committee should consider offering additional information through notes or tool tips so that the user understands how these data entries work.	The committee has made the best use of offering pop-ups in the Matlab platform to inform the user of data needs. Additional information on data needs is provided in the Phase II report, and those needs are elaborated on in this report. Addition of user-friendly features is certainly possible in future versions of SMART Vaccines if these versions are carried out in a Web-based domain, which the committee suggests as the next logical step in the development of the tool.
12. Results or outputs cannot be saved.	Provide the ability to save the output results.	As noted in Table A-1 response 1, the software now allows saving the results of any analysis through the option to print a table showing the "state of the software" with key variable values all listed.

Comment

Many of the feature enhancement requests the committee received from the user groups arose from uses that went beyond the intended use of the software. Future users will probably benefit from having specialized versions, one for the "prioritization of new vaccines" issue and another for "selection among existing vaccines" or perhaps for comparing a vaccine against another public health intervention for the same disease. The future versions of SMART Vaccines could be designed to include more refined age brackets for disease burden and vaccine program implementation, more refined entry of vaccine-related complications, and the granularity of Likert scales to describe attributes.

C

SMART Vaccines Software Updates

Scott Levin, Ph.D., Sauleh Siddiqui, Ph.D., and Patricia Satjapot, M.S.
Johns Hopkins University

Enhancements have been made to SMART Vaccines 1.1 to improve the user's experience. These include a new capability to perform vaccine candidate sensitivity analysis, a new reporting function, expanded population data for Organisation for Economic Co-operation and Development (OECD) countries, and simplified data input interfaces. These enhancements were based on structured feedback from three user groups and other stakeholder input. Details of these updates to the corresponding sections of the software are outlined below.

Specify

Population, disease, and vaccine candidate information is collected in separate views within the Specify portion of the software. Each of these views includes pre-loaded data to orient users. However, disease and vaccine data may be entered and saved to evaluate user-defined scenarios. The updates to these views include

Population: New populations have been added to supplement the previously available U.S. and South Africa populations. The new populations include populations of OECD member countries and of India, South Africa and New York State. A comprehensive list of the populations available is provided in Table 2-1. An interactive map based on World Health Organiza-

tion (WHO) regions has been added to guide population selection. Finally, the Health Utilities Index (HUI2) has been omitted from the population data because it has been shown to have negligible effects on health and economic outcomes and because it is not available for many populations.

Disease: Disease data input has been simplified to improve ease of use. The original requirements to itemize the costs of health care (inpatient, outpatient, medications) for the disease outcomes of morbidity and impairment have been collapsed to a single annual cost. Similarly, only a single cost of health care associated with death from disease is required.

Vaccine: The view has been re-organized and now offers a drop-down menu to enter one-time costs.

Evaluate

The evaluation portion of the software guides users through the process of attribute selection, weighting, and assessment in separate views. This culminates in SMART Score calculations that rank vaccine candidates based on the users' customized perspectives. Updates to this section include

Attributes: None.

Weights: None.

Priorities: SMART Scores are no longer bounded on a scale between 0 and 100. The health and economic values for vaccine candidates that fall beyond the "least" and "most" favorable bounds are extrapolated based on the predefined scale. For example, U.S. vaccine candidates averting 15,000 premature deaths (with case the least favorable bound being 0 and the most favorable bound being 10,000) would receive a value of 150. Vaccines with net direct costs of $2.2 billion (the least favorable bound is $2 billion and the most favorable is $0) would receive a value of –10. Thus, aggregate SMART Scores may be negative and may exceed 100. The SMART Score axes are now dynamic to accommodate changing scales. In addition, SMART Scores with negative component values are hashed diagonally with a notification.

Analysis

The Analysis section allows users to perform a sensitivity analysis that alters attribute weights and vaccine candidate characteristics and it now also includes a new reporting function. Updates to the Analysis views include

Weights: None.

Vaccine Profile: The new feature allows users to determine the effects of changing vaccine characteristics (the likelihood of licensure, coverage, effectiveness, the length of immunity, doses per person, cost per dose, cost to administer dose, and costs for research and development and for licensing) on SMART Scores interactively. Updated SMART Scores and values are highlighted in orange to make users aware of which vaccine profiles have been altered.

Print: The SMART Score, outputs, and selected inputs are displayed for each vaccine candidate evaluated. A comments field allows the users to label the scenario, and a new reporting function, Print, creates a PDF file of the view to promote transparency.

Updates to SMART Vaccines 1.1 were based on user feedback. In response to the feedback, the number of available populations was increased, data input views were simplified, and new sensitivity analysis and reporting functions were created.

D

Stakeholder Speakers

BRUCE GELLIN (*Co-Sponsor*), Deputy Assistant Secretary for Health; Director, National Vaccine Program Office, U.S. Department of Health and Human Services

STACEY KNOBLER (*Co-Sponsor*), Senior Scientific Program Director, Fogarty International Center, National Institutes of Health

DAVID KASLOW, Vice President, Product Development and Interim Program Leader, Drug Development, PATH

STEVEN REED, Founder, President, and Chief Scientific Officer, Infectious Disease Research Institute

DAVID SHOULTZ, Director, Grantee and Partner Engagement, The Bill & Melinda Gates Foundation

RAJEEV VENKAYYA, Executive Vice President and Head, Vaccine Business, Takeda Pharmaceuticals

GREG WIDMYER, Deputy Director, Vaccine Delivery, The Bill & Melinda Gates Foundation

E
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 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.

Paul Citron, M.S.E.E., retired as vice president of technology policy and academic relations from Medtronic, Inc., after a 32-year career there. His previous positions include vice president of science and technology, vice president of ventures technology, and vice president as well as director of applied concepts research. 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 University of California, San Diego. Citron received a B.S. in electrical engineering from Drexel University—where he later received an honorary doctorate—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, has twice won the American College of Cardiology Governor's Award for Excellence, and was inducted as a fellow of the Medtronic Bakken Society, the company's highest technical honor. Citron is a member of the National Academy of Engineering.

Rita Colwell, Ph.D., is a distinguished university professor both at the University of Maryland at College Park and at the Johns Hopkins 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 chair 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 also as president of the American Association for the Advancement of Science, the Washington Academy of Sciences, the American Society for Microbiology, the Sigma Xi National Science Honorary Society, and the International Union of Microbiological Societies. Colwell has been awarded 58 honorary degrees from institutions of higher education, including her alma mater Purdue University. Colwell holds a B.S. in bacteriology and an M.S. in genetics from Purdue University and a Ph.D. in oceanography from the University of Washington. Colwell is a member of the Royal Swedish Academy of Sciences, the Royal Irish Academy of Science, the American Academy of Arts and Sciences, and the American Philosophical Society. She is the recipient of the Order of the Rising Sun bestowed by the emperor of Japan and the National Medal of Science bestowed by the president of the United States. She is a U.S. science envoy and a member of the National Academy of Sciences.

Simon Mercer, D.Phil., is the 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 the 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 U.K. Medical Research Council to establish the Human Chromosome Abnormality Database, a health care resource subsequently adopted by the U.K. 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.

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 a senior staff economist and the 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 the director of the Public Policy Analysis Program and the chair of the Department of Community and Preventive Medicine in the School of Medicine and Dentistry. He served as the 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, 2010). Phelps has testified before congressional committees on health policy and intellectual property issues. He serves as the chairman of the board of directors of VirtualScopics, Inc., and as a consultant to

the division of research at Kaiser Permenante. He is a founding member of the Health Care Task Force of the Hoover Institution at Stanford University. He received his B.A. in mathematics from Pomona College, an M.B.A. in hospital administration, and 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 the global head of vaccines research for Novartis Vaccines. Previously, he was chief scientific officer and vice president of vaccines research for Chiron Corporation. Earlier, he served on various leadership positions in vaccine discovery and research within the company at IRIS, the Chiron S.p.A. Research Institute. 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 reviewer for numerous scientific publications. Rappuoli obtained his doctoral degree in biological sciences at the University of Siena. He has been awarded the Albert Sabin Gold Medal in recognition of his work in the field of vaccine discoveries and the Gold Medal by the Italian President for contributions to public health. He is a member of the National Academy of Sciences.

Edward Shortliffe, M.D., Ph.D., is a professor of biomedical informatics at Arizona State University, an adjunct professor of Biomedical Informatics at Columbia University, an adjunct professor of health policy and research (health informatics) at Weill Cornell Medical College, and a scholar in residence at the New York Academy of Medicine. Previously, he served as the 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 a professor of medicine and of computer science at Stanford University. He received his A.B. in applied mathematics from Harvard College and an M.D. and a Ph.D. in medical information sciences 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.

Peter Speyer, M.B.E., M.B.A., is the chief data and technology officer at the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, where he has directed the development of the Global Health Data Exchange and interactive data visualizations. Prior to joining IHME, Speyer spent most of his career in strategy and product management, working most recently for the image licensing company Corbis as its director of market strategy and director of product management. Speyer previously worked in the corporate strategy departments of the travel company Thomas Cook and the media conglomerate Bertelsmann in Germany, and he managed foreign licenses for the leading German TV network, RTL Television. Speyer holds an M.B.A. from Temple University in Philadelphia and a master's degree in business and engineering from the University of Karlsruhe, Germany.

Guy Steele, Ph.D., is a software architect for Oracle Labs, where he is responsible for research in language design, implementation strategies, and architectural and software support for programming languages. He received his A.B. in applied mathematics from Harvard College and his S.M. and Ph.D. in computer science and artificial intelligence from the Massachusetts Institute of Technology. Prior to becoming a member of Oracle Labs, he was an assistant professor of computer science at Carnegie Mellon University, a member of the technical staff at Tartan Laboratories, a senior scientist at Thinking Machines Corporation, and a distinguished engineer and then a Sun Fellow at Sun Microsystems Laboratories. He is an author or co-author of five books on programming languages and is a recipient of Grace Murray Hopper Award from the Association for Computing Machinery (ACM) and an ACM SIGPLAN Programming Languages Achievement Award. He is a fellow of the ACM, American Association for Artificial Intelligence, Institute of Electrical and Electronics Engineers, and the American Academy of Arts and Sciences. He is a member of the National Academy of Engineering.

Staff

Guruprasad Madhavan, Ph.D. (*Project Director*), is a senior program officer in 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, the 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. He has worked in the medical device industry as a research scientist developing cardiac surgical catheters for ablation therapy and has been a strategic consultant for technology startup firms and nonprofit organizations. Madhavan is a vice-president of IEEE-USA and a founding member of the Global Young Academy. Madhavan has co-edited five books. Among many honors, he has been named as 1 among 14 people as the "New Faces of Engineering" in *USA Today* and as a distinguished young scientist under the age of 40 by the World Economic Forum. Madhavan has received the National Academies' Innovator Award and the Cecil Award, the highest distinction for a staff member of the Institute of Medicine.

Kinpritma Sangha, M.P.H., was an associate program officer in the Board on Population Health and Public Health Practice at the Institute of Medicine until July 2014. Earlier, she worked at the National Women's Law Center as well as at the Association of State and Territorial Health Officials. She previously served as a research assistant in the University of California, Davis, Medical Center's Pediatric Emergency Care Applied Research Network. She received her B.S. in cellular and molecular biology and Asian American studies from the University of California, Davis, and an M.P.H. in health policy from George Washington University.

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 served 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 post-marketing, the soundness and ethical conduct of clinical trials to reduce mother-to-child transmission of HIV/AIDS, and chronic disease prevention. 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 was awarded 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 (PEPFAR), the U.S. commitment to global health, sustainable surveillance for zoonotic infections, global violence prevention, and setting priorities to build capacity for food and drug regulation in low- and middle-income countries. Prior to joining the National Academies, Kelley served on active duty in the U.S. Army for more than two decades as a public health physician–epidemiologist focusing on infectious disease surveillance and control and as a preventive medicine residency director and research program manager. In his last position within the U.S. Department of Defense, Kelley founded and directed the Global Emerging Infections Surveillance and Response System. He also served as the specialty editor for the two-volume textbook *Military Preventive Medicine: Mobilization and Deployment*. Kelley 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.

Proctor Reid, Ph.D., is director of the program office at the National Academy of Engineering (NAE). In this capacity, he oversees all NAE program activities and staff and directs the NAE policy research programs. He has served as the lead professional staff member for multiple NAE committee studies, workshops, and symposia on issues related to the globalization of engineering; the technological dimensions of competitiveness; international cooperation on energy and environment; systems approaches to

health and health care; the future of engineering education, research, and practice; and the vitality of the engineering workforce. Reid has served as a professorial lecturer at the Johns Hopkins University Paul Nitze School of Advanced International Studies, where he also received his Ph.D. in international relations. Reid formerly taught as an instructor in political economy at Oberlin College and worked as a consultant to the National Research Council and the Organisation for Economic Co-operation and Development. He is an elected fellow of the American Association for the Advancement of Science, and he served as a secretary to its section on industrial science and technology.

Consultants

Lori Adakilty, B.S., is a principal program manager for Microsoft Research Connections. She has 20 years of experience in software engineering efforts from inception through release, and has worked on many different projects, including Encarta, Windows, Visual Studio, and Xbox. She spent a few years working on process improvement efforts and earned her Six Sigma Black Belt, and she also created original courseware and conducted classes on how to get to the right metrics and measurements. Adakilty has served 20 years in the military, both on active duty and in the Air National Guard, where she gained experience in graphic design and information systems, helping to create a reporting analytics tool for area commanders long before such tools were common. She received her B.S. in computer science from St. Martin's College in Olympia, Washington.

Guthrie Birkhead, M.D., M.P.H., is the deputy commissioner at the Office of Public Health at the New York State Department of Health, where he is the chief public health physician. Birkhead is a graduate of the Epidemic Intelligence Service program and the preventive medicine residency program at the Centers for Disease Control and Prevention, is board certified in internal medicine and preventive medicine, and has a master's degree in public health. In addition to his work at the health department, he is also a professor of epidemiology at the School of Public Health, University at Albany. He is a past member of the federal Advisory Committee on Immunization Practices and past chair of the National Vaccine Advisory Committee.

Prasad Kulkarni, M.D., is the medical director of the Serum Institute of India Limited where he has been involved in the scientific development of new vaccines. He has carried out clinical trials for vaccines against measles; rubella; measles, mumps, and rubella; diphtheria, tetanus, and pertussis

(DTP); hepatitis B; Haemophilus influenzae type B (Hib); DTP–hepatitis B; DTP–hepatitis B–Hib; rabies; and H1N1 as well as trials for other therapeutic products. Kulkarni is a graduate and postgraduate of B.J. Medical College, Pune, with specialization in clinical pharmacology. Kulkarni has also been a faculty member at many institutes and workshops including the Annual Indian Vaccinology Course. He is an associate editor of *Human Vaccines and Immunotherapeutics* and has served as a temporary advisor to the World Health Organization.

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 Whiting School of Engineering. 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. Levin's research has been funded by the National Science Foundation, the National Institutes of Health, and the U.S. Department of Homeland Security. Levin received his Ph.D. in biomedical engineering from Vanderbilt University.

Eduardo Guzmán Morales, M.D., is a technical advisor to the undersecretary of prevention and health promotion at the Ministry of Health in Mexico. He has worked in the public health sector in Mexico since 2001. He has been involved in field work during natural disasters and has participated in preparedness planning efforts. He completed his medical degree at the Autonomous University of Puebla specializing in epidemiology.

Estefanía De La Paz Nicolau, M.D., M.P.H., is an advisor to the undersecretary of prevention and health promotion at the Ministry of Health in Mexico. Her prior research work has centered on obesity and chronic diseases at the National Institute of Medical Sciences and Nutrition in Mexico City. She obtained her medical degree at the Anahuac University in Mexico City and her master's degree in public health from the Johns Hopkins Bloomberg School of Public Health.

Patricia Satjapot, **M.S.,** is an associate director at Johns Hopkins Medicine International, where she oversees the business and project management division and the administrative residency program. She previously worked as a clinical analyst at University Health System Consortium and at

Bumrungrad International Hospital in Bangkok, Thailand. She is a graduate of Rush University, where she earned her M.S. in health systems management, and she is pursuing her Ph.D. in health services research (with a concentration in international health care) at Virginia Commonwealth University. Satjapot's professional interests include evidence-based management, analytics, and international health services research.

Sauleh Siddiqui, Ph.D., is an assistant professor in the Departments of Civil Engineering and Applied Mathematics and Statistics at the Johns Hopkins University Whiting School of Engineering, and he is affiliated with the Systems Institute. Siddiqui's research uses optimization, game theory, and probabilistic techniques to study large-scale systems in energy and environmental markets, transportation, and health care. Siddiqui received his Ph.D. in applied mathematics and statistics and scientific computation from the University of Maryland, College Park.

John Spika, M.D., is the 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 has widely published on subjects related to immunization, host defense, and food-borne and respiratory diseases.