ARTICLE IN PRESS

Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Beyond cost-effectiveness: Using systems analysis for infectious disease preparedness ☆

Charles Phelps Ph.D. [a], Guruprasad Madhavan Ph.D. [b,*], Rino Rappuoli Ph.D. [c], Rita Colwell Ph.D. [d], Harvey Fineberg M.D.,Ph.D. [e]

[a] University of Rochester, United States
[b] The National Academies of Sciences, Engineering, and Medicine, United States
[c] GlaxoSmithKline Vaccines, Italy
[d] University of Maryland, College Park, and Johns Hopkins Bloomberg School of Public Health, United States
[e] Gordon and Betty Moore Foundation, United States

A R T I C L E I N F O

Article history:
Available online xxxx

Keywords:
Cost-effectiveness
Systems analysis
Ebola
Infectious diseases
Global health
Preparedness
Zika

A B S T R A C T

Until the recent outbreaks, Ebola vaccines ranked low in decision makers' priority lists based on cost-effectiveness analysis and (or) corporate profitability. Despite a relatively small number of Ebola-related cases and deaths (compared to other causes), Ebola vaccines suddenly leapt to highest priority among international health agencies and vaccine developers. Clearly, earlier cost-effectiveness analyses badly missed some factors affecting real world decisions. Multi-criteria systems analysis can improve evaluation and prioritization of vaccine development and also of many other health policy and investment decisions. Neither cost-effectiveness nor cost-benefit analysis can capture important aspects of problems such as Ebola or the emerging threat of Zika, especially issues of inequality and disparity—issues that dominate the planning of many global health and economic organizations. Cost-benefit analysis requires assumptions about the specific value of life—an idea objectionable to many analysts and policy makers. Additionally, standard cost-effectiveness calculations cannot generally capture effects on people uninfected with Ebola for example, but nevertheless affected through such factors as contagion, herd immunity, and fear of dread disease, reduction of travel and commerce, and even the hope of disease eradication. Using SMART Vaccines, we demonstrate how systems analysis can visibly include important "other factors" and more usefully guide decision making and beneficially alter priority setting processes.

1. Introduction

During the recent Ebola outbreak, it became apparent that numerous groups pursued development of Ebola vaccines years ago, but shelved the efforts because of low commercial promise [1]. The most-recent epidemic—and the ensuing panic—made the development of Ebola intervention a high priority for countries and multi-national organizations [2,3]. Standard cost-effectiveness analyses—the formal standard of reference around the world for assessing health technology choices—did not capture important aspects of diseases like Ebola. Such factors include: disproportionate disease burden on low income populations, global public fear of contagion, incomplete understanding of the spread of infection and alternatives such as quarantine of travelers, contextual interaction with social customs (e.g., burial rites), and economic losses from reduction in trade and tourism. Ebola barely received mention in priority rankings for public health interventions in earlier analyses. How did we get into this situation, and how can we avoid it in the future? Stated differently, why did previous planning and modeling efforts fail? To answer that question, our focus first turns to the limitations of prevailing analytical practices for strategic planning in public health and health care, and then to the potential benefits of wide-ranging systems analysis mechanism.

2. Conventional cost-effectiveness analysis

Cost-effectiveness metrics calculate the ratio of incremental cost (e.g., dollars) over quality-adjusted life years gained (QALYs) gained or disability-adjusted life years (DALYs) averted. A lower

☆ The views expressed in this article are those of the authors and not necessarily of the National Academies of Sciences, Engineering, and Medicine.

* Corresponding author at: 500 Fifth St NW, Washington, DC 20001, United States.
E-mail address: gmadhavan@nas.edu (G. Madhavan).

http://dx.doi.org/10.1016/j.vaccine.2016.08.090
0264-410X/© 2016 Published by Elsevier Ltd.

incremental cost-effectiveness ratio indicates more health benefits per incremental dollar spent. An intervention is recommended if its cost-effectiveness ratio falls into an acceptable range, and it is well understood that allocating resources based on this criterion is economically efficient [4–6]. However, almost all published cost-effectiveness analysis studies are incomplete, typically ending with caveats such as the need to include and balance additional factors—often influential and sometimes determinative—to reach final decisions.

In addition to these issues, traditional cost-effectiveness analysis does not incorporate issues involving externalities. Examples include contagion and herd immunity with infectious diseases or non-health consequences for people only indirectly affected (e.g., second hand smoke, fear of travel or travelers involving virulent contagious diseases, loss of economic activity from reduced travel and such). Nor do cost-effectiveness models deal with issues of joint production (e.g., fit of a vaccine with extant programs or cold-chain and other supply-chain requirements) or the role that an intervention might have in achieving other governmental goals (e.g., defense and foreign policy). These sorts of issues can importantly affect major policy choices, yet they remain beyond the reach of cost-effectiveness methods.

3. Enhanced cost-effectiveness and cost-benefit analysis

The most recent recommendations from the World Health Organization support the use of a "generalized cost-effectiveness" approach that elaborates on the traditional method [8]. The generalized analysis brings in regional (sectorial) perspectives, but does not solve other problems associated with cost-effectiveness analysis as discussed earlier. Other analysts, attempting to circumvent some of these issues, recommend a standard cost-benefit analysis to evaluate vaccines and other health interventions, arguing (correctly) that this approach can effectively eliminate many of the shortcomings of cost-effectiveness analysis [9]. But those who urge this approach have not mitigated the dominant objection of analysts and policy makers: placing specific values on human life, either in terms of life years, QALYs or lives saved. Indeed, U.S. law forbids the use of quality-adjusted life years as a metric for ranking medical interventions [10].

Moreover, even full cost-benefit analyses cannot accommodate issues that are at the center of global and domestic policy debates focusing on disparities in health outcomes and distributional inequities in access to health care and (or) low incomes. For cost-benefit analysis to accommodate such issues will require inclusion of social preference about the distributions of health and wealth to the model (see for example [11]). But those methods are complex, difficult to explain even to those well versed in economics, and the data to support such models do not exist. Therein resides the problem and an opportunity.

Our recent experience in implementing a multi-criteria decision aid—Strategic Multi-Attribute Ranking Tool for Vaccines (SMART Vaccines)—suggests that there is potentially high value in employing a system explicitly stating those "other factors" that would otherwise remain obscure [7]. The SMART Vaccines prototype was employed on a trial basis by officials of the Public Health Agency of Canada, the New York State Department of Health, the Serum Institute of India Limited, and the Ministry of Health of Mexico. Decision makers have appreciated the clarity and transparency that SMART Vaccines brought to priority setting, and identified additional areas for application of the concept. We believe that this systems-based approach offers great promise in reducing or eliminating gaps in cost-effectiveness based analyses, and thereby improving priority setting.

4. Systems analysis

Decision support models based on multi-criteria systems analysis are widely used in other areas of society, including transportation engineering, military technology acquisition, environmental policy, land resource management, and urban planning [12]. Unlike cost-effectiveness ratios, multi-criteria models allow formal evaluation of many factors that can (and do) affect decisions. Although several approaches exist, we prefer a method with strong axiomatic support—multi-attribute utility theory—that offers better decision support and ease of use. This technique can also help improve planning and resource allocation decisions in a wide array of health and health care decisions [12].

To expand briefly (using SMART Vaccines as an example), multi-attribute utility analysis formally incorporates many disparate factors, each of which has a different yardstick of measurement. This technique allows the user to weight selected vaccine attributes to specify their relative importance (the weights adding up to 100%). The model converts the possible range of performance on each chosen attribute (e.g., $/QALY, lives saved, pandemic risk, public fear, or the vaccine's fit within an existing immunization schedule) into its own 0–100 scale. Subsequently, each vaccine's performance for each selected attribute is measured on a common scale, allowing appropriate summation of such scores. The final SMART Score for a vaccine is the weighted sum of each candidate's performance in achieving success for each attribute chosen by the user. This uses the same logic as valuing ten separate events in a decathlon track-and-field contest where each event has a different metric (time to run a distance, distance or height jumped, and so forth) that gets converted to a common scoring metric (historically) by using the single-event world record as the 1000 point "best" standard. While the decathlon uses equal weights for all events, multi-attribute utility models instead incorporate user specified weights applied to each selected attribute.

In theory, analysts can modify cost-effectiveness models to accomplish some of these goals using refined specifications of programmatic costs and consequences, and through increased complexity in defining the various utility states (outcomes) of the world. But in practice, this is not feasible. Cost-effectiveness analysis requires estimates of individual utilities for various disease states, derived from population surveys (for QALYs) or panels of experts (for DALYs). Further, standard cost-effectiveness models for vaccines completely omit persons without the disease whose lives are nevertheless affected, often profoundly, by fear of contagion and related concerns. Similarly, the possibility of disease eradication creates hope (and utility) for all. These types of factors cannot be built into standard cost-effectiveness analyses.

At this writing, Ebola has taken about 11,300 lives worldwide out of 28,600 known cases—a far lower toll than such common and widespread diseases as tuberculosis (1.5 million deaths per year), or malaria (1 million deaths per year), let alone deaths from tobacco use (over 5 million per year). Yet the mere mention of Ebola creates intense anxiety, often accompanied by panic and sometimes onerous public action—most likely related in part to Ebola's high rate of lethality and lack of the mechanistic understanding of disease transmission among the general public. Clearly, cost-effectiveness analyses miss something important here.

As noted earlier, for a wide range of health care interventions, many crucial attributes lie outside the realm of cost-effectiveness analysis, including distribution of effects by age, race, income, and other socioeconomic partitions, the fit of the intervention within a health care system, interaction with religious and philosophical beliefs, as well as privacy and individual autonomy [5] (as current debates about mandatory vaccination highlight). However, these other critical factors often dominate public and private

Please cite this article in press as: Phelps C et al. Beyond cost-effectiveness: Using systems analysis for infectious disease preparedness. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.08.090