perspective paper

INFECTIOUS DISEASE

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Selecting priority interventions to address infectious disease, injury and reproductive-health burdens: issues in economic evaluation

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I. Introduction

In the Copenhagen Consensus 2012 Challenge Paper "Infectious disease, injury and reproductive health" Jamison, Jha, Laxminarayan, and Ord select six "investment solutions" to address infectious-disease, injury and reproductive-health burdens in low-income countries (Jamison et al. 2012). We discuss issues in the approach the authors follow in selecting these six "investment solutions," focusing on the multi-criterion decision-making process they have chosen and on uncertainty and risk attitudes.

II. Multi-criteria decision-making

Using economic evaluation to inform the selection of health interventions for funding and implementation can be a useful exercise, because it allows systematic comparison of interventions accounting for benefits and costs (in the case of cost-benefit analysis, CBA) or for health outcomes and costs (in the case of cost-effectiveness analysis, CEA). The economic evaluation process can be broken down into the following steps:

1. Defining the universe of possible interventions
2. Estimating the benefit-cost ratios (BCRs), for CBA, or cost-effectiveness ratios (CERs), for CEA, for all individual interventions
3. Ranking the individual interventions by their BCR or CER in a league table
4. Selecting the interventions for implementation, starting with the one that has the most favorable BCR or CER, then the one that has the second most favorable ratio, and so on, until the available budget is exhausted

The first step will usually include defining the boundaries of the universe to be considered for the analysis at hand through explicit inclusion and exclusion criteria. Given the title of the Challenge Paper, "Infectious Disease, Injury and Reproductive Health," the boundary definition could have included criteria excluding all health interventions that do not address an infectious disease, injury or reproductive health burden. The result of the selection process summarized in steps 1.-4. will be that given a certain funding constraint the implementation of the selected interventions will maximize the social benefits that can be achieved with the interventions included in the universe of possible interventions.

Note that interventions whose discounted benefit streams exceed the discounted cost streams (i.e., BCR>1) are socially worthwhile and should always be implemented, independent of their rank in the BCR order – if there are no financial constraints. The economic evaluation process summarized in these four steps implies constraints in the ability of the decision-makers to fund all socially worthwhile interventions. If all socially worthwhile interventions can be funded, CBA requires only three steps: defining the universe of possible interventions, estimating BCRs, and selecting all interventions with BCRs>1 for implementation.

All of the six "investment solutions" that Jamison and colleagues select for funding have BCRs that are far greater than unity, implying that their implementation will increase social welfare. However, Jamison et al. do not present the BCRs of those interventions that were not selected as "investment solutions." The absence of BCRs of interventions that were part of the initial universe of possible interventions but are not part of the six "investment solutions" could imply that all other possible interventions in the universe have BCRs that are smaller than those of the six "investment solutions." However, judging from the description of the approach that Jamison and colleagues have taken in selecting the six "investment solutions," the reason for the absence of other BCR is a different one. The authors do not follow the four-step process outlined above but instead select the six "investment solutions" based on a range of arguments (described in sections of 4, 5 and 6 of the Challenge Paper) including BCR, which is required to indicate that the "investment solutions" are "highly cost effective" (or rather highly cost-beneficial) (Jamison et al. 2012):

> "… we have identified 6 solutions for investment in interventions that address a large disease burden highly cost effectively …"

The authors thus do not follow a standard economic evaluation approach to selecting the six "investment solutions." Their approach deviates from standard economic evaluation in two important respects: First, they do not maximize the benefits given the universe of possible interventions and a budget constraint; and, second, they do use multiple criteria for the selection of the interventions instead of the single criterion CER (or CBR). Rather than selecting the *most* cost-effective (cost-beneficial) interventions based on economic evaluation results covering the universe of possible interventions, Jamison and colleagues select the interventions based on a range of criteria, including some threshold of "high cost-effectiveness" whose precise value remains unspecified (Jamison et al. 2012).

> "Cost-effectiveness calculations provide important insights into the economic attractiveness of an intervention, but other considerations – such as consequences for financial protection and demands on health system capacity – need to be borne in mind. Even if factors such as system capacity remain difficult to quantify it may be useful to include a subjective judgment, for each intervention, of the extent of its demand on system capacity. We complement our quantitative (if imprecise) estimates of B:C with subjective judgments of this type in a dashboard comparison of interventions."

This selection process may reflect the experience of the author team, "realism," or an underlying theory of decision-making. It is important to note in this context, however, that the Copenhagen Consensus explicitly endorses an economic evaluation approach choosing "*the most* cost-effective" investment solutions rather than merely "*highly* cost-effective" ones (our emphasis) (Copenhagen Consensus Center 2012):

> "After deliberations, the Expert Panel's task is to create a prioritized list of solutions to the ten challenges, showing the most cost-effective investments."

Of course, the fact that the Copenhagen Consensus combines economic evaluation with deliberations of expert panels might be seen to indicate that in addition to the single criterion of maximizing effects or benefits given a budget constraint, the Consensus implicitly endorses the inclusion of other criteria in decision-making. It then would remain to be clarified whether the selection and application of these additional criteria in the process of the Copenhagen Consensus is intended to be left to the deliberations of the expert panel, or whether it should already take place in the earlier stages of the work for the Challenge Papers.

In addition to the intentions of the Copenhagen Consensus, we see a number of fundamental shortcomings of the particular multi-criterion selection process used by Jamison and colleagues (as it is described in the Challenge Paper).

First, the reasons for choosing a multi-criterion process of selecting the "investment solutions" are not explained. An alternative process could have been to capture the criteria of size of the disease burden, financial protection, feasibility of implementation, and relevance for development assistance budgets in exclusion criteria defining the universe of possible interventions. Then, the singly-criterion process of economic evaluation could have been used to select interventions for implementation, such that the benefits to society are maximized given the budget constraint. For instance, the universe should never include interventions that are not feasible and it could be constrained to include only interventions that are relevant for development assistance.

Second, it remains unclear how the authors used the criteria in selecting the "investment solutions." How did they trade the different criteria off against each other, when in the comparison of two interventions one scores higher on some criteria than the other but lower on other criteria? For instance, the intervention "Childhood diseases: expanded immunization coverage" scores lower on the "financial risk protection" criterion and the "relevance for development assistance" criterion than the intervention "HIV: accelerated vaccine development," but the former has a more favorable BCR than the latter. If we could only fund one of these two interventions, which one would we choose?

Third, while the authors provide some explanations why they included the five criteria in the selection process, in addition to cost-effectiveness, they do not explain why they did not include yet other criteria in the process. One meaningful additional criterion could have been whether existing organizations are already committed to supporting a particular intervention or not. It could for instance be argued that the intervention "Childhood diseases: expanded immunization coverage" is already sufficiently supported by the GAVI Alliance and thus does not need to be considered in the set of interventions for selection for future funding commitments. The distribution of benefits across populations in low- and middle-income countries could have been another criterion. For instance, on normative grounds, we might argue that, all else equal, we should prefer an intervention that benefits primarily poor populations in these countries over one that benefits primarily the wealth. The probability that an intervention would cause unintended

consequences (Bärnighausen et al. 2011a), and the severity of such consequences should they occur, might be yet other criteria that could have been justified to be included in the set of criteria used to select the "investment solutions."

Regarding the selection of multiple criteria for multi-criterion decision-making, it is important to note that in past applications of such approaches to selecting interventions to address infectious disease burdens, the criteria, and their relative weights, have commonly been based on empirically elicited stakeholder or community preferences (Youngkong et al. 2009; Youngkong et al. 2010; Youngkong et al. 2012), rather than on expert choice, as in this Challenge Paper.

Fourth, the possible reasons for including at least one of the criteria, "size of the disease burden," do not seem convincing. There are two possible reasons for a small disease burden. First, only a few people suffer from it; and, second, many people suffer from it but the per-person disease burden is on average small. In the first case, only because an intervention addresses a rare disease should not, in our opinion, exclude it from funding. Some characteristics of rare diseases, such as difficulty in identifying the people suffering from the disease, are indeed important, but can be captured in other criteria, such as the cost-effectiveness (it will be more costly to find those who suffer from the disease, the feasibility criterion (it might not be possible to identify them at all), or the relevance for development assistance criterion (particular funders may not be interested in funding interventions that benefit only a few for one reason or another). However, given that the BCR is favorable and the intervention possible and relevant for donor assistance, we see no reason why an intervention that improves the health of only a few people should not be implemented.

Given a favorable BCR, an implementation reaching a large proportion of the people suffering from the rare disease will not be expensive compared to the implementation of an intervention that benefits many, leaving most of the budget available for other funding opportunities. A similar argument can be made for the case of a disease that affects many but causes only comparatively little suffering in each person who has disease. In this case, a favorable BCR implies low costs per-person and implementing the intervention, so that it reaches a large proportion of the sufferers, will not be expensive, leaving most of the budget available for other funding. Of course, in this second case, we might be opposed to the funding for yet other reasons, such as a belief that funding of interventions that avert or successfully treat small individual disease burdens should be left to the individual sufferers. But this would be a different criterion than "size of the disease burden."

Fifth, it remains unclear how the authors derived the scores for the different interventions on the five criteria. Some of the scores lack face validity. For instance, it seems surprising to us that the intervention "Childhood diseases: expanded immunization coverage" scores low ("L") on the criterion "Financial risk protection provided" (Table 8). Some childhood diseases, such as measles or *Haemophilus influenzae* type B infection can lead to sequelae that severely impede a child's cognitive development and school attainment (Bärnighausen et al. 2011b), decreasing the

child's opportunities in adulthood to find gainful employment and thus rendering him or her financially vulnerable.

In sum, while a case could theoretically be made that instead of the single-criterion decision-making of economic evaluation a multi-criterion decision-making process should be followed, such a process would need to be aligned with the intentions and the existing process of the Copenhagen Consensus, i.e., selection of "the most cost-effective" investments after deliberations of an expert panel. The particular multi-criterion decision-making process should further be clearly justified in terms of the particular process chosen, the selection of the multiple criteria and how they are jointly used in decision-making, and the scoring of interventions on each of the criteria.

III. Uncertainty and risk attitudes

Jamison and colleagues take the following approach to deal with uncertainty in their economic evaluation results (Jamison et al. 2012):

> "Given these often broad ranges in CE [cost-effectiveness] ratios, and hence in cost-benefit ratios, it makes little sense to conclude with precise estimates of uncertainty or effect size. Rather we have identified 6 solutions for investment in interventions that address a large disease burden highly cost effectively even granted substantial uncertainty and variability in the underlying estimates."

This approach, to select "solutions for investment" that are highly cost-effective "even granted substantial uncertainty and variability in the underlying estimates," introduces yet another criterion for decision-making, robustness of the economic evaluation results to changing parameter estimates. While robustness checks in sensitivity analyses as the authors conduct are sensible, the dichotomous approach to dealing with uncertainty does not account for differential uncertainty between the different interventions selected as "investment solutions" and between the selected interventions and interventions that were not chosen as priorities.

Ignoring differential uncertainty is justified for government decision-making, if benefits and losses of an intervention are spread widely and fairly evenly across a population. However, as has been noted elsewhere, this prerequisite for justifying risk-indifferent decision-making in public investment is commonly violated in infectious disease prevention and control, because the diseases and the results of the prevention efforts affect different individual very differently (Dijkhuizen et al. 1994). HIV, tuberculosis, and malaria are not exceptions to this role, as they affect particular population sub-groups particularly commonly or severely. For these diseases, national policy-makers and international donors should thus arguably behave risk-aversely to arrive at the best public investment decisions. Risk aversion, however, implies that the degree of

uncertainty in results will matter in addition to the expected value of the results: It will be worthwhile to trade-off some expected value against reductions in uncertainty.

Jamison and colleagues do not account for differential uncertainty in their economic evaluations of "investment solutions" – at the same time, the interventions they select are likely to differ widely in their uncertainty. On one end of the spectrum is investment in research to develop an HIV vaccination, with extremely high levels of uncertainty about success; on the other end of the spectrum are the delivery of interventions with well-established efficacy and effectiveness, such as childhood vaccinations and deworming. It would seem likely that the BCR ranking of "HIV: accelerated vaccine development" (BCR 11:1) and "Deworming schoolchildren" (BCR 10:1) will be reversed, once the different levels of uncertainty in the results of these two investments is taken into account in risk-averse decision-making.

It is similarly likely that investment in the scale-up of medical male circumcision (MMC), an intervention with well-established efficacy and effectiveness in reducing HIV acquisition, would have outperformed investment in HIV vaccine development, had the authors taken uncertainty into account in their economic evaluations. MMC is equivalent to a vaccination with about 60% efficacy in reducing HIV acquisition in men (Auvert et al. 2005; Bailey et al. 2007; Gray et al. 2007; Newell and Bärnighausen 2007). Jamison and colleagues state that "[s]ustained investment in HIV vaccine development is, very recently, beginning to bear fruit" (Jamison et al. 2012). To our knowledge this statement is highly uncertain; thirty years of research to develop an HIV vaccine have not produced a convincing vaccine candidate, and the only vaccine that did show some promise in randomized controlled trials did not reach the efficacy levels of circumcision (Rerks-Ngarm et al. 2009).

IV. Conclusion

We examine in this Perspective Paper examining the Copenhagen Consensus 2012 Challenge Paper "Infectious disease, injury and reproductive health" by Jamison, Jha, Laxminarayan, and Ord a number of issues related to the multi-criterion decision making process and uncertainty. Our analysis suggests the following options for improving the process of selecting interventions for investment.

1. The multi-criteria decision-making approach could be replaced by a traditional economic evaluation process, coupled with clearly defined criteria for the initial selection of possible interventions into the choice set, or universe of possible interventions. These criteria could capture intervention characteristics over and above the estimated BCR, such as relevance for development assistance.

2. The multi-criteria decision making approach could be improved by clearly justifying (i) the selection of the different criteria, (i) the approach to score the criteria, and (iii) the

approach to trade the different criteria off against each other in selection the “investment solutions.” Such justifications could come from theory or empirical work, e.g., eliciting the preferences of relevant stakeholders.

3. Incorporating uncertainty estimates into the economic evaluation of the different interventions.

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