Appendix B: Value Framework for Economic Analyses of Vaccination Programs

Background

Traditional health economic evaluations of vaccination programs assess immediate health benefits and financial cost offsets to families and caregivers. However, in recent years, a growing body of research has suggested that vaccination programs can offer broader economic benefit at both individual and population level, and many of these hitherto unrecognized benefits could be of greater interest to different decision makers.

The impetus for investigating the broader economic impact of vaccination programs originated from a 2003 investigation by David Bloom and colleagues (2004) that linked poor health to reduced economic growth. This finding drew on older research by demographers (e.g., Dahan and Tsiddon, 1998) suggesting that decreases in child mortality rates can increase the investments of families in the human capital of their children while reducing fertility. Many of the reasons to link health with economic growth were presented in a guide by the World Health Organization (WHO) on the economic consequences of poor health (Evans et al., 2009).

These concepts were applied to vaccination programs by Til Bärnighausen and colleagues, who identified the benefits of vaccination programs that are often overlooked in traditional health economic evaluations as part of an examination of the investment case for vaccination programs in South Africa (Bärnighausen et al., 2008). This team subsequently expanded its initial list of benefits (Bärnighausen et al., 2011; 2012; 2014).

Bärnighausen and colleagues' work spurred numerous reviews by several independent groups of other proposed or established economic impacts of vaccination programs in the literature (Ozawa

et al., 2011; Deogaonkar et al., 2012). At the same time, groups explored such vaccination outcomes as increased educational attainment (Canning et al., 2011; Driessen et al., 2015a, 2015b), increased macroeconomic growth (Keogh-Brown et al., 2010), reduced antimicrobial resistance levels (Lipsitch and Siber, 2016), increased equity, and increased household financial risk protection (Verguet et al., 2013; Driessen et al., 2015b; Loganathan et al., 2016).

The WHO and Gavi, the Vaccine Alliance, have funded a series of expert consultations on the broader economic impacts of vaccination programs. These consultations culminated in the "Annecy declaration" of numerous global health experts on reassessing the value of vaccination programs (Bärnighausen et al., 2014).

Value Framework

The research by Bärnighausen and colleagues (2008; 2011, 2012; 2014) contributed to the development of a value framework for assessing all of a vaccination program's benefits (Jit et al., 2015). This value framework includes outcome measures typically used in narrow analyses of vaccination program benefits, such as healthcare cost reductions and work productivity gains because of disease avoidance in both the vaccinated population and those in contact with this population as a result of herd protection, although these benefits could be offset by serotype replacement in certain diseases. The framework also includes a broader set of outcomes, such as broader productivity gains and changes in behavior due to reduced disease risk, lower birth rates and increased investments in education; population-wide gains, reduced antibiotic resistance rates or greater economic stability; risk reductions; and utilitarian health gains.

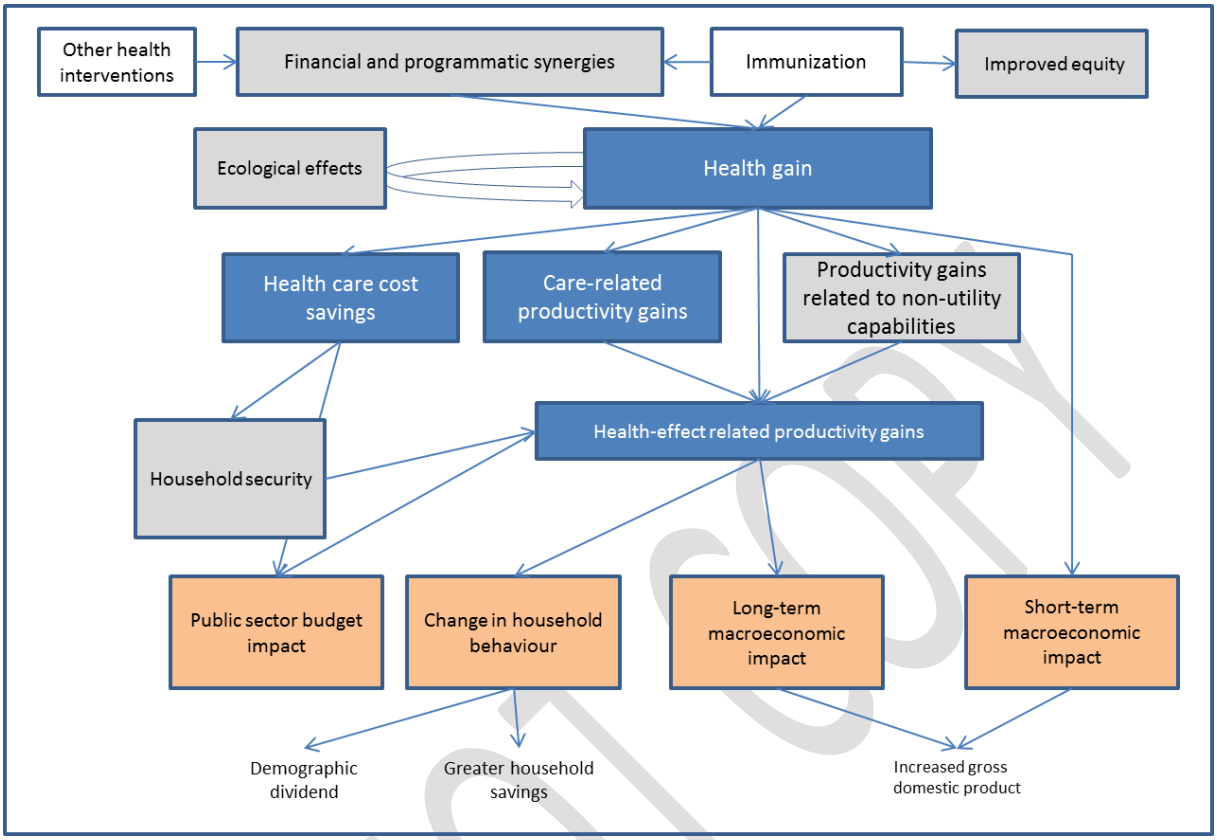
Meanwhile a literature review by Jit and colleagues (2015) demonstrated that these broader benefits of vaccination are rarely included in economic evaluations, partly because of the limited

data documenting the relationships between vaccination programs and the broader outcomes. Additional research is needed to document this relationship. To incorporate these outcomes into economic evaluations, it was suggested that cost-benefit rather than cost-effectiveness analysis would be the appropriate method of analysis. With cost-benefit analysis, all outcomes, health and non-health, can be valued in local currency, and a benefit-cost ratio can be calculated. Cost-benefit analysis that includes a broad set of health and non-health outcomes might be more meaningful than a typical cost-effectiveness ratio for ministers of planning, who must allocate funds across multiple sectors.

Jit and colleagues (2015) further explored putative causal links among the new outcome measures presented in the framework and the quantitative evidence supporting them. Disappointingly, the review indicated that empirical quantitative evidence based on observed data for the new outcomes are limited or absent. Values for the new outcome measures have been initially constructed only through modeling exercises. However, demonstrating the conceptual links among the measures is very useful and should inspire others to collect the evidence to the extent possible.

The links of this WHO-funded review are summarized in Figure A-1. Many of the new outcomes in the figure (those shown in orange and grey) are not typically considered in economic evaluations, and their placement is on the edges of the scheme and not in the core (middle). Being at the center of that scheme should indicate the high importance and attention we should give to those other measures and actually we don't. Many of these outcomes are related to externalities (i.e. community, household, equity, and finance), broad economic indicators (i.e. household behavior, net budget transfers, and short- and long-term macroeconomic indicators), or non-utility productivity gains (e.g. better education).

Figure A-1. Links Between Vaccination and Broad Economic Outcomes (Jit et al., 2015)



Jit and colleagues (2015) also found that economic evaluations of vaccination programs most often compare these programs with no vaccination and do not consider all possible prevention or treatment options. Evaluations must consider all relevant comparators to be transparent and objective.

One of the most striking difficulties to assess the impact of these extended outcome measures, such as on antimicrobial resistance levels (Atkins et al., 2017), educational outcomes, lifetime work productivity, and economies or cost savings is that it takes years to become evident, and as a consequence many confounding factors can influence them.

Finally, Jit and colleagues (2015) did not consider the information needs of those who decide whether to use vaccines or other healthcare interventions. Therefore, another WHO-supported

research by van der Putten and colleagues (2015) explored those needs and perceptions of stakeholders with respect to the economic benefits of vaccination programs. Interestingly this study found that key stakeholders perceived many of the potential non-health economic benefits of vaccination programs to be as important as the traditional outcomes of health economic analyses such as mortality and morbidity reductions.

Another review, one year later by Jit and Hutubessy (2016), focused on the methodological challenges to economic analyses of vaccination programs. In addition to reviewing the literature on the economic benefits of vaccination programs, they also addressed the decision maker's needs. For example, whether they would like to obtain the full value assessment of vaccination programs, incorporating the broader societal benefits (reduced work production loss, demographic dividend, household savings). Two critical points should be considered here. One is who is the decision maker since that is not always very easy to identify for vaccines because of donor involvement, co-payment status, or governments or third-party payment. The second point is from which budget the vaccines are funded as this will determine the perspective for the economic analysis. For example, if the vaccine is fully funded from the health care budget, it is likely that benefits with no impact on health care are less likely to be considered in the evaluations for health care budget holders.

A critical question addressed by Jit and Hutubessy (2016) is whether decisions about vaccination programs would have changed if a broader economic analysis approach had been used systematically. They argue that the decision would not have changed for most vaccines on the market, even for the newer ones (i.e. human papillomavirus, rotavirus, and porcine circovirus vaccines). However, to respond that question with a precise answer is difficult because the review was based on published literature only. Many vaccine reimbursement dossiers that are

requested by budget holders to grant funding are submitted with extensive evaluation modules without being published in peer-reviewed journals.

Evaluation Methods

When the benefits go beyond health gains and cost offsets, a cost-utility framework can still be used if the constraint (i.e. the cost-effectiveness threshold or opportunity cost) and/or the denominator (i.e. quality-adjusted life-years [QALYs] gained) is adjusted based on broader benefits that could be achieved. This approach has been applied in developed countries where there are formal guidelines for conducting CEA. For example, for vaccination programs, the UK generally use locally determined threshold values as the basis for their decisions but for meningitis they adjusted them to reflect disease severity levels because of catastrophic sequelae of meningitis (Christensen et al., 2014). An alternative approach that has been suggested is to adjust the QALY's gained for people with poor health to reflect the likelihood that a health gain may be worth more than an equivalent health gain in healthier individuals (Bleichrodt et al., 2004).

More transparent than the previous two examples of adjusting thresholds or selecting specific target groups is to expand the number of outcome maximands in the decision from one (e.g. number of QALYs gained) to several. For example, Verguet and colleagues (2016) developed the concept of extended CEA, in which the benefit of vaccination is presented as both health gained and financial risk protected for households in different income quintiles. The WHO's World Health Assembly supports this approach and notes that progress toward universal health coverage should be measured in three dimensions: health gains, health equity improvements, and financial risk protection (Evans et al., 2010).

As an alternative to extending the CEA framework, evaluations of new vaccination programs can be done to optimize a given objective by selecting a mix of available health care interventions using constrained optimization if the constraints (e.g. budget and logistic constraints) and decision variables (e.g. vaccination programs and other prevention interventions) to be considered are precisely defined (Earnshaw et al., 2003; Crown et al, 2017). Alternatively, a menu of choices and their various outcomes can be presented to decision makers using cost-consequence analyses where relative efficiency of alternative interventions would be assessed based on a broad set of costs and outcome values (Coast et al., 2004; Sanders et al., 2016).

To inform a broader range of stakeholders, it may be appropriate to adopt an entirely different economic framework designed to achieve goals including those that are not health related. An example is the welfarist framework in which all economic benefits of vaccination programs (and not just health) are valued in accordance with societal preferences. For example, Laxminarayan and colleagues (2014) recommend cost-benefit analysis using the value of a statistical life which is about how much people might pay for reducing the risk of dying, to express the health gains into monetary values. This analysis captures all benefits (health and non-health) in money terms that will facilitate the comparison. Ozawa and colleagues (2016) have explored the return on investment expected from vaccination programs also using a value-of-statistical-life approach. Narrower analyses that ignore health gains in favor of other economic outcomes—such as maximizing the overall gain in national outputs using the gross domestic product per capita in macroeconomic models (Smith et al., 2005) or maximizing public economic impact on the state (i.e. a fiscal health modeling framework)—might be appropriate in situations that illustrate important cost transfers from fiscal income to health care or vice versa with the introduction of new vaccination programs (Connolly et al., 2017).

The Task Force Report

Recent publications have identified several additional outcome measures to mortality and morbidity reduction that might be used to support decisions about healthcare interventions, including vaccination programs. Some of these outcomes are easy to measure, but others are more challenging and it may be premature to design analyses that require inputs that are not readily available. Recent reviews have identified that in addition to cost-effectiveness analysis, other economic evaluation approaches have been used for vaccines based primarily on mortality and morbidity effects. Some of these approaches like cost-effectiveness analysis and cost-benefit analysis have been used extensively, whereas others like constrained optimization and fiscal health modelling are less well understood and no guidelines for them are available.

In an environment with multiple decision makers who fund vaccination programs working in different decision contexts, these recent reviews indicate the importance of considering a broad range of approaches for economic assessments of vaccination programs. But these approaches should provide information in a format that adopt the relevant perspective of each stakeholder, are credible, useful and based on best practice for those making decisions about vaccination programs in different contexts. However, "cherry picking" should be avoided i.e only including the externalities for vaccination programs and not for non-vaccine interventions if they are compared. In this ISPOR task force report, we have presented guidelines for the traditional cost-effectiveness analyses of vaccination programs that are most relevant for HTA agencies and other decision makers in high, middle and low-income countries making decisions about the allocation of funds to alternative health programs. We have also provided guidelines for two alternative evaluation methods that have been used for vaccination programs: 1) constrained optimization, most relevant for a decision maker with a fixed budget and other constraints and

with an objective to allocate funds to alternative interventions in such as a way as to optimize the health outcomes for one or more diseases and 2) fiscal health modeling, most relevant for a decision maker assessing the impact on net public economics of government attributed to allocation of general government revenues to fund a vaccination program.

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