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Moving beyond Traditional Valuation of Vaccination: Needs and Opportunities

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Commentary

Moving beyond traditional valuation of vaccination: Needs and opportunities

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ABSTRACT

Economic evaluations of vaccination traditionally focus on a relatively narrow set of vaccine benefits, such as averted medical care costs among those who are immunized. In recent years, researchers have identified additional vaccination benefits that should be incorporated into economic evaluations in order to reflect vaccination's full value. Early efforts to estimate the magnitude of these broader benefits suggest that vaccination has been substantially undervalued, which has important implications for public and private vaccine policy and human health and welfare. More and better data will be required to advance this emerging line of research on the value of vaccination. The article discusses promising data sources and methods and research questions needing to be addressed.

1. Introduction

In 2013 a group of 25 global health experts led by Dean Jamison and Lawrence Summers set forth a goal of achieving a "grand convergence" in health over the next two decades. Specifically, the authors asserted that the world now has the capacity to reduce the rates of infectious, child, and maternal mortality in low- and middle-income countries (LMICs) to the levels seen in high-income countries by 2035 [1]. This is an ambitious goal, and realizing it will require a coordinated effort by national governments, nongovernmental organizations, and philanthropists to make improvements in many arenas, including basic sanitation, prenatal care, and poverty reduction.

Vaccination is also likely to play a prominent role in achieving this aim, but that is only possible if vaccine interventions receive appropriate levels of investment. This will be more probable if the full value of vaccination—as a means of promoting not only health, but also other forms of well-being, chiefly economic—is appreciated by those with the power to make or influence critical investment decisions. This article traces our current understanding of the value of vaccination and how it has evolved over time.

In the 220 years since Edward Jenner first inoculated eight-year-old James Phipps against smallpox, the world has recognized vaccination as one of its most potent tools for combatting the scourge of infectious disease, particularly among children. Indeed, the administration of basic childhood vaccines is acknowledged to be one of the most technically and economically effective means available for improving public health, and coverage rates for basic immunizations have risen fairly steadily over the past several decades (see Fig. 1) [2]. Vaccination has contributed to a dramatic reduction in under-five mortality, which fell by more than half from 1990 to 2015 (see Fig. 2) [3]. The societal impact of vaccination is so great that when *The Atlantic* asked a panel of experts to rank the 50 most important inventions since the wheel, vaccination came in at number eight—just edging out the internet [4].

Despite widespread appreciation for the role vaccines play in preserving health around the world, researchers have recently broached the question of whether they may actually be undervalued in economic terms. Traditionally, economic assessments of vaccines have focused narrowly on their ability to avert direct medical costs and lost productivity for an individual experiencing illness or death. Over the past decade, however, researchers have demonstrated that this understanding of vaccination's benefits does not accurately reflect the full magnitude of its social, economic, and health effects.

In 2005, Bloom et al. argued that accurate appraisals of vaccines' value must consider certain broader outcomes, including the effects of vaccination on cognitive development, educational attainment, labor productivity, income, savings, investment, and fertility [6]. Various scholars developed these ideas and other related ideas further in a series of articles [1,7–21]. In addition, academics, policymakers, and pharmaceutical industry representatives assembled six times over the past several years—in Canada

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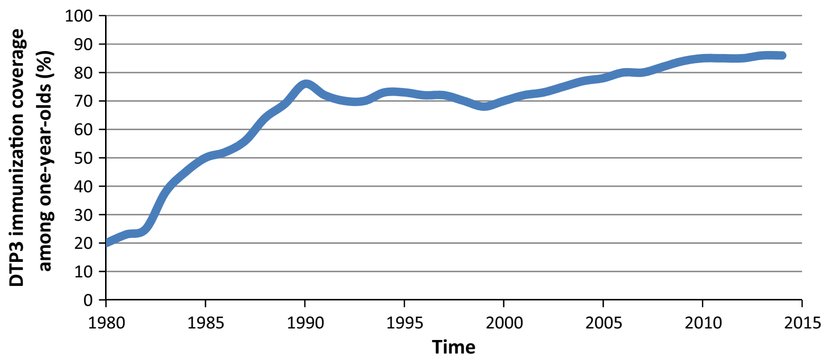

Fig. 1. Global DTP3 immunization coverage, 1980–2014. *Source:* [2].

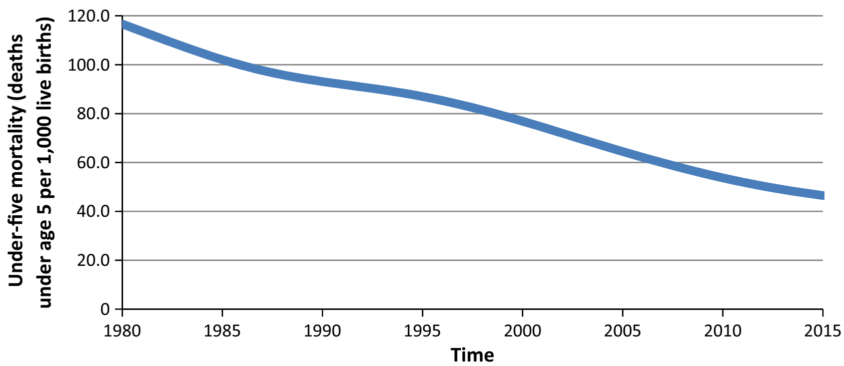

Fig. 2. Global under-five mortality, 1980–2015. *Source:* [5].

(2011), Switzerland (2012), France (2013), Australia (2013), Thailand (2014), and the United States (2016)—to discuss and develop robust frameworks for capturing the full range of vaccine effects.

Several publications on the value of vaccination are particularly noteworthy. Since its original conception, the Bloom framework has been expanded and updated on multiple occasions [12,22]. As currently envisioned, the framework divides vaccine benefits into two categories: narrow benefits consisting of health care cost savings and health gains, and broad benefits consisting of outcome-related productivity gains, care-related productivity gains, behavior-related output gains, health-based community externalities, reductions in co-morbidities, reductions in nosocomial infections, risk reduction gains, and increases in social equity (see Fig. 3).

In 2015, Jit et al. presented a compelling alternative value of vaccination framework based on work conducted in collaboration with the World Health Organization (WHO) [19]. This framework divides vaccination effects into four categories: health-related individual impacts, productivity-related individual impacts, community- or system-level impacts, and broader macroeconomic impacts. Health gains and health care cost savings fall under the category of health-related individual impacts. Care-related productivity gains, productivity gains related to nonutility capabilities, and health-effect-related productivity gains fall under productivity-related individual impacts. Improved equity, ecological effects, household security, and financial and programmatic synergies with other health intervention programs fall under community- or system-level impacts. Public sector budget impact, changes in household behavior, and short- and long-term macroeconomic impacts fall under broader macroeconomic impacts (see Fig. 4).

While researchers continue to debate the ideal formulation of a taxonomy of vaccine benefits, considerable agreement now exists that economic evaluations of vaccines must look beyond the traditional set of narrow benefits. At a minimum, vaccine assessment frameworks should consider the narrow benefits of health care cost savings and health gains and the broader benefits of outcome-related productivity gains, care-related productivity gains, behavior-related productivity gains, health-based community externalities, reduction of comorbidities and nosocomial infections, risk reduction gains, and improvements in social equity. These benefits must, of course, be offset by any negative effects associated with the use of vaccines, such as undesirable medical side effects.

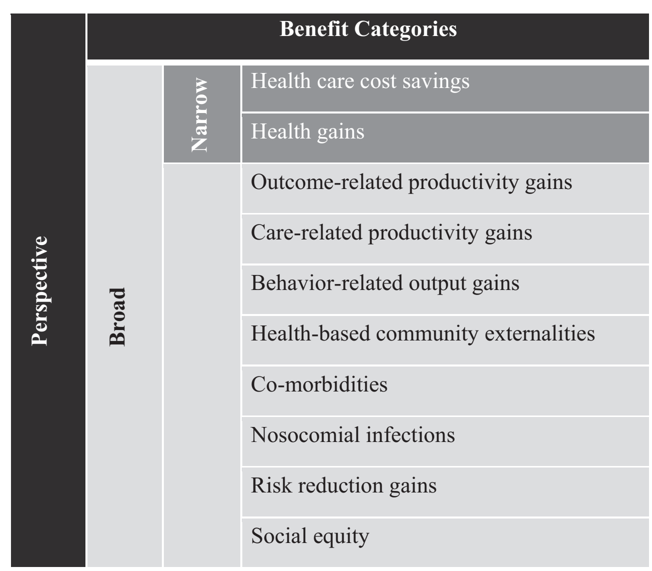

Fig. 3. Bloom framework 2016.

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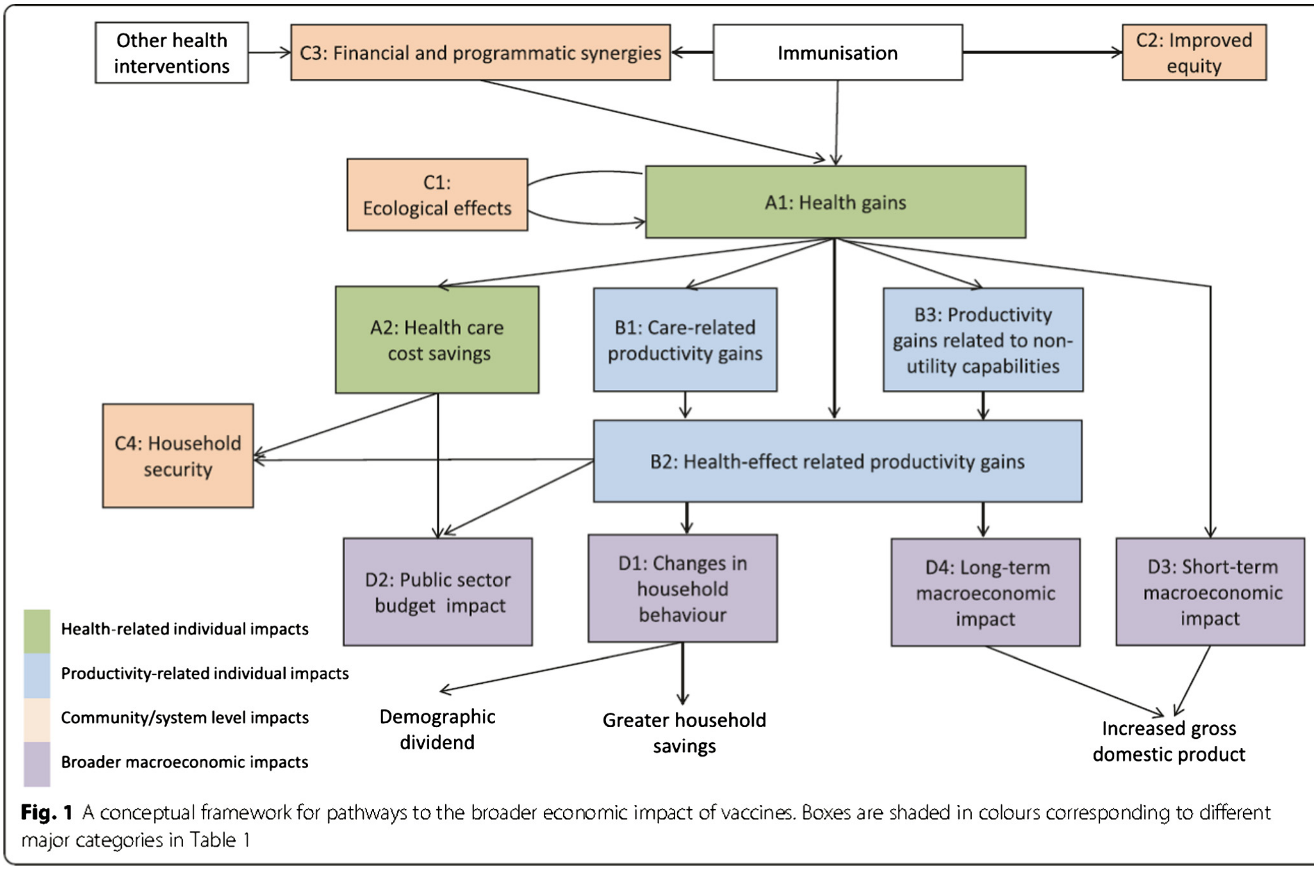

Fig. 4. Jit et al. framework, 2015. *Source:* [19].

2. Magnitude of the problem

Undervaluing vaccination potentially has significant implications. Despite the gains the world has made in vaccine coverage over the past several decades, the WHO estimates that nearly 20 million infants did not receive routine vaccines in 2015. Global coverage of pneumococcal vaccine, which helps protect against the leading infectious-disease-related cause of death among children, remained below 40% by the end of 2015 [23]. In 2008, roughly 1.5 million children under the age of five died from vaccine-preventable diseases [24].

Increasing vaccine coverage is not likely to become easier in the near future. The estimated cost of immunizing a child with the vaccines included in the WHO's Expanded Program on Immunization (EPI) has increased over recent years, in large part due to the introduction of new vaccines. In its 2013 report on the Global Vaccine Action Plan 2011–2020, the WHO estimated that the total cost of sustaining and scaling up current immunization programs, introducing new and underutilized vaccines, and conducting supplemental immunization activities needed to meet targets for disease elimination and eradication in all LMICs will amount to somewhere between US$50 billion and US$60 billion over the course of a decade [25]. Given this context, the potential underestimation of vaccine benefits could create problems for governments that must assess which vaccines to purchase and incorporate into their national vaccination programs. These assessments can only be made rationally if the full costs of vaccines and delivery of services are measured against their full benefits. A vaccine that is considered insufficiently beneficial to justify its costs under a narrow benefits framework could very well become justifiable once broader benefits are considered.

Unfortunately, the research community has not yet developed reliable mechanisms for capturing the data necessary to determine the actual magnitude of many of the broader benefits identified in theoretical frameworks. Systematic reviews by Ozawa et al. in 2012 and Constenla, Garcia, and Lefcourt in 2015 assessed the quality of evidence on vaccination's broader impacts and on the costs of vaccine-preventable diseases. Ozawa et al. found that the literature had not adequately captured data on many of the long-term social and economic benefits outlined in value of vaccination frameworks. As part of their review, the authors also considered two categories of broader vaccine benefits not previously included in value of vaccination frameworks: the value of statistical life and outbreak prevention savings [15]. While Ozawa et al. took a comprehensive approach by reviewing literature on the cost-effectiveness and economic benefits of multiple vaccines in LMICs, Constenla, Garcia, and Lefcourt focused specifically on literature related to the economics of dengue, for which a vaccine was first introduced in 2015. The authors found that inconsistent estimation of dengue costs and assessment of interventions in different contexts made drawing generalizations around costs difficult [20].

Despite the lack of compelling data, researchers have made several attempts to estimate how much vaccination has been undervalued. Initial evaluations based on empirical evidence suggest that the scale of underestimation is potentially quite large, and specific investigations into the value of both single vaccines and vaccine packages provide evidence of benefits to cognition and wages. One study of an early Gavi proposal to extend the use of various childhood vaccines to 75 low-income countries found that the labor productivity benefits resulting from expanded coverage alone suggested a return on investment of 12–18% from 2005 to 2020 [6,26].

Another study used data from the Philippines to examine the association between children's cognitive development and implementation of the EPI vaccine schedule in the first two years of life [27]. Based on a propensity score model designed to account for the nonrandom distribution of vaccination coverage, the study shows that vaccinated children achieved significantly higher test scores—high enough to suggest a 21% rate of return on vaccine spending.

A third study, which focused on the value of the Haemophilus influenza B (Hib) vaccine, considered cost reductions resulting from the fact that the Hib vaccine can only be delivered in pentavalent form and made adjustments to existing economic evaluations of the vaccine to better account for its full benefits [8]. Once these calculations were incorporated, the benefit-cost ratio moved from less than one to greater than one for most existing studies—enough of a shift to change from recommending against investing in the vaccine to recommending for it.

Yet another study found that by achieving coverage targets for basic vaccines, 72 LMICs could collectively avoid US$151 billion in costs after accounting for disease treatment costs, losses due to caretaker absences, and forgone income due to premature mortality [28].

More recently, in February 2016, Ozawa et al. estimated the expected return on investment for achieving projected vaccination coverage levels in 94 LMICs during the Decade of Vaccines (2011–2020). After accounting for some of the broader benefits of vaccination using a full-income approach and the value-of-statistical-life method, the authors found that achieving the projected coverage rates for the vaccines examined under the study would yield a net return on investment of more than 44 times the costs of immunization [14].

Finally, in October 2016, Ozawa et al. presented results from a modeling exercise designed to estimate the economic burden of vaccine-preventable diseases among adults in the United States [29]. The model estimated that these diseases accounted for a total economic burden of $9 billion through direct costs and productivity losses in 2015, and that unvaccinated individuals are responsible for roughly 80% of this burden.

Both individually and collectively, these studies indicate that the magnitude of vaccine undervaluation is potentially significant. However, it must again be acknowledged that the underlying data for studies on broader vaccine effects are not of the quality that researchers desire. The lack of large datasets containing health, education, labor, and economic data tailored to value of vaccination research has hindered more robust evaluations of these benefits. Consequently, much more research focuses on a limited set of conventional vaccination benefits than on the broader benefits of vaccination. For policymakers, health care providers, patients, and manufacturers, deeper knowledge of the broader benefits of vaccination is critical for making and adhering to evidence-based policies to maximize health gains. This information is important for ministries of finance and health to both mobilize resources and allocate them rationally.

3. The value of vaccination research agenda

Despite poor data quality and availability, great reason exists to be optimistic about the prospects for continued growth and development of value of vaccination research. With theoretical frameworks already well established, the most important next steps will involve identifying new sources of data, new tools, and new questions that will allow research to continue moving forward. This section sets forth a possible agenda for future value of vaccination research, outlining several concrete steps to move this work in the right direction. The following list of recommendations and caveats grew out of the collective efforts of value of vaccination researchers gathered at a workshop hosted by the Harvard T.H. Chan School of Public Health in April 2016 with the support of the Bill & Melinda Gates Foundation.

First, a great need for new and better data clearly exists. Researchers must prepare to shift from considering the broader effects of vaccination from a theoretical perspective to making new and concerted efforts at identifying and measuring appropriate indicators of those effects. In some cases, tracking broad vaccine effects back to their root causes will not be an easy task. For instance, outcomes related to educational attainment and long-term productivity must be measured long after vaccine exposure and are affected by multiple other factors, making it difficult to identify the individual contribution of a specific vaccine.

Gathering and coalescing useful data will most likely require researchers to adopt a portfolio of solutions, including matching existing data sets that are collected and maintained separately, improving modeling to extract the relevant signals from existing data, collecting wholly new data, and augmenting existing data collection efforts. Innovative study designs may also be needed. For example, natural experiments—such as the staggered rollout of pentavalent vaccine in India—offer opportunities for effectively studying the broader effects of vaccines in a manner that may not otherwise be feasible due to ethical concerns. Fostering effective partnerships with the private sector will be crucial throughout this process.

Some have proposed attaching economic analyses to clinical vaccine trials as a potential method for tracking long-term effects. However, representatives of the pharmaceutical industry caution that clinical trials may not always be appropriate for this type of study. Because the primary objective of clinical trials is to measure the efficacy and safety of vaccines, the design and statistical power of these trials may not meet the needs of economic assessment, and results may not be generalizable beyond the study population. Nevertheless, several pharmaceutical companies appear eager to collaborate with value of vaccination researchers. Fruitful collaborations require open communication and high levels of transparency around research methods and objectives, as well as respect for data privacy.

Second, researchers must be willing to tailor their studies and the presentation of their results appropriately. Some indicators of vaccination benefits are more relevant in certain contexts than in others. For example, economic evaluations of vaccines based in areas where tourism revenue plays a large role in the economy must consider potential losses to the tourism industry in the event of an outbreak of a vaccine-preventable disease. Other context-dependent variables that could factor into vaccine evaluations include the age structure of the local population, the epidemiological context, and the make-up of the labor force.

Tailoring studies to the audience may also involve re-evaluating the best methodology for economic analysis. At present, cost-effectiveness analysis (CEA) is most commonly used to assess interventions such as vaccination. However, benefit-cost analysis (BCA) may be better suited to the task of comparing vaccine prices and delivery costs against the full benefits of the intervention. BCA can account for diverse health and non-health outcomes and can be used to compare health and non-health interventions. It does both by translating multiple diverse outcomes into dollar measures that can be combined. By contrast, CEA has trouble handling more than one outcome at a time and cannot be used to compare health and non-health interventions.

For example, BCA can be used to simultaneously examine a particular health intervention's impacts on both days spent as an inpatient and incremental gains in employment and earnings. But CEA can only handle these outcomes one at a time, and therefore cannot offer a holistic assessment. BCA can also be used to compare the benefits of allocating resources to a health intervention (such as a vaccination program) with the benefits of allocating those same resources to a non-health intervention (such as a school lunch program). By contrast, CEA utterly fails with respect to such a comparison.

CEA continues to be the most directly applicable form of analysis for health ministers, who must set spending priorities while accounting for budgetary constraints. By contrast, BCA and estimation of return on investment for vaccination will naturally resonate with those, such as finance ministers, who are challenged to determine the most productive use of government resources in both health and non-health settings. Extended cost-effectiveness analysis and multi-criteria decision analysis may also be appropriate under certain conditions. The bottom line is that researchers should strive to generate the most relevant results for those tasked with making critical real-world decisions while also working to educate decision-makers on the relative virtues of different forms of analysis.

Finally, as the value of vaccination community focuses more on applied research and implementation, maintaining open communication with stakeholders will remain crucial. Academics and the private sector must foster trust with each other in order to collaborate on research effectively. Both researchers and private industry stakeholders must be willing to work with policymakers in relevant government ministries to help them better understand the implications of this work and make better decisions in prioritizing health investments. At the same time, policymakers must openly communicate their needs and limitations to researchers so that they can better orient their studies toward generating relevant data. Researchers must be prepared to continue their work at the implementation stage by gathering data on the effectiveness of vaccine-delivery programs and accounting for any unintended consequences.

4. Ideas for future study

The following topics represent the type of work that would yield relevant data for policy-oriented vaccine analyses.

1. Determine the value of vaccination in promoting school attendance, educational attainment, and cognitive development:

The effects of vaccination on schooling could be captured by comparing vaccinated and unvaccinated children with respect to school attendance, years of schooling, and cognitive development measured through standardized test scores. This analysis would need to control for other, confounding differences between the vaccinated and unvaccinated. Vaccinated children may, for example, have better-educated parents who are better informed about vaccine benefits and make independent contributions to their children's schooling. Possible data sources are longitudinal surveys, cross-sectional data that allows for examining educational differences between vaccinated and unvaccinated children within the same household, and analyses attached to randomized control trials.

2. Determine the value of vaccination in promoting labor force participation, hours worked, and earnings:

As in the preceding example, vaccinated and unvaccinated individuals could be compared with respect to labor force participation, employment, hours worked, and earnings. Data could come from the previously listed sources, including additional follow-up with the participants of randomized studies, to measure long-term labor market outcomes.

3. Examine how infant birthweight and neonatal health varies by mothers' immunization status:

Studies from Bangladesh and Nepal show that receipt of maternal influenza vaccination during pregnancy is associated with a significantly higher infant birthweight. Higher birthweight leads to better lifelong health, educational, and socioeconomic outcomes. These benefits of maternal vaccination are potentially large, monetizable, and worth measuring. Examining this effect in other geographic settings and for other vaccines could help build an evidence base for this benefit source.

4. Determine the value of vaccination in controlling the development of antimicrobial resistance:

Antimicrobial resistance (AMR) is costly in multiple respects. Resistance creates the need to use second- and third-line drugs—which are often more expensive, create more numerous and more severe side effects, and are less efficacious than standard treatments. Patients that must turn to second- and third-line drugs tend to experience longer recovery times and higher morbidity and mortality. Vaccines can reduce the pace at which AMR develops, translating into long-term health gains and cost reductions. This study would use epidemiological and economic modeling, along with empirically based estimates of key parameters and econometric analysis, to measure the benefits of vaccination in mitigating AMR costs. It would use welfare economic theory to monetize such benefits.

5. Develop and calibrate an epidemiological/economic model to estimate the value of vaccines:

Dynamic transmission models can trace the unfolding health impacts of an infectious disease. They can also model the health impact and reduced health costs of a vaccine that interrupts disease transmission. These epidemiological models could be expanded to incorporate economic behaviors, dynamics, and outcomes. This would involve modeling how epidemiological dynamics not only influence, but also are influenced by, economic decisions and their myriad outcomes such as fertility, education, labor productivity, and earnings. Models that integrate epidemiological and economic dynamics could better estimate the effects of a vaccine intervention on many economic outcomes. Such a study would also need to account for the costs of vaccine supply and delivery.

6. Determine the value of vaccination derived from herd effects stemming from the interruption of child-to-child, child-to-adult, adult-to-adult, and adult-to-child transmission:

Many economic evaluations of vaccines ignore the benefits associated with herd immunity, which is unsurprising given the challenges of measuring such benefits. But novel data sources and econometric estimators could address such challenges. Vaccine herd effects are age and disease specific. Given a sufficiently rich data source, these effects can be measured using an econometric estimator called the difference-in-difference-in-difference estimator, which measures health outcome differences across three dimensions. The first outcome difference exists in a time period before and after a vaccine's introduction. The second is between an age group that receives the vaccine and one or some that do not. The third is between a disease the vaccine protects against and one it does not.

A joint assessment of these three differences can help isolate the magnitude of herd effects at a population level, both between and within age groups and between and within disease categories.

In principle, this methodology can also measure unintended negative vaccine consequences such as serotype replacement—a phenomenon wherein vaccines protect against some disease subtypes, but other subtypes take their place, undoing at least some of the vaccines' benefits. Household-level data could be especially helpful in identifying transmission pathways and the magnitude of various herd effects.

7. Determine the anticipated value of prospective vaccines against HIV and emerging infectious diseases such as SARS, West Nile, H5N1, H1N1, MERS, MRSA, Ebola, and Zika:

Calculating the socioeconomic value of a prospective vaccine is also possible. Such a valuation exercise depends on the vaccine's expected impact on incidence and severity of the target disease, its side effects, its herd effects, its serotype replacement effects, and the consequences of these effects for economic dynamics, behaviors, and outcomes, which can be modeled or calibrated based on informed assumptions. Estimates of the value of prospective vaccines can be especially useful for informing decisions surrounding the allocation of resources to vaccine research and development.

8. Determine the insurance value of vaccines to individuals:

The full benefits of vaccination include its role as insurance against risks: a vaccinated person faces lower income and health risks—i.e., lower probabilities of deviations from normal levels of health or income. Such insurance value can be significant when risks are catastrophic, for example, involving death or severe lifelong disability. Research could quantify the degree to which people are willing to pay to avoid the health and financial risks associated with remaining unvaccinated. This could involve designing and solving a model of household welfare maximization with risk-averse members and solving for the monetary value to households of reducing the risks associated with vaccine-preventable diseases. It could also involve conducting stated-preference surveys of people's willingness to pay to avoid such risks, or econometric analyses of people's economic behaviors that implicitly reflect or reveal that willingness to pay.

9. Determine the value of vaccination in reducing social and economic inequality:

Evidence suggests that many vaccine-preventable diseases disproportionately burden the poor and worse-off in society. Many contemporary societies value equity in the distribution of health and income, even at the cost of foregoing efficiency in maximizing their aggregate values. As such, societies may be willing to sacrifice some of their total income to reduce inequality. Vaccination is one intervention that such a society would value for its contributions to equity. Research aimed at estimating social preferences regarding the equity-efficiency tradeoff and the effect of vaccines on promoting equity would help identify the magnitude of this potential benefit.

10. Determine the value of vaccination in triggering a fertility decline and a resulting demographic dividend:

When vaccination protects children's health, couples tend to reduce their fertility voluntarily, which can give rise to what demographers term a "demographic dividend" [22]. This refers to the boost in income growth that follows from diverting resources from feeding, clothing, housing, and educating large numbers of children to physical capital accumulation, human capital accumulation, and research and development—all proven drivers of economic growth and poverty alleviation. Research based on various microeconomic and macroeconomic datasets (e.g., the Demographic and Health Surveys and the World Development Indicators) could use modeling and econometric techniques to explore how much of a demographic dividend vaccine interventions can catalyze and create.

11. Determine the implications of childhood immunization for macroeconomic performance:

Health economists generally agree that poor health hinders macroeconomic performance. This is because a country's overall production is in part a function of its labor and human capital. When individuals are vaccinated and therefore healthier, they are better able to participate productively in the labor market and attain greater levels of training and therefore human capital. This shifts a country's production function upward. Estimating the degree to which childhood vaccines could bolster a country's economy would be useful for various policymakers.

The proposed study would involve building a macroeconomic model that focuses on the labor supply and productivity implications of mortality and morbidity associated with particular vaccine-preventable conditions. The model would also account for reduced rates of savings and investment due to diverting resources to treatment and care for vaccine-preventable conditions. The analysis would then require calibrating the model to account for these effects. The counterfactual would be disease elimination according to the effectiveness of the vaccine (if the vaccine provides immunity in 80% of the cases, then 80% of the disease would be averted; if a herd immunity effect exists, it should also be factored in). A rigorous analysis would also need to account for the cost of the immunization intervention. This could be done, for example, by multiplying the cost per dose by the number of required doses for full immunization and estimating the costs associated with distribution or administration of the vaccine.

5. Conclusion

The implications of proper vaccine valuation are not merely academic. How the value of vaccination is determined has consequences for vaccine pricing and policy, which in turn have consequences for human health and wellbeing—particularly among the world's most disadvantaged groups. Over the past decade, the global health community has come a long way in understanding the value of vaccination and has a solid understanding of the work that still needs to be done—we know the questions that remain open, and we have a good idea of the methods required to answer them. A lack of high-quality data, however, continues to represent the weak link in the chain from compelling theory to actionable evidence. Value of vaccination researchers must work closely with policymakers and industry leaders to close the data gap and continue advancing the state of knowledge in the field.

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