COMMENTARY: WHY HAS UPTAKE OF PNEUMOCOCCAL VACCINES FOR CHILDREN BEEN SO SLOW? THE PERILS OF UNDERVALUATION

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Abstract: Pediatric pneumococcal disease exacts a substantial burden on global health, much of which is vaccine-preventable. Despite this considerable burden and the demonstrably high efficacy of pneumococcal conjugate vaccines (PCVs), the overall level of PCV uptake remains concerningly low, especially compared with that of other childhood-recommended vaccines, such as tuberculosis and polio. A broad set of plausible explanations exists for this low uptake, including logistical challenges, psychosocial factors and affordability. One additional and systematic cause of low uptake, which is the focus of our discussion, is economists' and policymakers' tendency to undervalue vaccination in general by adopting a narrow health sector perspective when performing economic evaluations of vaccines. We present an alternative, societal framework for economic evaluations that encompasses a broader set of socioeconomic benefits in addition to health benefits. Quantifying a more comprehensive taxonomy of PCV's benefits will help to address potential undervaluation and may be sufficient not only to justify recommendation and reimbursement but also to stimulate efforts and investment toward closing coverage gaps.

Key Words: invasive pneumococcal disease, pneumococcal conjugate vaccine, economic evaluation, socioeconomic benefits

Accepted for publication October 4, 2019.

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This study and article development was led by Data for Decisions, LLC (DfD) and received financial support from Pfizer, Inc. S.P. is an employee and shareholder of Pfizer, Inc. Other than the named coauthor, the sponsor had no role in study design, data collection and analysis, decision to publish or preparation of the article.

A.S. was a full-time employee of Data for Decisions, LLC (DfD) during the development and drafting of the article. P.N.K. is a full-time employee of DfD. D.E.B. is a paid consultant to DfD and a member of the faculty at the Harvard T.H. Chan School of Public Health. He has received grant support from the Bill and Melinda Gates Foundation, the National Institute of Aging and the World Health Organization. He has also received grant support and/or personal fees from Merck, Pfizer, GSK, Sanofi Pasteur, Sanofi Pasteur-MSD and Gilead Life Sciences. S.P. is a full-time employee of Pfizer Inc.

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DOI: 10.1097/INF.0000000000002521

Pneumonia is the leading infectious cause of death in children 1–59 months of age worldwide, accounting for more than one in every five deaths in this age group in 2017 alone.[1] The most common cause of pediatric bacterial pneumonia, *Streptococcus pneumoniae* or pneumococcus, also causes severe but rare diseases like meningitis and bacteremia (jointly referred to as invasive pneumococcal disease or IPD), as well as mild but common diseases, such as otitis media, sinusitis, and bronchitis. These manifestations—known together as pneumococcal disease (PD)—collectively exact a substantial burden on global health. In 2015, an estimated 3.7 million episodes of severe PD and 318,000 resulting deaths occurred among children 1–59 months of age, with the majority of these deaths experienced in Africa (52%) and Southeast Asia (28%).[2]

Fortunately, much of this immense disease burden is vaccine-preventable. Pneumococcal conjugate vaccines (PCVs) protect against specific serotypes of *S. pneumoniae*. The 10-valent PCV (PCV10) and 13-valent PCV (PCV13), for instance, offer protection against 10 and 13 different serotypes of pneumococcus, respectively. Although decisions regarding PCV introduction and recommendation vary by country, an increasing number of both high- and low-income countries now incorporate PCV into their national immunization programs (NIPs). As of March 2019, 147 countries had introduced one or more PCVs into their NIPs (including 136 universal, five subnational, and three special risk programs), and 15 countries had announced future plans to introduce a PCV [Counts are based on authors' review of the International Vaccine Access Center's VIEW-hub report and database[3,4] and vaccination coverage estimates from the World Health Organization[5]]. These 147 countries include 60 low-income countries eligible for international assistance in procuring vaccines that introduced PCV after 2009 (the year in which funding from Gavi, the Vaccine Alliance, became available for PCVs).[3]

These vaccines provide immense public health benefits. Studies consistently indicate PCVs to be effective against pneumonia[6] and against IPD.[7] Furthermore, 49%–88% of IPD-related deaths in Africa and Asia in 2000 were caused by serotypes that are now included in existing PCVs.[8] The widespread adoption of these vaccines in recent years has contributed to significant reductions in the global burden of PD, especially in low-income countries with high child mortality. One study estimates that introducing PCVs prevented an estimated 250,000 cumulative PD-related deaths between 2000 and 2015 in children 1–59 months of age.[2] Another study modeling the potential effects of PCV13 use with high uptake across 180 countries projects that global use of the vaccine would avert a further 399,000 PD-related child deaths and 54.6 million disease episodes annually between 2015 and 2045.[9]

Despite considerable reductions in PD-related morbidity and mortality, the global burden of this disease among children remains substantial, and many countries have yet to recommend any PCV for routine vaccination.[3] Furthermore, even among countries that do recommend PCVs, uptake remains low compared with that of other common childhood vaccines, such as those against tetanus, polio, measles, and hepatitis B.[10] Pneumococcal vaccine routine uptake is low for various reasons, ranging from financial barriers and logistical obstacles to cultural influencers. Financially, vaccine expenditure has not increased in all countries in accordance with the scope of available vaccines[11–13] and gaps in funding and coverage are historically evident between older and newer-generation vaccines due to differences in cost and vaccine acceptance.[14]

One critical reason for low uptake, and a focus of this article, is economists' and policymakers' frequent failure to account for the full range of PCVs' benefits. Traditional economic evaluations adopt a narrow health sector perspective, focusing on benefits such as avoided medical expenses. An emerging literature finds that this conventional approach ignores or undercounts substantial portions of vaccines' full socioeconomic benefits, which can lead to systematic undervaluation and underinvestment in pediatric PCVs and other vaccines.[15–34] Such undervaluation in current economic evaluations may underlie many policymakers' decisions not to recommend or reimburse PCVs and other vaccines. Adopting a broader societal perspective may help address the gap between PCVs' measured benefits and the full benefits these vaccines actually offer, leading to better-informed vaccine development, recommendation, and reimbursement decisions.

This article discusses the various determinants of low uptake for pediatric PCVs and elaborates on how the shortcomings of existing valuation methods that adopt a narrow health-centric perspective may undermine efforts to increase vaccination. We

propose expanding the literature's taxonomy of vaccination benefits by adopting a societal perspective framework that includes a set of broader socioeconomic benefits in addition to conventionally measured health benefits. Such an expanded framework could reveal a greater rate of return to investment in PCVs than that estimated by traditional health-centric valuation methods.

REVIEW OF PCV UPTAKE

Reductions in the worldwide burden of childhood PD reflect widespread adoption of pneumococcal vaccines over the past two decades. Within the past 10 years, the total number of countries that have introduced PCVs (in at least one population and at least one region) has more than quadrupled (Fig. 1). Alongside this rise in recommendations, coverage rates for target childhood populations have also improved: in 2014 to 2018 alone, global uptake of the third dose of a pediatric PCV rose by almost 50% (Fig. 2).

Despite recent progress on this front and relative growth in coverage, the overall level of PCV uptake remains concerningly low. The World Health Organization (WHO) estimates that global coverage of the third dose of PCV, while notably greater than in 2014, still only reached 47% of its target population in 2018.[35] This coverage gap is especially striking when compared with rates for other childhood-recommended vaccines, such as the Bacille Calmette Guérin vaccine for tuberculosis (89%); the third dose of the polio vaccine (85%); the third dose of the diphtheria, tetanus, and pertussis vaccine (86%); and the third dose of the hepatitis B vaccine (84%) (Fig. 2). PCV uptake lags markedly behind even though by many measures PD is not necessarily less severe or lower priority than other higher-coverage vaccines. (One meta-analysis, for example, estimates that death caused by TB among patients who had initiated TB treatment was 3.0% for HIV-uninfected patients and 9.2% for HIV-infected patients (2011 estimates).[36] By comparison, case-fatality rates of PD manifestations,such as pneumococcal pneumonia (5%–7%) and bacteremia (20%), are notably higher (2018 estimates),[37] yet PCV uptake reaches only about half that of BCG, the vaccine that targets TB.) While global uptake remains low on average, important variability exists in the rate of uptake between countries. Some countries, such as Denmark, have achieved high uptake levels of the third dose of PCV in the range of 90%–100%, yet other countries have not had similar success.[35,38]

PLAUSIBLE REASONS FOR LOW UPTAKE

Many barriers and obstacles can impede PCV uptake. From a logistical standpoint, sustaining high coverage rates requires a dependable supply chain network, which has become increasingly challenging due to widening varieties of available vaccines, increasing supply costs and tightening infrastructure standards. Many existing immunization and supply chain logistics (ISCL) systems are not keeping pace with the changing vaccine landscape, often resulting in stock shortages, inventory unpredictability, the potential administration of ineffective vaccines and avoidable wastage.[39] The WHO estimates that in 2011, cold-chain failures in five countries resulted in the loss of 2.8 million vaccine doses.[39]

Even when existing ISCL systems are running smoothly and efficiently for the areas that they serve, accessibility often remains an especially important consideration for uptake in developing and rural areas. In underserviced areas, limitations such as travel opportunity costs, direct costs, and safety concerns may play a larger role in vaccination decisions. Children born to families living farther away from a road or clinic are at demonstrably greater risk of not being fully vaccinated, even where vaccines are reliably available and reimbursed.[40] One recent study in Kenya reported that only 39.1% of schoolgirls receive the third dose of the human papillomavirus (HPV) vaccine and found hospital distance to be a statistically significant predictor of HPV-immunization-course noncompletion.[41] Accessibility shortcomings and insufficient ISCL system funding both have far-reaching implications for vaccine coverage, uptake, and—in cases of noncompletion—efficacy.[39]

Behavioral and psychosocial considerations are also key determinants of vaccination uptake.[42] Vaccine hesitancy is one leading impediment to sustaining high coverage rates and is relatively common worldwide: according to one recent study, more than 90% of countries reported some level of vaccine hesitancy.[42] The top three reasons cited for vaccine hesitancy globally in 2016 were (1) risk-benefit concerns (such as vaccine safety concerns) (23% of responses); (2) lack of knowledge and awareness of vaccination and its importance (10%); and (3) religion, culture, gender, and socioeconomic issues regarding vaccines (12%).[42] The spread of misinformation through antivaccination lobbies and the media exerts a powerful influence on parents' vaccination decisions and perceptions of vaccine safety: for example, the use of mercury-based preservatives in some childhood vaccines such as the flu vaccine and the measles, mumps, and rubella vaccine caused controversy in the late 1990s, when an unfounded scare arose that these vaccines caused autism and other developmental disorders in children. Similarly, the 1970s saw an international movement against the diphtheria toxoid, tetanus toxoid, and pertussis vaccine when fears spread that it caused neurologic conditions.[43,44] Those with confidence in vaccines' safety may still refuse vaccination if they consider it unnecessary, perhaps due to excessive faith in the medical system's capacity to treat disease or the misconception that near-eradication of certain diseases means they are no longer a threat.[45] Public confidence in immunization's safety, necessity, and effectiveness is thus critical to ensuring high coverage levels.

Another central issue underpinning low pediatric PCV uptake is affordability. PCVs are more expensive than earlier generations of vaccines, and their prices have been rising in the United

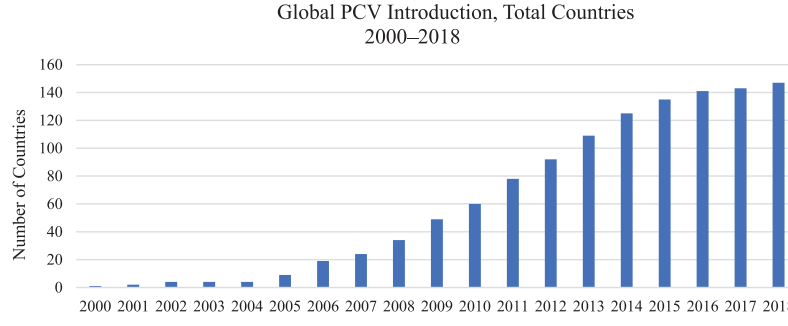

FIGURE 1. Global PCV introduction, total countries, 2000 to 2018.[3,4,5]

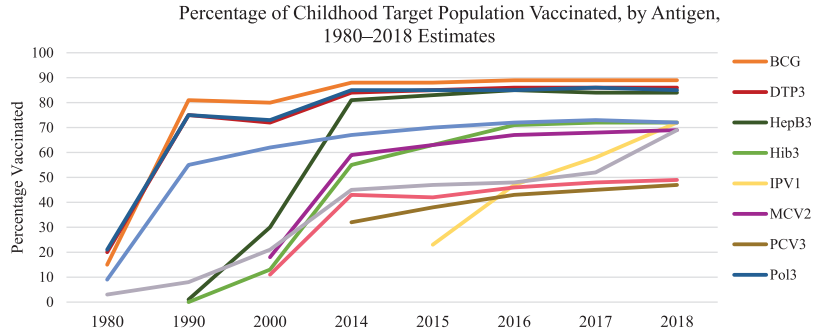

FIGURE 2. Percentage of childhood target population vaccinated, by antigen, 1980 to 2018 estimates.[35] BCG indicates Bacille Calmette Guérin vaccine for tuberculosis; DTP3, third dose of diphtheria toxoid, tetanus toxoid, and pertussis vaccine; HepB3, third dose of hepatitis B vaccine; Hib3, third dose of *Haemophilus influenzae* type B vaccine; IPV1, first dose of inactivated polio vaccine; MCV2, second dose of measles-containing vaccine; PCV3, third dose of pneumococcal conjugate vaccine; Pol3, third dose of polio vaccine.

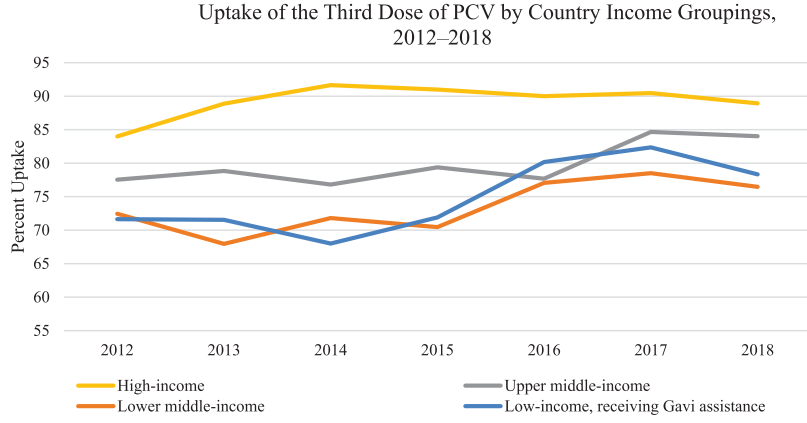

FIGURE 3. Uptake of the third dose of PCV by country income groupings, 2012 to 2018.[5,50,51]

States and globally.[46,47] Introducing PCVs into a NIP also typically represents a financial commitment of at least several years. PCVs should be continually administered to new cohorts for sustained protection against the target disease, and it is difficult to remove a vaccine from a NIP once it has been introduced. This long-term commitment to a relatively high-cost vaccine seems to place PCVs outside the financial reach of health authorities in many lower- and middle-income countries.

International funding from bodies like Gavi can also help eligible countries maintain their immunization programs and uptake rates by facilitating predictable, sustained access to costly vaccines like PCVs.[48] However, countries transitioning away from Gavi funding are especially vulnerable to affordability constraints. As these countries cross the income eligibility threshold for financial assistance and face the full vaccination costs, their uptake rates may actually fall below those of poorer countries because of an unsuccessful process of "graduation" from Gavi assistance. One review of middle-income countries finds that PCV uptake among lower middle-income countries was paradoxically much higher (71%) than that of upper middle-income countries (48%).[49] Our own analysis of WHO coverage data (Fig. 3) for the third dose of PCV similarly shows that in certain years lower middle-income countries reported lower average coverage rates than low-income countries receiving Gavi funding for pneumococcal vaccination, and even upper middle-income countries had a lower rate than low-income countries in 2016.

One other plausible major and systemic cause of low uptake is economists' and policymakers' tendency to undervalue vaccination in general, and PCVs in particular, by adopting a narrow health sector perspective when performing economic evaluations of vaccines. The conventional health sector perspective focuses on two benefit categories of vaccination: healthcare cost savings (stemming from reductions in visits to healthcare professionals, inpatient stays, and prescription drugs) and health gains (the value of reduced morbidity, mortality, and suffering from PD). These two benefit measures alone are insufficient to constitute a comprehensive assessment of PCVs' value, as they do not capture a much broader set of socioeconomic benefits to society. The gap between PCVs' measured benefits and their full benefits indicates that they are undervalued, which suggests that decisions to not recommend or reimburse their use are poorly founded, with avoidable mortality and morbidity and resulting downstream health, economic, and social implications an unfortunate result.

We present an alternative, societal framework for economic evaluations of vaccines that encompasses a broader set of socioeconomic benefits in addition to health benefits. Articulating and empirically measuring a more comprehensive taxonomy from the societal perspective will help to remedy gaps in the literature's consideration of pediatric PCVs' full benefits and to address potential

undervaluation. If the value of these additional benefits reveals a decisively higher rate of return to vaccination for society, the results may be sufficient not only to justify recommendation and reimbursement but also to stimulate efforts and investment toward closing coverage gaps. Such investment could include, for instance, allocating funds to improve accessibility by supplying additional clinics and sponsoring educational campaigns to raise awareness and combat vaccine hesitancy. If the benefits of supplying PCVs and increasing uptake are greater than the costs, then the costs, albeit high, may well be worth incurring.

A TAXONOMY OF THE FULL BENEFITS OF PEDIATRIC PCV VACCINATION

Our proposed taxonomy includes both traditionally captured narrow benefits, which we denote in italics, and additional broad benefits. We categorize all listed benefits along two dimensions: primarily health-related versus nonhealth-related benefits, and primarily internalized benefits (ie, those benefits enjoyed by the vaccine recipient and his or her household) versus externalized benefits (ie, those enjoyed by other members of society). This comprises a two-by-two matrix with four quadrants. Quadrant I, for example, includes internal health-related benefits while quadrant IV includes external nonhealth-related benefits. We assign benefits to these four quadrants according to what we believe would be the most relevant categorization for policymakers. Our categorizations, however, are not definitive: certain benefits may be internalized in some situations, while they are externalized in other situations. The assignment of such ambiguous benefits should, therefore, be considered according to each particular case. Table 1 presents our taxonomy. We now discuss each element within the taxonomy in turn.

Quadrant I: Internalized Health Benefits

Direct Health Gains

Direct health gains from disease prevention are most often measured in quality-adjusted life years (QALYs) or disability-adjusted life years gained. We characterize this as one of two narrow benefits because all cost-effectiveness analyses (CEAs) of vaccination necessarily measure its health impacts.[52–54] Oftentimes, however, CEAs fail to capture this benefit category comprehensively because they focus only on health costs related to the acute disease phase. A full-benefits approach would consider all disease outcomes and sequelae, which, for pediatric PD, can include various long-term complications, such as chronic renal failure, paralysis, muscle spasms or even death.[55] It would consider any potential nonspecific effects on health outcomes that are not directly related to the target disease. (For example, some observational studies find that BCG vaccination in infants is associated with a marked reduction in non-TB-related neonatal mortality rate[56] and influenza vaccination among elderly adults may lower all-cause mortality.[56] For a summary of the literature on this topic, including arguments that such benefits are overstated, see Simonsen et al.[57]) It would also consider any mitigating effect of vaccination on disease severity (because vaccines induce stronger immune responses against the target disease, vaccination may result in milder disease outcomes conditional on infection). Finally, insofar as PCVs cause adverse events, such as allergic reactions, any potential health costs should be counted against the overall benefits.

Household Health Externalities

Our first nonnarrow benefit category is comprised of household-level health externalities. Perhaps most importantly, a PCV recipient's household enjoys vaccine-related health benefits through herd protection. Because PD is contagious, preventing infection in one household member reduces the chances of it spreading to others and thus confers protection on the rest of the household. Households may enjoy additional health benefits, which are indirectly related to the burden of PD. For example, QALY losses related to ailments like anxiety and depression may occur at higher rates among household members living with a PD patient who suffers severe sequelae, especially in cases where the patient is a child (Al-Janabi et al[58] present findings on such outcomes for sequelae related to invasive meningococcal disease). Pediatric economic evaluations do not routinely capture disutility that may be experienced by caregivers,[59,60] yet this type of derivative household-level cost can be substantial. A recent review of pediatric cost-utility analyses found that including family spillover effects related to costs and health outcomes reduced cost-effectiveness ratios by 31% on average, or $40,000/QALY.[59] Such household spillover effects should certainly be considered along with PD-related health burdens.

Prevention and Amelioration of Comorbidities

Insofar as pediatric PD induces the development of new comorbidities or aggravates preexisting ones, PD patients have additional health burdens. For instance, studies show that childhood pneumonia, a common manifestation of PD, can impair long-term lung health.[61] Growing evidence suggest that sequelae

TABLE 1. Taxonomy of the Full Benefits of Pediatric Pneumococcal Conjugate Vaccination

	Health Benefits	Nonhealth Benefits
Internalized	*Direct health gains*	Education gains
	Household health externalities	Labor market productivity gains
	Prevention and amelioration of comorbidities	Nonmarket productivity and leisure gains
	Reductions in nosocomial infections	Caregiver productivity and leisure gains
	I	Risk reduction gainsII
Externalized	Full public health benefits	*Healthcare cost savings*
		Social preference fulfillment
		Outbreak control gains
		Macroeconomic gains
		Political implications
		Equity gains
	III	Health system efficiency gainsIV

Italicized benefits categories comprise narrow benefits. All listed benefits are broad benefits.

such as chronic obstructive pulmonary disease, restrictive lung disease, asthma, and chronic bronchitis later in life may be related to early childhood pneumonia[62] (for other comorbidities and sequelae related to pneumonia in other age groups, see Torres et al[63]). Preventing pediatric PD through early vaccination, therefore, could also prevent the incidence or worsening of comorbidity-related health burdens during the entire life course.

Reductions in Nosocomial Infections

Preventing pediatric PD prevents PD-related hospital visits, some of which could lead to the patient contracting a secondary nosocomial infection or to PD spreading to other patients and caregivers in the hospital.[64] Notably, studies and case reports indicate that nosocomial PD outbreaks are possible.[65–67] The prevention of hospital-acquired infections is, therefore, a benefit that should be considered for both the PD patient and other persons in the hospital.

Quadrant II: Internalized Nonhealth Benefits

Education Gains

Our first internalized nonhealth benefit category relates to potential educational interruptions for children who contract PD. Patients may miss days, or even weeks, of school while they are ill, depending on the manifestation and its severity. PD may also negatively impact cognitive functioning and therefore reduce how much children in school are able to learn and retain while in the classroom.[68–70] These effects may, in turn, lead to overall worse educational outcomes and attainment for children who contract PD.[71–73] Given the critical role of education in driving productivity, economic growth, and better health outcomes (both for the individual and for broader society),[74–77] the full value of preventing PD must include the long-term, downstream value of preventing these educational burdens.

Labor Market Productivity Gains

Pediatric PD can also affect productivity more immediately when its associated long-term burdens extend into working ages.[73] Potential long-term complications and sequelae of PD, such as organ failure, hearing loss, pericarditis, renal disease, chronic ear infections, or brain damage[78,79] can lead to missed workdays for continued treatment and appointments and can hinder productivity while at work (One study, for example, finds that work time missed for employees with chronic kidney disease exceeded 10 hours per week.[80] For example calculations of such market productivity costs related to adult pneumococcal disease, see Sevilla et al.[81]) Missed workdays and lower performance may have negative downstream implications for work-related skill development and career advancement. In the most severe case, a childhood death from PD would mean the loss of the decedent's entire lifetime's worth of market productivity.

Nonmarket Productivity and Leisure Gains

In addition to potential paid market productivity later in life, the same complications and sequelae discussed previously can affect patients' adulthood ability to engage productively in nonmarket activities, such as volunteering, caregiving, and performing housework.[81] Arguably even more immediately relevant for children, PD also affects leisure time or all nonproductive time besides self-care. This includes activities like socializing, participating in extracurricular clubs and sports, reading, and other activities that are critical to childhood development.[82]

Caregiver Productivity and Leisure Gains

Any potential caregivers—often parents or other family members—also enjoy productivity- and leisure-related benefits of PCVs. The burden of caring for a PD patient can be immense, imposing a potentially catastrophic demand on the quantity and quality of caretakers' time.[83] The value of avoiding these costs is especially pronounced for caregivers of pediatric PD patients because children with PD often require dedicated adult supervision. Overlooking these costs, therefore, risks substantial undervaluation.

Risk Reduction Gains

Risk-related costs of PD fall into several categories. First, risk-averse individuals are demonstrably willing to pay to reduce the types of severe health and financial risks that pediatric PD can impose.[84] As discussed previously, these burdens can fall on patients' parents or caretakers and potentially on the patients themselves if they reach adulthood with related complications. Parents, who often feel driven to protect their children from such costs, can be especially risk averse; studies have shown that becoming a parent substantially increases risk aversion among both men and women.[85] Second, pediatric PD vaccination helps to smooth health spending over time by reducing the financial risks of spending shocks for PD treatment.[86] Third, the protection conferred by vaccination may provide a sense of security and well-being to those who are anxious about themselves or their children becoming infected, especially during outbreaks (this effect is referred to as "utility in anticipation").[87–89] Insofar as pediatric vaccination mitigates negative emotions surrounding infection and serves as a source reassurance for caregivers, this benefit for quality of life should be counted.

Quadrant III: Externalized Health Benefits

Quadrant III contains only one, comprehensive category: the full public health benefits of vaccination (FPHV).[16] This broad set of benefits includes all health-related, externalized benefits that society as a whole enjoys when an individual child receives a PCV. Herd protection is one of the key benefits included in the FPHV category and is especially consequential for pediatric PD given that most children who die from PD reside in lower-income countries and are often unable to access lifesaving antibiotics.[90] Vaccination of other children in their communities reduces carriage and impedes transmission, conferring indirect protection to those most at risk of mortality. The effectiveness of pediatric PCVs at reducing carriage rates among nonvaccinated adults, slowing transmission among the general population for all age groups, has also been clearly demonstrated.[91,92]

A second facet of the FPHV of PCVs relates to antimicrobial resistance. Exposure to antimicrobials when they are used to treat and prevent PD has allowed *S. pneumoniae* bacteria to steadily build resistance.[93,94] Vaccinating, and thereby preventing many PD cases, obviates the need to use antimicrobials for chemoprophylaxis or for PD treatment in would-be patients.[95,96] Reducing the use of antimicrobials can slow the pace of antimicrobial resistance development and preserve their efficacy as a primary treatment.[55,97–102] Vaccines exercise a critical role in limiting antimicrobial exposure, and introducing vaccines against PD has been associated with decreased incidence of resistant strains.[103]

Quadrant IV: Externalized Nonhealth Benefits

Healthcare Cost Savings

The healthcare cost savings that stem from preventing PD can be immense in every country, regardless of income or development

level. The direct cost of PD among persons of all ages in the United States, for instance, was an estimated $3.5 billion in 2004.[104] Another study in Taiwan finds that families spent an average of $653 or $218 when their child was diagnosed with IPD or pneumonia, respectively (approximately 27%–81% of an unskilled worker's monthly salary)[105] (for similar estimates of economic costs of PD in The Gambia, see Usuf et al[106]). Such costs can easily mean not just financial hardship, especially for lower-income households, but medical impoverishment due to health (ie, when household income minus out-of-pocket healthcare spending falls below the poverty line). An analysis across 41 Gavi-eligible countries estimates that roughly 6.6 million more cases of catastrophic health costs (defined as out-of-pocket health spending exceeding 20% of household income) and 0.8 million more cases of medical impoverishment attributable to severe PD would occur over the period 2016 to 2030 in the absence of vaccine coverage against PD.[107] Such a hike in poverty cases would likely have detrimental impacts for the economies and development of these Gavi-eligible countries.

Note that healthcare cost savings can be flexibly categorized as either external (when public payers would cover the expenses) or internal (when individuals would pay the expenses of pocket). While healthcare cost savings often factor into economic evaluations of vaccines, many analyses only capture a subset of the direct costs and then focus just on those incurred during the acute disease phase. A comprehensive accounting of this category should consider a complete list of potential direct costs (eg, ambulance travel, drugs, and medical devices) as well as any costs associated with long-term care and rehabilitation (eg, physical therapy).

Social Preference Fulfillment

A growing body of literature finds that individuals are willing to pay disproportionate amounts to prevent severe disease.[108,109] This suggests a societal preference for preventing especially severe manifestations of PD, such as meningitis, over many milder diseases. Societal preferences may also exist for seeing benefits accrue to certain age groups (eg, the elderly or the very young) who are at elevated risk for PD.[110] An alignment may, therefore, exist between societal priorities and PCVs, which prevent potentially severe manifestations of PD in children. Failing to account for this fulfillment of preferences may underestimate the societal value of PCVs.

Outbreak Control Gains

Outbreaks are often accompanied by especially high prevention and treatment costs. An elevated number of cases requires an increased use of resources and can place strain on first responders and emergency medical providers. Responding to the outbreak may also involve escalated spending on chemoprophylaxis; precautionary medical tests; vaccine-related shipment, storage, administration, and labor; and public education and messaging efforts. Various studies focused on outbreak costs of other diseases demonstrate that the burden of infectious outbreaks can be immense.[111,112] Pediatric infection may spread quickly in settings such as childcare, where children, who have particularly high PD carriage rates, are in close contact.[113] To the extent that PCVs reduce the magnitude and consequences of outbreaks, their full benefits should incorporate any related costs savings.

Macroeconomic Gains

The relationship between health and economic growth is well-documented[114]; insofar as vaccines protect and promote good health, they also indirectly protect and promote economic growth. Valuing these gains for pediatric diseases like PD should capture both immediate productivity gains for caretakers as well as the eventual productivity gains accrued later in life by the would-be patients. In addition to productivity, there are other mechanisms through which vaccines contribute macroeconomic benefits. For example, disease can drive patients and their households into poverty cycles; it can hinder tourism, including routine tourism and tourism during special events like the Hajj or the Olympics;[18] and it is associated with lower foreign direct investment inflows.[115] The value of PCVs' effects on poverty reduction, tourism, and foreign direct investment should ideally be counted among its macroeconomic benefits.

Political Implications

One additional source of benefit that has been less prominent in the literature is the correlation between health status and political stability. High disease prevalence can weaken economic institutions, exacerbate social inequalities, and erode trust in governing institutions.[116,117] Research on multiple diseases such as Ebola and HIV/AIDS finds an association between poor or declining average health outcomes over time and a deterioration in state capacity, resulting in greater rates of conflict and unrest. (For example, the 2013 to 2015 Mano River Basin Ebola outbreak led to mass civil unrest and severely shook the regional stability.[118] Another study finds an association between HIV/AIDS and higher rates of violence.[119]) High rates of childhood mortality caused by PD[2,120] and debilitating complications for many survivors[55] may raise concerns about the effectiveness and reliability of state leaders who are seemingly failing to provide basic services needed to protect their citizenry. Such mistrust in the government may be especially important for developing nations: in a report on global trends for 2015, the US National Intelligence Council cautions that diseases and associated health problems can hurt prospects for transition to democratic regimes, which arguably depend greatly on political trust.[121,122] Although the potential costs to political stability may be small compared with other costs of pediatric PD, they are nevertheless part of a complete accounting of all vaccination benefits.

Equity Gains

The burden of infectious diseases, including PD, falls disproportionately on lower-income populations.[123–125] This stems in part from other factors associated with lower socioeconomic status that exacerbate poorer and younger individuals' vulnerability to PD. These include, for example, increased rates of malnutrition and undernutrition, lack of access to clean water and inadequate hygiene and sanitation,[126] all of which can increase the incidence and severity of infectious diseases. It may also stem from lower utilization of preventive care: if the cost of basic necessities represents a high share of household income, households may be less likely, or less able, to spend money on health interventions (such as vaccination) that prevent illness in an uncertain future as opposed to addressing an immediate need.[86]

In addition to higher incidence rates, the overall health and economic burden of pediatric PD can be higher for low-income patients. In lower-income countries, medical diagnoses are frequently incorrect for pneumonia and other serious conditions, and doctors may provide treatment too slowly for conditions that require quick action, such as meningitis caused by *S. pneumoniae.*[127] Insufficient or untimely care can lead to unnecessary

suffering, persistent symptoms, worsening conditions, increased likelihood of long-term disability (which, in turn, would exacerbate the educational and productivity losses discussed previously), and increased mortality. The health costs of a PD episode, while substantial across countries, can thus be disproportionately severe for the very poor and other vulnerable groups without access to high-quality care. Unbudgeted and unanticipated health costs can also be disproportionately and catastrophically expensive for low-income and uninsured households.[86]

Research shows that vaccination, therefore, yields greater benefits for low-income groups than for middle- and high-income groups, on average. The same analysis of 41 Gavi-eligible countries discussed previously finds that the majority of catastrophic health cost cases would occur in the lowest two income quintiles in the absence of vaccination.[107] Another study in Bangladesh finds that providing pediatric measles vaccination has a low impact on early childhood mortality risks for children from high-income families, but a pronounced impact for children from low-income families.[128] The distributional impact of vaccines, therefore, has an important role to play in poverty reduction, especially for lower socioeconomic groups.

In addition to socioeconomic disparities, racial, ethnic, and geographic disparities in IPD rates have also been documented. IPD incidence in the US has historically been higher among some racial minorities, including black children and Alaskan Native infants.[129,130] Following the introduction of the PCV7 series in 2000, however, these disparities declined significantly.[129,130] Similarly, one study in Tennessee finds that IPD rates in children under two years of age were higher in east Tennessee than middle-west Tennessee before PCV13's introduction, but this difference was no longer significant in the post-PCV13 era.[131] Because vaccine benefits often accrue disproportionately to poorer communities, some racial and ethnic minorities, and certain geographic regions, vaccines have additional value as a method to promote health equity across subpopulations.[132]

Health System Efficiency Gains

Our final benefit category relates PCVs and the sustainability of healthcare systems. Fewer pediatric PD cases means medical supplies and professionals' time can be reallocated more efficiently (eg, to other patients or to research and development efforts), easing the strain on hospital budgets and benefiting other patient groups with unmet needs.[133] It may also reduce any costs or system inefficiencies related to planning hospital capacity around seasonal or outbreak-related surges in the incidence of PD.[134] Given the particularly substantial time and care demands involved in treating severe manifestations of pediatric PD,[105–107] the financial and medical resources saved through prevention merit consideration.[134]

The broad benefits categories we outline here are general enough to span all segments of the life course. Admittedly, certain categories will be more salient for particular age groups: for instance, educational benefits accrue predominantly from childhood vaccination, while productivity gains are likely empirically small for pediatric vaccination relative to those for adult vaccination. But, for the sake of completeness, a full benefits framework should nevertheless count them. Because the same taxonomy can be used to evaluate other diseases, additional value exists in creating a methodical, comprehensive framework that can be applied to numerous health technology assessments of infectious diseases. Assessments that aim to measure the benefits of these broad categories must necessarily adopt a societal perspective that employs such a framework.

ANALYSES FROM THE SOCIETAL PERSPECTIVE: IMPLEMENTATION

Proper analyses that apply a societal perspective and consider all relevant benefits will help to remedy undervaluation of PCVs by closing the gap between vaccines' full benefits and those most frequently considered by policymakers. Capturing and accurately measuring this full spectrum of health and socioeconomic benefits is a crucial but complicated undertaking. Successful implementation requires a structured process for systematically evaluating a complex set of relevant information. Fortunately, evaluation methods and decision-making tools exist that enable us to perform these societal-perspective analyses.

CEAs represent one widely used evaluation method in public health. These analyses compare alternative health intervention programs on the basis of budget dollars spent per unit of outcome, where the outcome measure is a single, common effect such as frequency of medical visits or QALYs. In the case of pediatric PD, for instance, a CEA might model and compare the impacts of a hypothetical new PCV10 or PCV13 vaccination program on incidence rates. Because both programs have the same outcome of interest, this approach offers a straightforward way to compare the relative monetary costs of each and their differential success in achieving the desired outcome. CEAs are thus especially useful in situations where a decision-maker, operating within a set budget, faces a limited range of alternative options with comparable outcome goals.

Traditionally, CEAs have adopted a health sector perspective, but they also lend themselves to a societal perspective (CEA-S). In addition to the direct financial costs of implementing a given health intervention, CEA-S would incorporate the monetized value of each benefit category in our societal taxonomy (Section IV) into the total estimated program costs (monetary gains from these benefits would count negatively against the overall cost of the program). This results in an aggregated, comprehensive societal cost per unit of the desired outcome, facilitating comparisons across health interventions.

One potential drawback to the CEA-S approach is that certain outcome indicators may be insufficient to properly capture a health intervention's total benefit. The value of lowering PD incidence rates, for instance, may depend on the average severity of a PD episode, which is, in part, a function of the availability of treatment options and access to medical care. Another aspect of this approach that draws much debate is its underlying assumption that all health outcome units are comparable, sometimes termed the "QALY is a QALY is a QALY" assumption[135,136] (QALYs are a frequent unit of measure for CEAs). CEAs do not allow for the measured broad benefits of a program to vary across units of the given health outcome measure (which may be a QALY or any other specified outcome variable). This means, for example, that permanently increasing the quality of life of a two-year-old by one unit produces the same societal benefits as permanently increasing the quality of life of a 65-year-old by the same amount. Critics of this CEA assumption may argue that scenarios exist for which this structure inaccurately models reality: saving the life of a two-year-old could be considered more beneficial to society than doing so for a 65-year-old since a younger individual has more to offer society in terms of productive work years, fertility, and future consumption. (Admittedly, this line of logic does not hold true for all health improvements, such as the utilitarian value of comfort.) Proponents of the "QALY is a QALY is a QALY" aspect of CEAs, however, may contend that it is important from a social equity perspective. If the young are assigned greater productive potential than the elderly (or other measure of greater 'worth' to society), this disparity could justify deprioritizing health interventions for older adults. Uniformity serves as a form of insurance against policymakers using

relative potential benefits as a basis to prioritize some groups or individuals over others.

One alternative method, cost-benefit analysis (CBA), does not assume this "QALY is a QALY is a QALY" foundation. Because its more flexible structure allows the broad benefits of an intervention to vary across QALYs and other health outcome units,[11] a CBA is, in this respect, empirically superior to a CEA-S. Nevertheless, the nature of this approach invites controversy and is not universally accepted. To vary the assignment of benefits, CBAs in essence assign more value to some lives than to others, which is less palatable to many and is, therefore, politically risky for policymakers. Efforts to assign monetary value to human life and suffering are inherently controversial and may be open to moralist criticism.[137] One important response to this criticism is that policy decisions involving such valuations must unavoidably be made on a regular basis, and standardized, economic approaches to these valuations help to ensure policy decisions are made more consistent and transparent.[137]

CBAs also explicitly calculate and assign a monetary value to all potential benefits and outcomes of interest, which presents an additional set of limitations and challenges. A common approach is to set valuations using prices that are revealed in the markets, or, in the absence of a relevant functioning market, to model society's hypothetical willingness to pay for different outcomes. For many potential benefits, quantifying the associated monetary benefits can be empirically difficult to calculate or model with certainty.

Deliberative discussion by an expert panel is one process for assessing CEA and CBA results and making recommendations to policymakers. Expert panels may help ensure a broad range of expertise and may be especially helpful when conclusive data or scientific certainty are lacking, or when policymakers need assistance interpreting and understanding the evidence.[138] A common critique of expert panels, however, is that they are subject to a lack (or perceived lack) of objective independence, transparency, and consistency.[139]

Multi-criteria decision analyses (MCDAs) have arisen as an alternative to expert panels, offering an explicit, transparent structure for decision-making that increases the credibility and accountability of policymakers' public health and priority-setting decisions. In general, this process involves defining an intervention's objectives, identifying alternative programs and relevant stakeholders, selecting evaluation criteria, assigning each criterion a scoring scale and relative weight, and measuring the performance of each alternative health program to produce an overall estimate of its value. CEAs and CBAs can be incorporated as one of these criteria and are, in this sense, complementary to an MCDA framework. Because no limitations are placed on the number or types of criteria that could theoretically be included, MCDA is a helpful framework for integrating different concerns about policy objectives, market conditions, innovations, program safety, and other considerations beyond the scope of CEAs and CBAs.[140]

One criticism of MCDAs focuses on the underlying subjectivity of criteria selection, weight assignments, and scaling design. MCDAs do not mandate uniformity or standardization of these inputs, which gives rise to potential internal inconsistencies in final estimates across MCDAs from different ministries (which often have competing budget applications and interests). Selecting nonoverlapping criteria is also critical for an MCDA's accuracy, yet identifying a completely independent set of criteria with no overlaps is challenging to satisfy and has not yet been realized. Finally, the relationship among criteria is assumed to be additive in an MCDA as scores for each criterion are added together to generate the final value estimate, whereas many economists argue that criteria's true relationship is in fact multiplicative.[141]

A third framework, referred to as the social welfare function, proposes a more rigorous, multiplicative way to aggregate criterion data that is more theoretically meaningful and interpretable. It offers superior axiomatic foundations and is possibly the best approach among existing methods to reconcile MCDA criteria into a single result. One trade-off of social welfare functions, however, is that these frameworks are much more difficult to operationalize and less easy for policymakers to understand than MCDAs.

CONCLUSIONS

Policymakers' and health technology assessors' use of a narrow health sector perspective in economic evaluations reinforces the undervaluation of vaccines' worth. Undervaluation may drive many nonrecommendation and nonreimbursement decisions for PCVs or result in inefficient resource allocation strategies that underinvest in PCVs' development and uptake. Given the disproportionate share of childhood deaths worldwide that pneumonia and other manifestations of pneumococcus cause, addressing the concerningly low global uptake of PCVs is critical for protecting the health of younger generations. Undervaluing and underinvesting in PCVs leaves money on the table and permits unnecessary, preventable disease with potentially severe and burdensome long-term health consequences.

Improving this issue requires expanding conventional, narrow valuation methods to implement a societal perspective that instead captures the broad, comprehensive set of PCVs' full benefits. Although measuring all components of the societal taxonomy may not be outright or immediately feasible in some cases, it is important to begin to move the conversation forward by including those benefit categories for which data is available when vaccines are assessed against other health-related interventions. Quantifying a wide-ranging, inclusive set of socioeconomic benefits whenever possible, in addition to health benefits, may expose a higher rate of return to vaccination than previously estimated. If these findings are decisive, they may reverse existing nonrecommendation decisions and spur efforts to mitigate other obstacles to PCV uptake.

Implementing this updated societal framework will require proper evidence, data, and methodologies. Various methodologies exist that offer a structured, systematic process for properly investigating this more comprehensive perspective on PCVs' value. The most suitable method depends in part on the context of each valuation, influenced by factors such as the resources available to dedicate to valuation efforts and whether particular criteria of interest are directly comparable or can be readily monetized. The most critical aspect of whichever method is selected will be that it is compatible with a societal framework and that it offers a structured approach to improve the quality and transparency of decision-making.

This new framework provides some apparent directions for future research. First is to empirically quantify in monetary terms as many of these benefits as are feasible. Once quantified, these benefits should be included in analyses of the value of pediatric pneumococcal vaccination.

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