Conference report

Estimating the full public health value of vaccination

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ABSTRACT

There is an enhanced focus on considering the full public health value (FPHV) of vaccination when setting priorities, making regulatory decisions and establishing implementation policy for public health activities. Historically, a therapeutic paradigm has been applied to the evaluation of prophylactic vaccines and focuses on an individual benefit-risk assessment in prospective and individually-randomized phase III trials to assess safety and efficacy against etiologically-confirmed clinical outcomes. By contrast, a public health paradigm considers the population impact and encompasses measures of community benefits against a range of outcomes. For example, measurement of the FPHV of vaccination may incorporate health inequity, social and political disruption, disruption of household integrity, school absenteeism and work loss, health care utilization, long-term/on-going disability, the development of antibiotic resistance, and a range of non-etiologically and etiologically defined clinical outcomes.

Following an initial conference at the Fondation Mérieux in mid-2015, a second conference (December 2016) was held to further describe the efficacy of using the FPHV of vaccination on a variety of prophylactic vaccines. The wider scope of vaccine benefits, improvement in risk assessment, and the need for partnership and coalition building across interventions has also been discussed during the 2014 and 2016 Global Vaccine and Immunization Research Forums and the 2016 Geneva Health Forum, as well as in numerous publications including a special issue of Health Affairs in February 2016.

The December 2016 expert panel concluded that while progress has been made, additional efforts will be necessary to have a more fully formulated assessment of the FPHV of vaccines included into the evidence-base for the value proposition and analysis of unmet medical need to prioritize vaccine development, vaccine licensure, implementation policies and financing decisions. The desired outcomes of these efforts to establish an alternative framework for vaccine evaluation are a more robust vaccine pipeline, improved appreciation of vaccine value and hence of its relative affordability, and greater public access and acceptance of vaccines.

1. Introduction

Historically, vaccines have been assessed for inclusion into public immunization programs based on safety and efficacy against severe etiologically-confirmed disease or against serious sequelae [1]. In randomized controlled trials, many factors, including geography, inclusion and exclusion criteria, age, diagnostic methods, and epidemiological issues, may affect vaccine efficacy. One example of geographic disparity is a group of randomized controlled trials of rotavirus vaccine, where high efficacy against severe rotavirus-confirmed gastroenteritis was seen in the developed world [2,3] with lower efficacy against the same outcome among infants in developing countries [4–6]. Appropriately quantifying the value of vaccines was critical to the WHO decision on the use

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of rotavirus vaccine, and continues to be critical in promoting and sustaining vaccine programs, particularly in resource poor-settings where a strong argument must be made to justify prioritizing immunization programs among many other health priorities competing for scarce resources.

In June 2015, a group of experts discussed criteria to be considered to assess the full public health value (FPHV) of vaccination in addition to efficacy measured in individually randomized clinical trials [7]. It was clear for this group of experts that considering additional outcome measures (e.g., vaccine preventable disease incidence), and designs (e.g., vaccine probe studies and community randomized trials) were valuable, as was the consideration of indirect or community protection and economic and other non-health benefits of vaccines. They also considered that in addition to benefit-risk assessments based on the information collected through the traditional clinical development process, a substantial body of additional information is necessary to more fully inform policy and other required decision-making at the global, national and sub-national levels. Therefore, to assess the wider scope of vaccine benefits, there needs to be an enhanced expectation that studies – including licensing studies – incorporate measurement of these benefits; that greater connections are developed between partners who work on distinct but complementary aspects of vaccine valuation including health, economics, education, productivity, and economic gains; and that data and methods across these domains are shared widely across the vaccine community.

With such an enhanced paradigm and with a focus on low and middle-income countries (LMIC), alternative regulatory pathways could be considered that focus on conditional licensure of vaccines based on outcome results relevant to regulatory and public health decision-makers. This process could increase the development and introduction of vaccines in these countries. These issues will be particularly relevant to inform decision-making for vaccines on the near-term horizon such as those against malaria and dengue.

The components of this new paradigm having been defined [7], the Fondation Mérieux organized a second conference from 5–7 December 2016 ("Les Pensières" Conference Centre, Annecy-France), to evaluate the feasibility of an encompassing assessment of the FPHV of vaccines. The main objectives of the meeting were to advance discussions on the definition, evidence and communication of the FPHV of vaccines by:

- challenging and refining the definition of what constitutes the FPHV of vaccination;
- reviewing examples of FPHV with existing vaccines used in outbreak settings and others used in endemic disease settings;
- proposing designs, measures, and outcomes for assessing the FPHV of vaccination in phase III trials and phase IV assessments and integrated/hybrid phase III/IV strategies;
- applying these concepts to specific vaccines particularly those targeting malaria, dengue, Group B Streptococcus (GBS), Respiratory syncytial virus (RSV), *Neisseria meningitidis* B (NMB), and cholera, and;
- strategizing on how to communicate the FPHV of vaccination to regulatory and program policy makers.

In this paper, we argue for as robust a measure as possible of the FPHV of vaccines to allow authorities to make accurate decisions on whether it will be efficient to invest in a particular vaccine for use in a particular setting and for a particular population, in the context of other public health interventions and programs remaining constant. As an example, the adoption of dengue vaccine should be considered in the context of an integrated management strategy while cholera vaccination should be considered in the context of clean water, sanitation, and hygiene.

2. Defining and assessing the FPHV of vaccines

Vaccine efficacy (VE) (Table 1), usually measured for etiologically-confirmed clinical outcomes, is often given the most weight among vaccine outcome measures considered in regulatory and policy recommendations. However, VE is not a static, robust, universal 'true' value as is commonly understood. Rather, it belongs within a list of measures that are useful for informing policy decisions. Indeed, VE can only be interpreted in the context of the population studied and the chosen trial design and can change based on factors such as microbial flora (enteric vaccines), force of infection, serotype distribution of the pathogen, pre-existing immunity, and the local epidemiological situation. Furthermore, VE by itself only indicates if the vaccine works against the target outcome, not whether it represents a good investment for a country.

Currently, most of the economic evaluation of vaccines focuses on a narrow set of vaccination-mediated health benefits [8], measured in quality adjusted life years (QALYs) (Table 1). One of the strengths of this focused view is that it yields a natural decision criterion, the incremental cost effectiveness ratio (ICER), that a policymaker can compare across competing programs. ICER requires comparison with a benchmark value or "threshold". Demand side estimates of this threshold are generally based on how much individuals are willing to pay or give up to improve their health. However, demand side estimates cannot tell us about opportunity cost imposed by an intervention [9,10]. By contrast, supply side effects – i.e., what improvement in health is possible given existing resources – can be obtained from estimates of the health effects of changes in health expenditure [11,12] and estimates are available for LMICs [13]. Supply side estimates are useful for decision-makers, donors and for prioritizing between a set of cost-effective interventions.

A broader perspective includes non-health benefits of vaccines such as productivity, risk reduction, equity/fairness, and fiscal impacts. A Social Welfare Function (SWF) and Social Rates of Return (SRR) framework could replace the QALYs and ICERs framework. The SWF is the most flexible framework for representing social preferences regarding health. However, since QALYs have important informational content, they remain an important part of SWF/SRR analysis.

To assess the broader economic impact of vaccination (BEIV), the WHO established a conceptual framework of the pathways between vaccines and their proposed benefits [14]. Applying the BEIV framework in practice showed that any broadening of the methodology for economic evaluation must also involve evaluations of non-vaccine interventions, and hence may not always benefit vaccines given a fixed health-care budget [15]. Furthermore, the scope of evaluation should be based on the budget holder and its priorities [15]. Nevertheless, relative to other public health interventions, vaccines have had a large impact on global public health with a relatively low cost. This outcome has been achieved both through the direct protection of vaccinated individuals and indirect protection of unvaccinated persons through reduction in transmission. Furthermore, for some infections – such as those due to measles, rotavirus, pertussis, meningococci, pneumococci, and *Haemophilus influenzae* type b (Hib) – few other effective prevention measures exist. For other infections, prevention measures have proven globally insufficient (e.g., dengue), or insufficient in specific contexts (e.g., malaria and cholera). This is evidenced, for example, by high Hib meningitis rates in Europe and the US in the pre-vaccine era, and the recent resurgence of measles and pertussis cases in the developed world in the context of insufficient vaccination coverage and possibly inadequately efficacious vaccine (see Table 1).

Table 1
Summary of measures used to assess vaccine benefits.

	Strengths (what it measures)	Weakness (what it does not measure)
Vaccine effectiveness (VE)	• The percentage of an outcome reduced by vaccine • Can be measured for direct, indirect, total, or overall protection • For non-etiologically confirmed outcomes provides a means to infer outcome specificity • Can be used to calculate VPDI when multiplied by background disease incidence • Can be of potential value to initiate policy discussions	• Does not measure the incidence rate reduction of outcomes achievable by vaccine • Does not incorporate quantification of underlying disease burden in the absence of vaccine • For non-etiologically confirmed outcomes, values will vary substantially depending on the proportion of the outcome due to etiologies not prevented by vaccine • Does not measure population impact and its measurement may reinforce false and strong perceptions of the need for high effectiveness before implementation
Vaccine-preventable disease incidence (VPDI)	• Also known as the vaccine attributable rate reduction or the incidence rate reduction • Measures the reduction in disease incidence due to vaccine use • Can be measured for direct, indirect, total, or overall protection • For non-etiologically confirmed outcomes provides a measure of outcome sensitivity • For non-etiologically confirmed outcomes, values don't depend on the incidence of outcomes due to etiologies not prevented by vaccine • Incorporates and depends on the underlying disease burden in the absence of vaccine • Can be estimated from any robust data source and can be calculated for any vaccine relevant outcome • Can assist health systems planning for outbreak preparedness and policy decisions by estimating impact of immunization program in reducing disease burden over the long-term	• Requires incidence data, which is not available from case-control studies • Should be based on complete ascertainment of incidence • Fully quantifying the preventable disease incidence of all relevant outcomes requires community-based and not just hospital-based surveillance data, from various sources, to account for outpatient illness and ill persons who do not present for care
Quality adjusted life years	• A year of life adjusted for its quality or value, with perfect health assigned a value of 1.0 • Incorporates the quality of life, in addition to its duration, when measuring vaccine impact • Allows broader advocacy for the value of vaccination over the entire life course of an individual going beyond just the health sector (quality of life arguments)	• Relies on value judgments • Varies by society, and quality adjustment values not ascertained for most societies • Cannot be measured directly for children below a certain age, who can't assess the value of different health states • Perfect health, as the reference standard, difficult to define • Values may change over time in a society or as individuals age • May overweigh value of interventions for younger, healthier people and thus reduce equity, since by definition it incorporates length of life, and healthier people may have a greater change in the value of health states from baseline • Quality of life is assigned to only an individual experiencing illness, which ignores broader impacts on households, communities, and society as a whole • Quality adjustment factors infrequently updated, so do not account for improvements over time in mitigating and overcoming health problems, improvements in health care delivery and economic development more broadly
Incremental cost effectiveness ratio	• The difference in cost between two interventions divided by their difference in effect; difference in effect often measured using quality adjusted life years • Can be used as an absolute or relative decision rule for determining whether or not to implement a vaccination program • Provides a relative measure for comparison of different interventions • Can assist in priority setting under urgent scenarios of outbreaks vs routine programs	• Requires accurate assessment of costs and burden reduction • May underweight value of preventing potentially epidemic diseases (such as Ebola) until crises have occurred • May undervalue political and equity issues, as these are difficult to cost • May result in widening inequities and disadvantaging some sub-population if cost-effectiveness is higher in wealthier groups (e.g., those with higher costs of medical services)
Social Welfare Function	• Places the value of vaccination in the broader sphere of better policies to improve social welfare, e.g. education, poverty reduction, gender equality, empowerment of women, etc.	• Difficult to measure and disaggregate the various functions, which may vary by time and place
Social Rates of Return	• Places vaccination in the broader context of greater social impact on populations, including better health, more robust school attendance, equality between males and females, better economic outcomes, etc. • Social justice and equity arguments may have greater political weight than arguments limited to health benefits	• Difficult to measure and disaggregate the various components, which may vary by time and place • Can create unintended competition and turf battles between various sectors (e.g. health, education, welfare, etc.)
Multi-criteria decision-making processes	• Allows for a more robust, inclusive and holistic decision-making process and framework, which takes into account the linkages between various dimensions of immunization programs and beyond	• Difficulty to define the nature and strength of the linkages, which criteria are important and, then, assigning appropriate weighting to various criteria • Outcomes that can be measured may not be the most important outcomes for decision-making
Extended cost-effective analysis	• Allows more rational policy decisions and stronger advocacy especially in situations in many developing countries of limited resources and competing priorities • Allows evidence-based articulation of effectiveness and benefits beyond health outcomes	• Difficulty in obtaining appropriate data and subjectivity in defining effectiveness in a broader sense • Inherent limitations in the many analytical and modelling tools used and the many underlying assumptions of such analyses

There are a variety of methods to make sure vaccines are appropriately valued. Replacing the present common practice of relying on cost-effectiveness with multi-criteria decision-making processes where the full value of vaccines is captured is an example that has been used by the SMART vaccines initiative of the Institute of Medicine [16]. Extended cost-effective analysis (ECEA) is another tool that enables quantifying the equity and financial risk protection benefits of vaccination, supplementing the quantification of health benefits provided by traditional cost-effectiveness analysis [17]. Applying ECEA to evaluate vaccine policy in LMIC provided evidence that ECEA captures important health and non-health implications of scaling up vaccine programs [18]. It incorporates financial risk protection and distributional consequences into the systematic economic evaluation of vaccine policy. It enables selection of vaccine packages based on quantitative inclusion of information of equity and of how much financial risk protection is being bought, in addition to how much health is being achieved for a given expenditure on specific vaccines, which may be useful for progressive prioritization toward universal health coverage and the Sustainable Development Goals [17].

More accurate measurement of vaccination-mediated health benefits should include measures beyond efficacy and safety. Such measures include vaccine preventable disease incidence (VPDI) (also known as the vaccine attributable risk or the incidence rate reduction) and number needed to vaccinate (NNV) as well as assessment of these measures against non-etiologically confirmed clinical outcomes. Use of non-etiologically confirmed outcomes is useful in all situations [21] but particularly in situations where etiologic confirmation is difficult, such as with non-bacteremic Hib and pneumococcal pneumonia [5,6,19–23]. Other parameters that should be considered beyond efficacy and safety include, case fatality ratio, transmissibility, severity, sequelae, duration of immunity, age distribution, outbreak potential and predictability of disease occurrence, and disruption of health systems.

The latter point was illustrated in the three West African countries severely affected by the Ebola epidemic in 2013–2015. In that case, loss of health care workers to disease and reassignment of health staff towards Ebola response likely led to a decrease in other health services and increase in mortality. A similar situation likely exists for dengue and cholera during large outbreaks or epidemics. For all outbreak driven diseases, given the unpredictability of disease occurrence, it is usually impossible to have adequate resources (staff, facilities, medicines, supplies) available to respond in an efficient way to maximize health through reactive interventions. Vaccines also can be used to mitigate the effects of protracted armed conflicts, where much of the associated morbidity and mortality results from disruption of public health services. This point has long been acknowledged by the WHO-SAGE, and an economic framework for decision making was developed and endorsed by SAGE in 2012 [14]. This was followed by a series of meetings to agree on a package of documents and solutions to guide vaccination in humanitarian emergencies.

Vaccination is also an essential element for promoting (i) health equity, (ii) economic equity (through reducing medical and non-medical costs associated with cases of vaccine-preventable diseases), (iii) social equity (e.g. access to the health care system) and (iv) vertical equity intervention (e.g. vaccines for diseases of poverty). In addition, childhood vaccination is an entry point to the health system for the poor [24], and as such can have effects on other health outcomes. For example, studies on measles case fatality ratios showed drastic differences according to socio-economic group [25,26] and a global literature review revealed how the risks of meningitis sequelae varied substantially according to income [27]. Out-of-pocket costs are the largest source of health expenditures in many LMICs and vaccine preventable diseases can lead to catastrophic health expenditures for poor households

[28,29]. By averting cases of disease, vaccination averts the need for these health expenditures and when delivered equitably can help break cycles of poverty and ill health, which can then lead to improvements in health and economic security.

3. Case studies of the need for full public health value of vaccination analysis

3.1. Vaccines being adopted

3.1.1. Rotavirus

Diarrheal disease caused by rotavirus is a public health problem in young children. The two available vaccines have shown significant impact in reducing all-cause acute gastroenteritis and rotavirus-related hospitalization [30] but also indirect benefits to older children and young adults in the USA [2,3]. These vaccines conferred lower efficacy in the developing world [4–6]. While there were key differences in study design and methodology [31], the lower efficacy in developing countries was likely due to factors such as interference from other co-infecting pathogens, malnutrition, and gut enteropathy.

From a regulatory perspective, this lower efficacy might suggest rotavirus vaccine is a poorer investment in developing countries. However, from a FPHV perspective, where additional criteria should be taken into account when deciding on vaccine implementation of rotavirus vaccine, a different picture emerges. For example, in spite of lower efficacy, the absolute public health impact of these vaccines is anticipated to be higher than in high income settings because of the greater burden of rotavirus disease [20,22,32,33]. This impact is likely to be even greater outside of a clinical trial setting, where access to health care services may be limited [20,22,34]. Enteric infection during early childhood could also lead to early stunting, obesity, metabolic and cardiovascular diseases and cognitive impairment [35]. Assessment of the FPHV of rotavirus vaccination should take into consideration the cost of this triple burden of diarrhoea at the individual and population level and the longer-term benefits on child health of disease prevention. Further, rotavirus vaccines illustrate the importance of health equity, as children in rural areas with poor access to treatment have high incidence of preventable severe gastroenteritis [20].

3.1.2. Maternal immunization with influenza vaccine

Globally, significant morbidity and mortality from vaccine-preventable diseases occurs in pregnant women and in young infants. Immunization of pregnant women against selected infectious diseases is therefore a potential strategy to reduce several diseases in mothers and their new-born infants and may also prevent infection-related foetal outcomes [36–41]. For influenza, uncertainties and logistical challenges have led to limited financing for and demand by low-income countries to implement maternal influenza vaccine [42]. A lack of assessment of the FPHV of maternal influenza immunization also adversely effects decision-making. Areas for additional research include the degree to which influenza precipitates other illness, the impact of influenza illness on prenatal care, and broader issues such as the impact of the lack of a seasonal influenza vaccine strategy in many countries on their ability to access vaccine during a pandemic.

3.1.3. Dengue

Countries have had limited success using traditional strategies to control the geographical spread and increasing burden of dengue. Several vaccine candidates are in the pipeline. The recent first licensure of CYD-TDV (Dengvaxia®, Sanofi-Pasteur, Lyon France) was followed by a WHO recommendation to vaccinate in endemic populations with seroprevalence not lower than 50%, as part of an

integrated management strategy for the control of dengue (IMS-Dengue) [45,47]. Traditional approaches to estimating the value of CYD-TDV have shown efficacy against severe dengue (93%), hospitalized dengue (80%) and laboratory-confirmed clinical dengue (65%), with variable efficacy against the four dengue serotypes (47–83%) and by previous exposure (52–81%) [46]. CYD-TDV is now approved in 17 countries and public sector programs have been initiated.

Calculation of VPDI for the dengue vaccine phase III trial helps illustrate the vaccine's FPHV by illustrating the large preventable burden of disease (Fig. 1). When combined with calculation of NNV, these data demonstrated that dengue vaccine had a public health impact that compared favourably with other vaccines already in use in the trial regions [48]. Moreover, dengue vaccine showed a high VPDI against less severe clinical disease, which is the disease outcome that may have the largest impact on health service utilization [48].

3.2. Vaccines under evaluation

3.2.1. Malaria

RTS,S/AS01, the only malaria vaccine to receive positive regulatory approval so far, provides protection for a few months but this wanes rapidly during subsequent years [43]. Despite these deficiencies, there may still be an important role for imperfect malaria vaccines in malaria control if these are used strategically. Seasonal vaccination might be an appropriate use for a vaccine which has a high level of initial efficacy but which provides only short lived protection. Moreover, a vaccine of limited efficacy could be useful as one component of a mass control campaign aimed at elimination. A malaria vaccine could also have indirect effects including reduction in invasive bacterial infections, especially non-typhoidal salmonella infection; improvement in nutrition; improvement in school attendance and performance; and improvement in productivity. Using mathematical modelling, routine use of the RTS,S/AS01 vaccine in African settings turned out to be highly cost-effective with significant public health impact [44]. From a FPHV point of view, local and national economic benefits as well as gains in productivity are among factors that should be taken into consideration when evaluating malaria vaccines.

3.3. Vaccines in pipeline

3.3.1. Group B Streptococcus

Invasive Group B Streptococcus (GBS) is a leading cause of neonatal sepsis, morbidity and mortality in both high and low income settings [49,50] even when intrapartum antibiotic prophylaxis during labour of colonized women has been successful in reducing early-onset invasive disease in newborns. Recent advances in the prevention of invasive GBS disease have renewed interest in polyvalent polysaccharide protein conjugate vaccines [51]. The licensure of a GBS vaccine for pregnant women aimed at protection against invasive GBS disease of their newborns will, however, require studies with large sample sizes for an invasive disease endpoint. An alternate licensure pathway, as was the case for meningococcal vaccine, could be premised on establishing a sero-correlate of protection against invasive disease and using this information to license the vaccine based on immunogenicity and safety. This could be followed by post-licensure effectiveness studies against invasive GBS disease, GBS carriage, and non-etiologically confirmed clinical outcomes such as pneumonia or sepsis of unknown etiology, and low birth weight or preterm birth.

3.3.2. Respiratory syncytial virus

The recognized importance of prevention of acute lower respiratory illness (ALRI) caused by respiratory syncytial virus (RSV)

has led to a robust research and development pipeline with more than 60 vaccines or prophylactic monoclonal antibodies in development and more than 15 being evaluated in clinical trials [52]. Moreover, bacterial-RSV interactions are only beginning to be understood, and suggest that prevention of RSV ALRI could potentially have direct effects on invasive bacterial pulmonary disease [53,54] or indirect effects through alterations in the respiratory microbiome [55,56]. A link between early RSV disease and long-term lung health such as recurrent wheezing [57,58] or childhood asthma [59] has also been reported. A proper assessment of the full impact of RSV vaccines should therefore include indirect outcomes (e.g. all-cause pneumonia, pathogen-pathogen interactions, and pathogen replacement).

4. Discussion

Vaccines are an important contributor to the increase in life expectancy from less than 50 years in 1900 to more than 80 years now. During the last 15 years, there has been substantial advancement in vaccine innovation, a massive increase in the number of countries introducing several new vaccines into National Immunization Programs, and increased coverage with others, e.g., measles. Progress in introduction of three key vaccines supported by Gavi, the Vaccine Alliance (i.e., Hib in the form of pentavalent vaccines, rotavirus vaccine, and pneumococcal conjugate vaccine), has led to protection against some of the major vaccine-preventable causes of child mortality. In spite of their social value, the economic value of vaccines has been underestimated using current traditional economic evaluation methods and the standard evaluation criteria for vaccine licensure. As a consequence, future vaccines are likely to face substantial constraints on policy decision making with the *status quo* approach. This is particularly likely to occur for vaccines that have VE less than currently adopted vaccines, a situation that may occur despite lower efficacy vaccines having broader public health impact as measured by VPDI and NNV.

As illustrated by case studies, application of FPHV of vaccination would change decision-making (e.g., vaccine development timelines, vaccine introduction decisions). Modern cost-benefit vaccine studies have moved beyond safety and efficacy to additional impact measures and strategies which assess reduction of disease burden and reduced inequities among populations, but more efforts are still needed to include wider direct and indirect parameters. Other concepts such as outbreak control, family integrity, local and national economic issues, and different types of inequities should be considered to measure the FPHV of vaccines accurately. However, we face an impasse, with a wall between the traditional approach and an approach that considers a vaccine's FPHV (Fig. 2). To move from the former to the latter, the following questions must be answered: (1) what evaluations should be considered; (2) when should they be done, pre- or post-licensure; and (3) who will see this as their responsibility?

Economic evaluation of vaccination is a key tool to inform effective spending on vaccines. However, traditional methods are too narrow and not always easy to communicate to ministries of finance. To support ministers of health and immunization program directors, Anderson and colleagues identified ten attributes that could help them to prepare better and to provide more convincing arguments before they start negotiation with their ministries of finance [60].

The broader economic evaluation of vaccines include: use of clinically defined outcomes in addition to etiologically-defined outcomes; wider societal benefits (e.g., improved educational achievement, economic growth and political stability); reduced health disparities; medical innovation; reduced pressure on hospital beds; and synergies in economic benefits with non-vaccine
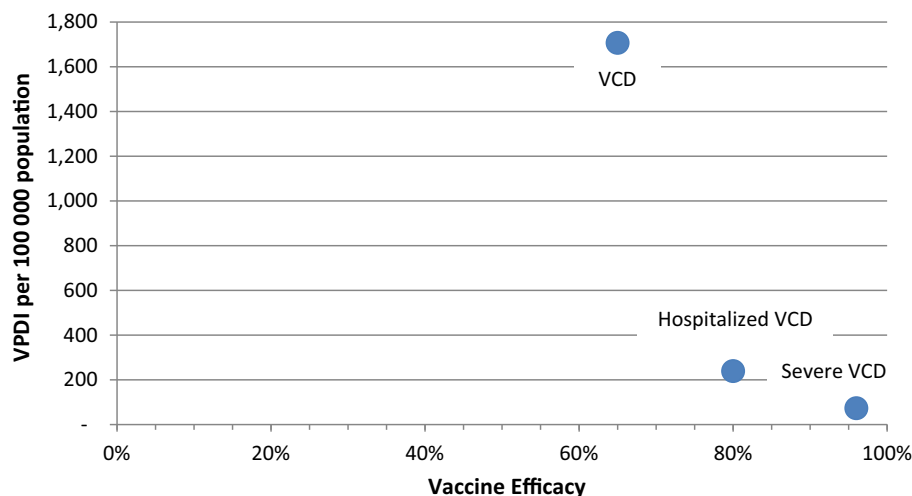
Fig. 1. Comparison of dengue vaccine efficacy and vaccine preventable disease incidence (VPDI*) in Latin America. Moderately efficacious interventions can have high public health value when the background rate of an outcome is high. For example, while the prevention of clinically severe virologically confirmed dengue (severe VCD) and the reduction in the demand for health services such as hospitalization (hospitalized VCD) are public health priorities, the value of dengue vaccination is also reflected in a much higher reduction in less severe clinical disease outcomes, outcomes that result in direct health expenses and loss of productivity at school and work [48]. *High VPDI indicates a greater reduction in disease burden through use of vaccine.
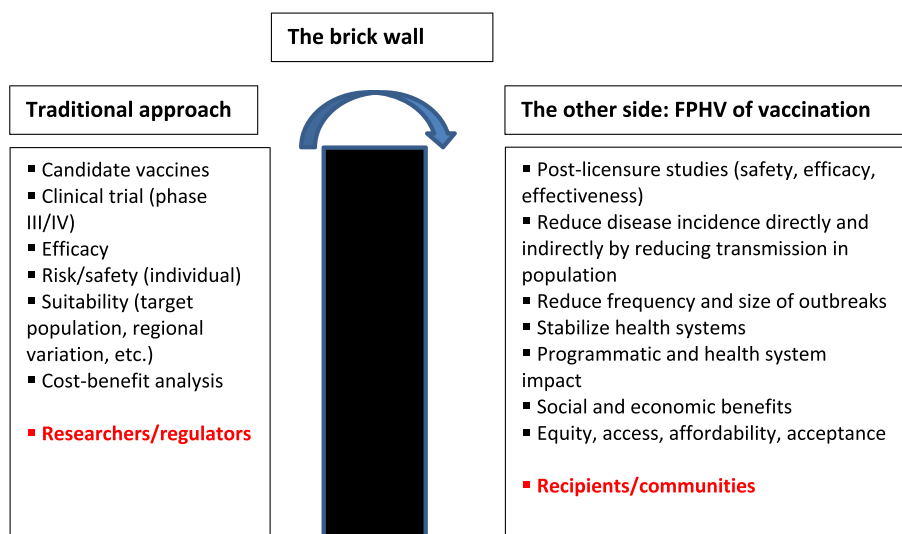
Fig. 2. The brick wall: Moving from vaccines to vaccination.

interventions. Also, the fiscal implications of vaccination programs are not always made explicit. Many of these topics could be incorporated into licensing trials to provide quantitative estimates of these measures.

The scope of a broader economic evaluation should also consider the budget from which vaccines are funded, and the decision-maker's stated objectives for such budgets. As an example, gross domestic product (GDP)-based thresholds show lack of country specificity, which can lead to lack of prioritization, as evidenced by one country electing not to fund vaccination programs demonstrated to be 'very cost effective'. In this and other similar cases, it is likely that other factors beyond cost effectiveness, including the overall budgetary impact, dictate decision-making in LMICs [10]. Information on cost–effectiveness should be used alongside other considerations – e.g. budget availability [10], budget impact and feasibility considerations – rather than in isolation

based on a single threshold value. Additionally, economic and decision-making analysis should go beyond dependence on QALYs as a single outcome measure and incorporate the concepts of SWF/SRR. Once a more context specific decision-making process is developed, this should be supported by legislation; have stakeholder buy-in, for example the involvement of civil society organizations and patient groups; and be transparent, consistent and fair [61]. Such a country-specific process may emphasize to a greater extent the FPHV of vaccines, but final expansion of immunization programs may still be restricted by budget limitations, especially in LMICs.

Strategies for scaling the brick wall (Fig. 2) will require (1) the development of a comprehensive framework for FPHV of vaccines as part of end-to-end vaccine development programs; (2) a research question gap analysis and prioritization, (3) an inventory of FPHV evidence, by vaccine, (4) set-up of an annual score card for

Table 2
Points to be considered by policy makers to achieve the full public health benefits of vaccination.

Broader, non-health impacts and externalities and use of methods to capture the full benefits of vaccination (e.g. VPDI, NNV, SRR, BEIV, ECEA, cost/QALY)
More balanced view of cost-effectiveness data and balancing value versus access and profit versus public good
Accurate assessment of the disease burden reductions and other benefits of moderately effective vaccines; vaccines may have moderate effectiveness yet high public health value if they target diseases that are common, severe, or outbreak driven
Knowledge of previously unknown causal associations which can be broken by vaccination (e.g. viruses that predispose to bacterial disease, an association between measles and malnutrition, influenza and chronic disease exacerbation, etc.)
Value of post-licensure studies to gather evidence for example on real world effectiveness, indirect protection and herd immunity, number of protective doses needed and duration of immunity
Flexibility and local/sub-national contextual factors
The need for political commitment, good communication, and evidence-based decisions (e.g. technical aspects of vaccines, vaccine hesitancy and confidence)

VPDI: Vaccine Preventable Disease Incidence; NNV: Number Needed to Vaccinate, SRR: Social Rates of Return; BEIV: Broader Economic Impact of Vaccination; ECEA: Extended Cost-Effective Analysis; QALY: Quality Adjusted Life Years.

progress on completeness of evidence, (5) advocacy to apply the FPHV approach to novel product development, and (6) dialogues with manufacturers and policy makers. Additional information also will be required including (Table 2): when do policy makers assess vaccine benefits, which benefits count, and assuming the boundaries of the relevant benefits have been defined, what is the best metric for quantifying those benefits?

In conclusion, vaccines have wide-ranging benefits but these benefits are often poorly quantified and not typically captured in regulatory and implementation policy discussions. This was highlighted during the meeting with discussions on the FPHV of vaccines already adopted, i.e., rotavirus and maternal influenza immunization, vaccines being considered for licensure and implementation, i.e., malaria and dengue, and others in clinical development, i.e., GBS and RSV candidates. A change in mind set and further innovations are necessary when considering the FPHV of prophylactic vaccines in the evidence-based decision-making process of vaccine licensure and public health use. Vaccines should be seen not only or even primarily as a cost that increases public health budget needs, but as an investment with sustainable, long term, and large-scale impact. Accurately measuring the FPHV of vaccines will increase the likelihood of adopting this approach by increasing political will and allowing for more accurate prioritization of available resources.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

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Conflict of Interest

CBN is employee of Sanofi Pasteur. BDG performed this work as an employee of AMP and is currently employed by Pfizer. Other authors declare that they have no conflicts of interest to report.

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