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Current issues in the economics of vaccination against dengue

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ABSTRACT

Dengue is a major public health concern in tropical and subtropical areas of the world. The prospects for dengue prevention have recently improved with the results of efficacy trials of a tetravalent dengue vaccine. Although partially effective, once licensed, its introduction can be a public health priority in heavily affected countries because of the perceived public health importance of dengue. This review explores the most immediate economic considerations of introducing a new dengue vaccine and evaluates the published economic analyses of dengue vaccination. Findings indicate that the current economic evidence base is of limited utility to support country-level decisions on dengue vaccine introduction. There are a handful of published cost-effectiveness studies and no country-specific costing studies to project the full resource requirements of dengue vaccine introduction. Country-level analytical expertise in economic analyses, another gap identified, needs to be strengthened to facilitate evidence-based decision-making on dengue vaccine introduction in endemic countries.

Introduction

Dengue – a mosquito-born viral infection caused by four distinct dengue virus serotypes from the genus Flavivirus – is a major public health concern with explosive epidemic potential in tropical and subtropical areas of the world [1–6]. A recent study put the upper bound of population at risk of dengue infection at a preliminarily 3.97 billion [7], corresponding to 56% of the world’s population in 2012. Dengue had the largest increase in age-standardized incidence and prevalence rates (nearly 447%) among all common causes of infectious disease, including HIV and malaria, during the period from 1990 to 2013 [8]. An increase in years lived with disability due to dengue was observed during this period, highlighting its steadily growing non-fatal burden of disease [8].

Dengue outbreaks are notoriously difficult to predict and control, develop rapidly and frequently, and cause massive hospital overflows in endemic countries [2,4,5,9]. Another concerning trend is the rising incidence of severe dengue disease, which drives the increase in the hospitalization rates for dengue, particularly among children [2–6]. Unmet medical needs exist for dengue, there is no therapeutic drug or a rapid test to identify at-risk patients early on during the acute phase of the disease, posing a major challenge to clinicians in endemic areas [10–12]. Clinical management of cases, therefore, relies on intensive supportive care. This can keep case fatality rates low [13,14], but requires use of considerable health care resources, placing a major strain on the public health infrastructure, particularly during outbreaks [5,15,16]. A growing body of literature shows that dengue illness causes considerable social and economic disruption at the household level, requiring one or multiple visits to a health care provider and resulting in missed days of school and work, medical and non-medical expenditures, and foregone household productivity and income [17–19]. Despite their high cost, vector control programs are implemented in endemic countries, but have proved largely ineffective to control dengue transmission or epidemics [9,15,20–22]. Further expansion of dengue is expected because of favorable conditions provided by rapidly growing urban centers serving as epicenters for dengue outbreaks and increased worldwide travel and trade [23].

The prospects for dengue prevention have recently improved with the results of three efficacy trials of a recombinant live chimeric tetravalent vaccine (CYD-TDV developed by Sanofi-Pasteur) involving more than 35,000 children aged 2–16 years in Asian Pacific and Latin American countries [24–26]. Pooled vaccine efficacy against dengue of any severity and any serotype in participants who were aged 9 years or older was 65.6% (95% CI, 60.7–69.9), as compared with 44.6% (95% CI, 31.6–55.0) in children aged 9 years or under [27].
Vaccine efficacies were lower among children aged 9 years or older who were seronegative at baseline than among children who were seropositive in the same age group [27]. The candidate vaccine showed a good safety profile during the acute vaccination period and up to 1 year following the completion of the three-dose series [24,25]. The results of the long-term follow-up studies in years 3 and 4 showed that while the risk of hospitalization for dengue was consistently lower among children aged 9–16 years who received the vaccine, an elevated risk of hospitalization was observed in children younger than 9 years of age, particularly among those 2–5 years of age [27]. Despite being partially effective and despite these safety concerns, if licensed, the introduction of the candidate vaccine can be attractive and even become a public health priority in heavily affected countries because of the perceived public health importance of dengue at the household and national levels [28–32].

Vaccination is considered one of the most cost-effective prevention strategies to lower the burden of infectious diseases, particularly in children, in both developed and developing countries [33–35]. Wide variation exists in vaccine coverage levels across countries, however tremendous progress has been made in introducing new vaccines and increasing coverage levels since the launch of the Expanded Programme of Immunization of the World Health Organization (WHO) in 1974 and the Global Alliance for Vaccination and Immunization (GAVI) in 2000 [36,37]. While maintaining vaccination coverage and infrastructure remains to be a challenge for most developing countries, the major lingering problem is the long delay between vaccine licensure and availability in developing countries [34,38–40]. If licensed and endorsed by the WHO, the new dengue vaccine – likely to be expensive and limited in supply at first – would be introduced against such an economic and political backdrop in developing countries where dengue is endemic.

Economic considerations around a new dengue vaccine

When new lifesaving vaccines become available, developing countries face a series of difficult decisions regarding their introduction into national immunization programs (NIPs). The WHO recommends that country policy makers should consider the cost-effectiveness, affordability and sustainability of a new vaccine before its introduction [44]. While NIPs are under pressure to make new vaccines accessible to populations in need, they are usually more expensive than those currently in use [45]. Furthermore, most NIPs will need resources to increase their financial and operational capacity to strengthen supply chain and logistics systems to manage larger volumes of higher-value vaccines with different handling requirements and monitor and evaluate their impact given their different vaccination schedules and target populations [44,45]. This places an added pressure on NIPs as they strive to strengthen the effectiveness and efficiency of existing systems to expand the coverage of routine immunization in an environment where developing countries are increasingly expected to cover the full costs of NIPs [46].

Cost-effectiveness

Because of limited health care budgets, investment decisions in vaccination have to be traded off against those in other preventive and therapeutic interventions to facilitate the optimal allocation of resources in developing countries. Cost-effectiveness analyses have become an important component of health policy decisions for planners, providers and funders of healthcare to ensure value for healthcare expenditure. Consequently, the number of cost-effectiveness analyses focused on vaccination has been growing rapidly [40].

Cost-effectiveness analyses of vaccination programs against infectious diseases necessitate the consideration of demographic, clinical, epidemiological and economic data and the use of modeling approaches to simulate disease transmission dynamics, synthesize data from multiple sources and extrapolate data beyond the duration of clinical trials [47]. There are methodological issues involved in modeling of the potential impact of vaccination at the population level [48]. An important one is the consideration of the indirect effects of vaccination on nonvaccinees, known as herd immunity effects, in addition to the direct protective effects on vaccinees [49]. In the case of dengue, herd immunity is a particularly challenging concept because of the complex dynamics of dengue infection,
mainly owing to four co-circulating dengue virus serotypes in many endemic areas, cross-protection and possible antibody dependent enhancement among the four serotypes [50]. An added challenge is the explicit representation of complex temporal–spatial interactions between human hosts and mosquito vectors so as to estimate the critical vaccination threshold to eliminate dengue transmission [50]. The use of dynamic disease transmission models addressing these two challenges are important to study the impact of different vaccination strategies such as age targeting, vaccine dosing, catch-up campaigns, and the impact of pre-existing immunity in high and low transmission settings [48]. Recent reviews indicated that dynamic dengue transmission models are limited but growing in number and they vary significantly in their incorporation of mosquito vector populations, permanent and transient cross-protection and antibody-dependent enhancement of infection [50,51].

In the case of the candidate dengue vaccine, estimating its public health impact gets further confounded because of its reported serotype specific efficacy and the potential immunopathogenic effects of vaccine derived immunity [24,25,52]. The potential impact of mass vaccination with an imperfect dengue vaccine was only recently explored, using an age-stratified dengue transmission model that included cross-protection and infectiousness enhancement between four dengue serotypes and explicit vector-host dynamics [53]. The study found that a vaccine with high efficacy against dengue serotype 1, 3, 4 and low efficacy against dengue serotype 2 resulted in a 50% or greater reduction in the number of dengue cases in a hyperendemic population in Thailand over 10 years. Longer-term simulations indicated that vaccination might lead to a shift in the mean age of dengue cases towards younger age groups, and this implied that vaccinating immunologically naive children might predispose them to clinically apparent disease earlier in life if vaccine derived immunity enhanced severity of dengue infections. Nonetheless, the study concluded that partially effective vaccines could have the potential to be an important tool for dengue control at the population level.

We identified two other modeling studies that assessed the impact of mass vaccination in a multi-strain framework with vector–host dynamics, but these studies did not consider serotype specific vaccine efficacies [54,55]. One of the models further made simplified assumptions on the risks and consequences of secondary infections (i.e. cross-protection and cross-immunity), did not consider waning vaccine efficacy, and concluded that children should be prioritized for vaccination to reduce dengue cases and hospitalizations and adults should be vaccinated along with children to control dengue transmission [54]. The other model, which included all the aforementioned features likely to influence the dynamics of dengue transmission, concluded that while vaccination would decrease the incidence of dengue and the frequency and magnitude of outbreaks it would modify the transmission dynamics of infection and the age distribution of dengue cases [55].

There are gaps in our understanding of dengue virus serotype dynamics, age-specific risk of severe disease, immune enhancement of susceptibility and infectiousness, and immunopathogenic effects of vaccine-induced immunity [50,51,53,56]. Accordingly, modeling approaches for projecting the public health impact of vaccination against dengue are evolving and expected to be more complex than those for other infectious diseases [50,51]. On the other hand, these models require extensive empirical data, ideally obtained from longitudinal cohort studies, which is currently very limited [50,51].

There are only five published cost–effectiveness studies of dengue vaccines [57–61]. All studies investigated the threshold price per vaccinated individual below which dengue vaccination would be cost-effective based on narrow categories of economic benefits of vaccination, such as averted health care spending and productivity losses. Only one of these studies modeled herd immunity to capture health gains by the community, including non-vaccinees, under two different vaccine efficacy scenarios in Brazil [61]. At a 70% vaccine efficacy, the study found that vaccination might be cost-effective for up to US$ 534 and cost-saving for up to US$ 204 per vaccinated individual. The price per vaccinated individual for which vaccination stopped being cost-effective was US$ 237, and cost saving was US$ 93 per vaccinated individual at a vaccine efficacy of 30%. The other four studies, focusing on Southeast Asian settings, employed static models that either did not consider herd immunity effects or made linear assumptions between vaccination coverage and health outcomes, and hence potentially underestimated the effectiveness and cost–effectiveness of dengue vaccines.

Although the concept of herd immunity has commonly been incorporated in studies of the public health impact of mass vaccination, it has not been fully explored in the context of cost–effectiveness studies of dengue vaccination. Furthermore, given the limited number of cost–effectiveness studies, more country-level evidence is needed from dengue endemic
countries to justify future investments in dengue vaccination programs.

There is limited analytical expertise and limited quality surveillance data in developing countries to develop and run models of complex interventions [62,63], such as vaccination programs [64,65]. Hence, the practice of adapting existing models under limited guidance is reported to be common [66]. A further challenge is translating the results of economic analyses into conclusions that are useful to country policy makers. In particular, policy makers need to understand the type of programmatic and policy questions that economic models can address and the caveats around model results in view of data shortcomings and parameter uncertainties [66]. Some important programmatic and policy questions include: What are the benefits of immunization programs? When is it best to introduce a new vaccine into an NIP? What is the budget impact of a new vaccine on an NIP? How can we achieve equitable vaccination coverage levels, given a budget constrain?

Affordability

In addition to cost–effectiveness, country decision makers need to assess resource implications and affordability of introducing a new vaccine. Several new life-saving vaccines have become available over the past decade, such as those for human papillomavirus, rotavirus and pneumococcal disease [44]. Although the price of the candidate dengue vaccine is not known yet, almost all aforementioned new vaccines emerged from a strictly commercial process directed at developed country markets [67] and were introduced in those settings at prices higher than US$ 50 per dose [68]. Consequently, the uptake of these new vaccines has been slow in developing countries, particularly in lower middle-income countries that are not eligible for GAVI assistance [69].

When the high price of new vaccines present a formidable financing challenge, it is necessary to justify that these vaccines address a public health priority. In the case of dengue, multi-country surveys of policy makers and opinion leaders showed that dengue was a highly political disease and governments would be under tremendous pressure to introduce a dengue vaccine when available because of the difficulty in preventing and managing the disease [28,31].

Parents identified dengue as a particular source of fear and concern, especially when children developed fever during outbreaks [70,71]. Recent studies suggested that households would be willing to pay US$ 23.30 per dose in Thailand, US$ 8.70 per dose in Vietnam, US$ 7.50 in Colombia and US$ 1.94 in Indonesia, and placed more value on vaccinating young children than school age children or adults [30,72]. The results of these studies indicate the presence of a private sector market for dengue vaccines in these countries if governments set user fees below average willingness-to-pay amounts for a dengue vaccine. A recent review indicates that the private sector already plays an active role in introducing new and underutilized vaccines and provides services to higher-income clients in middle-income countries that are ineligible for GAVI assistance [73]. In low-income countries, the private sector is engaged with providing services particularly to the poor through contracting and financing strategies. However, the extent to which these immunization services are regulated and what type of regulation is most effective to ensure service quality has not been documented, particularly in middle-income countries.

Consequently, developing countries may decide to allocate more resources from national budgets while simultaneously tapping into the private market for partial cost recovery without loss of demand and seek international assistance in the form of grants, budgetary support and loans from development banks to cover the costs of key inputs, particularly the higher cost of new vaccines.

A recent economic analysis estimated the production cost of a tetravalent dengue vaccine in Brazil not to exceed US$ 0.20 per dose in 10 dose vials and US$ 0.70 per dose in single dose vials when producing 60 million doses annually [68]. While the production cost is important, the final cost of a new vaccine reflects high investment costs in research and investment and marketing, and usually falls through gains in productivity (increased know-how) and economies of scale (increased production volume) [74]. It is unclear how the entrance of manufacturers from developing and emerging economies into the vaccine market, which has been historically dominated by a few multinational companies, will affect the prices of existing and new vaccines in the future [10].

As for the candidate dengue vaccine which is expected to be licensed in the near future, Sanofi Pasteur has made a commitment to make the vaccine available at an affordable price in dengue endemic countries where the need is greatest [75]. Accordingly, the Dengue Vaccine Initiative (DVI) and the International Vaccine Access Center at Johns Hopkins University has undertaken a multi-year project to estimate the potential demand for a dengue vaccine and its drivers in Latin American countries that are ineligible for GAVI support to inform financial resource
requirements and strategies [76]. Some preliminary results for Brazil and Mexico have been presented at scientific meetings [77,78], but the findings of these strategic demand forecasting (SDF) studies have not been published yet.

Although the price of vaccine per dose is a key consideration in country decisions to introduce a new vaccine, additional resources will be needed for training of health workers, strengthening supply chains and logistics in the light of increased number and volume of vaccines (e.g. cold chain, vehicles, transport, quality assurance), program management (information systems, monitoring and evaluation), social mobilization (information, education and communication efforts and advocacy) and disease surveillance (vaccine safety and impact) [43]. The cost of vaccination per fully immunized person also depends on these non-vaccine immunization costs and is expected to vary across countries according to the cost of key inputs, the mix of vaccine delivery strategies and the scale of vaccination programs [79].

Despite recent progress in dengue vaccine development efforts, no studies detailing country-specific cost estimates of a dengue vaccination program were found in the published literature, corroborating the findings of an earlier review [16]. Admittedly, the findings of such studies for a vaccine that is in the development pipeline need to be interpreted in the light of its main limitations pertaining to uncertainties associated with vaccine schedules, target groups, delivery strategies and vaccine prices. However, country-specific costing studies are needed and could assist national governments and donors to project the full resource requirements for introducing new vaccines [80–82]. Such country-specific costing studies also provide essential cost data to assess the cost–effectiveness of new vaccination programs for evidence-based decision-making [82].

**Sustainability**

Since 2000, the GAVI Alliance has supported more than 70 countries with a gross national income per capita of US$ 1550 or less in the introduction of new and underused vaccines into NIPs [83]. Overall, there have been increases in the financial commitment of national governments to NIPs, particularly when increased co-financing and ownership are required for the receipt of supplementary external funds [84], for example, through the GAVI Alliance [85]. There is, however, a wide variation in the domestic and external mix of financing for NIPs across developing regions of the world [46,86]. For instance, in Latin America, all NIPs are fully domestically funded, except in Guyana which receives support for immunization from the GAVI Alliance [87]. The introduction of a new vaccine is expected to be less challenging in Latin American countries because of the limited demand it will place on their health budgets. Countries in this region have been working on their dengue vaccine introduction strategies in collaboration with the DVI [67,88]. Furthermore, the Pan American Health Organization (PAHO) backs immunization advocacy efforts in the region and provides technical assistance to countries through the ProVac Initiative to make evidence-based decisions on new vaccine introductions [89,90].

The absence of a similar enabling environment in Asia where the majority of the dengue disease burden lies has recently been noted [91].

Historically, important financing gaps exist in GAVI-supported countries [46]. It has been argued that earmarked donor funding does not necessarily increase the allocation of developing country resources towards programs that yield the greatest health benefits [92]. In the short term, recipient governments adjust their spending to offset donor-funding preferences, whereas the risk in the long-term is that country ownership of programs is often compromised and governments are less likely to allocate resources to fully fund program activities. A review showed that <20% of the vaccine introductions in GAVI-supported countries were decided by a national advisory body [93]. An underlying reason for this is the wide variation in the availability and functional quality of national immunization technical advisory groups (NITAGs) in these countries [90,94], which is the main objective of another multi-year international initiative, established in 2008 and funded by the Bill & Melinda Gates Foundation, to support NITAG creation and strengthening in low- and middle-income countries [95].

By 2020, more than 20 countries are projected to graduate from GAVI assistance. [83] A graduation planning exercise recently identified financial sustainability a major challenge because current domestic funding for NIPs is small in most GAVI-supported countries, and the extent to which graduated countries will have access to GAVI-negotiated lower vaccine prices remains unclear [46]. The prospects for immunization financing ultimately depend on the level of government spending on health and the political prioritization of NIPs. National governments will need to improve the efficiency of NIPs and explore alternative sources of financing to meet the resource requirements [96]. Although a high public health priority in endemic countries, dengue has a low profile in the global health community because of its low mortality rates [10,97]. Concomitantly, efforts must continue to reduce vaccine
prices to ensure equitable access to new life-saving vaccines, including for dengue. The most effective strategies to reduce vaccine prices are to incentivize the development of alternative quality vaccines and encourage and take advantage of competition when it occurs. Reducing the unit cost of vaccines through innovative manufacturing processes, pricing and procurement modalities, and increased transparency on vaccine pricing are some of the other recommended strategies to drive down vaccine prices [43].

Developing economic evidence on dengue vaccination

As the costs of new vaccines continue to rise, economic evidence is likely to play an increasingly important role in country-level decisions to introduce and sustain a new vaccine. The results of existing economic analyses focusing on dengue vaccines, which are limited in quantity and quality as discussed above, are not easily generalizable to different country contexts, owing to large differences in local factors such as burden, epidemiology and transmission of dengue and characteristics of health care systems. The published literature focuses on only three dengue-affected countries, namely Thailand, Brazil and Singapore. More country-specific studies are needed to estimate the benefits and costs of dengue vaccination programs to determine appropriate vaccine introduction strategies, such as optimal target populations and catch-up vaccination programs and their cost-effectiveness.

Countries considering dengue vaccine introduction also need to evaluate their fiscal space to support the introduction and maintenance of a dengue vaccination program. SDF studies are under way to estimate the potential demand for dengue vaccines and the costs of dengue vaccine introduction in Latin American countries. Similar studies are urgently needed for dengue endemic countries in other regions, particularly in Southeast Asia. The quantification of the potential demand for dengue vaccines and the costs of dengue vaccine introduction inform national financing strategies and reduce access barrier to dengue vaccines in endemic countries while enabling vaccine suppliers and donors to make informed decisions about dengue vaccine supply.

Discussion

There are several dengue vaccines in clinical development [98], and at least one is expected to become available imminently. The experience to date, however, suggests that it takes about 10–20 years for a new vaccine to reach developing countries following its licensure in developed countries [39,40], as was in the case of the hepatitis B vaccine despite its high disease burden [99]. It has been speculated that it would be 2030 or later before a dengue vaccine would be widely available if no pre-planning were undertaken by dengue endemic countries [67].

The introduction of new lifesaving vaccines can be justified on many grounds, including that vaccination equitably promotes and protects health. However, developing countries are often faced with difficult decisions on the allocation of scarce health resources in view of competing national health priorities. So far, there are only a handful of analyses that evaluated the cost-effectiveness of dengue vaccines. The choice of analytical models in most of these studies was not optimal given specific methodological issues surrounding vaccination, such as the consideration of herd immunity effects.

None of the cost-effectiveness studies went beyond the narrow benefit categories of averted health care spending and shorter-term productivity gains, while there is a steadily growing literature on the broader economic benefits of vaccination [40,100–102]. In the case of dengue, these broader economic benefits include but not limited to productivity gains related to overall improved health status and changes in household choices, reduced spending on dengue vector control or outbreak surveillance, positive impacts on foreign investment and tourism [103]. It has been argued that the undervaluation of vaccination may lead policy makers towards underinvestment in expanding coverage with more costly vaccines [101]. However, it is still unclear how to quantify, value and incorporate these broader economic benefits in economic assessments.

There are currently no country-specific cost estimates for delivering a dengue vaccine. As we now know more about the characteristics of the candidate dengue vaccine, such projections should be developed speedily to articulate the costs and financing requirements for vaccine introduction and scale-up to support financial planning and forecasting at a national level. Historically, vaccine introduction has led to substantial increases in the cost of NIPs. It is important to tie these projections to an assessment of the domestic and external mix of funding sources to carefully examine the possibility of sustaining new vaccinations.

Country-level decisions on new vaccine introduction should be transparent and evidence-based. Given the inherent complexities involved with the economic analyses of vaccination programs and the limited availability of fully functional NITAGs, country policy makers often support recommendations to introduce vaccines in the absence of a transparent and independent review process and under considerable pressure from...
many stakeholders and vaccine advocates [64]. Capacity building in economic analyses is a key step in promoting evidence-based decision-making on vaccination introduction in dengue endemic countries and can drive the political will by bridging the gap between the high-level recommendations made by the WHO and stakeholders and the specific challenges faced at a country level.

**Expert commentary**

The WHO recommends that country policy makers should consider cost–effectiveness, affordability and sustainability of a new vaccine before its introduction into NIPs. A new dengue vaccine is expected to become available imminently. Current economic evidence base on dengue vaccination programs is, however, severely limited to support country-level decisions on vaccine introduction in endemic countries and needs to be strengthened based on available information on the candidate dengue vaccine. Although the new dengue vaccine is expected to be more expensive than existing vaccines, its introduction can become a national priority in endemic countries given the perceived public health importance of dengue at the household and national levels. Capacity building in economic analyses at a national level is a critical step in promoting the rational use of economic principles and analytical tools to support evidence-based vaccine introduction decisions, which addresses the specific challenges faced at a country level.

**Financial & competing interests disclosure**

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- • of considerable interest


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