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Review

Valuing the broader benefits of dengue vaccination, with a preliminary application to Brazil

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ABSTRACT

The incidence of dengue has been on the rise since at least the 1960s, bringing greater urgency to the need for a vaccine to prevent the disease. Recent advances suggest that the scientific world is moving closer to an effective dengue vaccine. However, there are concerns that the price of a future vaccine could limit its uptake. High prices, in addition to other challenges, have already weighed negatively in government decisions to include other new vaccines in national immunization programs, e.g., the pneumococcal, rotavirus, and human papillomavirus vaccines. Recent research on the value of vaccination, however, suggests that vaccination confers benefits that are often neglected by traditional economic evaluations. In the case of dengue, commonly overlooked benefits are likely to include reduced spending on outbreak control, averted losses in tourism flows, and avoided productivity losses due to long-term dengue sequelae. Accounting for these and other broader benefits of dengue vaccination could reveal significantly greater economic value and strengthen the case for inclusion of dengue vaccination in national immunization programs. In this article we discuss a framework for the broader value of vaccination and review its application in the context of dengue vaccination for Brazil.

1. Dengue vaccination: an overview

Since the 1960s, the world has witnessed at least a 30-fold increase in the global incidence of dengue [1]. Dengue is a vector-borne viral disease transmitted primarily by the mosquito *Aedes aegypti* (*A. aegypti*), and, to a lesser extent, by *Aedes albopictus* (*A. albopictus*) [2,3]. Disease is caused by one of four dengue virus strains (DENV1–4), and in many settings all four strains are present. According to the World Health Organization (WHO), some 2.5 billion people (more than one-third of the world's population) are currently at risk for contracting dengue [2]. The disease is now endemic in more than 100 countries, many of which lie on or near the equator [2]. According to another estimate, dengue is currently present in 128 countries and the at-risk population is as large as 3.97 billion [4]. WHO estimates that there are 50 million new dengue infections per year [2]; estimates from other sources reach as high as 200 million [2]. Similar to the situation involving many infectious diseases, reported cases are a small fraction of estimated total cases (see Fig. 1).

Researchers have cited multiple possible causes for the increase in incidence of dengue, including global warming [5]. Some argue that changes in climate have expanded the habitat of the *A. aegypti* mosquito, allowing it to survive in new settings and infect new populations. While mosquitoes transmit the disease from person to person, humans host the virus. Thus increases in population size (and, more importantly, in population density), and migration of infected people can increase the number of susceptible people and thus increase the number of new cases of dengue. Indeed, the same areas that now host the *A. aegypti* mosquito are also experiencing the most rapid rate of population growth [5,6]. Population growth is most acute in urban areas, where high population density encourages further spread of dengue [5,7]. In addition, increased international travel also helps to spread dengue if the mosquito vectors are present in the destinations visited by infected persons [5].

Once infected, dengue can present as a mild rash and fever or as a severe headache and muscle and joint pain [2]. About one percent of all dengue infections can result in dengue hemorrhagic fever (DHF), characterized by high fever, enlarged liver, and circulatory failure [8]. Prior infection by one of the four types of dengue is an important risk factor for DHF. Convulsions and other complications may arise from DHF, and in very severe cases, shock and death may occur. According to the 2010 *Global Burden of Disease Study*, roughly 14,700 people die from dengue or DHF annually [9]. Shepard et al. report 36 million symptomatic cases per year, resulting in 24,000 deaths, predominantly among children [10].

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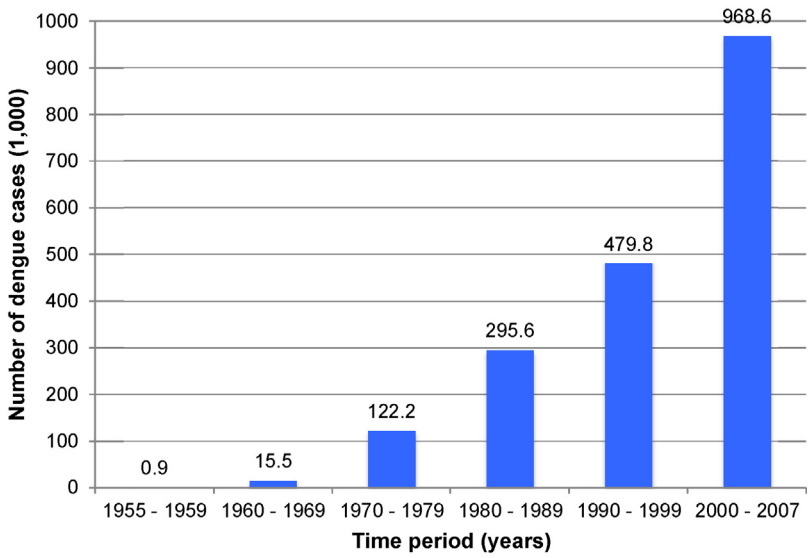

Fig. 1. Average annual number of dengue cases reported to WHO, 1955–2007.

Source: [3].

Despite the scale of the problem, there is no specific treatment for dengue. Current treatment consists of general oral rehydration therapy, intravenous fluids, and blood plasma transfusions [2]. In many settings, however, proper treatment is not available, and communities rely on care provided by informal caregivers. While such caregivers may have little-to-no formal medical training, they commonly charge fees for their services, leading to the imposition of substantial costs on families. Inadequate treatment of dengue can result in preventable complications and death [11,12].

To date, there is no vaccine for dengue, owing to a host of scientific challenges [13]. According to WHO, these include [2]:

- Technical challenges surrounding development of a vaccine that protects against all four strains of dengue, which is important to prevent potential vaccination-induced antibody dependent enhancement; ADE could lead to more severe dengue disease when a patient is infected with a strain against which the vaccination does not protect.
- Limited understanding of how the disease typically behaves and how the virus interacts with the immune system.
- Lack of laboratory animal models available to test immune responses to potential dengue vaccines (because dengue virus does not naturally infect non-human species).

In the absence of a vaccine, prevention efforts have instead consisted of vector control, largely through elimination of the habitat of *A. aegypti*. This involves using insecticides or reducing pools of standing water. In recent years, however, there have been a number of vaccine candidates in both clinical and preclinical development [14–17]. Researchers at Sanofi Pasteur have developed the candidate vaccine that is furthest along in development. The candidate vaccine, "CYD-TDV," currently in Phase III clinical trials, is designed to protect against all four strains of dengue virus. The company recently completed Phase IIb clinical trials of CYD-TDV among 4002 schoolchildren in Thailand [18]. The currently available results suggest that the Sanofi Pasteur dengue vaccine provides about 60 percent protection against dengue virus 1 (DENV1) infections and 80–90 percent protection against types 3 and 4 (DENV3, DENV4) infections. While the vaccine did not demonstrate significant protection against type 2 (DENV2) – a concern given the potential for ADE – the trial proved that a safe dengue vaccine is possible [18]. A final-stage Phase III trial with 31,000 participants in Asia and Latin America is currently underway and should provide further information on vaccine efficacy and safety.

The prices at which a future dengue vaccine will sell are, of course, currently unknown. Like all vaccines, the prices will likely depend on a mix of market forces and procurement agreements between national governments, pharmaceutical companies, and multilateral agencies, and can differ in the public and private sectors. Recent vaccines added to national immunization programs (NIPs) – such as those that protect against pneumococcal disease (Pneumo), rotavirus (Rota), and human papillomavirus (HPV) – tend to have much higher prices, in both the public and private sectors, than the original EPI vaccines (Fig. 2). This is one reason why many low- and middle-income countries are struggling to achieve widespread coverage of these new vaccines (Fig. 2). Whether this will be an issue for inclusion of a dengue vaccine in NIPs in countries where the incidence of dengue is highest remains to be seen.

In the context of rising healthcare costs and competing budget priorities, it is especially critical to properly assess the value of vaccination so that governments can make informed spending decisions [19]. Robust data on the economics of vaccination could therefore be important for national-level decision-making in all countries, including countries where dengue is endemic. In this article we review emerging arguments that suggest that important economic benefits of vaccination have been ignored in past economic evaluation studies and should be included in future assessment of the value of vaccination programs. We discuss what these arguments could mean for dengue vaccination, and apply this thinking to Brazil.

2. New thinking on health and wealth

Economists and health specialists have long believed that a strong economy is an important foundation for a healthy population. More recently, this wealth-to-health relationship has been viewed in reverse, with many researchers noting that the health of a population is an important ingredient underlying a strong economy [25]. Population health can, in theory, contribute to economic growth through a number of important pathways – e.g., healthier people can work more, longer, and harder, and they tend to be more and better educated [25–27]. Moreover, healthier populations typically have lower fertility and a correspondingly reduced burden of youth dependency [28], and as such tend to save larger fractions of