

Perspective

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Dengue vaccination: Availability and relevance to low- and middle-income countries

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1. Background

Dengue, commonly known as "Break Bone Fever", is expanding widely, resulting in increased morbidity, mortality, and hospitalizations. Between 2000 and 2019, global dengue incidence surged tenfold from 0.5 to 5.2 million cases across 129 countries, reaching a historic high of over 6.5 million cases and 7 300 dengue-related deaths in more than 80 countries by 2023[1]. Driven by urbanization and climate change, the primary mosquito vector for dengue, *Aedes aegypti*, is spreading extensively into new areas, while the less effective vector, *Aedes albopictus*, is also rapidly expanding its range. While most infected individuals are asymptomatic, severe cases may require hospitalization, and fatalities can occur.

Dengue infection is caused by four distinct, immunologically cross-reactive DENV serotypes, with infection providing life-long immunity to that serotype and temporary cross-protection against others for up to two years[2]. Currently, there are no specific treatment for dengue. Prophylactic and supportive measures are practiced that can reduce mortality. Vector control remains the primary preventive measure but has been only partially successful in reducing the dengue disease burden. New approaches, like integrated control, *Wolbachia*-infected, and genetically modified mosquitoes, show promise but are years away from broad use. In this context, tetravalent dengue vaccines present a valuable option; even with partial effectiveness, they could help reduce epidemic spread and improve the effectiveness of vector control efforts.

A safe, effective, and affordable tetravalent dengue vaccine that is effective against all four serotypes of the dengue virus, has long been sought. On May 1, 2019, the United States Food and Drug Administration (US FDA) approved a vaccine named "Dengvaxia", prepared by Sanofi Pasteur, for preventing dengue[3]. On May 10, 2024, another vaccine Qdenga (TAK-003), developed by Takeda, received prequalification from the World Health Organization (WHO)[4]. So far, Dengvaxia has received market authorization as a vaccine for dengue prevention, from the US FDA, while Qdenga has received such authorization from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicine Agency (EMA)[5]. However, Takeda has withdrawn its application at the US FDA and Sanofi has announced plans to halt its manufacturing of Dengvaxia in the US, despite the increasing number of infections[6].

Dengvaxia is designed for individuals with prior dengue exposure, specifically for children aged 6-16 years. Administered in three doses at 0, 6, and 12 months, it has shown 65.6% efficacy in children over 9 years and 44.6% in those under 9 years, with variable effectiveness by serotype, primarily targeting DENV-4[7]. Meanwhile, Qdenga, a live-attenuated, recombinant vaccine targeting all four dengue serotypes, is recommended by the WHO for children in high-burden areas aged 6-16 years. Given in two doses three months apart, it has

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shown efficacy rates of 69.0% for DENV-1, 90.8% for DENV-2, and 51.4% for DENV-3, with inconclusive results for DENV-4[7]. Over three years, Qdenga demonstrated a 62.0% overall efficacy against virologically confirmed dengue and 83.6% against hospitalized cases, with stronger efficacy in seropositive individuals than in seronegatives[7]. Safety assessments found no significant issues, with serious adverse events occurring in 2.9% of the Qdenga group *versus* 3.5% in the placebo, confirming its effectiveness and safety profile.

2. Vaccination in low- and middle-income countries (LMICs)

Since early 2023, dengue transmission has surged, resulting in over five million reported cases and more than 5 000 deaths across more than 80 countries, affecting all WHO regions: Africa, the Americas, Southeast Asia, the Western Pacific, and the Eastern Mediterranean. The rising case fatality rates, especially in low- and middle-income countries (LMICs) like Bangladesh and Nepal, emphasize the urgent need for improved response measures. In 2023, intensified outbreaks were recorded in countries such as Bangladesh, Brazil, Burkina Faso, Fiji, Pakistan, the Philippines, and Vietnam, highlighting the demand for effective vaccines[1].

In the WHO Southeast Asia Region (SEARO), where dengue is endemic in 10 out of 11 countries, significant rises in dengue cases have been recorded. By November, Bangladesh reported 308 167 cases with 1 598 deaths, while Thailand saw 136 655 cases with 147 deaths[1]. Nepal is also severely impacted, with 76 of its 77 districts affected in 2024, totaling 28 212 cases and 12 deaths. Also, WHO's 2024 data show that while cases have declined slightly, they remain high across SEARO, highlighting the critical need for effective dengue vaccination initiatives to curb outbreaks and lessen health impacts.

In fact, even though all these data suggest the high need for vaccination, the Philippines was the first, and for a long time, the only LMIC to implement a dengue vaccination program on a national scale. The program began in 2016 with Dengvaxia[8]. However, after safety concerns and public controversy surrounding adverse effects—particularly among children who had not been previously exposed to dengue—the program was suspended in 2017, and Dengvaxia's use became highly restricted[8]. The reason behind the suspension was early rollout without thorough evaluation of safety for specific populations that were intended to be protected.

3. Cost and availability of vaccines

Dengvaxia is approved in 20 countries, including Brazil and the European Union (EU), but not by the US FDA for those without prior dengue exposure[9]. Likewise, Qdenga is allowed to be used by children and adults in private markets in European countries, as well as in Indonesia and Thailand, and some private and public programs in Argentina and Brazil.

Pricing varies globally: Dengvaxia costs about $197.99 per course in the US, around $263.679 for Dengvaxia and $98.94 for Qdenga per course in Thailand, and $520 for a course of Dengvaxia in Singapore. Qdenga costs £240 per dose in the UK, €400 in Sweden, and $86 to $200 in Brazil. In Malaysia, a course of Qdenga regimen costs over $134-$160[10].

4. Can LMICs afford dengue vaccines?

Given the GDP per capita of LMICs, the prices for both vaccines may be prohibitively high for many people. This high cost may limit vaccination uptake significantly. For instance, the cost of one course of the Qdenga vaccine represents about 7.4% to 22.66% of Nepal's GDP per capita ($1 324)[11]. Given that a significant portion of the population in Nepal lives on less than $2 a day, even a relatively low-cost vaccine like Qdenga may be considered expensive for many households. The proportion of income that would need to be allocated for vaccination could be burdensome for low-income families. Efforts to reduce the cost of the Qdenga vaccine have been made, with the contract Biologicals E. Limited, an Indian company on multidose vials and in large volume. Biologicals E. Limited plans on producing 50 million doses per year, assuring Takeda's blueprint of producing 100 million annual doses.

Also, while some individuals may afford the vaccine out-of-pocket, healthcare financing mechanisms in LMICs like Nepal, including government programs and international aid, play a crucial role in making vaccines accessible to broader segments of the population[12]. If provided through public health initiatives, the cost may be subsidized or covered entirely for eligible individuals.

5. Conclusion

In conclusion, the high incidence of dengue fever and

hospitalizations in LMICs highlights an urgent need for effective strategies to manage such a disaster. Vaccination as a prophylactic measure is a better option. Qdenga can be a more inclusive vaccination option. LMICs like Bangladesh and Nepal face significant barriers to access, highlighting the need for improved distribution and affordability measures in regions heavily affected by dengue. Improving access to dengue vaccines in such nations requires financial support mechanisms such as subsidies and public funding, as high out-of-pocket costs are typically unaffordable.

Nevertheless, access to dengue vaccines is essential in high-risk countries, but early rollout should align with each nation's health system and regulatory capacity to assess cost-effectiveness, safety, and impact. Premature implementation, without thorough evaluation, may bring unforeseen challenges. Successful vaccine deployment depends on a context-specific approach to maximize uptake and long-term health benefits.

Conflict of interest statement

The authors declare that they have no competing interests in the preparation of this manuscript.

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