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Dengue vaccine an optimistic beginning

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Abbreviations: WHO, World health organization; DVI, dengue vaccine initiative; CCID50, cell-culture infectious doses; YF, yellow fever

Mini review

Dengue, also known as "break bone fever," is caused by a virus transmitted by Aedes mosquitoes. With more than half of the world's population living in areas at risk for infection and 32 million reported cases in 2015,[1] dengue virus has become a leading cause of illness and death in tropics and subtropics. The disease is now endemic in more than 100 countries with estimated annual incidence about 50-100 million symptomatic cases occurring in recent years, predominantly in Asia, Latin America and Africa.[2] Factors such as rapid unplanned urbanization, population growth, globalization and travel, and climate change have facilitated the transmission of dengue viruses both in urban and rural settings.[3]

Dengue virus belongs to the genus Flavivirus, having four distinct serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) sharing about 60%–75% identity at the amino acid level. Dengue viruses primarily infect cells of the myeloid lineage, including macrophages, monocytes, and dendrite cells.[4] The incubation period is usually 4–7 days with the majority of dengue virus infections being asymptomatic.[5] The most common presentation is the sudden onset of fever accompanied by headache, retro-orbital pain, generalized myalgia and arthralgia, flushing of the face, anorexia, abdominal pain and rash frequently seen on the trunk.[6] For clinical management, the World Health Organization (WHO) has reclassified the old case definitions like dengue fever, dengue hemorrhagic fever and dengue shock syndrome by the new 2009 cases definitions like dengue without warning signs, dengue with warning signs and sever dengue.[7] The most fatal severe dengue includes any sign of plasma leakage leading to shock or fluid accumulation with respiratory distress, bleeding, or serious organ impairment.

The immune response to dengue viruses is poorly understood and a bit complicated. Natural infection and recovery by one serotype induces high-titer neutralizing antibody and provides lifelong immunity against that particular serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue.[8,9] There is no specific anti-viral treatment for dengue illness. Clinical management is based on supportive therapy with case fatality rate as high as 20%. The control and prevention of dengue virus infection has been classically through vector management.

Although a search for an effective dengue vaccine started in 1940s, due to the limited appreciation of the global burden of the virus, no advancement was achieved during the 20th century. However, recent years have seen a dramatic increase in dengue vaccine progress. The Dengue Vaccine Initiative (DVI) is the major force driving global dengue prevention and control strategies It is an international consortium composed of the international vaccine institute, the WHO initiative for vaccine research, the international vaccine access center at the Johns Hopkins University Bloomberg School of public health and the Sabin vaccine institute that specializes in research, health economics, policy and advocacy to equip countries with objective information and scientific evidence to fight dengue fever.[10] The initiative is supported with funding by the Bill & Melinda Gates foundation Under this initiative, several vaccine candidates are undergoing clinical development with some of the are in advanced stage.

The first dengue vaccine, Dengvaxia® (CYD-TDV) by Sanofi Pasteur, has been registered for use in individuals 9-45 years of age living in endemic areas in late 2015 and early 2016. Since then, Dengvaxia® has been approved by the regulatory authorities in South American countries including Mexico, Brazil, El Salvador, Paraguay and Costa Rica In Asia, the Philippines remain the first country to approve this vaccine for its population.[11] Dengvaxia® is a prophylactic, tetravalent, live attenuated (recombinant) viral vaccine the vaccine is indicated for individuals 9–45 years living in dengue endemic areas.[12] The shelf-life of CYD-TDV is 36 months when stored between 2 °C and 8 °C The active substances contained in the CYD-TDV dengue vaccine are live attenuated recombinant viruses representing serotypes 1, 2, 3, and 4 Each of these serotypes counts approximately about 45 to 6 log10 median cell-culture infectious doses (CCID50) in the final formulation of the vaccine Each monovalent CYD recombinant is obtained separately by replacing the genes encoding the prM and E proteins of the attenuated yellow fever (YF) 17D virus genome with the corresponding genes of the 4 wild-type dengue viruses.

CYD-TDV induces neutralizing antibodies against all 4 dengue virus serotypes, as measured by PRNT50 Similarly, T-cell response is also induced against structural antigens of dengue viruses Individuals who were seropositive at the time of vaccination developed higher titer of antibodies compared to individuals who were seronegative.[13] Vaccine efficacy varied by infecting serotype, previous exposure to dengue, age and severity. Also, vaccine efficacy varied by country, with efficacy ranging from 313% (95% CI 13%–519%) in Mexico to 790% (95% CI 523%–915%) in Malaysia. This variability in efficacy

likely reflects at least in part the baseline sero positivity and circulating serotypes, both of which affect the performance of the vaccine.[14,15] The duration of protection of the CYD-TDV vaccine is yet to be clear except for suggestions that a potential waning of protection across all age group is likely.[16] The CYD-TDV is a safe vaccine following vaccination, local and systemic adverse reactions were comparable to those recorded for other live attenuated vaccines. The most common systemic side effects are headache, malaise and myalgia.

The vaccine contraindications are similar to most live vaccines including individuals with a history of severe allergic reaction, individuals with congenital or acquired immune deficiency that impairs cell-mediated immunity, individuals with symptomatic or asymptomatic HIV infection, pregnant or breastfeeding women. the vaccine is also not indicated in children less than 5 years of age due to safety concerns.

According to the WHO, a dengue vaccine complements but does not replace prevention methods, such as vector control which is already in place.[17] Like other vaccine-preventable vector-borne diseases, effective surveillance, vector control, vaccines and outbreak response tools must continue to complement each other in reducing the burden of dengue virus in the affected countries. Currently, the WHO recommends that countries should consider introduction of the dengue vaccine Dengvaxia® only in geographic settings where epidemiological data indicate a high burden of disease. It has also developed well established recommendations to ensure the quality, safety, and efficacy of this live attenuated tetravalent dengue vaccines.[18]

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Conflicts of interest

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