The role of new dengue vaccines in curtailing the emerging global threat of dengue outbreaks arising from mass gathering sporting and religious events

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Editorial

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The risk of outbreaks of arthropod-borne pathogens arising from mass gathering events is ever increasing due to the rising number of travellers from arbovirus endemic areas, and the expansion and adaptation of arthropod vectors such as mosquitoes worldwide due to climate and environmental change [1-4]. Indeed, introduction of dengue virus (DENV) was a concern at the recent Olympic Games in Paris 2024, Japan 2020 and Brazil 2014 but outbreaks did not happen [5-7].

Recurring mass gathering sporting, religious, festival, and political events attract millions of people from across all continents, which is associated with the risk of outbreaks and onward transmission of a range of communicable diseases. The risk of introducing DENV can be estimated from the number of travellers from dengue endemic areas [8]. Countries hosting recurrent mass gathering religious events have the arduous task of reducing the risks of importation, amplification, and transmission of infectious diseases between pilgrims and indigenous populations, and exportation overseas after the event. Therefore, it is important to adopt a risk-based approach towards dengue and other potential deadly vector-borne pathogens.

Over the past decade, Zika, Chikungunya, Yellow fever (YF), Rift valley fever, West Nile fever, Japanese encephalitis, Oropouche and dengue fever (DF), have been on the radar of global public health authorities and countries organizing mass gathering religious events since they are endemic in countries of origin of pilgrims [9-12]. Furthermore, several of these diseases are endemic to host countries posing threat to attendees and the local population. The spread of arboviruses by infected people depends on the appropriate vector being available and the climate allowing the intrinsic development of the virus in the vector.

DENV is the most rapidly spreading mosquito-borne arbovirus in the world and while the majority of infections are mild, serious debilitating lethal cases of dengue occur. DENV is a single-stranded RNA virus of the genus *Flavivirus*, family *Flaviviridae*, with four serotypes (DENV1, DENV2, DENV3, and DENV4). People who acquire a second DENV infection caused by a different serotype are at an elevated risk for severe dengue once cross-protection induced by the first infection wanes. DENV is estimated to infect up to 400 million people every year, with more than half of the world's population now at risk [13-14]. Recent studies have predicted that more than several billion people could be at risk of dengue by 2080. As of August 2024, over 10 million cases of dengue have been reported from 176 countries across all WHO regions [15]. Several factors have been suggested for this increase and rapid spread including the changing distribution of the mosquito vectors *Aedes aegypti* and *Aedes albopictus* in previously dengue-free countries such as climate change with increasing temperatures, high rainfall and humidity.

Prevention of spread of dengue at recurring mass gathering religious events such as the Hajj in Saudi Arabia, the Grand Magal of Touba in Senegal West Africa, and the Kumbh Mela in India is now a priority control issue for global public health authorities [16]. Saudi Arabia is host to the largest annually recurring pilgrimage, the Hajj. It has one of the largest burdens of DENV in the Middle East. The first case of dengue detected in Saudi Arabia was in Jeddah in 1993 and the number of cases in 1994 rose to 289 with sporadic cases detected since then [17]. Between 2004 and 2015, outbreaks occurred outside Jeddah in Makkah, Al-Madinah, Jizan, and Najran. In 2022, 3647 cases of dengue were reported, some with history of travel outside Saudi Arabia [17]. Currently there has been a surge in the number of dengue cases arising from urbanization, high rainfall, and *Aedes spp* mosquito geographical expansion, insecticide resistance and climate change. According to WHO, Saudi Arabia is one of the top three countries reporting dengue cases in the Eastern Mediterranean Region and dengue infections reached 4,099 during the first half of 2024, a significant increase compared to previous years. Dengue fever appeared in Oman in 2018-19 a country previously with no local transmission [18].

Similarly, dengue cases in India and Bangladesh, other countries in Asia and Africa have increased for similar reasons [19,20]. The Kumbh Mela is held in various locations across India, including cities like Prayagraj (Allahabad), Haridwar, Ujjain, and Nashik. Some of these areas are in regions where dengue is endemic, particularly during the monsoon season when mosquito populations are at their peak. The large influx of people, living near mosquito breeding grounds creates a conducive environment for transmission of arboviruses such as DENV. Local and state health authorities typically ramp up vector control measures, health surveillance, and public health messaging during the event to prevent outbreaks. Dengue was first detected in Senegal in 1979 and frequent outbreaks have occurred every year. A study of the dengue outbreak at the Grand Magal of Touba recorded 263 confirmed cases out of 832 collected samples [16]. There was co-circulation of DENV serotypes 1 and 3. Phylogenetic data showed the origin

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Table 1
Current dengue vaccines and new developmental pipeline.

AVAILABLE DENGUE VACCINES
1). Dengvaxia (CYD-TDV): Manufacturer: Sanofi Pasteur
Dengvaxia was the first dengue vaccine to be approved, receiving regulatory approval in several countries, including the Philippines, Mexico, Brazil, and more. The World Health Organization (WHO) also endorses its use under specific conditions.
Efficacy: Dengvaxia is a live attenuated tetravalent vaccine designed to protect against all four dengue virus serotypes. Its efficacy varies depending on the serotype and prior exposure to dengue. It is more effective in individuals who have had a previous dengue infection. The WHO recommends Dengvaxia primarily for people aged 9-45 years (preferably seropositive) who live in endemic areas. For those who have never been infected by the DENV (seronegative), the vaccine poses a risk of severe dengue upon a subsequent infection. Dengvaxia is generally not recommended for seronegative individuals.
2. TAK-003 (QDENGA): Manufacturer: Takeda Pharmaceutical Company
TAK-003, has shown promising results in clinical trials, providing protection against all four dengue serotypes.
Efficacy: TAK-003 has good efficacy in both seropositive and seronegative individuals, making it a potentially safer option compared to Dengvaxia for a broader population. TAK-003 has shown promise for vaccination programs, especially in endemic regions. WHO recommends the use of TAK-003 in children aged 6–16 years in settings with high dengue burden and transmission intensity. The vaccine should be administered in a 2-dose schedule with a 3-month interval between doses. The TAK-003 vaccine should not be administered to people who are pregnant or planning to become pregnant at least 1 month following vaccination; people who are breastfeeding; people with congenital or acquired immune deficiency, including those receiving immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids (for example 20 mg/day or 2 mg/kg body weight/day of prednisone for 2 weeks or more) within 4 weeks prior to vaccination; and people with symptomatic HIV infection or with asymptomatic HIV infection associated with evidence of impaired immune function.
DENGUE VACCINE CANDIDATES IN DEVELOPMENT
1). Butantan-DV: Manufacturer: Butantan Institute, Brazil
This vaccine is currently in Phase III clinical trials. Early data suggest it is effective against all four dengue serotypes.
2). TV003/TV005: Manufacturer: National Institutes of Health (NIH), USA
This is a live attenuated tetravalent vaccine candidate that has shown promising results in early trials and is under trial evaluation in several countries.

of DENV-3 and its spread between African countries and subsequent dissemination after the religious mass gathering Grand Magal event. Subclinical cases exist and contribute to the spread.

Whilst all countries hosting mass gathering events have arbovirus control programs in place, it's obvious these are not sufficient to protect pilgrims or the local populations. 'Prevention is better than cure' as the old adage goes. This has been highlighted by the introduction and widespread use of yellow fever vaccines which are mandated for pilgrims travelling for the Hajj and which have been very effective. There are several available dengue vaccines, some under clinical evaluation in trials and other in development (Table 1) [21-23]. Two dengue vaccines have been licensed, Dengvaxia® (CYD-TDV), developed by Sanofi Pasteur, and Qdenga® (TAK-003), developed by Takeda. Two others are under development and evaluation – the Butantan-Dengue Vaccine (Butantan Institute in São Paulo state, Brazil) and TV003/TV005 (National Institutes of Health, USA) [24,25]. A single dose of Butantan-DV was generally well tolerated and efficacious against symptomatic VCD (caused by DENV-1 and DENV-2) for a mean of 3·7 years. These findings support the continued development of Butantan-DV to prevent Dengue disease in children, adolescents, and adults regardless of Dengue serostatus.

The licensing of new dengue vaccines now brings forth dialogue on opportunities for vaccination for pilgrims travelling to mass gathering religious events. Many travellers may come from non-endemic areas, where they have little to no immunity to Dengue since they have no prior exposure to dengue. Dengue virus-infected travellers returning to non-endemic countries could potentially introduce DENV into regions where the *Aedes spp* mosquito is present, but where Dengue is not yet widespread, for instance southern Europe [26]. Furthermore, dengue outbreak during or after a mass gathering event could overwhelm local healthcare systems, especially if the event is held in regions with limited medical and public health infrastructures. The question arises – should dengue vaccination be made mandatory for all travellers to mass gathering events in host countries where DENV is endemic, or *Aedes spp* vector is present and DENV may be introduced and transmission cycles propagated?

Mandating dengue vaccination is complex and depends on several factors. Risk-benefit analysis is an important consideration when recommending Dengue vaccines. For pilgrims coming from dengue endemic countries, the benefits of vaccination may outweigh the risks, especially for those who are seropositive. Given the risks associated with vaccinating seronegative individuals with the Dengvaxia vaccine, mandatory vaccination is not advisable and pre-vaccination serostatus must be determined. Thus before mandating vaccination, healthcare systems must establish infrastructure to screen for dengue serostatus, to ensure that only those who would benefit from the vaccine receive it. Mandatory vaccination raises ethical concerns, particularly regarding informed consent and individual autonomy. It is crucial to ensure that individuals or parents (in the case of children) understand the risks and benefits before receiving the vaccine. Ongoing surveillance would be needed to monitor vaccine effectiveness, and any potential adverse events and local pharmacovigilance capacities supported to monitor these.

Attendees of mass gathering events should now be considered 'high-risk groups' for acquiring dengue. Vaccination could be offered to travellers from non-DENV-endemic areas attending religious mass gatherings held in dengue endemic areas such as Saudi Arabia, Senegal and India, particularly for those staying for a few weeks. Prior to travel, pilgrims must be provided with detailed information on the risks of acquiring dengue, the availability of vaccines, their side effects and efficacy, and limitations. This needs to be coupled with educational leaflets on the importance of mosquito bite prevention measures and advised to use mosquito repellents and wear protective clothing. Organizers of mass gatherings must focus on implementing mosquito control measures before and during the event, around venues, and provide mosquito nets, and distribute insect repellents. Pilgrims must be encouraged to seek advice before traveling including the option of vaccination. Travelers returning from pilgrimage should be advised to look out for dengue symptoms and seek medical attention as soon as possible.

In conclusion, there appears a growing case for considering adding dengue vaccination for travellers to mass gatherings religious events in dengue-endemic regions of Saudi Arabia, India and West Africa, and this must be included as part of a broader infectious diseases' prevention strategy. However, due to the limitations of current vaccines, particularly the need for serostatus testing with Dengvaxia, and more evidence base of TAK-003 vaccine and Butantan-DV under evaluation is awaited, a blanket recommendation for mandatory vaccination is not yet practical. The Saudi and India public health authorities have pre-travel guidelines and regulations for pilgrims attending the Kumbh Mela or the Hajj and have a list of mandated and optional vaccines, Dengue vac-

cines should now be added to the list of optional recommended vaccines for travellers, with the caveat that serostatus screening to assess likely benefit be carried out prior to an individual receiving the vaccine.

Author declarations

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