

Review

Current status of dengue fever epidemics and vaccine development

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ABSTRACT

Dengue fever, an acute mosquito-borne infectious disease caused by dengue virus (DENV), is primarily endemic in tropical and subtropical regions. In recent years, the global incidence of dengue has increased dramatically. Since 2023, widespread outbreaks have been reported across numerous countries in the Americas, Asia and Africa. According to the World Health Organization, more than 5 million dengue cases were reported globally in 2023, while the number surged to over 14 million cases with more than 10,000 deaths in 2024—marking the highest global burden ever recorded. A similar upward trend has been observed in China, which experienced its largest dengue outbreak in a decade in 2024, with Guangdong Province accounting for the majority of domestically reported cases. These epidemiological patterns highlight the rapid expansion of dengue transmission, driven by climate change, accelerated urbanization and increased human mobility. In this context, vaccine development has become a public health priority. To date, two vaccines—Dengvaxia and Qdenga—have been licensed for clinical use. Six other vaccine candidates are currently in clinical trials, among which the tetravalent live-attenuated vaccines TV003/TV005 are considered the most promising. Despite considerable advances in dengue vaccine research, significant challenges remain, including the need to elicit balanced immune responses against the four serotypes and to reduce the risk of antibody-dependent enhancement (ADE). Taken together, this review systematically summarizes recent global and regional trends in dengue fever and the current progress in dengue vaccine development, collectively offering a valuable resource for informing prevention and control strategies.

INTRODUCTION

Dengue virus (DENV) belongs to the genus *Orthoflavivirus* in the family *Flaviviridae*. The genome is an approximately 11 kb, positive-sense and single-stranded RNA, encoding three structural proteins [the capsid protein (C), the precursor membrane protein (prM) and the envelope protein (E)] and seven non-structural proteins (NS1~NS5). Based on antigenic differences in the E protein, DENV is classified into four distinct but antigenically related serotypes (DENV-1–DENV-4) (Ma et al., 2022).

DENV is mainly transmitted by the bites of *Aedes aegypti* and *Aedes albopictus* mosquitoes. The clinical manifestations of infection are complex and varied. Most patients present with self-limiting dengue fever with nonspecific signs and symptoms, including fever, malaise,

nausea, vomiting, diarrhea, severe headache, and muscular and joint/bone pains. A small proportion of patients, however, may progress to life-threatening severe dengue, characterized by symptoms such as hemorrhage and shock.

It should not be overlooked that dengue fever has become a serious public health challenge in recent years, with expanding global outbreaks and a significant increase in morbidity. However, the pathogenic mechanism of dengue fever is still unclear. Antibody-dependent enhancement (ADE), which occurs during secondary infection with a heterologous serotype, is a major risk factor for severe dengue and a key obstacle to the development of an effective dengue vaccine. Therefore, this paper reviews the current epidemiological situation of dengue fever, especially the progress of vaccine investigation to provide reference for dengue prevention and control.

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CURRENT STATUS OF DENGUE FEVER EPIDEMICS

Status of the global epidemics of dengue fever

Dengue fever is the fastest spreading mosquito-borne viral disease worldwide. An estimated 390 million people are infected with DENV annually, of whom approximately 96 million develop clinical symptoms, posing a serious global health challenge. Dengue fever is currently endemic in more than 100 countries/regions, mainly in tropical and subtropical regions of the Americas, Asia, Africa and Australia (Cattarino et al., 2020).

According to reports from the World Health Organization (WHO), global dengue cases increased nearly tenfold between 2000 and 2019 (WHO, 2023a), placing approximately half of the world's population at risk of infection. In 2019 alone, approximately 5.2 million cases were reported, with 3.1 million concentrated in the Americas (Togami et al., 2023). Consequently, dengue was listed among the top ten global health threats that year (WHO, 2019b). At the same time, Bangladesh in Southeast Asia also experienced a major outbreak, recording 101,000 dengue cases and 164 deaths (Kayesh et al., 2023). Between 2020 and 2022, global dengue cases declined, likely due to the impact of the Coronavirus Disease 2019 (COVID-19) pandemic. This reduction in transmission increased the proportion of the population lacking immunity to certain DENV serotypes (Sharma et al., 2022; WHO, 2023a).

In 2023, the number of global dengue cases rose again. The WHO reported over 5 million cases and 5000 deaths across more than 80 countries/regions, with up to 4.1 million (nearly 80% of the total) in the Americas (WHO, 2023a). In Southeast Asia, Bangladesh recorded a significant increase in dengue infections, with 308,167 cases and 1598 deaths by November 2023 compared to 62,382 cases and 281 deaths reported in 2022 (Subarna and Saiyan, 2024). In Southeast Asia, Thailand experienced a threefold surge, with cases rising from 46,678 (34 deaths) in 2022 to 136,655 (147 deaths) in 2023. In Africa, the WHO reported 171,991 cases and 753 deaths in 2023 (WHO, 2023c). Notably, over 154,000 suspected cases (nearly 90% of the continental total) and 700 deaths were concentrated in Burkina Faso (Biohub, 2025). Meanwhile, countries and territories in the Western Pacific region reported over 500,000 infections and 750 deaths, with the Philippines being the hardest hit (WHO, 2023a, 2023b).

The global dengue epidemic intensified further in 2024. Since the beginning of 2024, a staggering 14 million dengue cases and more than 10,000 dengue-associated deaths were documented, marking an unprecedented peak (Venkatesan, 2024). The majority of cases remained concentrated in the Americas, where over 12 million suspected dengue infections were reported, indicating a dramatic escalation in risk (Venkatesan, 2024). In particular, Brazil has experienced the most severe dengue outbreak on record, with over 9.8 million cases reported as of November (European Centre for Disease Prevention and Control, 2024).

Building on this upward trend, dengue activity has remained persistently high in 2025. Between January and July 2025, more than 4 million cases and over 3000 dengue-associated deaths were reported across 97 countries, highlighting that the rapid global expansion of dengue transmission has continued unabated (WHO, 2025).

Current status of dengue fever epidemic in China

DENV is also prevalent in some regions of China (Yuan and Wang, 2005). In the early 1940s, dengue fever became endemic in the southeastern provinces of China (Mao and Zhang, 2007). Since the beginning of the 21st century, accelerated urbanization, increased tourism, expanded commercial trade, and population migration have further expanded the endemic areas of dengue fever in China, thereby increasing the risk of transmission as well as the difficulty of prevention and control (Liu, 2020). Currently, it is estimated that about 168 million people live in high-risk areas in China (Wu et al., 2022).

Notably, the number of provinces reporting indigenous cases of dengue fever has continuously increased, with notable epidemic peaks occurring in 2014, 2019 and 2023 (Fig. 1). For instance, in 2014, China experienced an unprecedented outbreak, recording 46,105 autochthonous cases, the majority of which were in Guangdong. Between 2014 and 2018, a total of 59,183 autochthonous cases (distributed in 314 districts and counties of 13 provinces) and 5458 imported cases (distributed in 734 districts and counties of 29 provinces, with 50% in Yunnan) were reported in the mainland of China (Yue, Y. et al., 2019). During the period 2019–2023, case numbers of dengue fever in China showed a distinct epidemiological pattern. The years 2019 and 2023 were characterized by large-scale outbreaks, with a notably high incidence of 1.57/100,000 (22,188 cases) in 2019 and 1.38/100,000 (19,541 cases) in 2023, accounting for 96.83% of the total number of reported cases in the last five years (Li et al., 2024). During 2020–2022, COVID-19 restrictions significantly reduced dengue cases in China, resulting in only 1185 autochthonous cases and 217 imported cases, primarily distributed in Yunnan, Guangdong, and Guangxi. These numbers were substantially lower than those recorded in 2019 and 2023 (Yue, Y.J. et al., 2023a; Yue, Y.J. et al., 2023b).

According to the National Disease Control and Prevention Administration (<https://www.ndcpa.gov.cn/jbkzzx/c100016/common/list.html>), a total of 24,330 dengue cases were reported nationwide in 2024. The epidemic was sporadic during the first half of the year, with fewer than 200 cases reported monthly from January to June. Case numbers surged from July onwards, reaching a peak between August and October, with October recording the highest monthly count of 11,083 cases. The epidemic also exhibited clear regional differences, with localized outbreaks most severe in Guangdong, where over 8000 cases were reported in October, representing the majority of infections nationwide. Although severe cases occurred, no fatalities were documented (Guangdong Provincial Center for Disease Control and Prevention, https://cdcp.gd.gov.cn/zwgk/yqxx/content/post_4581884.html).

From January to December 2025, a total of 10,007 dengue cases were reported nationwide (<https://www.ndcpa.gov.cn/jbkzzx/c100016/common/list.html>). The epidemic remained relatively mild during the first six months, with monthly cases below 100. Beginning in July, cases rose steadily through August, September, and October, with the highest monthly count reaching 3737 in October, indicating an overall improvement compared with the previous year. Localized outbreaks continued, with Guangdong reporting 1610 cases from October 1 to October 30, accounting for the majority of infections nationwide (https://wsjkw.gd.gov.cn/gkmlpt/content/4/4796/post_4796639.html#2571).

Risk factors for dengue epidemic

In recent years, global warming has accelerated the worldwide spread of dengue fever, while also extending the active season of vector mosquitoes, leading to a longer transmission cycle. Temperature and rainfall have been found to play a more critical role in mosquito reproduction and virus transmission. Higher temperatures accelerate the rate of DENV multiplication in mosquitoes and shorten the external incubation period of infection (Modak et al., 2023). Rainfall creates standing water that provides ideal breeding sites for *Aedes aegypti*, significantly influencing its population density and composition (Kraemer et al., 2015). Moreover, driven by climate change, dengue fever is spreading to higher altitude in temperate and colder regions. For example, new dengue epidemics have been recorded in Spain, Portugal, the southern United States and Nepal (Kraemer et al., 2015; Pandey and Costello, 2019; Kretschmer et al., 2023).

In addition, increased urban population density, expanded global trade, and travel have facilitated the movement of DENV-infected people across regions, leading to further expansion of transmission (Guo, 2018; Messina et al., 2019). Finally, public sanitation, which shapes the

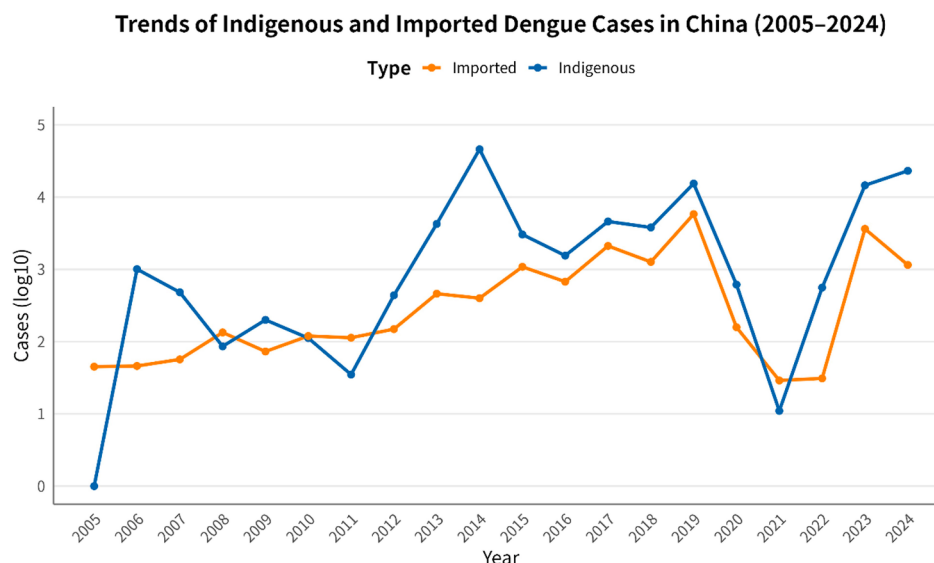


Fig. 1. Trends of indigenous and imported dengue cases in China (2005–2024). Data on dengue cases in China from 2005 to 2024 were compiled from published reports (Yue Y. et al., 2022; Yue et al., 2023a; Yue Y. et al., 2025) as well as from official statistics provided by the National Disease Control and Prevention Administration and the Guangdong Provincial Center for Disease Control and Prevention. Blue line indicates indigenous (locally transmitted) dengue cases in China, while the orange line represents imported dengue cases in China.

living environment of mosquito vectors, also influences the distribution and transmission of dengue fever (Messina et al., 2019).

Indeed, DENV can also gain transmission advantages through antigenic drift and genotype replacement. It has been suggested that the evolutionary success and continued prevalence of DENV are due in part to the interactions among its serotypes. Such interactions, through the mechanism of antibody-dependent enhancement (ADE), can exacerbate disease severity (Williams et al., 2014), which may indirectly influence transmission dynamics.

Meanwhile, it has been shown that two adjacent mutations at residues 226 (T226K) and 228 (G228E) on the DENV envelope protein can synergistically enhance viral infectivity in both mosquito vectors and mammalian hosts. This synergistic effect not only drives lineage replacement but also promotes the widespread circulation and epidemic expansion of DENV-2 in Southeast Asia (Chen et al., 2022). These findings not only offer a scientific explanation for the large-scale sustained epidemics of dengue fever from the perspective of genetic evolution but also provide an important basis for early warning of future dengue pandemics (Pollett et al., 2018).

RECENT DEVELOPMENTS OF DENGUE VACCINES

There is currently no specific treatment for dengue fever, so it is imperative to develop an effective dengue vaccine. Given that DENV has four serotypes, an ideal vaccine should be safe and able to induce a relatively balanced immune response against all serotypes. However, the presence of ADE is a major challenge in dengue vaccine development. Two licensed vaccines (Dengvaxia and Qdenga) and one vaccine in Phase III clinical trials (TV003/TV005) are the most advanced, while other candidates are in earlier stages of development (Table 1).

Licensed dengue vaccines

Dengvaxia (CYD-TDV)

Dengvaxia (CYD-TDV) is the world's first dengue vaccine developed by Sanofi. It is a tetravalent, live-attenuated vaccine consisting of four chimeric viruses. In other words, the *prM* and *E* genes of the yellow fever

vaccine (YF17D) were replaced by the corresponding genes from each of the four DENV serotypes (Fig. 2A) (Thomas and Yoon, 2019). Administered on a three-dose schedule (0, 6, and 12 months), CYD-TDV demonstrated satisfactory safety and immunogenicity in preclinical studies and Phase I/II clinical trials involving both flavivirus-naïve and flavivirus-exposed individuals, thereby inducing both humoral and cellular immune responses against all four serotypes. Building on these findings, CYD-TDV entered larger clinical trials to assess its efficacy in children. As part of its clinical development, Sanofi conducted three main efficacy trials. A proof-of-concept Phase IIb clinical trial (CYD23) in a Thai population aged 4–11 years evaluated the efficacy of CYD-TDV against virologically confirmed dengue (VCD). The vaccine efficacy was 30.2% (95% confidence interval [CI]: –13.4–56.6), but poor protection against DENV-2 was observed with an efficacy rate of 3.5% (95% CI: –59.8–40.5) (Sabchareon et al., 2012).

Sanofi subsequently completed two pivotal Phase III trials in Asia (10,275 children aged 2–14 years, CYD14) (Capeding et al., 2014) and Latin America (A total of 20,869 children and adolescents aged 9–16 years, CYD15) (Villar et al., 2015). In these two trials, the overall efficacy against virologically confirmed dengue (VCD) was 56.5% (95% CI: 43.8–66.4) in CYD14 and 60.8% (95% CI: 52.0–68.0) in CYD15. The number of serious adverse events was 647 (402 in the vaccine group and 245 in the control group) and 983 (630 in the vaccine group and 353 in the control group), respectively (Capeding et al., 2014; Hadinegoro et al., 2015). In addition, the serotype-specific vaccine efficacy against VCD in CYD14 ranged from 35% (DENV-2) to 78.4% (DENV-3). In CYD15, vaccine efficacy was highest against DENV-4 (77.7%) and lowest against DENV-2 (42.3%) (Capeding et al., 2014; Hadinegoro et al., 2015). Both CYD14 and CYD15 demonstrated relatively low efficacy against DENV-2. Consequently, in the long-term follow-up, CYD-TDV showed more protective in individuals over 9 years old which has the lowest risk of hospitalization for VCD (Hadinegoro et al., 2015).

Collectively, these two clinical trials encompassed data from ten countries across diverse populations (varying in age and ethnicity) and epidemiological seasons (differing in prevalent serotypes and epidemic intensity), thereby providing consistent and comprehensive evidence on the efficacy and safety of CYD-TDV (Hadinegoro et al., 2015). Based on

Table 1

Brief overview of licensed and investigational dengue vaccines.

Vaccine name	Vaccine type	Research and development phase	Main features	Recommended people and vaccination schedule	Limitations
Dengvaxia (CYD-TDV)	Tetavalent, live attenuated vaccine	Approved for marketing	A chimeric vaccine, developed by Sanofi, was constructed based on the yellow fever 17D backbone (Thomas and Yoon, 2019).	CYD-TDV should be limited to use in people aged 9–45 years with previous DENV infection. The schedule consists of three doses, with a six-month interval (WHO, 2024).	Moderate efficacy overall, poor protection against DENV-2, and increased risk of severe disease and hospitalization in seronegative or younger children (<9 years).
Qdenga (TAK-003)	Tetavalent, live attenuated vaccine	Approved for marketing	A chimeric vaccine, developed by Takeda Pharmaceuticals, was built with attenuated DENV2 (PDK-53) cDNA backbone (Huang et al., 2013).	WHO recommends 6–16-year-olds in high dengue disease burden and high transmission intensity areas receive 2 vaccine doses, 3 months apart (Freedman, 2023).	Waning efficacy over time, limited protection against DENV-3 in seronegative populations, and insufficient evaluation of efficacy against DENV-4.
TV003/TV005	Tetavalent, live attenuated vaccine	Of the two, only TV003 is in Phase III trials	A chimeric vaccine, developed by the NIAID, was constructed by deleting 30 or 31 nucleotides from the 3'UTR of a wild strain (Kirkpatrick et al., 2015; Durbin et al., 2016).	The TV003/TV005 vaccine is administered with a single dose (McArthur and Edelman, 2015).	No phase III efficacy data for TV005, limited evaluation for DENV-3/4, and waning immunity in young children.
TDENV-LAV & TDENV-PIV	Live attenuated vaccine & purified inactivated vaccine	Clinical Phase I or II trials completed	Two vaccines developed by GlaxoSmithKline (Lin et al., 2020, 2021).	Heterologous prime-boost vaccination showed superior efficacy over homologous. Two schedules: LAV at 180 or 90 days post PIV (General and Army, 2019).	Early-phase data only, limited efficacy, and long-term protection unconfirmed.
V180	Tetavalent, recombinant subunit vaccine	Clinical Phase I trial completed	A subunit vaccine, developed by MSD, was composed of 4 serotypes of truncated E proteins (DEN-80 E)	It has not yet been determined.	Phase I only; efficacy and long-term protection unknown.
TVDV	Tetavalent DNA vaccine	Clinical Phase I trial completed	Vaccine developed by the US Naval Medical research Center based on the sequences of four serotypes of prM and E proteins.	It has not yet been determined.	Phase I only; mainly T-cell responses, limited antibody induction, long-term efficacy unknown.
PepGNP-dengue	Gold nanoparticle-based multivalent synthetic peptide vaccine	Clinical Phase I trial completed	Multivalent synthetic peptide vaccine developed by Emergex, UK	It has not yet been determined.	Phase I only; T-cell responses only, long-term efficacy unknown.

these data, CYD-TDV was first approved in Mexico in December 2015 and is now licensed in twenty dengue-endemic countries/regions.

However, subsequent clinical studies have shown that CYD-TDV provides poor protection in younger children (aged 2–8 years) and increases the risk of severe illness and hospitalization in seronegative vaccinees (Sridhar et al., 2018). As a result, WHO revised its position paper to recommend that CYD-TDV be limited to use in people aged 9–45 years with a previous DENV infection (WHO, 2019a). In May 2019, the US Food and Drug Administration (FDA) approved Dengvaxia for use in children and adolescents aged 9–16 years residing in dengue-endemic areas who have a laboratory-confirmed prior DENV infection (FDA, 2023).

Qdenga (TAK-003)

Qdenga (TAK-003), developed by Takeda Pharmaceuticals (Takeda), is also a quadrivalent, live-attenuated vaccine based on an attenuated DENV-2 (PDK-53) backbone containing the *prM* and *E* genes of the other three types of DENV (Fig. 2B) (Huang et al., 2013). The vaccine should be administered in two doses separated by a three-month interval. TAK-003 demonstrated both safety and immunogenicity in flavivirus-seronegative individuals aged 18–45 years in Phase I clinical trials (Osorio et al., 2014; George et al., 2015; Rupp et al., 2015). The following Phase II clinical data in children and adolescents aged 2–17 years in Asia and Latin America showed that TAK-003 induced immune responses against all four DENV serotypes in both seropositive and seronegative participants, regardless of baseline serostatus. Meanwhile, antibody responses persisted for up to 48 months post-vaccination, and no significant safety risks were observed. Especially, the risk of symptomatic dengue reduced persistently in vaccinated individuals (Sáez-Llorens et al., 2017, 2018; Tricou et al., 2020).

To further evaluate the efficacy, safety and immunogenicity of TAK-003 in healthy children, Takeda undertook the largest Phase III clinical trial to date (Tetavalent Immunization against Dengue Efficacy Study, TIDES), which recruited more than 20,000 children and adolescents (aged 4–16 years) from 8 dengue-endemic countries in Asia and Latin America, with a pre-vaccination dengue seroprevalence rate of approximately 70% in the study population (Wilder-Smith, 2024b). To assess the safety and long-term efficacy of the vaccine, Takeda conducted follow-ups at 1, 1.5, 3, and 4.5 years after the primary two-dose schedule (Biswal et al., 2019, 2020; Rivera et al., 2022; Tricou et al., 2024). Although the vaccine's efficacy against VCD diminished with time, the 4.5-year data still demonstrated long-term protection (Tricou et al., 2024), and the cumulative vaccine efficacy of TAK-003 was 61.2% (95% CI: 56.0–65.8) against VCD and 84.1% (95% CI: 77.8–88.6) against hospitalized dengue. Vaccine efficacy varied by baseline serostatus and serotype, with higher efficacy observed in seropositive populations, ranging from 52.3% against DENV-3 to 80.4% against DENV-2. Especially, TAK-003 provided the best protection against DENV-2, irrespective of the population's serostatus. Overall, TAK-003 was well tolerated, and no significant safety risks or enhancement of infection was indicated during the observation period. Of note, in the seronegative population, TAK-003 was effective against DENV-1 (45.4%) and DENV-2 (88.1%) but not DENV-3, and Takeda did not evaluate the protective effect of DENV4 due to the low prevalence of DENV-4 during the study period (Tricou et al., 2024). Furthermore, the rate of serious adverse events were similar between the TAK-003 and placebo groups, irrespective of baseline serostatus (For the seropositive subjects: 6.0% (291/4854) adverse events in the placebo group and 5.0% in the TAK-003 group (481/9663); For seronegative subjects: 5.7% (105/1832) adverse events in the placebo group and 4.9% (183/3714)

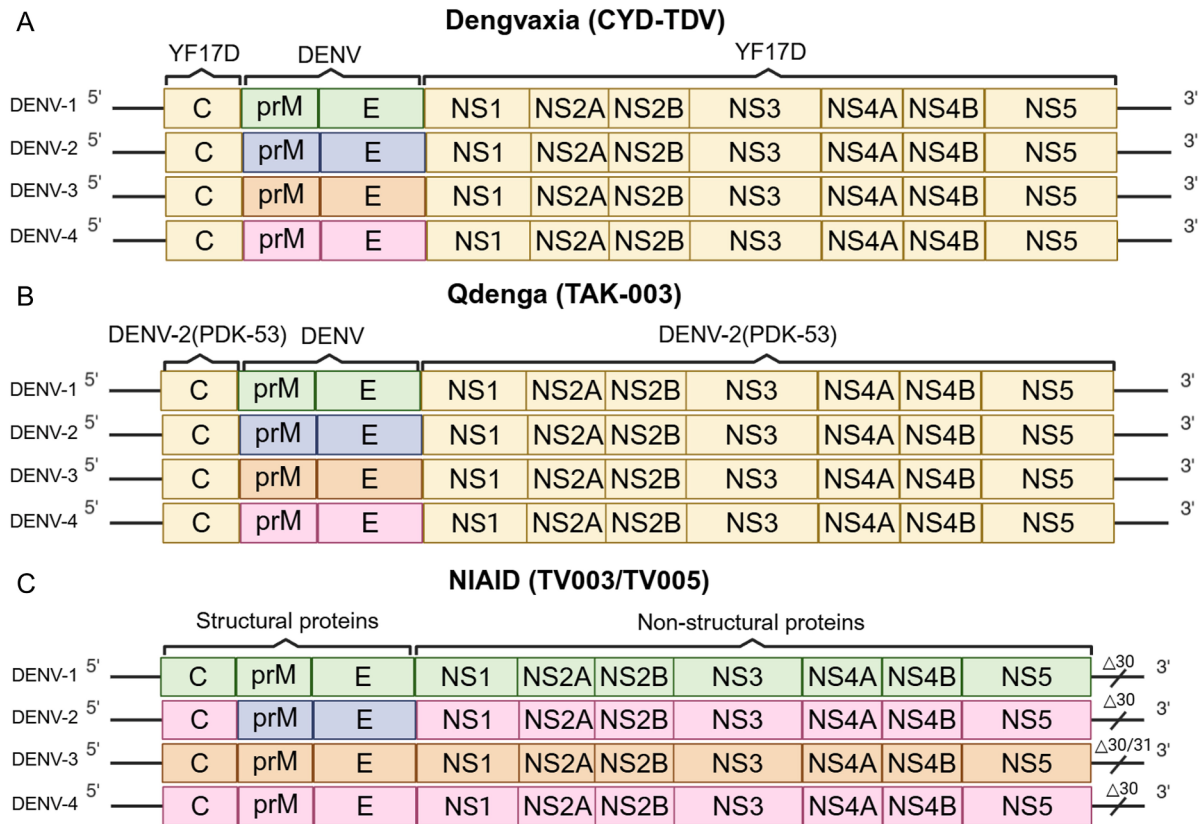


Fig. 2. Vaccine Structure Diagrams. **A** Dengvaxia (CYD-TDV) contains four chimeric viruses, where the *prM* and *E* genes of YF17D are replaced by those from each DENV serotype. **B** Qdenga (TAK-003) is a quadrivalent, live-attenuated vaccine based on an attenuated DENV-2 (PDK-53) backbone with *prM* and *E* genes from the other three DENV types. **C** TV003/TV005 (LAV Δ_{30} or TetraVax-DV) is an attenuated vaccine constructed by deleting 30 or 31 nucleotides from the 3' untranslated region (3'UTR) of the genome, and the DENV-2 component was a chimeric strain based on the rDENV-4 Δ_{30} backbone.

in the TAK-003 group) (Tricou et al., 2024). Clinical studies of TAK-003 are still ongoing to further evaluate long-term safety and protective efficacy.

In August and December 2022, TAK-003 was approved in Indonesia for individuals aged 9–45 years and in the European Union for those aged 4 years and above, respectively. However, Takeda withdrew the biologics licence application (BLA) for TAK-003 from the US FDA in July 2023 due to the insufficient data collection during the review cycle (Takeda, 2023).

There is no doubt that TAK-003 has superior efficacy compared to CYD-TDV in children under 9 years of age. In September 2023, WHO's Strategic Advisory Group of Experts on Immunisation (SAGE) recommended the inclusion of TAK-003 in routine immunisation programmes for individuals aged 6–16 years in high-burden areas, defined as a population seropositivity threshold of 60% or higher. Specifically, SAGE mentioned that pre-vaccination background screening is unnecessary. However, WHO has not yet endorsed the planned vaccination with TAK-003 in low and medium endemic areas, pending a more comprehensive assessment of its efficacy and risk profile against DENV-3 and DENV-4 in seronegative populations (Freedman, 2023). In a recent update, TAK-003 reached a significant milestone by receiving prequalification from WHO on May 10, 2024, making it the second dengue vaccine to achieve this recognition.

Other dengue vaccine candidates

TV003/TV005

TV003/TV005 (LAV Δ_{30} or TetraVax-DV), developed by the National Institute of Allergy and Infectious Diseases (NIAID) of the National

Institutes of Health (NIH), was constructed by deleting 30 or 31 nucleotides from the 3' untranslated region (3'UTR) of the genome of a wild strain to obtain an attenuated strain (rDENV Δ_{30}). Since rDENV-2 Δ_{30} is not sufficiently attenuated, the DENV-2 component of the vaccine was created by substituting the *prM* and *E* genes of DENV-2 into the rDENV-4 Δ_{30} backbone to produce the chimeric strain rDENV2/4 Δ_{30} (Fig. 2C) (Whitehead, 2016). Five single-dose tetravalent formulations were developed by NIAID, of which TV003 and TV005 were the most promising vaccine candidates due to their optimal immunogenicity and safety. TV003 and TV005 share the same four monovalent components (rDENV-1 Δ_{30} , rDENV-2/4 Δ_{30} , rDENV-3 $\Delta_{30}/31$, and rDENV-4 Δ_{30}), with the only difference being that TV005 contains a 10-fold higher dose of rDENV-2/4 Δ_{30} component to compensate for its relative under-attenuation in the TV003 formulation. TV003 and TV005 have been extensively tested in Phase I and II clinical trials, and the vaccines have been shown to generate a robust and balanced tetravalent neutralising antibody response with a single dose (Kirkpatrick et al., 2015; Durbin et al., 2016).

TV003/TV005 are currently licensed to several manufacturers in low-to middle-income countries (e.g., Instituto Butantan in Brazil, Vabiotech in Vietnam, Panacea Biotech and Serum Institute in India). The technology transfer, covering validation of core assays, vaccine preparation and regulatory expertise, is expected to help build local capacity for conducting clinical vaccine trials (Whitehead, 2016; Wilder-Smith, 2024a).

Butantan received the authorisation for TV003 from NIH in 2009 (i.e., Butantan-DV). Completed Phase II studies have shown that a single dose of Butantan-DV induces a robust and balanced neutralising antibody response, with a seroconversion rates of exceeding 76% against all

four serotypes of DENV, and significant CD8⁺ T-cell responses (Kallas et al., 2020). Theoretically, Butantan-DV could induce a safer and broader protective immune response than vaccines that express only DENV structural proteins or those that contain non-structural proteins from a single DENV serotype. On this basis, Butantan initiated a Phase III clinical study in Brazil in 2016 and partnered with Merck Sharp & Dohme (MSD) in 2018 to accelerate the development of Butantan-DV (Butantan, 2022-12-16; Butantan Institute, 2022). Preliminary data obtained so far have shown that the overall vaccine efficacy at 2 years post-vaccination is 79.6% (95% CI: 70.0–86.3), regardless of serum background (Butantan Institute, 2022). A single dose of Butantan-DV protects against symptomatic DENV-1 and DENV-2 irrespective of seroprevalence. No efficacy data are available for DENV-3 and DENV-4, as these serotypes were not endemic in Brazil during the trial period (Kallás et al., 2024), and follow-up is still ongoing.

In addition, facilitated by the Dengue in Dhaka Initiative (DIDI), a Phase II clinical study of TV005 has just been completed in Bangladesh to assess its safety and immunogenicity. Irrespective of age and baseline serostatus, TV005 triggered a robust multi-serotype immune response, with the majority of vaccinated adults and adolescents remaining seropositive throughout the three-year period. However, the rapid decline in neutralising antibody concentrations in younger children (1–4 years) raises concerns, and further clinical studies are required to determine whether booster doses are necessary for this age group (Walsh et al., 2024). The efficacy of the TV005 vaccine has not been evaluated in a Phase III trial yet.

Other vaccines already in clinical trials

GlaxoSmithKline (GSK) has developed two dengue vaccines: a quadrivalent live-attenuated vaccine (TDENV-LAVPDK) and a purified inactivated vaccine (TDENV-PIV), with each having completed Phase I or Phase II clinical trials, respectively. In particular, a prime-boost heterologous immunisation strategy, in which inactivated vaccines are followed by live-attenuated vaccines, has been shown to elicit a robust immune response (Lin et al., 2020, 2021).

MSD's quadrivalent recombinant subunit vaccine, V180, is based on the N-terminal 80% fragment of the E protein (DEN-80E) from each of the four serotypes. This design ensures extracellular secretion and ease of purification while preventing serotype interference. When formulated with ISCOMATRIX™ adjuvant, V180 demonstrated good tolerability and high immunogenicity in Phase I studies (Manoff et al., 2019). In addition, in subsequent studies conducted in collaboration with NIAID, V180 was shown to further enhance the immune response in individuals previously vaccinated with TV003 or TV005 (Durbin et al., 2020).

The US Naval Medical Research Center developed a tetravalent DNA vaccine (TVDV) based on the prM and E protein sequences of the four serotypes. In a Phase I trial, TVDV formulated with Vaxfectin adjuvant induced specific T-cell responses but not neutralising antibodies in most participants, possibly due to the type of adjuvant, immunisation strategy or route of administration (Danko et al., 2018).

Emergex in the UK has developed a gold nanoparticle-based multi-valent synthetic peptide vaccine (PepGNP-Dengue) to minimize the risk of ADE. Results from a recently completed Phase I trial in Switzerland showed that PepGNP-Dengue successfully induced virus-specific CD8⁺ T cells and dextramer⁺ memory T cell subsets, but not DENV-specific antibodies (Miauton et al., 2024). This vaccine represents a novel strategy for dengue vaccine development.

Emerging technologies in dengue vaccine development

In recent years, the integration of innovative biotechnological approaches has ushered in a new era of transformative opportunities in dengue vaccine development. Messenger RNA (mRNA) vaccines and artificial intelligence (AI)-driven strategies offer promising solutions to the long-standing challenges in dengue vaccination, including achieving

broad coverage across all serotypes, minimizing the risk of ADE and inducing a balanced immune response.

mRNA-based dengue vaccines

In contrast to traditional vaccines that employ live-attenuated or chemically inactivated viruses, mRNA vaccines make use of artificially designed RNA molecules that encode dengue virus proteins. After entering host cells, these transcripts are processed by the cellular translation machinery to generate viral antigens, which subsequently trigger both antibody-mediated and T cell-mediated immune responses. To ensure stability and efficient intracellular delivery, the RNA is packaged within lipid nanoparticles (LNPs), which protect it from degradation and enhance its expression in target cells, thereby improving the overall potency and reproducibility of the vaccine (Anumanthan et al., 2025).

Using this platform, investigators have recently developed an mRNA-LNP vaccine that expresses the prM-E proteins of dengue virus serotype 1 (DENV-1). This vaccine has shown strong immunogenicity in experimental models. In immunocompetent mice, it elicited high titers of neutralising antibodies along with a robust cellular immune response, while in immunodeficient mice it provided significant protection against lethal viral challenge. Notably, the immune protection generated by this vaccine was serotype-specific and did not induce ADE (Wollner et al., 2021).

Additional studies on dengue virus serotype 2 (DENV-2) have highlighted the role of the N8 epitope within the E protein in mediating cross-reactivity and contributing to infection enhancement. When the N8 site was modified (N8R-mRNA-LNP), vaccinated animals developed stronger neutralising responses, exhibited reduced ADE, and showed improved protection compared with those given the wild-type construct. These results demonstrate that mRNA-LNP vaccines represent a promising strategy for developing a safe and broadly protective tetravalent dengue vaccine, effectively addressing the limitations associated with conventional vaccines (Kumari et al., 2025).

Artificial intelligence in vaccine design

The application of artificial intelligence (AI) to vaccine research has accelerated the identification and optimization of immunogenic targets through data-driven methodologies. Leveraging machine learning, structural bioinformatics, and immunoinformatics, AI has redefined the paradigm of vaccine discovery, especially under the framework of reverse vaccinology. In the context of dengue, where epitope variability and serotype cross-reactivity complicate traditional vaccine development, AI provides a means to model and predict immune interactions at an unprecedented scale and resolution.

Recent studies have demonstrated that AI algorithms can accurately predict B-cell and T-cell epitopes across all DENV serotypes, rank them by immunodominance and population HLA coverage, and design multi-epitope constructs to minimize the risk of ADE. Additionally, AI facilitates the identification of novel adjuvants and delivery systems by screening vast chemical and biological libraries. For instance, recent studies have demonstrated that the deep learning models can rapidly narrow down thousands of antigenic candidates for further experimental validation (Asediya et al., 2024; Elfatimi et al., 2025). These methodologies have already contributed to the preclinical design of dengue vaccines (Ali et al., 2017), with implications extending to other flaviviruses such as West Nile virus and Japanese encephalitis virus.

Moreover, AI-guided modeling can simulate host-pathogen interactions, forecast antigen evolution under selective immune pressure, and personalize vaccine formulations based on regional serotype prevalence and host genetic profiles. This integrative approach enhances both the precision and efficiency of vaccine pipelines. As the availability of high-quality viral sequence data and host immunological datasets increases, AI-driven platforms are expected to play an increasingly important role in the rational development of next-generation dengue vaccines.

CONCLUSION

This review summarizes the current status of the global dengue epidemic and the progress of vaccine development. Multiple interrelated factors—including climate change, rapid urbanization, expanding global trade, increased international travel, and the continuous evolution of DENV genotypes—have collectively accelerated the global spread of dengue and led to the annual expansion of its endemic range. The situation remains critical, with more than 10 million cases and thousands of deaths reported annually across many regions.

Although no specific antiviral treatment is available, significant advances in dengue vaccine research have been made. To date, two vaccines, Dengvaxia and Qdenga, have been licensed for prophylactic use. However, challenges remain, such as unbalanced immune responses among different serotypes, limited protection in younger children, and the persistent risk of ADE. These obstacles continue to hinder the development of safe and broadly effective vaccines.

Emerging technologies offer promising solutions. In particular, the mRNA platform enables the design of vaccine candidates encoding conserved or chimeric antigens to achieve cross-serotype protection and balanced immunity. Precise epitope targeting, codon optimization, nucleotide modification, and improved delivery vectors further enhance antigen expression and immune responses, while potentially reducing the risk of ADE. Preclinical studies have already demonstrated that dengue mRNA vaccines can elicit both neutralising antibodies and T-cell responses. At the same time, the rapid progress of AI-assisted vaccine design—including epitope prediction, immunogen optimization, and adjuvant screening—has greatly accelerated the identification of promising candidates. AI-driven reverse vaccinology approaches have shown great potential for developing future vaccines against DENV and other flaviviruses.

Beyond vaccines, the following measures remain indispensable: strengthening epidemic surveillance, implementing sustainable vector control, raising public awareness, and advancing antiviral drug research. Looking forward, continued international collaboration and knowledge sharing will be crucial to overcoming the challenges of dengue and reducing its global public health burden.

CONFLICT OF INTEREST

The authors declare no conflicts of interest. Prof. Jing An is an editorial board member for *Virologica Sinica* and was not involved in the editorial review or the decision to publish this article.

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