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Dengue: Tetravalent Live-Attenuated Vaccine Towards the Triumph

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Abstract

Dengue is an expanding global health problem causing millions of infections each year. There is no exact medication for dengue other than case management. Therefore, the potential use of an efficient tetravalent vaccine against dengue would denote a remarkable addition to the prevention of this disease. This review will provide a survey of trials and tribulations on the path of developing a live-attenuated dengue vaccine. Most vaccine efforts against dengue have been focused on formulating a live-attenuated vaccine and these are the furthest along in clinical development. The induction of antibodies that are effective against all four dengue virus serotypes and provide protection in all age groups, regardless of dengue baseline serostatus, are considered as major challenges of developing a live attenuated vaccine for dengue. After decades of research, the development of a dengue vaccine has achieved a major milestone with the approval of Sanofi's Dengvaxia (CYD-TDV) in twenty countries. However, as recent clinical trial data of Dengvaxia suggests a signal of vaccine-related harm among seronegative individuals, the necessity of a safe vaccine which is effective regardless of the serostatus remains crucial.

Keywords

Dengue; Vaccine; Live-Attenuated; Trivalent; Tetravalent; Antibodies; Serotype; Immunogenic; Efficacy; Formulation

Introduction

Dengue is a *Flavivirus* with a single-stranded positive sense RNA genome. The mature virion is comprised of multiple copies of three structural proteins; envelope (E), pre-membrane (prM), capsid (C), and seven non-structural (NS) proteins which are necessary for the virus replication [1]. There are four dengue virus serotypes (DENV1-4) which are genetically diverse and differ by 25% to 40% at the amino acid level. The genetic variations between serotypes have enhanced the adaptation of dengue virus (DENV) strains, resulting in mutant variants that differ in their ability to transmit and cause the disease [2,3].

The disease has distributed in most tropical and many subtropical regions, generating a significant burden and economic cost in endemic countries [4]. From 2010 to 2015 the number of cases reported to the World Health Organization (WHO) has increased from 2.2 million to 3.2 million [5]. In Sri Lanka, the first documented dengue outbreak occurred in 1965-1966 [6], and in 2017, there were 186,101 reported cases of dengue [7].

The virus is transmitted to humans mostly by *Aedes aegypti* and *Aedes albopictus*, which are urban day-biting mosquitoes. Hence, insecticide-treated bed nets that have been vital for malaria control are ineffective [8]. Since vector control is difficult to sustain, public health authorities called for the development of a vaccine against dengue. The indication of formulating a tetravalent dengue vaccine which could induce antibodies against all four serotypes was nominated at the WHO South East Asian regional conference in Singapore as early as 1978 [9]. The feasibility of development of a dengue vaccine was mainly influenced by the successful development of a live-attenuated vaccine for Yellow Fever (YF) virus, which is a virus belonging to the same family as dengue [10].

Challenges in the Development of a Vaccine for Dengue

Infection with dengue has been shown to confer lasting protection against homotypic re-infection, supporting the feasibility of a dengue vaccine. Studies show that neutralizing antibodies can mediate the protective immunity against dengue, particularly those targeting the E glycoprotein [11]. However, limited cross-protection among the four DENV serotypes have combined with the risk that pre-existing heterotypic immunity may enhance the disease severity leading to Dengue Shock Syndrome/Dengue Hemorrhagic Fever (DSS/DHF). The existence of viral interference among strains, where the immune response against one or more serotypes dominates over the other, is problematic in tetravalent dengue vaccine development [12].

As dengue is a significant health problem in many resource-poor countries, the vaccine must be manufactured economically, which is challenging as the vaccine must comprise antigens from all four serotypes and must be tested among different ethnicities [13].

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Moreover, due to the vague immunity against DENV infection [14,15] and lack of reliable animal models [16], the vaccine efficacy must be measured as protection from infection following vaccination of humans [17], which further complicates the dengue vaccine development.

Approaches of Live-Attenuated Dengue Vaccine

The first successful dengue vaccine was stated in 1945 by Sabin and Schlesinger, who attempted to serial passage the "Hawaiian" strain of DENV through mouse brain which resulted in virus attenuation in humans [18]. The fifteenth mouse-passaged virus was used as a vaccine to defend sixteen volunteers against dengue infection and the approach reported to be safe [18,19]. In 1963, this work concluded in a field efficacy trial in Puerto Rico in which partial defense of individuals who administered DENV-1 vaccine was observed during a heterologous DENV outbreak [20]. However, in 1971, the US Army ultimately drove the production of mouse brain vaccine towards a theoretically safer production substrate, initiating the modern era of DENV propagation in tissue culture testing [21].

The Tissue Culture Passaging

Following the discovery by Halstead that DENV could be propagated serially in cell lines including Primary Dog Kidney (PDK) and Green Monkey Kidney (GMK) cells [21], the passaging was done simultaneously at Walter Reed Army Institute of Research (WRAIR) and Mahidol University. The WRAIR-produced initial vaccine formulation strains were tested in flavivirus-naive adults as monovalent or tetravalent vaccines. Some recipients who were subjected to the tetravalent vaccine did not seroconvert to all four serotypes suggesting the potential risk of DHF in partially immune individuals [22].

Later, influenced by the possibility that one or more serotypes in the tetravalent combination could either improve or suppress the immunogenicity, replication, or reactogenicity of other vaccine serotypes, another sixteen live-attenuated vaccine formulations were developed. Although seven formulations induced at least a trivalent response, no formulation was detected to induce a tetravalent response in every individual [23].

Subsequently, a new formulation (Formulation 17) was designed to induce a balanced tetravalent neutralizing antibody and cell-mediated immunity response in cynomolgus macaques [24]. Following the assurance of safety of this formulation [25], the study was expanded in a phase II trial where the formulation 17 was tested side by side with two of the previous formulations (Formulation 13 and 14). Compared to the older formulations, the formulation 17 found to be less reactogenic and more immunogenic [26], thus, selected for advanced studies including a phase I/II trials in infants which further assured its safety [27]. Later, this formulation (designated F17/Pre) was used as a precursor to produce two different formulations of a new DENV vaccine designated TDEN (F17 and F19). Although new formulations were seemed to be immunogenic and safe, the protective efficacy required advanced evaluations [28].

The initial formulations of vaccine strains produced at Mahidol University were tested in Thai adults. Although the vaccine was safe, some tetravalent recipients did not seroconvert to DENV4 [29]. The vaccine strains designed by Aventis Pasteur were found to be more reactogenic in tetravalent formulation and neutralizing antibody responses were directed primarily towards DENV3 [30]. The vaccine was capable of inducing the virus specific T-cell responses but those responses were not equivalent to the four serotypes [31].

With the purpose of achieving a more balanced antibody response, Sabchareon and his colleagues selected seven tetravalent vaccine formulations of Aventis Pasteur and tested in Thai adults. The selected formulations were differing in the total viral dose and relative concentration of each virus. It resulted in a trivalent response in 76% of subjects and tetravalent response in 71% of subjects. However, the DENV3 component was detected to be dominant in viremia [32]. Hence, using less DENV3 than the previous formulations, another two formulations were tested in Thai children. Although the vaccines were moderately reactogenic and recipients seroconverted to all four serotypes. However, the DENV3 component was found to be still dominant [33]. Due to imbalanced immunity and unacceptable reactogenicity observed in some volunteers, later trials were halted the further clinical testing [34,35].

DENVax

The DENVax vaccine is a combination of attenuated DENV2 strain which was previously developed at Mahidol University (DENV2 PDK-53) and chimeric DENV1, DENV3 and DENV4 cloned with DENV2 PDK-53 as the backbone. The DENV2 PDK-53 vaccine was designed by 53 serial propagations of a wild-type DENV2 strain in PDK cells. The vaccine strains for rest of the serotypes were produced by substituting the structural proteins of the DENV2 PDK-53 with the genes from respective wild-type serotypes [36,37].

Three different formulations of the tetravalent chimeric DENVax vaccine were tested in cynomolgus macaques for safety, immunogenicity, and efficacy. The formulations were well-tolerated and virus neutralizing antibody titers were induced against all four serotypes after one or two administrations of the vaccine [38]. Subsequently, Mono and tetravalent formulations of DENVax formulations were tested in AG129 mice and found to be immunogenic and elicited primary and secondary neutralizing antibody responses to all four serotypes. However, responses to certain serotypes were found to be more dominant [39].

Later, a phase 1 study was conducted in dengue non-endemic Colombia, evaluated the high and low dosages of DENVax along with intradermal or subcutaneous routes of administration. Both admixtures were well tolerated with generally mild and transient systemic or local reactions. Immunization with either high or low dose DENVax formulations induced neutralizing antibody responses to all four DENV serotypes. The results also showed that either subcutaneous or intradermal routes of administration can provoke tetravalent responses against dengue. However, the subcutaneous vaccination was more favored as it caused lower rates of local adverse reactions compared to intradermal [36].

Conversely, another phase 1 dose-escalation study (high and low dose) of a recombinant live-attenuated tetravalent dengue vaccine candidate, termed as TDV (formerly DENVax) was studied in the United States (US). Both dosages of TDV were immunogenic and well tolerated. The reduced local reactogenicity following subcutaneous delivery, associated with the higher neutralizing antibody titres, higher seroconversion rates and induction of neutralizing antibodies for three or more serotypes in more than 90% of recipients suggested that subcutaneous administration of the high-dosage formulation deserves to move forward in development [40].

Based on the results of these two studies, a phase 1b study was conducted to evaluate the safety and immunogenicity of TDV in 140 participants aged 18-45 years. In this study, three different dosages of TDV; (i) initial TDV dosage, (ii) a vaccine in which TDV-4 had been augmented three-fold, and (iii) a one-tenth TDV dosage were assessed. The TDV formulations were well tolerated and immunogenic. The results confirmed that all TDV admixtures, dosages, and dosing rosters were well tolerated in these flavivirus-naive adults [41].

A multicenter, phase 2 study, with two subcutaneous vaccinations 90 days apart, was carried out in Puerto Rico, Singapore, Colombia, and Thailand. The study was designed for age de-escalation followed by expansion in 1.5-45 year olds in endemic countries. The only solicited adverse events experienced by TDV recipients were the pain in the injection site, itching, and erythema. After two TDV dosages, higher percentages of seropositivity were observed in all the groups and the results confirmed that TDV was immunogenic and well tolerated in participants who were 1.5-45 years of age, disregard of pre-vaccination to dengue exposure [42].

Conversely, the characteristics of CD8+ T-cell responses to the TDV vaccine were also studied in flavivirus-naive individuals. In this trial, individuals were given 2 doses of TDV by subcutaneous or intradermal administration. The observed results confirmed the ability of TDV to induce cross-reactive T-cell-mediated responses that could possibly afford a broad protection against dengue [43].

An ongoing phase 2 trial of a TDV is being done at dengue-endemic countries in Asia and Latin America to determine its safety and immunogenicity in 2-17 year old healthy individuals. The aim was to compare the immune responses to TDV given in different dosage schedules subcutaneously. Due to the previously observed higher immunity against DENV2 and relatively lower immunity against DENV-4 [36,41,42], the dosage of the attenuated DENV-2 virus strain (TDV-2) in this vaccine was condensed by one log relative to the other serotypes to induce a more balanced immune response. The two-dose schedule of TDV induced a higher immunogenicity in seronegative children, against DENV-3 and DENV-4. The study further assured the well tolerability, safety, and immunogenicity of TDV in 2-17 years old individuals, irrespective of previous exposure to dengue [44].

TV003/TV005

With the aim of attenuating the virus without significantly reducing immunogenicity, the US National Institute of Health (NIH) introduced a new era in investigating the potential strains of vaccine which can be combined to form an effective tetravalent vaccine candidate for dengue. The NIH examined several monovalent vaccines using strains with the similar genetic mutations, in flavivirus-naive candidates, to ensure the vaccine safety and immunogenicity. The vaccine strains for both DENV1 and DENV4 were designed by a removal of 30 nucleotides in the 3′ untranslated region (3′UTR) from a wild-type serotype 1 and 4 strains, respectively (rDEN1Δ30 and rDEN4Δ30). Early studies revealed the high immunogenicity of both of these monovalent vaccines [45,46]. However, application of the same mutation to wild-type DENV2 and DENV3 in animal models, discovered to be not much effective in attenuation, hence other attenuation methods were examined [47,48].

Similar to other strains, the serotype 3 strain was designed by applying the 30 nucleotides deletion in 3′UTR, but an additional 31 nucleotides were also deleted from upstream of the Δ30 mutation (rDEN3Δ30/31). Another DENV3 vaccine strain (rDEN3-3′D4Δ30) which has replaced the 3′ UTR of rDEN3 with the 3′ UTR of the DENV4 vaccine candidate (rDENV4Δ30) was also inspected. Both vaccine strains were well attenuated and found to induce broad neutralizing antibody responses [49]. The vaccine for serotype 2 was created by using the DENV4 vaccine strain (rDEN4Δ30) and replacing the prM and E proteins for that of serotype 2 (rDEN2/4Δ30(ME)). This approach led to a safe monovalent vaccine which was capable of inducing 100% seroconversion to DENV2 [46].

Following the observed broad neutralizing antibody responses induced by each monovalent vaccine, four different tetravalent admixtures (TV001-TV004) were initially produced by combining different monovalent vaccine candidates to evaluate the immunogenicity and safety [50]. Each of these formulations was immunogenic and well tolerated, eliciting a greater antibody response in 75%-90% of flavivirus-naive adult subjects following a single dose. The TV003 (rDEN1Δ30, rDEN2/4Δ30, rDEN3Δ30/31, rDEN4Δ30) induced a broader and most balanced antibody response with a trivalent or greater response in 90% of participants following a single subcutaneous dose. Moreover, this vaccine reported high seroconversion rates for serotype 1, 3 and 4 (85-100%), but the rate was lowest for serotype 2 (50%). Based on the immunogenicity and safety profile of the observed four different formulations, TV003 was selected for further development and evaluation [50].

In a follow-on trial, TV003 was compared with a novel tetravalent formulation termed as TV005, which shared the same four monovalent components as TV003 but a 10-fold increase in dosage of the DENV2 component. One dose of TV003 formulation resulted in 92%, 76%, 97%, and 100% of seroconversion frequencies for DENV1–4, respectively. A total tetravalent response was observed in 74% of individuals. Conversely, one dose of TV005 resulted in seroconversion rates of 92%, 97%, 97%, and 97% for DENV1–4, respectively and 90% of recipients mounted a tetravalent response. The enhanced DENV2 dosage of TV005, significantly improved the frequencies of seroconversion and overall antibody titres to the DENV2 constituent of the vaccine while upholding the immunogenicity of the other serotypes [51].

Later, for a better evaluation of the protective efficacy of TV003, a placebo-controlled study was conducted among flavivirus-naive individuals. In this study the recipients of TV003 were challenged with a DENV-2 strain (rDEN2D30) 6 months later. As the result, all the recipients of TV003 showed complete protection against rDEN2D30 infection without viremia, neutropenia or rash, following the challenge. The study further suggested that a controlled dengue human challenge model can improve the vaccine development by assessing the protection presented by the vaccine [52].

Subsequently, the safety and immunogenicity of TV003 was further evaluated in a flavivirus-experienced population. As in previous studies among flavivirus-naive individuals, flavivirus-experienced volunteers were subjected to two doses of TV003 six months apart. The results supported the well tolerability of TV003 with few adverse events. One does of TV003 resulted in a tetravalent response 87% of recipients indicating a robust immunity. The second dose was not associated with a sustained increase in antibody titers suggesting that a single dose is sufficient to prevent viral replication and protect against dengue [53].

Recombinant, Live-Attenuated Tetravalent Dengue Vaccine (CYD-TDV)

The successful approach formerly described for the production of ChimeriVax-JE [54] was applied to construct a chimeric strain of DENV2; ChimeriVax- DENV2. In this process, the prM and E genes from the DENV2 PUO-218 strain were cloned into a cDNA infectious clone of a yellow fever strain (YF 17D). Resultant ChimeriVax-DENV2 was non-neurovirulent for 4-week-old mice, genetically stable and provided complete protection from wild-type DENV2 infection [55]. This influenced the construction of DENV1, DENV3, and DENV4 chimeras using the prM/E sequences from the respective DENV clinical isolates. All chimeras replicated to high titres in cells approving its acceptability for good manufacturing practices and elicited neutralizing antibodies against all four serotypes in almost all animals after a single dose [56].

The initial clinical trial of CYD, which only assessed the DENV2 vaccine strain (ChimeriVax-DENV2) in healthy adults, found that its immunogenicity and safety profile is consistent with that of YF-VAX. Immunization with ChimeriVax-DENV2 did not get affected by the pre-immunity to YF virus but induced a long lasting and cross-neutralizing antibody response to all four serotypes [57].

In an attempt to investigate the vaccine induced-protection, ChimeriVax-DENV1-4 immunized cynomolgus monkeys were exposed to wild-type DENV strains 6 months later. All monkeys seroconverted to all four serotypes and suggested that the ideal tetravalent formulation(s) for humans may contain equal amounts of each of four ChimeriVax-DENV serotypes and could be administered twice, to ensure complete seroconversion [58]. However, viral interference was observed in cynomolgus monkeys vaccinated with the ChimeriVax-DENV vaccines, with the dominance of DENV4 [59]. The ChimeriVax strains were discovered to be highly attenuated for A. albopictus and A. aegypti mosquitoes [60], and less hepatotropic than YF 17DV vaccine in humans [61].

Based on ChimeriVax technology, a Tetravalent Dengue Vaccine (TDV) containing each recombinant dengue serotypes was first developed and tested in adults who were flavivirus-naive. The study compared a three-dosage regimen at 0, 4, and 12-15 month to a two-dosage regimen at 4 and 12-15 months. All participants in the three-dosage group seroconverted to the four serotypes, and nearly all seroconverted following two doses given 8-11 months apart [62].

With the purpose of examining the immunogenicity, safety, and infectivity of TDV in individuals who were pre-exposed to dengue and YF, a phase 2a study was conducted among healthy adults. These individuals were flavivirus-naive or vaccinated with YF vaccine or monovalent, live-attenuated Vero cell-derived dengue vaccine against DENV1 (VDV1) or DENV2 (VDV2) one year before. The study revealed that the existing immunity against dengue or YF has no evident adverse effects but enhance both the humoral and cellular immunity to following TDV vaccination [63].

Consequently, a first phase 1 trial of TDV, conducted in the dengue non-endemic Mexico, presented a favorable safety profile in children and adults with tetravalent neutralizing antibody responses following three TDV vaccinations [64]. A phase 1 study was then carried out in Philippine, a dengue-endemic country, which supported its tolerability and safety in flavivirus-endemic populations. Following each successive vaccination of TDV, increased seropositivity rate against each serotype and the safety profile of the vaccine was consistent with that of previous reports from flavivirus-naive populations. Either, three immunizations over a year or two immunizations more than 8 months apart, presented a balanced antibody reaction to all the serotypes, as well as in children, who are most susceptible to this infection [65].

Numerous phase 2 trials have been performed globally in children and adults. A study conducted in the dengue-naive individuals of Singapore evaluated the safety of TDV, which contained four live attenuated, recombinant viruses (CYD-TDV). The results showed that 66.5% of recipients to be seropositive to all four serotypes following three dosages of CYD-TDV at 0, 6, and 12 months while seroconversion rates were found to be high in children [66]. Supporting these results, the third dose of CYD found to cause seropositivity to all four serotypes in children of dengue-endemic Peru, who were seropositive to YF at baseline. The vaccine found to be immunogenic and resulted in 94% of individuals seroconverting to all four serotypes [67].

Later, in order to upsurge immunogenicity, with a balance immune reaction in naive individuals by limiting viral interference, the studies proceeded with 0, 6, and 12-month dosing regimen [68-70]. The initial clinical study of CYD with a primary endpoint of Vaccine Efficacy (VE) was conducted in 4-11 years old Thai children. Children were randomly grouped to vaccine or placebo with three dosages at 0, 6, and 12 months. The main objective of this study was to evaluate the protective efficacy against dengue, regardless of serotype or severity, occurring one month or longer following the third vaccination. The observed result presented a 30.2% (95% Confidence Interval (CI): -13·4 to 56·6) of efficacy which varied by serotype. Although the VE against serotype 1, 3 and 4 was statistically significant, against DENV2, the efficacy found to be low. Hence the observed lack of efficacy against DENV2 required further investigations [68].

Subsequently, two phase 3 efficacy studies were completed in Latin America and Asia. In contrast to the previous study, the primary endpoint of these trials was VE to be more than 25% for the lower bound of the 95% CI [69,70].

In a study performed in five Asian countries among 2-14 years old children, the estimated efficacy was 56.5% (95% CI: 43.8-66.4). The VE following three injections for dengue hemorrhagic fever (88.5% (95%CI: 58.2-97.9)), severe dengue (80.8% (95%CI: 42.7-94.7)) and hospitalized dengue (67.2% (95%CI: 50.3-78.6)) were recorded to be statistically significant. In comparison to the trial in Thailand, the large-scale trial reported here showed high immunogenicity for all four serotypes, while the serotype-specific VE for serotype 2 was not statistically significant but efficacies for DENV1, DENV3 and DENV4 were significant [69].

In the Latin American, a study among 9-16 years old children, estimated a 60.8% of VE (95% CI: 52.0-68.0) following three injections. All serotypes were presented with a statistically significant serotype-specific VE ranging from 42.3% for DENV2 to 77.7% for DENV4. A 79.4% of individuals in the immunogenicity subset, were found to be dengue seropositive for any serotype at baseline. There was an increased VE among children who were seropositive at the baseline (83.7% (95%CI: 62.2-93.7)) compared to children who were seronegative (43.2% (95%CI: 61.5-80.0)). The reported efficacy results found to be consistent with those of Asian trial; both successfully achieving their primary endpoint [70].

Later, convened by the WHO, several other supportive studies were conducted to make model-based predictions on the public health impact of CYD-TDV (Dengvaxia), reflecting the long-term safety, population-level effectiveness, and economic considerations on routine vaccination. Considering seroprevalence levels among 9-y-olds (SP9), eight independent modelling groups were assembled to predict the burden of dengue disease following vaccination with Dengvaxia [71-74].

In 2016, modelers from Sanofi Pasteur concluded that the vaccination with Dengvaxia can reduce the disease burden significantly over 10 years following vaccine introduction and beyond. The most efficient age for vaccination, which varied according to the transmission intensity, was found to be 9 years of age [72]. However, analysis of year 3 results of phase III trials demonstrated the high risk of hospitalization in CYD recipients who were under 9 years of age, compared to that of placebo recipients. The risk was highest in recipients who were 2 to 5 years of age [73]. In addition, VE among all age groups was found to be lower during the hospital-based phase than during the active phase, suggesting waning of vaccine-induced protection [73,74]. Further analysis reported that in high-transmission endemicity settings (SP9 ≥ 70%), the burden of dengue disease could be reduced by 13%-25%, and in moderate to high dengue settings (SP9 ≥ 50%) by 6%-25%. However, the models predicted that the vaccination can cause a substantial increase in hospitalization due to dengue in low transmission intensity settings (SP9 ≤ 30%) [74].

Following the analysis of risk of hospitalization for Virologically Confirmed Dengue (VCD) and clinically severe dengue occurring up to 4 years after the first dose (years 1 to 4), the efficacy trials of CYD-TDV assured that the vaccine holds a positive benefit-risk profile in the population aged ≥ 9 years old [75]. However, in order to obtain precise risk estimates of CYD-TDV according to observed dengue serostatus, after 13 months following third vaccination, blood samples were subjected to a dengue anti–nonstructural protein 1 (NS1) IgG enzyme-linked immunosorbent assay to determine serostatus in a post hoc analysis. The study allowed the reanalysis of vaccine safety and efficacy of CYD-TDV based on the serostatus. Vaccination with CYD-TDV found to confer protection against dengue for at least 5 years among dengue-seropositive participants. The study demonstrated 70% lower rates of severe VCD and hospitalization for VCD in all ages considered (2 to 16 years of age) over a 5-year period and 80% lower rates among the population aged ≥ 9 years in comparison to the control groups. However, over the same period, among dengue-seronegative participants, the rates of severe VCD and hospitalization for VCD were found to be higher in the vaccine group compared to the control group. Although the exact reason for observed results are unknown, it is suggested that similar to the naturally occurring second dengue infection, in the absence of previous exposure to dengue, the CYD-TDV vaccine may partially mimics the primary infection, increasing the risk of severe dengue during following infection [76].

The first dengue vaccine, Dengvaxia was first approved in 2015 and currently licensed in twenty countries. Mathematical modelling suggested the potential of Dengvaxia to significantly reduce the burden of dengue in moderate to high transmission intensity settings [77]. However, due to the high risk of hospitalized dengue reported among seronegative trial individuals, WHO Global Advisory Committee on Vaccine Safety (GACVS) concluded that individuals, who are seronegative, should not be vaccinated with CYD-TDV [78].

Conclusion

Years of vaccine research have finally achieved the end-point of having a licensed vaccine. Although Sanofi's CYD-TDV and TV003 are promising vaccine candidates currently present, due to the extent of global dengue burden, many more vaccine candidates would be required to certify a satisfactory supply of vaccine in the long-term.

Several studies investigating vaccines for immunogenicity and safety have been conducted in the last few years. Significantly, there is no established correlation between efficacy and protection for the dengue vaccine. Evaluation of neutralizing antibodies for all serotypes in immunogenicity studies has been a necessity to proceed with a candidate vaccine. However, cellular immunity, which is not much examined, could be equally essential. Although CYD confirmed a robust antibody reaction to all four serotypes in early studies, serotype-specific VE for DENV2 was not significant in large phase 2b

and phase 3 studies. The reason for the vaccine to be less efficacious against serotype 2 regardless of its capability to elicit neutralizing antibodies is indistinct. The quality of the antibody provoked and the protective role of cytotoxic T cell reaction are currently under investigations.

The observed high risk of hospitalization identified among seronegative individuals following the vaccination, in latter safety studies of CYD-TDV, indicates that the serostatus of recipients should be thoroughly confirmed prior to the vaccination. In address to this, a rapid, reliable test to determine the dengue serostatus would be ideal. However, as many initial infections are asymptomatic and currently no such test has been extensively registered for this indication, pre-vaccination screening is challenging to implement. Hence the development of safe dengue vaccines which are effective regardless of the serostatus remains a high priority. Despite the abundance of work that required to decide how a dengue vaccine, once approved, could be positioned, its role in the control of disease is certain.

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