The first licensed dengue vaccine: can it be used in travelers?

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Purpose of review: The first dengue vaccine (Dengvaxia®) was endorsed by the European Medicine Agency and the US Food and Drug Administration. Given the excess risk of severe dengue in seronegative vaccinees, use is restricted to seropositive individuals. Dengvaxia confers high protection against severe dengue in seropositive vaccinees.

Recent findings: With increasing global travel, the probability of travelers being seropositive increases. Such seropositive travelers may be at increased risk of severe dengue as a result of a second dengue infection during repeat travel. Nevertheless, the use of Dengvaxia in travelers requires a careful analysis of all the factors. Seropositive travelers only present a minority of all travelers. A validated rapid diagnostic test to screen for dengue serostatus is not yet available. Such a test should be highly specific to avoid inadvertent vaccination of seronegative individuals. The 3-dose regimen precludes the use in most travelers who tend to present at travel clinics less than 6 weeks prior to departure. Furthermore, questions about potential sub-optimal immunogenicity in seropositives in non-endemic settings, and the need and timing of boosters remain unanswered.

Conclusions: Although there could potentially be substantial protection against severe dengue in seropositive travelers, Dengvaxia is far from an ideal travel vaccine.

Key words: severe dengue, screening test, immunogenicity, pre-vaccination screening strategy, individual risk

Introduction:

More than 125 countries are endemic for dengue infection, and the number of at risk countries for dengue is increasing[1]. The Global Disease Burden study documented a 400% increase in dengue incidence, and dengue is now being the leading arboviral disaese globally[2]. Many dengue endemic countries are popular travel destinations[3, 4]. With the global increase of dengue transmission intensity, dengue has become a frequent cause of febrile illness among travelers returning from Southeast Asia, Latin America or the Caribbean[5-7] and has

overtaken malaria as the leading cause of febrile illness for those traveling to South East Asia[8]. Dengue affects not only tourists[9, 10], but also business travelers[11], expatriates[12], persons visiting friends and relatives (VFR)[13], and migrants[14]. Dengue occurs mostly in adult[8, 10] and also in pediatric travelers[15, 16].

The objectives of this paper are to review whether a dengue vaccine would be indicated for travelers, to critically appraise the first licensed dengue vaccine – Dengvaxia- and to examine whether Dengvaxia should or could be used in travelers.

I Risk of dengue in travelers:

Sentinel surveillance provides data on disease trends. GeoSentinel, a global network of travel medicine providers for ill-returning travelers[17] documented an increase of dengue in returning travelers over the past decades[18, 19]. In Southeast Asia, annual proportionate morbidity increased from 50 dengue cases per 1,000 ill returned travelers in non-epidemic years to an average of 159 cases per 1,000 travelers during epidemic years[8]. The intensity of dengue transmission is influenced by various factors within dengue endemic countries, including population density, social, economic, cultural, demographic and ecological factors such as temperature, season, rainfall and altitude[20-22]. Accordingly, the risk of dengue for travelers varies widely between and within countries, from year to year, and season to season. In addition, the risk of dengue for travelers depends on the duration of travel, and activities during travel.

US travelers to dengue endemic countries with a median length of travel of 21 days had a seroconverson rate by either anti-DENV IgM or IgG ELISA between 2.9 and 6.8%.[23]. A tripling of hospitalization for dengue in US travelers was reported between 2000-2007[24]. There has been a corresponding increase in dengue reported in European travelers[9, 25]. The attack rate of symptomatic dengue in Swedish travelers was 13.6 (95% CI 12.7, 14.4) to Thailand, 45 for Sri Lanka and 43 for per 100,000 travelers[25]. Attack rates were reported to be as high as 5.51 cases per 1000 travel-months in peace corps volunteers[26]. Prospective studies of seroconversion rates in both asymptomatic and symptomatic travelers revealed a seroconversion rate of 2.9 percent (after a mean of one month of travel)[9]. In a study from London, 86% had a primary infection compared to 14% with secondary infections[27].

Compared to classical travel vaccine preventable diseases such as yellow fever, hepatitis A and B, rabies, and Japanese encephalitis[28], dengue is the most frequent infectious disease in travelers to the tropics and subtropis that could potentially be vaccine-preventable.

In most travelers, dengue is a self-limiting acute febrile disease[29]. However hospitalization for dengue in travelers is fairly common[30], dengue illness often disrupts travel resulting in evacuations[3] and travelers incur substantial direct and indirect costs because of dengue-related illness[31]. Given that travelers have low compliance rates with anti-vectorial protective measures[32], pre-travel vaccination would be a great tool to reduce the risk of dengue when traveling to dengue-endemic countries.

II Dengvaxia

Currently, there is only one licensed dengue vaccine: CYD-TDV (Dengvaxia®). Dengvaxia, developed by Sanofi Pasteur. is a live attenuated, recombinant tetravalent vaccine employing the attenuated YF virus 17D strain as the replication backbone. The vaccine was first licensed in 2015 on the basis of efficacy trials conducted in 10 highly dengue endemic countries in Asia and Latin America involving more than 30,000 children. Pooled rates of efficacy for symptomatic dengue during the first 25 months were 65.6% (95% CI, 60.7 to 69.9) for those 9 years of age or older[33] with higher efficacies aginst hospitalized and severe dengue. Those trial results showed a varied vaccine performance depending on age, severity of the disease, and serostatus. The serostatus-dependent vaccine performance was only fully documented in 2018 when Sanofi Pasteur published the results of retrospective analyses of the trial population by serostatus. Although blood samples at baseline were taken for an immunogenicity subset of the trial, involving about 13% of all trial participants, the sample size was too small to conclusively address the effect of serostatus on risk for severe dengue as severe dengue is a relatively rate event. The company therefore developed a new NS1 based ELISA assay, designed to distinguish prior infection from prior vaccination, so that they could use the blood samples taken 13 months after vaccination (which had been stored for all participants). The assay results, combined with statistical imputation methods, enabled the serostatus of trial participants prior to vaccination to be inferred retrospectively. Though this new method has limitations with respect to sensitivity and specificity, the assays were able to tease out the effect of serostatus on efficacy and safety.

The vaccine efficacy in seropositive vaccinees in the first 25 months was 76% (CI 63.9- 84.0) based on the NS1 antibody assay. Vaccine efficacy based on the NS1 antibody assay likely underestimates the true efficacy due to misclassification as a result of the NS1 assay. Based on the PRNT results in the immunogenicity subset of 13% of the trial population, vaccine efficacy was (81.9%, 95%CI 67.2-90.0). The Hazard Ratio of hospitalized dengue over the observation time of approximately 5 years was 0.21, and for severe dengue 0.16.

Number of Subjects with Cases					
	Vaccine Group n (N)	**Placebo Group n (N)**	**Vaccine Efficacy (%)**	**95% Confidence Interval**	**p-value**
Symptomatic VCD (M0-M25)	192.7 (1441.4)	372.1 (697.3)	76	(63.9, 84.0)	<0.001
Number of Subjects with Cases					
	Vaccine Group n (N)	**Placebo Group n (N)**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Hospitalized dengue (M0-M60-72)	58.8 (1502.9)	137.7 (729.8)	0.21	(0.138, 0.307)	<0.001
Severe dengue (M0-M60-72)	11.2 (1502.9)	33.4 (729.8)	0.16	(0.068, 0.371)	<0.001

The vaccine efficacy against symptomatic VCD in the first 25 months after first vaccination in seronegative trial participants aged was 39% (CI -1; 63). The long-term safety follow up to 66 months, expressed as Hazard Ratio against hospitalized dengue and severe dengue in inferred baseline seronegative subjects 9-16 years of age….

The excess risk was apparent from month 30 of the trial (17 months after the 3rd dose) in seronegatives aged 9 years and above and persisted throughout the 66 months of available observation time. Clinical manifestations of severe dengue were similar in vaccinated seronegative persons compared to unvaccinated seropositive persons, consistent with the working hypothesis that CYD-TDV vaccination mimics a primary-like dengue infection. The majority of severe cases were classified as DHF I and DHF II and all recovered.

In the epidemiological settings of the trials, in those seropositive children prior to vaccination, the incidence of severe dengue was 1.0 per 1,000 in those vaccinated and 4.8 per 1,000 in those not vaccinated. In those seronegative prior to vaccination, the incidence of severe dengue was 4.0 per 1,000 in those vaccinated and 1.7 per 1,000 in those not vaccinated.

Potential explanations for the excess risk in seronegative vaccinees

The most plausible hypothesis for the increased risk in seronegative individuals is that the live attenuated CYD-TDV initiates a first immune response to dengue in seronegative persons that predisposes them to a higher risk of severe disease when they experience their first natural dengue infection. That is, the vaccine acts as a "primary-like" infection and a subsequent infection with the first wild type dengue virus is then a "secondary-like" clinically more severe infection[34]. Statistical analyses suggested that Dengvaxia is a dengue serotype 4 (DENV4) immunodominant vaccine[35]. This is further corroborated by studies on viremia levels where mainly viremia was only or mainly detected for serotype 4[36, 37]. The PRNT is an admixture of homotypic and heterotopic antibodies. Depletion assays teasing out homotypic (eg serotype specific) versus heterotypic antibodies (cross-reactive) demonstrated that DENV4 was mainly neutralized by type-specific antibodies whereas DENV1, DENV2, and DENV3 were mainly neutralized by serotype cross-reactive antibodies[38]. In other words, serotype specific antibodies dominated the DENV-4 response (CYD-4 most often detected post-vaccination), while cross-reactive antibodies dominated the DENV-2 response.

Licensure and in-country experiences to date:

First licensed in 2015 in Mexico, with subsequent licensures in the Philippines and Brazil, Dengvaxia is now licensed in 20 dengue-endemic countries in Asia, Latin America and Australia, typically for use in persons aged 9-45 years, (exceptions are: Singapore (12-45 year-olds), Indonesia (9-16 year-olds) and Paraguay (9-60 year-olds). Despite widespread licensure, it is not used routinely in any country. In some countries such as Singapore it is only used in the private market. Only two countries introduced the vaccine in a subnational programme: in the Philippines and in Brazil. Following the Sanofi Pasteur press release in November 2017 that reported on the excess risk of hospitalized and severe dengue in seronegative vacccinees, the Philippines discontinued the programme. The Philippines experience showed the speed of social media and public outcry that resulted in loss of vaccine confidence in general. Political turmoil ensued, parents of vaccinated children went to the streets, and several researchers, regulators and the former Secretary of Health were indicted[39]. The result was broken public trust around the dengue vaccine and heightened anxiety around vaccines in general[40]. The Vaccine Confidence Project™ compared confidence levels in 2015, before the crisis, with levels in 2018, and found a dramatic drop in vaccine confidence from 93% "strongly agreeing" that vaccines are important in 2015 to 32% in 2018[40]. Major measles outbreaks are now occurring in the Philippines[40], at a time when MMR vaccine coverage rates are also declining globally with global resurgence of

measles[41-45]. In Brazil, there was no public outcry as dengue incidence had declined by 2016-2018, possibly due to the preceding Zika virus outbreak.

In 2018, Dengvaxia was approved by the European Medicine Agency for use in seropositive individuals aged 9 to 45 in dengue endemic areas or countries; use in travelers was not endorsed. In May 2019, Dengvaxia was also approved by the U.S. Food and Drug Administration (FDA), for the use in seropositive individuals aged 9 to 16 in dengue endemic areas. The recommendations by American Committee on Immunization Practices (ACIP) whether it will be recommended for travelers is still outstanding. To date, Dengvaxia has not been in use in Europe, the United States, Australia or any Territories. The label in Australia states "Vaccination is not recommended for individuals living in non-endemic areas and travelling to endemic areas short-term."

WHO position on the use of Dengvaxia (published in July 2018)

After the WHO SAGE discussions and recommendations in April 2018, WHO published its position in July 2018 with the following statement[46]: "Countries should consider introduction of the dengue vaccine CYD-TDV only if the minimization of risk among seronegative individuals can be assured. For countries considering vaccination as part of their dengue control programme, pre-vaccination screening is the recommended strategy. With this strategy, only persons with evidence of a past dengue infection would be vaccinated (based on an antibody test, or on a documented laboratory confirmed dengue infection in the past)." No country to date has implemented such a pre-vaccination screening strategy.

Pre-vaccination screening:

Screening tests would need to be highly specific to avoid vaccinating truly seronegative persons, and to have high sensitivity to ensure that a high proportion of seropositive persons are vaccinated[46]. The required sensitivity to achieve a high positive predictive value (PPV) will depend on the seroprevalence in the population on which the test is conducted and on the test specificity. The PPV of a test would be a unifying indicator for an acceptable safety profile of a pre-vaccination screening strategy[47]. Furthermore, it has been argued that an additional reasonable criterion for the selection of a screening test is that those who are deemed ineligible for vaccination as a result of the test, should be at a lower risk of hospitalised or severe dengue disease if they are left unvaccinated than if they are vaccinated[48]. For the time being, no rapid diagnostic test has been validated and licensed for the purpose of determining dengue serostatus.

III Should Dengvaxia be used in travelers?

Clearly, Dengvaxia should not be used in seronegative travelers. However, with increasing global travel including repeated travel to dengue endemic countries, the probability of travelers being seropositive increases. Such seropositive travelers may be concerned about repeat travel to a dengue endemic country for fear of severe dengue, given that a second infection is clearly linked with a higher risk of severe dengue[29] with a relative risk to a primary dengue infection of about 7[49]. In Australia, Dengvaxia is not licensed for short-term travelers, but the wording of the label suggests it could be considered for long-term travelers such as expatriates. From an occupational medicine perspective, it is paramount to protect expatriates who had a primary dengue infection and will therefore be at increased risk of more severe dengue at a time of a second infection when being deployed to dengue endemic areas[50]. As Batchelor writes, protecting expatriates via dengue vaccination is not only an appealing prospect but -if safe and effective- could also be considered a requirement for some expatriates under Australian Work Health and Safety legislation. The use of the CYD-TDV vaccine in selected travelers could be considered a reasonably practicable method to substantially reduce the risk of subsequent dengue infections[51]. In seropositives, Dengvaxia offers protection against severe which is greater than 90%[33, 52]. Nevertheless, its use in travelers is not straightforward and requires a careful analysis of all the factors.

Pre-vaccination screening for travelers

A documented history of a past laboratory confirmed dengue infection would not require an additional screening test. However, many primary dengue infections can be asymptomatic, hence screening travelers who have visited dengue endemic countries before would be necessary. The dengue seroprevalence in Australian travelers to Asia was 4.4%; a greater number of prior trips to Asia was a predictor for dengue seropositivity[53]. Obviously, the seroprevalence in travelers in any given setting will depend on the frequency and duration of travel as well as the epidemiological situation of dengue in the destination country[54], and could be higher in some other settings. The best screening test for past dengue infection still needs to be determined, given the cross-reactivity of dengue IgG with other flaviviruses and flavivirus vaccines such as yellow fever and Japanese encephalitis vaccines that are frequently used in the travel medicine setting. For settings with low seroprevalence (and travelers would belong to this category), a screening test with a higher specificity would be needed compared to high seroprevalence settings, in order to mitigate risk. For travelers, the

most specific screening test would be the plaque reduction neutralization assay (PRNT$_{50)}$, but this assay requires a specialized laboratory, takes time and is costly[55].

Benefit-risk assessments

Only benefit-risk assessments in populations living in highly dengue endemic countries are available. The number of averted hospitalised and severe disease in seropositive subjects substantially outnumbered those precipitated in seronegative participants[56]. On a population level, a trade-off therefore exists between the population benefit conferred by vaccination, and the enhanced risk experienced by a subset of seronegative vaccine recipients. The population level benefit versus individual risk will depend on the level of dengue seroprevalence in the target age group for vaccination, and the annual dengue incidence in a given setting. Based on the incidence in the epidemiological settings of the trials, for persons aged 9 years and above, the 5-year risk of severe dengue in vaccinated seronegative persons (4.04 per 1,000 seronegative persons vaccinated) is similar to the risk of severe dengue in unvaccinated seropositive persons (4.8 per 1,000 seropositive persons unvaccinated). The risk of severe dengue is lower in unvaccinated seronegative persons (1.7 per 1,000 seronegative persons unvaccinated). The risk of severe dengue in vaccinated seropositive persons is the lowest (less than 1 per 1,000 seropositive persons vaccinated). Thus over 5 years, there was a reduction of about 15 cases of hospitalized dengue and 4 cases of severe dengue per 1,000 seropositive persons vaccinated. For 1,000 seronegative persons vaccinated, there was an increase of about 5 cases of hospitalized dengue and 2 cases of severe dengue[57]. Thus, in high transmission settings, Dengvaxia brings forward the risk period for severe dengue (associated with a natural second infection) but does not increase the lifetime risk of severe dengue except in low transmission settings where not everyone is likely to experience two natural dengue infections in their lifetime.

In the benefit-risk assessment in travelers, the risk of several sequential dengue infections is far lower than in the endemic population. Therefore, the benefit-risk assessments cannot be extrapolated to travelers. This is particularly important when considering that pre-vacccination screening may lead to false-positive results which would result in advertent vaccination of a truly seronegative person. This risk is particularly high in low seroprevalence settings such as travelers.

Immunogenicity in endemic versus non-endemic populations

In vaccinees seropositive before vaccination, neutralizing antibodies titres were higher following vaccination compared to the seronegative vaccinees[58]. The GMTs post-dose 3 for

serotypes 1–4, respectively, were 580, 741, 827 and 341 for participants who were seropositive at baseline and 34.6, 101, 174 and 119 for those who were seronegative. After the third injection, serotype-specific seropositivity rates were 94.2% or higher, and 100%, 98.6% and 93.4% of participants were baseline seropositive for at least 2, at least 3 and all 4 serotypes, respectively. The $PRNT_{50}$ assays used in the trials to measure GMT do not allow for reliable differentiation between monotypic and heterotypic (temporarily cross-protective) antibodies, hence all the GMT titres may be a mixture of long-lasting monotypic and transient heterotypic antibodies, neutralizing and non-neutralizing antibodies. No correlate of protection for dengue has been established to date, although some correlation has been described between vaccine-induced neutralizing antibody titres and protection from VCD for a given serotype [59, 60]. From natural cohort studies in Nicaragua for example, it appears that a high titer protects against severe dengue, and instead, the risk of severe dengue disease is highest within a narrow range of preexisting anti-DENV antibody titers[61].

Of particular importance for the travel medicine context is the observation that immunogenicity was shown to be different in highly endemic versus low or non-endemic populations, even in seropositives. Of participants who received ≥1 CYD-TDV injection in Singapore and Vietnam after four years, geometric mean titers (GMTs) for those in Vietnam ranged from 30.2 1/dil (95% CI 23.9-38.3) to 73.7 (49.3-110) 1/dil while GMTs were only 9.73 1/dil (95% CI 8.28-11.4) to 21.8 (18.9-25.1) 1/dil in Singapore[62]. It is unclear what these lower GMT despite the same regimen in non-endemic areas mean. In highly dengue endemic countries, natural boosting will occur with circulating dengue viruses. We are also increasingly learning that other flaviviruses[63, 64] may have a booster effect and may even increase the efficacy and safety of Dengvaxia. Obviously, such booster effects would be missing in the travelers population.

Dosing regimen

The current dosing regimen for which the vaccine is licensed is a 3 dose schedule, 6 months apart, hence requiring a full year to complete. This makes this vaccine unfeasible for most travelers, as the vast majority of travelers seek pre-travel advice usually within 6 weeks prior to departure[65]. Maybe business or expatriate travelers, or those in planning for overseas postings would be able to complete such a series prior to departure.

The 3-dose regimen was pursued by the company many years ago because of the observation that in the combined group of seropositive and seronegative indiviuals 3 doses were needed to achieve an overall high immunogenicity (GMTs titers in seronegatives are notoriously low). However, the immunogenicity data in seropositive vaccinees suggest that maybe it is possible to use a primary schedule with reduced doses. The Geometric Mean

Titres measured by the PRNT50 assay in seropositive subjects immunogenicity are as high after one dose as after 3 doses[58]. Furthermore, the vaccine efficacy between the first and second dose, and second and third doses, was similar to the vaccine efficacy after the third dose, in the overall trial population in the multi-centre Phase 3 trials[33]. However, no long-term efficacy data for one or two dose schedules exist because the completion rate of 3 doses was very high in the trials. It is expected that in the very near future the company will provide more data on immunogenicity in seropositives after one or two doses. With regards to the need and timing of booster doses, no data are available for the time being. Dengue neutralizing antibody persistence data in 2 studies (CYD22 and CYD28) with longer follow-up to 4 years post-dose 3 also show that GMTs remain 1.2–3.2-fold higher than baseline.

A 3-dose regimen will be an obstacle to travelers, however it would not be the main deterrent. Expatriates may be deployed to countries where the vaccine is licensed, thus being able to commence or complete the vaccine course during their deployment. Frequent travelers or expatriates with multiple deployments could complete the series during their periods "at home"[51].

A question that has not yet been answered is 'how soon after a confirmed clinical case of dengue infection can an individual be safely and effectively vaccinated with the CYD-TDV vaccine?' [50]. This is a really important question, however, there are no clinical trial data to define an optimal window for dengue vaccination following recent dengue infection. During the clinical efficacy and safety studies for Sanofi Pasteur dengue vaccine, participants who had a recent dengue infection were not excluded from the study, as long as they were not acutely unwell, and met all other inclusion criteria[66]. Anaturally acquired dengue infection, there is cross-protection to all other dengue serotypes for a period of possibly up to one year, even two years[67]. If dengue infection is taken as a proxy for vaccination (as CYD-TDV mimics a silent infection), there may be some merit towards waiting at least 4 weeks.

Indicated age range for CYD-TDV in travelers

The Phase 3 efficacy trials in ten countries in Asia and Latin America only included the age range of 2 to 16 years[33, 68]. Due to the lower efficacy and the safety issue observed in the Phase 3 trials in younger age groups, licensure was only sought for the age of 9 and above. No efficacy data exist in individuals older than 16 years of age. However, immunogenicity and safety data up to the age of 45 are available[69]. EMA has endorsed the age range from 9 to 45, but FDA has restricted the use of Dengvaxia to the age range of 9 to 16[27, 70, 71].

Most travelers that present with dengue upon return are above the age of 16. Thus, the use in travelers is restricted.

Conclusions

Although there could potentially be substantial protection against severe dengue in seropositive travelers if vaccinated with Dengvaxia[72], Dengvaxia is far from an ideal vaccine in the travel medicine context. First of all, seropositive travelers only present a minority of all travelers. Second, we do not have a validated rapid diagnostic test to screen for dengue serostatus. Third, the requirements for extremely high specificity for such a test are even more pressing compared to high seroprevalence settings in endemic populations, and the risk of litigation in case of breakthrough dengue will be high. Fourth, the 3-dose regimen precludes the use in most travelers who tend to present at travel clinics usually less than 6 weeks prior to departure. Furthermore, questions about potential sub-optimal immunogenicity in seropositives in non-endemic settings, and the need and timing of boosters remain unanswered at this stage. There is a need to redefine priorities in research for travel medicine[73], which should include addressing some of the unanswered questions for dengue vaccination.

For the time being, Dengvaxia is not endorsed for the use in travelers from Europe, the United States and Australia. In the US, it is only licensed for ages 9 to 16, thus restricting its use even further. It is unlikely that travel medicine providers will opt for off-label use given all the uncertainties of this vaccine.

What is the prospect of alternative dengue vaccines in the near future? Two other live-attenuated chimeric dengue vaccines are currently in Phase 3 trials, the results of which should be available by end 2019 or early 2020. One is a mixture of attenuated dengue 2 and chimeric dengue 1, 3 and 4 with backbone containing only the dengue 2 NS1 antigen, the other contains attenuated NS1-containing dengue 1, 3 and 4 viruses and a dengue 2/4 chimera[74]. These vaccines are expected to result in a very different serostatus dependent performance from that of CYD-TDV, but we should await the results of the long-term efficacy data beyond 3 years before making any premature conclusions.

Key Points

1. The first licensed dengue vaccine- Dengvaxia- should not be used in seronegative travelers.

2. Pre-vaccination screening is required, and only those found to be seropositive should be offered the vaccine

3. In low seroprevalence settings such as in the travel medicine context, a screening test with extremely high specificity is needed

4. Benefit-risk assessments conducted in endemic populations cannot be extrapolated to travelers

5. The 3-dose regimen of Dengvaxia where one year is necessary to complete the series is impractical in travel medicine practice

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