Serostatus-dependent performance of the first licensed dengue vaccine: implications for travelers

Wilder-Smith A
London School of Hygiene and Tropical Medicine, UK

The number of international travelers from non-dengue endemic countries to dengue-endemic countries has increased exponentially, and is poised to increase further.[1] These evolving travel patterns, in particular increased travel to Southeast Asia, combined with the fact that dengue has experienced an unprecedented rise and geographic spread in recent decades[2] are the reasons that travelers are increasingly at risk of dengue. Recent attack rates were reported to be as high as 5.51 cases per 1000 travel-months in Peace Corps volunteers.[3] Dengue is now the leading cause of fever in returning travelers, having overtaken malaria for travelers to Southeast Asia.[4] Since travelers often have low compliance rates with anti-vector protective measures,[5] pre-travel immunization against dengue may be the best way forward to reduce the risk of dengue when traveling to dengue-endemic countries.

Currently, there is only one licensed dengue vaccine: CYD-TDV (Dengvaxia®) is a tetravalent live-attenuated vaccine, developed by Sanofi Pasteur. CYD-TDV is licensed in 20 dengue-endemic countries in Asia, Latin America and Australia for use in persons aged 9-45 years. Efficacy results from two large multi-centre trials in 10 countries in Asia and Latin America revealed a vaccine performance of unprecedented complexity with varying efficacy dependent on serostatus, age, serotype, and clinical severity.[6] In 2016, WHO therefore recommended the use of this vaccine *only* in settings with a very high dengue disease burden, as measured by seroprevalence of 70% and above.[7] It was hence not regarded to be suitable as a travelers`vaccine.

Additional post-hoc studies conducted in 2017 shed more light on the impact of baseline serostatus on vaccine performance.[8] Serostatus refers to whether a person has had a previous dengue infection: a seronegative person is dengue-naïve; a seropositive person has had at least one dengue infection in the past. Utilizing a novel NS1-antibody ELISA assay, Sanofi Pasteur retrospectively determined baseline serostatus in blood samples obtained from all trial participants at month 13 of the trial. The analyses showed significant differential performance

of CYD-TDV in those who were seropositive versus seronegative at the time of receiving the first vaccine dose. Vaccine efficacy in persons ≥9 years of age was relatively high in seropositive vaccinees: 76% (95%CI: 63.9, to 84.0), but non-significant among seronegative participants: 38.8% (95%CI: –0.9 to 62.9%). After the first 25 months of the trial, the trial design changed to hospital-based surveillance for another four years. The hospital-based surveillance only documented dengue related hospitalizations and severe dengue, expressed as hazard ratio compared to the unvaccinated trial population. The long-term safety data obtained through the hospital-based surveillance revealed an increased risk of hospitalized and severe dengue in seronegative vaccinees starting in year 3 after the first dose compared to unvaccinated seronegative individuals. Among seronegative participants 9 to 16 years of age, the cumulative incidence of severe dengue was 0.40% among vaccine recipients and 0.17% among controls, with a hazard ratio of 2.44 (95% CI, 0.47 to 12.56).[8] The reasons for the excess cases of severe dengue in seronegative vaccine recipients are not fully understood, but a plausible hypothesis is that the vaccine may initiate a first immune response to dengue in seronegative persons that predisposes them to a higher risk of severe disease. 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.[7]

What are the implications for travelers?

Most travelers from non-dengue endemic countries are seronegative, and should therefore not receive this vaccine, as the vaccine induces an immune status in seronegative vaccinees that predisposes to more severe dengue when exposed to a subsequent natural dengue infection. However, the vaccine is efficacious and safe in seropositive individuals. The main concern for travelers who experienced a dengue infection during their previous travel is acquiring a second infection when traveling again to a dengue endemic area, which would put them at increased risk of more severe disease.[9,10] The documented risk of more severe dengue in secondary infection may therefore be a rationale for using this vaccine in seropositive travelers. The vaccine efficacy against dengue illness of any severity in the first 25 months in seropositive individuals, based on the results in the immunogenicity subset, was 81.9% (95%CI 67.2-90.0).[6] The hazard ratio of severe dengue was 0.16 (95% CI 0.07-0.37) in seropositive individuals throughout 60 months of trial observation.[8] This translates into a substantial long-term protective efficacy of 84% against severe dengue in seropositive persons. In the absence of any other proven effective intervention to reduce the risk of dengue acquisition in travelers, vaccinating seropositive travelers with CYD-TDV may thus be justified.

How does one determine whether a traveler is seropositive?

A documented history of a laboratory confirmed dengue infection would not require an additional screening test. However, many primary dengue infections can be asymptomatic, and hence screening for serostatus is needed for all travelers who are interested in receiving a dengue vaccine prior to repeat travel to dengue endemic countries. The seroprevalence of dengue infection in one Australian study in travelers to Asia was 4.4% and a greater number of prior trips to Asia was a predictor for dengue seropositivity.[11] The seroprevalence in travelers in any given setting will depend on the extent of exposure to dengue such as frequency and duration of travel as well as dengue transmission intensity in the destination country. Screening will therefore need to be prioritized for travelers according to the extent of previous exposure to dengue. Pre-vaccination screening is not new in the travel medicine context: blood samples are often taken in travelers to check for hepatitis B status to ascertain the need for hepatitis B vaccination, for example. Cost and waiting time may also not pose such a problem compared to the use of a pre-vaccination strategy in a public health programme. The best screening test for previous 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. Although dengue IgG ELISA is widely available and can be used to determine serostatus, it lacks specificity due to cross-reactivity with other flaviviruses.[12] 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. Rapid diagnostic tests to determine serostatus are urgently needed to facilitate pre-vaccination screening of travelers.

How many vaccine doses are needed?

The efficacy trials were done with a three-dose schedule, 6 months apart. In other words, to complete the primary schedule it would take 12 months. No traveler, except maybe business or expatriate travelers, would be able to complete such a series prior to departure. However, the immunogenicity data in seropositive individuals are encouraging. In seropositive subjects immunogenicity appears to be as high after one dose as after 3 doses.[13] 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.[6] 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. Thus, for the time being the schedule remains a 3-dose schedule, 6 months apart, and deviating from this schedule would be off-label use. However, one could argue that for seropositive travelers the priority is the protection for the period of travel to dengue endemic countries, which is in most cases less than 6 months. A single dose prior to travel may suffice, followed by completion of the

primary schedule after return in order to achieve long-term protection for subsequent travel plans to dengue endemic countries.

The use of CYD-TDV in travelers from non-endemic to endemic countries is at this point in time only of theoretical nature. Except for Australia, CYD-TDV is not licensed in any of the non-endemic countries. However, licensure with the European Medicine Agency is being sought, and may possibly also be filed with the US Food and Drug Administration in the near future. Hence, the travel medicine community needs to start developing strategies how best to use this complex vaccine in travelers to countries with high dengue transmission intensity. The first step is to develop a highly sensitive and specific point-of-care screening test for serostatus. Furthermore, there is an urgent need to study one or two dose vaccination schedules in seropositive individuals in order to enhance the uptake of CYD-TDV. At this point in time, the need and timing of booster doses are unknown and we need to await the results of currently ongoing booster studies.

It is important to note that two second-generation dengue vaccines are now in Phase 3 trials. Due to their different composition, they may not exhibit the same safety issue in seronegative vaccinees as CYD-TDV does, but obviously we need to await the trial results. As WHO has recommended long-term safety follow-up[14], it will still take several years before a second-generation dengue vaccine will enter the market.

Conflict of interest: AWS is consultant to the Initiative for Vaccine Research at the World Health Organization (WHO). The author alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO. The author declares no conflicts of interest.

References

1. Glaesser D, Kester J, Paulose H, Alizadeh A, Valentin B. Global travel patterns: an overview. *J Travel Med* 2017; **24**(4).
2. Jentes ES, Lash RR, Johansson MA, et al. Evidence-based risk assessment and communication: a new global dengue-risk map for travellers and clinicians. *J Travel Med* 2016; **23**(6).
3. Ferguson RW, Henderson SJ, Lee EA, Jung P. Dengue in Peace Corps Volunteers, 2000-14. *J Travel Med* 2016; **23**(3).
4. Leder K, Torresi J, Libman MD, et al. GeoSentinel surveillance of illness in returned travelers, 2007-2011. *Ann Intern Med* 2013; **158**(6): 456-68.

5. Lalani T, Yun H, Tribble D, et al. A comparison of compliance rates with anti-vectorial protective measures during travel to regions with dengue or chikungunya activity, and regions endemic for *Plasmodium falciparum* malaria. *J Travel Med* 2016; **23**(5).
6. Hadinegoro SR, Arredondo-Garcia JL, Capeding MR, et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. *N Engl J Med* 2015; **373**(13): 1195-206.
7. Wilder-Smith A, Vannice KS, Hombach J, Farrar J, Nolan T. Population Perspectives and World Health Organization Recommendations for CYD-TDV Dengue Vaccine. *J Infect Dis* 2016; **214**(12): 1796-9.
8. Sridhar S, Luedtke A, Langevin E, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. *N Engl J Med* 2018.
9. Wilder-Smith A, Tambyah PA. Severe dengue virus infection in travelers. *J Infect Dis* 2007; **195**(8): 1081-3.
10. Salje H, Cummings DAT, Rodriguez-Barraquer I, et al. Reconstruction of antibody dynamics and infection histories to evaluate dengue risk. *Nature* 2018; **557**(7707): 719-23.
11. Ratnam I, Black J, Leder K, et al. Incidence and seroprevalence of dengue virus infections in Australian travellers to Asia. *Eur J Clin Microbiol Infect Dis* 2012; **31**(6): 1203-10.
12. Arien KK, Wilder-Smith A. Dengue vaccine: reliably determining previous exposure. *The Lancet Global health* 2018.
13. Villar LA, Rivera-Medina DM, Arredondo-Garcia JL, et al. Safety and immunogenicity of a recombinant tetravalent dengue vaccine in 9-16 year olds: a randomized, controlled, phase II trial in Latin America. *Pediatr Infect Dis J* 2013; **32**(10): 1102-9.
14. Vannice KS, Wilder-Smith A, Barrett ADT, et al. Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines. *Vaccine* 2018; **36**(24): 3411-7.