Author/s:
Thevarajan, I;Torresi, J;Simmons, C

Title:
Exploring the role of a recently licensed dengue vaccine in Australian travellers

Date:
2020-02-01

Citation:
Thevarajan, I., Torresi, J. & Simmons, C. (2020). Exploring the role of a recently licensed dengue vaccine in Australian travellers. Medical Journal of Australia, 212 (3), pp.102-103.e1. https://doi.org/10.5694/mja2.50471.

Persistent Link:
https://hdl.handle.net/11343/275238

Article type : Perspective (2-pp)

Article begins on page three of this document.

Title	Exploring the role of the recently licensed dengue vaccine (Dengvaxia, CYD-TDV) in Australian Travellers

Authors:

	Title	First name	**Mid inits**	Last name	Postnom (eg, PhD)	Position1	Address1	Position2	Address2	Tel	Email
1	Dr.	Irani		Thevarajan	FRACP, PhD		1		2		irani.thevarajan@mh.org.au
2	Prof.	Joseph		Torresi	FRACP, PhD		2				joseph.torresi@mh.org.au
3	Prof.	Cameron		Simmons	BS, PhD		3				cameron.simmons@worldmosquito.org
4											
5											

Number of corresponding author:	1
Number of alternative corresponding author:	

Addresses:

	Institution		City	State		Nation
1	Victorian Infectious Diseases Services		Melbourne			
2	Doherty Institute		Melbourne			
3	Institute of Vector-Borne Diseases, Monash University		Melbourne			
4						
5						

Postal address of first corresponding author (if different from the institutional address given above)	

Primary Keywords [Office use only]	Infectious diseases; Environment and public health
Secondary keywords [Office use only]	Dengue; Vaccine preventable disease
Notes:	

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/MJA2.50471

Article details (press ctrl – 9 to enter details):

Article type	Perspective
Blurb	

Office use

Ms. Number	mja19.00154.R1
Medical editor	Francis Geronimo
Medical editor email	fgeronimo@mja.com.au
Structural editor	Graeme Prince
Structural editor email	gprince@mja.com.au
Section/Category	Perspective (2-pp)
Strapheading	Perspective
Substrap	

Elsevier – file data:

Filename for copyediting	the_mja19.00154_ms
Accompanying graphics	
Stock images	
Appendices	

Office use – history:

Event	Date
Original submission received	20/02/2019

Event	Date
Accept	28/08/2019

Proof sent to author	
Proof returned by author	
Published (date format xx/xx/xx)	17/02/20
Issue	3
Vol	212
DOI	10.5694/mja19.00154
Journal	The Medical Journal of Australia
Original article DOI (for response)	

Exploring the role of a recently licensed dengue vaccine in Australian travellers

CYD-TDV (Dengvaxia) use in travellers should be considered on a case-by-case basis, with a detailed discussion of risks and benefits in light of its safety and efficacy profile

Dengue has a significant impact on global health and is a leading cause of illness in travellers who visit dengue endemic countries. There are four serotypes of dengue virus, belonging to the *Flaviviridae* family, that are transmitted to humans by *Aedes spp.* mosquitoes. Infection with dengue virus can be asymptomatic or cause a self-limited febrile illness, but can also cause severe infection. Secondary infection is a risk factor for severe dengue and one of the proposed mechanisms for this is antibody-dependent enhancement of dengue infection. It has been shown that antibody-dependent enhancement results from the presence of pre-existing antibodies arising from a primary dengue virus infection that bind to an infecting dengue virus particle in a secondary infection with a different serotype. This results in an antibody–antigen complex that enhances virus entry and replication in monocytes and increases risk of severe illness.[1] A key consideration for the development of an effective dengue vaccine has been how best to achieve efficacy against all four serotypes without significant safety concerns.

CYD-TDV (Dengvaxia, Sanofi Pasteur) is the first dengue vaccine licensed for use in 20 countries in Asia, Latin America and Australia. CYD-TDV is a tetravalent live attenuated chimeric vaccine administered as three doses (months 0, 6, 12) with no current indication for a booster dose. It is registered with the Australian Register of Therapeutic Goods but is not currently available in Australia, and can only be obtained on a case-by-case basis through the Therapeutic Goods Administration using the Special Access Scheme online system (https://www.tga.gov.au/form/special-access-scheme).

In phase 3 clinical trials, the vaccine has been shown to provide protection against dengue virus infection in dengue seropositive individuals, and reduce hospitalisations. However, long term safety analyses have raised concerns over its use in dengue seronegative individuals in endemic countries. The role of the vaccine in travellers needs careful consideration. The Australian Technical Advisory Group on Immunisation recently advised against the use of this vaccine in short term travellers and recommended limited use only in Australian travellers with past dengue infection, who are planning to reside in dengue endemic areas, if the risk–benefit consideration favours vaccination.[2] This article considers the role of the vaccine for Australian travellers in the context of both the Australian Technical Advisory Group on Immunisation recommendations and the recently revised Strategic Advisory Group of Experts on Immunization (SAGE) recommendations on its use (Box 1).[3]

In July 2016, the World Health Organization endorsed the recommendation for the use of CYD-TDV in people over the age of 9 years in regions with > 70% seroprevalence. The early findings of CYD-TDV efficacy trials in individuals aged 2–16 years in the Asia–Pacific and Latin America regions underpinned the SAGE recommendation. The key findings of the trials were overall vaccine efficacy of 65.6% (notably lower efficacy for dengue virus serotype 2); reduction in severe dengue by up to 93%; and reduction in dengue hospitalisation by up to 82%.[4,5]

However, at the 3-year follow-up there was a clear trend, despite a low number of cases, of an increased risk of hospitalisation for virologically confirmed dengue in vaccine recipients in the younger age groups.[6] This risk was most notable in Asian–Pacific children aged 2–5 years (relative risk [RR], 7.45; 95% CI, 1.15–313.80; although very wide due to the low number of cases, the confidence interval did not cross zero, indicating the trend of increased risk in vaccine recipients in the younger age group). Pooled risk estimates supported this observation with an RR of 1.58 (95% CI, 0.83–3.02) in vaccine recipients under 9 years of age compared with 0.57 (95% CI, 0.18–1.86) in children aged 9 years and older.[6] At the 4-year follow-up, the trend of higher risk in the < 9 years age group, while less pronounced compared with the 3-year follow-up, was still present. In the immunogenicity subgroups which captured pre-vaccination status of a small proportion of the study participants (7.5–20%, depending on the trial), a higher risk of hospitalised virologically confirmed dengue was apparent for seronegative vaccine recipients.[7] Experts in the field raised concerns about the broader use of the vaccine in young children in endemic countries and highlighted the need for further examination of the role of age and pre-vaccination serostatus with CYD-TDV vaccination.[8]

A recent study added to the growing safety concerns by demonstrating that in seronegative vaccine recipients the risk of hospitalisation and severe dengue was higher than in individuals who were seropositive at baseline regardless of age.[9] In this study, all cases of virologically confirmed dengue were reassessed for hospitalisation and severe dengue by serostatus and age groups. A subset of 10% ($n = 3578$) of the study participants underwent repeat testing with a novel non-structural protein 1 (NS1) IgG antibody enzyme-linked immunosorbent assay (ELISA) to determine their pre-vaccination serostatus. Hospitalisation for severe dengue was increased in the younger age group of 2–8 years, with hazard ratios (HRs) of 1.95 (95% CI, 1.19–3.19) for hospitalisation and 3.31 (95% CI, 0.87–12.54) for severe virologically confirmed dengue in seronegative vaccine recipients versus unvaccinated controls. Similar increased risks of hospitalisation (HR, 1.75; 95% CI, 1.14–2.70) and severe virologically confirmed dengue (HR, 2.87; 95% CI, 1.09-7.61) were observed for seronegative participants aged 2–16 years. The increased risk of more severe infection in seronegative vaccine recipients was observed up to 30 months after vaccination. In contrast, vaccine efficacy in all age groups was significantly higher in seropositive individuals (76%) compared with seronegative individuals (39%).[9] Based on these findings, the World Health Organization reconvened SAGE and in 2018 revised the recommendations for the use of CYD-TDV (Box 1).[3]

In Australia, there has been a recent trend of increasing dengue notifications,[10] with

reports indicating that dengue infection is a leading cause of fever and illness in returning Australian travellers.[11,12] Local dengue infection occurs in far North Queensland, but the introduction of a *Wolbachia* program in this region has led to a reduction in the annual outbreaks among local residents.[13]

For travellers visiting Bali, a common destination for Australians, a prospective study found that dengue occurred in 66.2% (133/201) of travellers who presented to a hospital with fever, and in that cohort, 13.5% were classified as having dengue haemorrhagic fever.[14] In a study of Australian travellers returning from Bali, dengue was the most common laboratory-confirmed diagnosis, reported in 5% of travellers.[15] An effective and safe vaccine would therefore be a valuable addition to the pre-travel vaccines offered to travellers. However, given the findings of the phase 3 clinical trials and the most recent SAGE recommendations, it would be essential to first determine whether a traveller can reliably report past dengue infection, with results from corresponding supportive diagnostic tests with high sensitivity and specificity for dengue, such as direct virus isolation, nucleic acid detection (polymerase chain reaction) or antigen detection (NS1 antigen assay). Without a clinical history or record to demonstrate past dengue infection, it is challenging to interpret positive dengue virus antibody serology in individuals who may have been previously infected with other flaviviruses, or received a vaccination (eg, yellow fever, Japanese encephalitis, Kunjin) that elicited cross-reactive antibodies in dengue virus ELISA. NS1 IgG antibody ELISA assay overcomes the challenge of flavivirus cross-reactivity but is currently not widely available.

Vaccination with CYD-TDV for the prevention of primary infection with dengue is not recommended in travellers. In Box 2, we discuss scenarios where vaccination can be discussed with dengue seropositive travellers who spend prolonged periods of time or intend to reside in dengue endemic countries; or who repeatedly and frequently travel to dengue endemic areas. In addition, the vaccine's long term efficacy (> 5 years) and long term risks associated with incomplete compliance to the schedule are not yet known. Another dengue vaccine, currently in phase 3 studies, may prove to be a more suitable option for travellers.[16]

Our recommendations are similar to those proposed by other experts.[17] Despite CYD-TDV being registered in Australia for use from July 2017, its use in travellers should be considered on a case-by-case basis, with a detailed risk– and cost–benefit discussion in light of its safety and efficacy profile.

Competing interests: Joseph Torresi has received an unrestricted research grant from Sanofi Pasteur, and speaking honoraria from Sanofi and Takeda Pharmaceutical Company, manufacturers of dengue vaccine.

Provenance: Not commissioned; externally peer reviewed.

Author details

Irani Thevarajan[1,2]
Joseph Torresi[2]
Cameron Simmons[3]

1 Victorian Infectious Diseases Services, Melbourne.

2 Doherty Institute, Melbourne.

3 Institute of Vector-Borne Diseases, Monash University, Melbourne.

irani.thevarajan@mh.org.au

doi: 10.5694/mja19.00154

References

1 Katzelnick LC, Gresh L, Halloran ME, et al. Antibody-dependent enhancement of severe dengue disease in humans. *Science* 2017; 358: 929-932.

2 Australian Technical Advisory Group on Immunisation. ATAGI clinical advice for immunisation providers regarding use of Dengvaxia for Australians. Canberra: Australian Government Department of Health, 2019. https://www.health.gov.au/news/clinical-advice-atagi-statement-on-use-of-dengvaxiar-for-australians (viewed Dec 2019).

3 World Health Organization. Revised SAGE recommendation on use of dengue vaccine. 19 Apr 2018. Geneva: WHO, 2019. https://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/ (viewed Dec 2019).

4 Capeding MR, Tran NH, Hadinegoro SR, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *Lancet* 2014; 384: 1358-1365.

5 Villar L, Dayan GH, Arredondo-Garcia JL, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med* 2015. 372: 113-123.

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: 1195-1206.

7 Arredondo-Garcia JL, Hadinegoro SR, Reynales H, et al. Four-year safety follow-up of the tetravalent dengue vaccine efficacy randomized controlled trials in Asia and Latin America. *Clin Microbiol Infect* 2018. 24: 755-763.

8 Simmons CP. A candidate dengue vaccine walks a tightrope. *N Engl J Med* 2015; 373: 1263-1264.

9 Sridhar S, Luedtke A, Langevin E, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. *N Engl J Med* 2018; 379: 327-340.

10 Rowe SL, Thevarajan I, Richards J, et al. The rise of imported dengue infections in Victoria, Australia, 2010-2016. *Trop Med Infect Dis* 2018; 3: 9.

11 O'Brien D, Tobin S, Brown GV, Torresi J. Fever in returned travelers: review of hospital admissions for a 3-year period. *Clin Infect Dis* 2001; 33: 603-609.

12 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: 1203-1210.

13 Ritchie SA. *Wolbachia* and the near cessation of dengue outbreaks in Northern Australia despite continued dengue importations via travellers. *J Travel Med* 2018; 25: tay084.

14 Masyeni S, Yohan B, Somia IKA, et al. Dengue infection in international travellers visiting Bali, Indonesia. *J Travel Med* 2018; 25: tay061.

15 Sohail A, McGuinness SL, Lightowler R, et al. Spectrum of illness among returned Australian travellers from Bali, Indonesia: a 5-year retrospective observational study. *Intern Med J* 2019 49: 34-40.

16 Takeda. Takeda's dengue vaccine candidate meets primary endpoint in pivotal phase 3 efficacy trial. 30 Jan 2019. https://www.takeda.com/newsroom/newsreleases/2019/takedas-dengue-vaccine-candidate-meets-primary-endpoint-in-pivotal-phase-3-efficacy-trial/ (viewed Dec 2019).

17 Wilder-Smith A. Serostatus-dependent performance of the first licensed dengue vaccine: implications for travellers. *J Travel Med* 2018; 25: tay057.

[Boxes]

Current Strategic Advisory Group of Experts on Immunization recommendations[3]

- In countries considering dengue as part of their vector control program, the preferred option is a pre-vaccination screening strategy where only dengue seropositive individuals are vaccinated.
- Conventional serology, with sensitivity and specificity assessed within the local context, should be considered. In dengue endemic countries, standard dengue serological assays are challenging because of cross-reactivity with other circulating flaviviruses; dengue non-structural protein 1 antibody assay, although not widely available, may be more useful in this context.
- In high transmission settings, rapid diagnostics could be used, although lower specificity is accepted as a limitation.
- The indicated age range for vaccination should be 9–45 years. The optimal age group to target is the age at which severe dengue disease incidence is highest, as indicated by local surveillance data. The vaccination schedule is a three-dose series given at 0, 6 and 12 months.

2 Scenarios where vaccination for dengue can be discussed with travellers

Dengue seropositive travellers who spend prolonged periods of time (expatriate) or intend to reside in dengue endemic countries

This traveller type may adopt the same risk profile for dengue virus infection as the local endemic population given the prolonged exposure times to vectors that transmit dengue. Expatriates may also have past exposure to dengue virus or have received Japanese encephalitis or yellow fever vaccines, thereby making the interpretation of baseline dengue serology difficult. Careful consideration of a clinical history to support past dengue infection and reliable diagnostic tests plus consultation with an expert (ie, travel medicine specialist, infectious disease physician or virologist) in flavivirus infection should be considered before vaccination.

Dengue seropositive travellers with repeat and frequent travel to dengue endemic areas

This traveller type includes those who visit friends and relatives and who have been infected with dengue previously. They may have a higher likelihood of exposure to a second strain of dengue virus from cumulative exposure time and therefore may experience a more severe illness following infection with a second serotype of dengue virus. The three-dose schedule of CYD-TDV may still limit the applicability of the vaccine to such travellers who may wish to visit a dengue endemic area before the schedule is complete. Currently, an abbreviated immunisation course is not supported by vaccine efficacy or safety data and vaccination should therefore only be offered to travellers who can complete the three-dose schedule prior to travel to a dengue endemic country.