



## ATAGI CLINICAL ADVICE FOR IMMUNISATION PROVIDERS REGARDING USE OF DENGVAXIA® FOR AUSTRALIANS

*It is important to read this statement in conjunction with other travel sections of the current online version of The Australian Immunisation Handbook available at <https://immunisationhandbook.health.gov.au/>*

### Key points

- The dengue vaccine, Dengvaxia is NEVER indicated for primary prevention of initial dengue infection. Dengvaxia's only role is in prevention of subsequent, more serious secondary infections in specific groups who fulfil ALL of the criteria listed below.
- The dengue vaccine, Dengvaxia®, should **NOT** be used in people who have never had a dengue infection, as it is potentially harmful. In these people, vaccination appears to increase their risk of hospitalisation and serious disease if they are subsequently infected by the dengue virus.
- Australian travellers are **NOT** recommended to receive Dengvaxia® for short-term stays in dengue-endemic areas, even in people who have had previous dengue infection, as the risks most likely outweigh any potential benefits.
- There are only very rare occasions when Dengvaxia® may be considered for use, on a case-by-case basis. This should only be considered for Australians who meet all of these conditions:
  - a) aged 9–45 years; AND
  - b) have had previous dengue infection; AND
  - c) are intending to reside in highly dengue-endemic regions for an extended period; AND
  - d) only if the potential benefits are deemed to outweigh the risks.

Factors to be assessed should include:

- *a sufficiently high risk of dengue infection – taking into account the intended duration of stay in an area considered at risk from dengue infection, due to the local level of endemicity, seasonal risk and/or current outbreaks of dengue. For example, Australians being deployed to areas where there is a high dengue risk, such as military personnel, or workers or volunteers for Government agencies or NGOs.*
- *evidence of previous acute dengue infection confirmed by laboratory testing at the time OR current serology suggestive of previous infection, in conjunction with a consistent clinical history.*
- *the feasibility of completing the 3-dose vaccination schedule over 12 months.*

The decision to advise vaccination should then be made on a case by case basis by medical staff who have expertise in dengue, which may include physicians in travel medicine, infectious diseases or occupational health.

- Serological tests that are currently available may cross-react and give false positive results from infections with and/or previous vaccination against other non-dengue flaviviruses; interpretation is often complex and requires an assessment of the pre-test probability of past true dengue infection based on a full travel, vaccination and medical history. It is recommended that clinicians seek expert advice, for example via the laboratory that performs the test, on interpreting serological results.
- For Australians, prevention of dengue while travelling or residing in dengue-prone areas should primarily be through use of strategies to avoid mosquito bites.

### What is dengue?

- Dengue is a mosquito-borne disease caused by the dengue virus. There are 4 distinct serotypes of the virus. Infection with one serotype provides lifelong protection against that serotype only, but not against the other serotypes<sup>1</sup>.
- Mild dengue disease may include symptoms such as an influenza-like illness with high fevers, headaches, muscle and joint pains, and a rash.

<sup>1</sup> World Health Organization. WHO Fact Sheet: Dengue and severe dengue. Available from: <https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue> (Accessed 13/12/18).

- Severe dengue disease most commonly occurs after a subsequent dengue infection with a different serotype of the virus, and may result in death<sup>2</sup>. Evidence suggests that the initial infection primes the immune system of an individual, which leads to a potentially more serious disease when a second infection occurs. Potential mechanisms include antibody-dependent enhancement whereby falling antibody titres reach an intermediate level at which viral entry and replication in immune cells is enhanced<sup>3</sup>.
- Dengue is not endemic in any region in Australia. It is, however, widespread in many countries that are popular destinations for Australian travellers<sup>4</sup>. While the primary mosquito species (*Aedes aegypti*) responsible for transmitting dengue is present in north Queensland, only small local outbreaks from occasional imported cases occur.

### What is Dengvaxia®?

- Dengvaxia® (manufactured by Sanofi Pasteur) is a live-attenuated recombinant tetravalent dengue vaccine registered for use in some countries in people aged 9–45 years<sup>2</sup>. Current evidence does not support use of Dengvaxia in any situation outside this age range. It is currently the only licensed dengue vaccine in the world. A complete course of vaccination requires 3 doses, to be given at 0-, 6- and 12-month time points. Dengvaxia® is registered with the Therapeutic Goods Administration (TGA) in Australia, but is not currently marketed in Australia. It is available only via the Special Access Scheme (SAS), on a case-by-case basis, through specific application to the TGA. The recommendations in this statement are consistent with the TGA registered indication for use.

### Clinical trial results of Dengvaxia® regarding its efficacy against dengue infection and safety

- Dengvaxia® is a moderately effective vaccine in populations in which it was tested. It reduces symptomatic laboratory-confirmed dengue disease by 55–60%. However, it has only been tested in people living in countries with high rates of dengue exposure ( $\geq 70\%$  of the population with previous infection)<sup>5,6</sup>.
- It is important to note that an overall benefit from vaccination is seen only in individuals who have had dengue infection before vaccination; it reduces the risk of subsequent infection in these people<sup>7</sup>. In people of all ages who have not had dengue infection before vaccination and who are vaccinated with Dengvaxia®, there is a longer-term increase in the risk of hospitalisation and severe disease during a dengue infection in the future compared to those who are unvaccinated.
- At a population level, the clinical trials of Dengvaxia®, which were conducted in areas of high dengue prevalence, showed that people aged 9–16 years who had no previous dengue infection before vaccination experienced the following risks of harm<sup>7</sup>:
  - *risk of dengue hospitalisation over the 5 years after vaccination was 1.4 times (95% CI: 0.74–2.68) that of the unvaccinated*
  - *risk of severe dengue was 2.4 times (95% CI: 0.47–12.56) that of the unvaccinated.*
- Vaccination with Dengvaxia® appears to act like a primary infection in those with no prior exposure to the virus, increasing the risk of severe disease if the person gets a dengue infection after vaccination. In contrast, Dengvaxia® reduces the risk of subsequent disease in those with previous dengue infection before vaccination and who live in highly endemic areas<sup>7</sup>. However, since the beneficial effects shown in the clinical trials were in people living in highly endemic regions of dengue, they may not be the same for those seeking vaccination for short-term stays, even in individuals who have been previously infected with dengue. In these people, the benefits may not sufficiently outweigh the risks.

### When should Dengvaxia® NOT be used?

- Dengvaxia® should NOT be used:
  - *in persons without laboratory, clinical and epidemiological evidence consistent with previous dengue infection*
  - *in individuals aged less than 9 years or older than 45 years*
  - *as a travel vaccine for Australians planning short stays in endemic areas – in most circumstances using it for Australians planning long-term stays in endemic areas would also be inappropriate – refer to the Key points on page 1 above*
  - *for protection against getting a dengue infection in Australia (including north Queensland), as dengue is not endemic.*

<sup>2</sup> World Health Organization. Updated Questions and Answers related to the dengue vaccine Dengvaxia® and its use. 22 December 2017. Available from: [https://www.who.int/immunization/diseases/dengue/g\\_and\\_a\\_dengue\\_vaccine\\_dengvaxia\\_use/en/](https://www.who.int/immunization/diseases/dengue/g_and_a_dengue_vaccine_dengvaxia_use/en/) (Accessed 13/12/18).

<sup>3</sup> Katzelnick LC, Gresh L, Halloran ME et al. Antibody-dependent enhancement of severe dengue disease in humans. *Science* 2017;358:929-32

<sup>4</sup> Tai AY, McGuinness SL, Robosa R, et al. Management of dengue in Australian travellers: a retrospective multicentre analysis. *Medical Journal of Australia* 2017; 206:295-300.

<sup>5</sup> 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;384:1358-65.

<sup>6</sup> Villar L, Dayan GH, Arredondo-Garcia JL, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med* 2018; 379: 327-40.

<sup>7</sup> Sridhar S, Luedtke A, Langevin E, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. *N Engl J Med* 2018; 379: 327-40.

## Important notes regarding blood tests for previous dengue infection in the absence of laboratory confirmation of infection at the time of acute disease

- Currently there is no point-of-care test, with adequately high sensitivity and specificity, to accurately confirm past dengue infection and which is suitable for use immediately before vaccination<sup>2,8,9</sup>.
- For Australian residents believed to have had previous dengue infection, dengue serology consistent with this and an appropriate clinical history of infection following travel to a dengue endemic area should be verified before considering whether the benefits outweigh the risks of vaccination. Even a history of a past “laboratory-confirmed” dengue infection should be interpreted with caution.
- Cross-reactivity with current or previous infection by a related flavivirus (e.g. Zika, Japanese encephalitis, or yellow fever) or vaccination with a flavivirus vaccine makes correct interpretation of dengue serology tests difficult; consultation with an expert in dengue serology is strongly advised.

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<sup>8</sup> World Health Organization. Revised SAGE recommendation on the use of dengue vaccine. April 2018. 2018 Available from: [https://www.who.int/immunization/diseases/dengue/revised\\_SAGE\\_recommendations\\_dengue\\_vaccines\\_apr2018/en/](https://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/) (Accessed 13/12/18)

<sup>9</sup> World Health Organization. Dengue Position Paper September 2018. 2018. Available from: <http://apps.who.int/iris/bitstream/handle/10665/274315/WER9336.pdf> (Accessed 13/12/18).