

Vaccination against dengue fever for travellers

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Summary

Dengue fever, endemic to most tropical and subtropical countries, is a major cause of illness in travellers, but severe dengue, hospitalisation and death are considered rare in this population. Two vaccines against dengue fever, Dengvaxia[®] and Qdenga[®], are available. While there is no recommendation for the use of Dengvaxia[®] in travellers, Qdenga[®] has been licensed for travellers in many European countries since December 2022, most recently (29 July 2024) in Switzerland by Swissmedic.

The Swiss Expert Committee for Travel Medicine (ECTM), having assessed available data on the Qdenga[®] vaccine, issues the following recommendations:

(1) Vaccination against dengue fever virus with Qdenga[®] is not recommended for persons with no previous dengue fever infection.

(2) Vaccination with Qdenga[®] may be recommended for travellers aged 6 years and older who have evidence of previous dengue infection, defined as (a) a laboratory-confirmed dengue infection (PCR, antigen or seroconversion) or (b) a compatible history of dengue infection with a positive IgG serological test AND expected exposure to a region with significant dengue transmission.

Travel medicine advisors should provide clear information in accessible language on the complexity of dengue vaccines and the risk/benefit evaluation for their use in travellers.

Current epidemiological situation and immunological specificity of dengue fever

Dengue fever, caused by an arthropod-borne virus (arbovirus) of the family *Flaviviridae*, occurs in most tropical and subtropical countries. It is transmitted by the bite of the female *Aedes aegypti* mosquito and, to a lesser extent, *Aedes albopictus*. Its global incidence has gradually increased over the decades, with 5 million cases reported in 2023 [1] and more than 10 million already in 2024 [2]. The seroprevalence of dengue is heterogeneous, differing both by age and by world region, even within the same country [3]. Most cases are recorded in South Asia, Southeast Asia and Latin America. However, due to the spread of potential vector species, human mobility and the effects of global warming, the epidemiology of dengue is changing, with an increase in dengue cases in Africa and the appearance of autochthonous dengue cases in North America and Southern Europe [4, 5]. In addition to its socioeconomic implications, dengue fever is recognised as a prominent contributor to mortality among children in Asia. The burden of dengue fever in travellers to endemic areas is lower but not negligible, representing the main identified cause of fever on return from travel to (sub-)tropical areas outside sub-Saharan Africa. The incidence rate of dengue infection among travellers is estimated to be 2 to 60 per 1,000 person-month, with up to 80% asymptomatic infections [6]. Among symptomatic patients, few present with complicated dengue (1.6%) or severe dengue (0.5%) [7, 8].

There are four different serotypes of dengue virus (DENV-1, DENV-2, DENV-3 and DENV-4), which circulate concurrently in most endemic countries worldwide.

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However, the predominance of one serotype over another fluctuates across epidemics [9, 10]. Except in rare situations, there is no surveillance of the circulating serotype, and this information is usually unknown during outbreaks. Recovery from infection results in long-term (sterilising) immunity against the specific serotype, mainly through neutralising humoral immunity (homotypic antibodies) [11]. The specific pathogenesis of severe dengue fever, with an increased risk of complications associated with a second infection by a serotype other than that causing the primary infection, is explained by an immunological mechanism known as antibody-dependent enhancement (ADE). The presence of non-neutralising, non-serotype-specific (heterotypic) antibodies facilitates the invasion of cells of the myeloid lineage (the main target) and leads to an increase in viral load and severe disease [12–14]. Treatment for dengue virus infection remains symptomatic, with no specific treatment currently available.

Rationale for dengue fever vaccines

Given the impact of dengue fever in endemic countries, a safe and effective vaccine is of major public health interest for the local population. In non-endemic countries such as Switzerland, while public health interest lies in preventing the introduction of dengue fever and its local transmission, the main aim of vaccination for travellers is to reduce morbidity, including absenteeism or treatment costs, since the risk of severe dengue fever and mortality in a seronegative population is low [8, 15].

Several vaccines against dengue fever are currently being developed but only two ever reached approval (in chronological order of submission to the authorities): Dengvaxia[®] and Qdenga[®]. While both vaccines are licensed by the European Medicines Agency (EMA), only Qdenga[®] is commercially available in certain European countries since 2022. In early 2023, Takeda Pharmaceutical Co. Ltd. applied for the marketing authorisation of Qdenga[®] in Switzerland, which was approved at the end of July 2024.

One of the main challenges of vaccination against dengue virus infection – as highlighted by the World Health Organization (WHO) in 2011 [16] – is the induction of persistent immunity against each of the four serotypes. This is crucial because a decline in neutralising antibodies could not only fail to provide protection but also increase the risk of severe dengue following a natural infection with a different serotype due to antibody-dependent enhancement.

Dengvaxia[®]

Dengvaxia[®] has been licensed since 2018 by the EMA for seropositive patients aged 6 to 45 years but is not currently available in Europe and is not recommended for travellers. In June 2024, Sanofi-Pasteur announced that the production of Dengvaxia[®] for children would be halted due to a lack of demand. Nevertheless, some key points and lessons learned from Dengvaxia[®] must be highlighted and are summarised below [17].

Dengvaxia[®] was the first dengue vaccine to be authorised and used. It is a live-attenuated, tetravalent, chimeric vaccine against all four dengue virus serotypes (DENV 1–4) based on a 17D yellow fever vaccine backbone, with the introduction of precursor-membrane protein (prM) and en-

velope protein (E) domains. The vaccination schedule includes three doses injected subcutaneously at months 0, 6 and 12 (M0, M6 and M12). While studies showed a cumulative vaccine efficacy (cVE) against dengue overall of nearly 60% at 25 months after the first vaccine dose, the efficacy was unbalanced across serotypes, favouring DE NV4 (cVE ~80%) and showing the lowest value against DENV-2 (cVE ~40%). Moreover, overall cVE was ~35% in patients under 5 years of age, as well as in seronegative patients, compared to ~75% in children over 12 years of age and seropositive patients [18, 19]. In 2016, a sub-group analysis revealed a significant increase in the relative risk of severe dengue fever in the vaccinated under-5 population compared to unvaccinated children [6, 20]. In 2018, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommended a pre-vaccination screening strategy limiting vaccination to seropositive individuals only without discussing the problem of serological test reliability (e.g. specificity, cross-reactions). As stated by Da Silva et al., [21] “a lesson learned from that experience was the importance of balanced immunity achieved by independent replication and immunogenicity of the four vaccine components”.

Qdenga[®]

In December 2022, the EMA granted marketing approval for Qdenga[®], and it has been available in certain European countries since early 2023. In July 2023, Takeda withdrew its application for approval by the United States Food and Drug Administration (FDA) due to “aspects of data collection, which cannot be addressed” [21]. Regarding Switzerland, Qdenga[®] was approved by Swissmedic at the end of July 2024.

Qdenga[®] is a tetravalent, chimeric, live-attenuated vaccine (DENV 1–4) based on a DENV-2 backbone, with the introduction of the prM and E domains of DENV 1, 3 and 4. Unlike Dengvaxia[®], it encompasses the domains of DENV-2 non-structural (NS) proteins [23].

Vaccination schedule

The vaccination schedule for individuals aged 6 years and older, as recommended by the WHO [10], is two doses subcutaneously on day 0 and at 3 months (M0 and M3). Exploratory data show sufficient protection (81%) in the short term (90 days) after a single dose [10, 24, 25]. Currently, the need for a Qdenga[®] booster dose remains unknown, particularly for individuals residing in non-endemic areas that cannot rely on natural boosters.

Vaccine efficacy data against virologically confirmed dengue infection

Cumulative vaccine efficacy (cVE data) until 57 months (4.5 years) post-primary vaccination are available [26].

In summary, the overall cVE is reported as ~80%, 73% and 61% at 12 months, 18 months and 57 months after the second dose, respectively, with a final vaccine efficacy of ~54% in seronegative patients. Efficacy varied significantly between serotypes regardless of baseline immunological status: in seropositive patients, the rates were 56%, 80%, 52% and 71% for DENV-1, DENV-2, DENV-3 and DENV-4, respectively, at month 57. In seronegative pa-

tients, the cVE was 45% and 88% for DE NV1 and DENV-2, respectively, while data were insufficient to confirm efficacy and safety against DE NV3 and DENV-4 (cVE -16% and -106%, respectively; see table 1).

Vaccine efficacy against hospitalisations

Vaccine efficacy against hospitalisations at month 57 was ~86% in seropositive patients and 79% in seronegative patients, with marked differences between serotypes: high efficacy (>95%) was observed against DENV-2 regardless of initial serological status, consistent with its use as the vaccine backbone. However, efficacy data for other DENV serotypes were less conclusive: while the vaccine showed reduced but substantial efficacy (74%) against DENV-3 in seropositive patients, its efficacy was inconclusive or potentially indicated increased risk (-88%, not statistically significant) in seronegative patients infected with DENV-3 [27]. Data were insufficient to draw conclusions about protective effects (or safety) against hospitalisation regarding DENV-4 owing to the limited circulation of this serotype during the study period.

Conclusion and recommendations

To date, cases of dengue in Switzerland are exclusively travel-related, and severe cases are very rare in travellers. Regarding vaccination against dengue fever, and in line with the WHO recommendation issued on 3 May 2024 [10], the Swiss ECTM concludes the following:

1. Vaccination with Qdenga® is not recommended for travellers with no evidence of a previous dengue fever infection.

This recommendation considers the following points:

- an estimated (very) low seroprevalence against dengue in the Swiss population, and consequently, the low risk of a potentially severe second infection in the Swiss population;
- a lack of balance in vaccine efficacy across serotypes, particularly in seronegative subjects;
- insufficient data to establish efficacy and safety against DENV 3 and 4 in vaccinated seronegative individuals;

- limited data on adults, especially those older than 60 years.

2. Vaccination with Qdenga® may be recommended for travellers aged 6 years and older who have evidence of previous dengue infection and will be exposed to a region with significant dengue transmission.

- Definition of previous dengue infection: Previous dengue infection is defined as (a) a laboratory-confirmed dengue infection (PCR, antigen or seroconversion) or (b) a compatible history of dengue infection with a positive IgG serological test.

This ECTM recommendation reflects the current knowledge as of the publication date. These guidelines will be revised when more data become available.

Communication

Travel medicine advisors should provide clear information in accessible language on the complexity of dengue vaccines and the risk/benefit evaluation for their use in travellers.

Serological screening

General serological screening is not recommended. It should be noted that serology alone without a compatible history should be interpreted with caution given cross-reactions with other flaviviruses or their vaccines (such as yellow fever, tick-borne encephalitis and Japanese encephalitis) [28, 29], especially in patients living outside endemic areas where the positive predictive value is low. Ideally, dengue serology should be performed in laboratories with experience in interpreting cross-reactive arboviral disease results. Rapid diagnostic tests are considered inappropriate. In case of doubt, consultation with a specialist in tropical and travel medicine or infectious diseases is recommended.

Vaccine schedule

Preferably, the two doses on day 0 and at month 3 (M0 and M3) should be administered before travel to a dengue-endemic area. In case of time restrictions, completion of the primary schedule with the second dose given upon return can be considered (if future exposure is planned). The

Table 1:

Cumulative vaccine efficacy against virologically confirmed dengue fever, from first dose to 54 months post-second dose [25]

	Vaccine efficacy (in %) in preventing virologically confirmed dengue fever (95% CI)	Vaccine efficacy in preventing hospitalisation due to virologically confirmed dengue fever (95% CI)
Overall	61.2 (56.0, 65.8)	84.1 (77.8, 88.6)
Baseline seronegative		
Any serotype	53.5 (41.6, 62.9)	79.3 (63.5, 88.2)
DENV-1	45.4 (26.1, 59.7)	78.4 (43.9, 91.7)
DENV-2	88.1 (78.6, 93.3)	100 (88.5, 100)
DENV-3	-15.5 (-108.2, 35.9)	-87.9 (-573.4, 47.6)
DENV-4	-105.6 (-628.7, 42.0)	Not provided (too few cases)
Baseline seropositive		
Any serotype	64.2 (58.4, 69.2)	85.9 (78.7, 90.7)
DENV-1	56.1 (44.6, 65.2)	66.8 (37.4, 82.3)
DENV-2	80.4 (73.1, 85.7)	95.8 (89.6, 98.3)
DENV-3	52.3 (36.7, 64.0)	74.0 (38.6, 89.0)
DENV-4	70.6 (39.9, 85.6)	Not provided (too few cases)

CI: confidence interval

interval of 3 months between the first and second dose should not be shortened.

Booster dose

None is recommended, as currently, there are no corresponding data for Qdenga[®]. As there is a lack of knowledge about the duration of protection after vaccination, the need for a booster must be considered for vaccinees living in a non-endemic area.

Adverse events

Some rare anaphylactic reactions have been reported in vaccinees. Consequently, Qdenga[®] should only be administered in settings where anaphylaxis can be treated and vaccinees observed for at least 15 minutes following vaccination.

Moreover, as adverse events, such as headaches, weakness, rash and fever, start to occur in the second week after vaccination, vaccine doses should ideally be given at least 14 days prior to departure [30].

Contraindications

- Allergy to the active substances or any of the excipients or allergy to a previous dose of Qdenga[®]
- Individuals with congenital or acquired immune deficiency, including due to immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids (e.g. ≥ 20 mg/day or ≥ 2 mg/kg body weight/day of prednisone for 2 weeks or more) within 4 weeks prior to vaccination, as with other live-attenuated vaccines
- Individuals with HIV infection if CD4 cell counts < 200 cells/ μ L or if viremia is uncontrolled
- Pregnant women (delay pregnancy by 1 month following vaccination)
- Breast-feeding women (it is unknown whether Qdenga[®] is excreted in human breast milk)

Checklist: practical considerations for the use of Qdenga[®]

General information to be given to travellers

Qdenga[®] has been licensed in Switzerland since the end of July 2024.

- Qdenga[®] costs are not reimbursed by basic health insurance. Supplemental health insurance plans can pay a part or the entirety of the cost.
- Provide detailed information on the cons and pros of the vaccine.

Dengvaxia[®] is not an option.

Before vaccination, inform the vaccinee about the following points:

- **Mosquito bite prevention measures are still very important, also to protect against other arboviruses.**
- Dengue infection can still occur after Qdenga[®] vaccination.
- Qdenga[®] does not provide the same level of protection against all serotypes of infection.

Indications

Qdenga[®] may be recommended for travellers who have evidence of previous dengue infection.

Check the following criteria:

- Previous laboratory-confirmed dengue infection (PCR, antigen or seroconversion) *or* a compatible history of dengue infection with positive IgG serology
- *and* expected exposure to a region with significant dengue transmission

Absolute contraindications

Immunodeficiency (individuals with congenital or acquired immune deficiency, including persons using immunosuppressive therapies).

Pregnancy or breastfeeding.

Age < 6 years.

Allergy to any substance included in the vaccine or hypersensitivity to a previous dose of Qdenga[®].

Relative contraindications (great caution)

Age > 60 years (due to a lack of data). Vaccination can be considered for individuals over 60 years, but the recipient must be informed about the lack of data.

Administration of immunoglobulins within the last 3 months.

Vaccine schedule

Dose 1: day 0. Dose 2: month 3 (M0-M3). Of note: The interval between dose 1 and dose 2 cannot be shortened. Dose 2 can be given upon return (or before the next exposure) if time does not allow vaccination with two doses before travel.

Route of administration: subcutaneous injection.

Due to rare anaphylactic reactions, Qdenga[®] should only be administered in settings where anaphylaxis can be treated and the vaccinees observed for at least 15 minutes following vaccination.

Minimum interval between dengue infection and the first dose of Qdenga[®]: 6 months.

Co-administration with other vaccines

Concomitant vaccine with hepatitis A or yellow fever vaccine has been studied and is considered safe.

If possible, avoid other concomitant vaccinations with Qdenga[®] due to missing data on immunogenicity.

If co-administration with another injectable vaccine is unavoidable, the vaccines should be administered at different injection sites.

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Potential competing interests

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