Vaccination against Dengue fever for Travellers – Statement of the Swiss Expert Committee for Travel Medicine, March 2024

Summary

Dengue fever, endemic in most tropical and sub-tropical countries, is a major cause of illness in travellers, but severe dengue, hospitalisation or death are considered rare in this population. Two vaccines against dengue fever exist, Dengvaxia® and Qdenga®. While there is no recommendation for the use of Dengvaxia® in travellers, Qdenga® is licensed for travellers in many European countries since December 2022. Approval by Swissmedic for its use in Switzerland is still pending. This decision is expected for the second half of the year 2024.

The Swiss Expert Committee for Travel Medicine (ECTM) assessed the published and unpublished data for the Qdenga® vaccine and issues the following recommendation:

1. Vaccination against dengue fever virus with Qdenga® in persons with no previous dengue fever infection is not recommended.

2. Vaccination with Qdenga® **can be recommended** for travellers 4 years of age or older **with confirmed previous dengue infection**, defined as i) a laboratory confirmed dengue infection (PCR, antigen or seroconversion) or ii) a clear clinical history with a positive IgG serological test. **AND** who **will be exposed in a region with significant dengue transmission.**

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

Current epidemiological situation and immunological specificity of dengue fever

Dengue fever, caused by an arthropod-borne virus (arbovirus) of the flaviviridae family, is present in most tropical and sub-tropical countries. It is transmitted by the bite of the female mosquito of *Aedes aegypti* and, to a lesser extent, *Aedes albopictus*. Global incidence has gradually increased over the last decades, with 5 million cases reported in 2023.(1) There is heterogeneity in seroprevalence according to age but also according to regions of the world, and even within the same country. Most cases are recorded in South Asia, South-East Asia and Latin America. However, as a result of the spread of potential vector species (also in Switzerland), human mobility and also the effects of global warming, epidemiology is changing, with an increase in dengue cases in Africa and the appearance of autochthonous dengue cases in North America and Southern Europe.(2,3) Apart from the socio-economic impact of morbidity, dengue fever is considered to be one of the leading causes of death among children in Asia. The burden of dengue fever in travellers to endemic areas is low but not negligible, since it represents the main identified cause of fever on return from travel to (sub-) tropical areas outside sub-Saharan Africa.(4)

There are four different serotypes of dengue virus (DENV-1, DENV-2, DENV-3, DENV-4) which circulate concurrently in most endemic countries worldwide. However, the predominance of one serotype over another fluctuates from one epidemic to another. Recovery from infection results in long-term (sterilising) immunity against the specific serotype, mainly through neutralising humoral immunity (homotypic antibodies). The particular pathogenesis of severe dengue fever, with an increased risk associated with a second infection by a serotype other than the primary infection, is explained by a specific immunological mechanism known as antibody-dependent enhancement (ADE). The presence of non-neutralising non-serotype-specific (heterotypic) antibodies facilitates invasion of cells of the myeloid lineage (the main target) and consequently leads to an increase in viral load and severe disease.(5–7) Treatment for dengue virus infection remains symptomatic, there is currently no specific treatment.

Rational regarding 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 is to avoid the introduction of dengue fever and its local transmission, the main aim of vaccination for travellers would be to improve individual health and to reduce morbidity, such as absenteeism, cost of treatment, since the risk of severe dengue fever and mortality in a seronegative population is low.(8,9)

Several vaccines against dengue fever are currently being developed but only two are approved or available: 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.) submitted an application for marketing authorisation of Qdenga® in Switzerland. The decision on the submission is expected for the second half of the year 2024.

One of the main difficulties of vaccination against dengue virus infection - as highlighted by WHO in 2011(10) - is the importance to induce persistent immunity against all 4 serotypes, since a decline of 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 ADE.

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 not recommended for travellers.

Dengvaxia®, developed by Sanofi®, was the first dengue vaccine authorised and used. It is a live-attenuated tetravalent chimeric vaccine against all four serotypes (DENV 1-2-3-4) based on a 17D yellow fever backbone, with the introduction of the prM (precursor-membrane protein) and E(nvelope protein) domains. The vaccination schedule includes three doses injected subcutaneously at months 0, 6 and 12 (M0, M6, M12). While studies showed a vaccine efficacy (VE) against dengue disease overall of nearly 60% at 25 months after the first vaccine dose, there was an unbalanced efficacy between serotypes in favour of DENV-4 (VE ~80%), and least against DENV-2 (VE ~40%). Moreover, overall VE was ~35% in patients under 5 years of age as well as in seronegative patients compared to ~75% VE in children over 12 years of age or seropositive patients.(11,12) In 2016, a sub-group analysis revealed a significant increase in the relative risk of severe dengue fever in the vaccinated under-5 years population compared to the non-vaccinated.(4,13) 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 the reliability of serological tests (e.g. specificity, cross-reactions). As written by Da Silva et al.,(14) "a lesson learned from that experience was the importance of balanced immunity achieved by independent replication and immunogenicity of the 4 vaccine components".

Qdenga®

On December 2022, the European Medicine agency granted marketing approval for Qdenga® and it has been available in certain European countries since early 2023. In July 2023, Takeda withdrew the application for the approval by the Food and Drug administration (FDA) in the United States, due to requirements of missing data.(15)

For Switzerland, Takeda has submitted Qdenga® to Swissmedic, the decision on its submission is expected for the second half of the year 2024.

Qdenga®, developed by Takeda, is a tetravalent chimeric live attenuated vaccine (DENV 1-2-3-4) based on a DENV-2 backbone, with the introduction of the prM and E domains of DENV-1-3-4. Unlike Dengvaxia®, it possesses the domains of (DENV-2) non-structural (NS) proteins.(16)

Vaccination schedule for individuals from 4 years old as investigated by Takeda: 2 doses subcutaneous, on day 0 and at 3 months (M0, M3). Unpublished exploratory data show sufficient protection (81%) for short term (90 days) after one dose.(17) To date the need for a Qdenga® booster dose is unknown, particularly for persons living in non-endemic areas that cannot rely on natural boosters.

Vaccine efficacy data until 57 months (4.5 years) post primary vaccination are available.(18) In summary, the overall cumulative vaccine efficacy against symptomatic dengue fever 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. There was considerable variability in reported efficacy between serotypes regardless of immunological status at baseline: in seropositive patients 56%, 80%, 52% and 71% were reported for DENV-1, DENV-2, DENV-3 and DENV-4 respectively at month 57; and in seronegative patients 45%, 88%, -16% and -106%.

Vaccine efficacy against hospitalizations at months 57 was ~86% in seropositive patients and 79% in seronegative patients, with major differences between serotypes: excellent efficacy (>95%) was seen against DENV-2 irrespective of initial serological status; this was to be expected since DENV-2 constitutes the backbone of the vaccine. However, for all other DENV serotypes data are less clear: reduced but robust efficacy (74%) was observed for DENV-3 in seropositive patients but it was absent or might even show an increased risk (-88%, not significant) in seronegative patients infected with DENV-3.(19) There was insufficient data to come to any conclusion regarding a protective effect against hospitalization for DENV-4, due to a lack of DENV-4 circulation at the time of the studies.

Conclusion and recommendations

To date, cases of dengue in Switzerland are exclusively travel-related and severe cases are very rare in travellers. With regard to the vaccination against dengue fever, the Swiss Expert Committee for Travel Medicine concludes:

1. Vaccination with Qdenga® for travellers with no previous dengue fever infection is not recommended. This recommendation takes into account the following points:

- an estimated (very) low seroprevalence against dengue in the Swiss population
- the limited risk in the Swiss population of primary dengue infections and - even more so - of a second infection - the main risk of severe dengue
- the limited documented efficacy in seronegative subjects, esp. for DENV-1, 3 and 4
- a lack of balance in vaccine efficacy between serotypes, particularly in seronegative subjects
- insufficient data on the risk (or its absence) of severe dengue fever in vaccinated seronegative subjects
- few data on adults, especially in people older than 60 years

2. **Vaccination with Qdenga® can be recommended for travellers** from **4 years old with confirmed previous dengue infection* AND** who **will be exposed in a region with significant dengue transmission.**

***definition of previous dengue infection:**
Previous dengue infection is defined as i) a laboratory confirmed dengue infection (PCR, antigen or seroconversion) or ii) a clear clinical history with a positive IgG serological test

Of note:

- **Travel medicine advisors should provide concise communication** in accessible language on the complexity and risk/benefit evaluation for the use of dengue vaccines in travellers.

- **General serological screening is not recommended**. It should be noted that serology alone without a compatible history should be interpreted with caution given the cross-reactions existing with other flaviviruses or their vaccines (such as yellow fever, tick-borne encephalitis, Japanese encephalitis),(20,21) especially in patients living outside endemic areas where the positive predictive value is low.

- **Vaccine schedule:** Preferably, the 2 doses at day 0 and month 3 (M0, M3) should be administered before travelling to a dengue endemic area. In case of time restriction, completion of the primary schedule with the second dose given upon return can be considered (if future exposure is planned). The interval of 3 months between the first and second dose should not be shortened.

- **Booster dose:** None recommended, as currently there are no corresponding data for Qdenga®. As there is lack of knowledge about the duration of protection after vaccination, the need for a booster needs to be taken into account for vaccinees living in a non-endemic area. Consultation with a specialist in tropical and travel medicine or in infectious diseases is recommended.

- **Contraindications to Qdenga®**:
  - Allergy to the active substances or to any of the excipients, or allergy to a previous dose of Qdenga®
  - Individuals with congenital or acquired immune deficiency, including 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 are <200 cells/µl or if viremia is uncontrolled
  - Pregnant women (delay pregnancy by one month following vaccination)
  - Breast-feeding women (it is unknown whether Qdenga® is excreted in human breast milk)

This ECTM recommendation reflects the current knowledge as of publication date. These guidelines will be revised when more data become available, particularly data on serotypes DENV-3 and DENV-4.

Table 1: Cumulative vaccine efficacy in virological confirmed dengue fever, data from Takeda(18)

	Vaccine efficacy (in %) in **preventing virologically confirmed dengue fever** (95% confidence interval)	Vaccine efficacy in **preventing hospitalisation** due to virologically confirmed dengue fever (95% confidence interval)
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)
DEN-4	70.6 (39.9, 85.6)	Not provided (too few cases)

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PRACTICAL CONSIDERATIONS FOR THE USE OF QDENGA®

Expertenkomitee für Reisemedizin
Comité d'experts pour la médecine des voyages
Comitato di esperti per la medicina di viaggio
Expert committee for travel medicine

General information to be given to traveller

- ☐ Qdenga® is not licensed in Switzerland. The current vaccine has been imported from Germany. It has been approved by the European Medicines Agency and is available in some European countries;
  - ☛ Inform the vaccinee on the "off label" use in Switzerland and document in the patient file that the patients has been informed on this. Qdenga® will not be reimbursed by the health insurance.
  - ☛ Provide detailed information on con's and pro's to the vaccine.
- ☐ Dengvaxia® is not an option
- ☐ Before vaccinating: Inform the vaccinee about:
  - ☐ **Mosquito bite prevention measures are still very important, also as protection from other arboviruses.**
  - ☐ Dengue infection can still occur if vaccinated with Qdenga®.
  - ☐ Qdenga® does not provide the same level of protection against all serotypes of infection.

Indication

Qdenga® can be recommended for travellers with confirmed previous dengue infection. Check the following criteria:

- ☐ Previous laboratory confirmed Dengue (PCR, antigen or seroconversion) or clinical history with a serological test IgG positive
- ☐ Exposed in a region with significant dengue transmission

Absolute contraindication

- ☐ Immunodeficiency (individuals with congenital or acquired immune deficiency, including immunosuppressive therapies)
- ☐ Pregnancy or breastfeeding
- ☐ Age < 4 years
- ☐ Allergy to any substance included in the vaccine or hypersensitivity to a previous dose of Qdenga®

Relative contraindication/ great caution

- ☐ Age > 60 years (due to missing data). Vaccination can be considered for individuals over 60 years, but the recipient must be informed about the lacking 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 2 doses before travel.
- ☐ Route of administration: subcutaneous injection
- ☐ Minimal interval between dengue infection and first dose of Qdenga®: 6 months

Co-administration with other vaccines

- ☐ If possible, avoid concomitant vaccinations at the same time with Qdenga® due to missing data on immunogenicity.
- ☐ If coadministration with another injectable vaccine is not avoidable, the vaccines should always be administered at different injection sites.