Vaccination against Dengue fever for Travellers – Statement of the Swiss Expert Committee for Travel Medicine, an organ of the Swiss Society for Tropical and Travel Medicine, July 2024

on behalf of the Swiss Expert Committee for Travel Medicine (members listed at the end)

Summary

Dengue fever, endemic in most tropical and subtropical 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 before the end of 2024.

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

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 aged 6 years and older **who have evidence of previous dengue infection**, defined as i) a laboratory confirmed dengue infection (PCR, antigen or seroconversion) or ii) a compatible history of dengue infection with a positive IgG serological test.
   AND will be exposed in a region with significant dengue transmission.

Travel medicine advisors should provide clear 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 subtropical countries. It is transmitted by the bite of the female *Aedes aegypti* mosquito 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.[2] Most cases are recorded in South Asia, South-East Asia and Latin America. However, as a result of the spread of potential vector species, 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.[3,4] In addition to the socioeconomic implications of illness, dengue fever is recognized 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, as it represents the main identified cause of fever on return from travel to (sub-) tropical areas outside sub-Saharan Africa. The incidence rate for dengue-infection among travellers is estimated to be 2 to 60 per 1,000 person-month with up to 80% asymptomatic infections[5]. Among symptomatic patients, few presented complicated dengue (1.6%) or severe dengue (0.5%).[6,7]

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.[8,9] 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).[10] 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.[11–13] Treatment for dengue virus infection remains symptomatic as there is currently no specific treatment.

Rationale 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 lies in preventing the introduction of dengue fever and its local transmission, the main aim of vaccination for travellers would be to reduce morbidity, including absenteeism or treatment costs, since the risk of severe dengue fever and mortality in a seronegative population is low.[7,14]

Several vaccines against dengue fever are currently being developed but only two are approved or available (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 marketing authorisation of Qdenga® in Switzerland. A decision on the submission is expected before the end of 2024.

One of the main challenges of vaccination against dengue virus infection - as highlighted by WHO in 2011[15] – is the importance of inducing persistent immunity against each of the four serotypes. This is crucial because 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. Sanofi-Pasteur announced in June 2024 that production of Dengvaxia® for children will be halted due to a lack of demand. Despite this, some key points and lessons learned from Dengvaxia® need to be highlighted and will be summarised below.(16)

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 vaccine 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 cumulative vaccine efficacy (cVE) 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 (cVE ~80%), and least 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% cVE in children over 12 years of age or seropositive patients.[17,18] 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.[5,19] 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.,[20] "a lesson learned from that experience was

the importance of balanced immunity achieved by independent replication and immunogenicity of the 4 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 the application for the approval by the Food and Drug administration (FDA) in the United States, due to "aspects of data collection, which cannot be addressed".[21] **For Switzerland, Takeda has submitted the application for Qdenga® to Swissmedic, and the decision about its registration is expected before the end of 2024.**

Qdenga® 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 encompasses the domains of (DENV-2) non-structural (NS) proteins.[22]

Vaccination schedule for individuals aged 6 years and older as recommended by WHO[9]: 2 doses subcutaneously, on day 0 and at 3 months (M0, M3). Exploratory data show sufficient protection (81%) for short term (90 days) after a single dose.[9,23,24] 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 against virologically confirmed dengue infection: cumulative vaccine efficacy (cVE) data until 57 months (4.5 years) post primary vaccination are available.[25]

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: for seropositive patients, rates were 56%, 80%, 52% and 71% for DENV-1, DENV-2, DENV-3 and DENV-4 respectively at month 57. In seronegative patients cVE was 45%, 88% for DENV-1 and DENV-2 respectively, while data were insufficient to confirm efficacy and safety against DENV-3 and 4 (cVE – 16%, respectively – 106%; see Table 1).

Vaccine efficacy against hospitalizations at months 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 seropositive patients showed reduced but substantial efficacy (74%) against DENV-3, efficacy was inconclusive or potentially indicated increased risk (-88%, not statistically significant) in seronegative patients infected with DENV-3.[26] Data were insufficient to draw conclusions about protective effects (or safety) against hospitalization for DENV-4, owing to 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. With regard to the vaccination against dengue fever, and in line with the WHO recommendation issued on 3 May 2024,[9] the Swiss Expert Committee for Travel Medicine concludes:

1. Vaccination with Qdenga® for travellers with no evidence of a previous dengue fever infection is not recommended. This recommendation considers the following points:

- an estimated (very) low seroprevalence against dengue in the Swiss population, and consequently the limited risk of a potentially severe second infection in the Swiss population
- a lack of balance in vaccine efficacy between 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® can be recommended for travellers aged 6 years and older who have evidence of previous dengue infection* AND 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 compatible history of dengue infection with a positive IgG serological test.

Of note:

- **Travel medicine advisors should provide clear 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),[27,28] 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 diseases results. Rapid diagnostic tests are considered inappropriate. In case of doubt, consultation with a specialist in tropical and travel medicine or in infectious diseases is recommended.

- **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 a 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.

- **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.

- **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 <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.

Table 1: Cumulative vaccine efficacy in virological confirmed dengue fever, from first dose to 54 months post second dose[25]

	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)
DENV-4	70.6 (39.9, 85.6)	Not provided (too few cases)

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CHECKLIST

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 about the "off label" use in Switzerland and document in the patient file that the patients has been informed. Qdenga® is not reimbursed by the basic health insurance. Supplemental health insurance plans can pay part or the totality of the cost.
  - ☛ Provide detailed information on con's and pro's to the vaccine.
- ☐ Dengvaxia® is not an option
- ☐ Before vaccinating: inform the vaccinee about the following points:
  - ☐ **Mosquito bite prevention measures are still very important, also as protection against 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 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 a positive IgG serology
- ☐ AND expected exposure in 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 contraindication/ 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 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
- ☐ Due to rare anaphylactic reactions, Qdenga® should only be administered in settings where anaphylaxis can be treated and vaccinees observed for at least 15 minutes following vaccination.
- ☐ Minimal interval between dengue infection and first dose of Qdenga®: 6 months

Co-administration with other vaccines

- ☐ Concomitant vaccine with hepatitis A or yellow fever vaccine was studied and is considered to be safe
- ☐ If possible, avoid other concomitant vaccinations at the same time with Qdenga® due to missing data on immunogenicity.
- ☐ If coadministration with another injectable vaccine is unavoidable, the vaccines should be administered at different injection sites.