Report of the Standing Committee on Vaccination
at the Robert Koch Institute
The STIKO recommendation on vaccination against dengue with the Qdenga vaccine

Following its 106th meeting on 6th/7th November 2023, the Standing Committee on Vaccination (STIKO) has agreed on a recommendation for vaccination with the tetravalent live attenuated vaccine Qdenga for certain travellers prior to exposure in dengue-endemic regions, and for laboratory personnel outside of dengue-endemic regions. Preliminary discussions were held in multiple meetings of the joint working group of the STIKO and the German Society of Tropical Medicine, Travel Medicine, and Global Health (DTG). In addition, statements from the Joint Federal Committee (G-BA), the top health agencies of the German Federal States, and affected professional societies were considered.

Background

The live attenuated dengue vaccine Qdenga has been approved for travellers in the European Union (EU) since 8th December 2022. The vaccine is distributed by the company Takeda and is based on an attenuated live virus of the dengue virus serotype 2 (DENV-2), which forms the genetic "backbone" of the tetravalent vaccine. The vaccine was developed to protect against all four DENV serotypes.

The **primary immunisation** consists of 2 vaccine doses separated by 3 months and is licensed for use from the age of 4 years. The goal of the STIKO's vaccine recommendation is to prevent illness, severe clinical courses, and death due to a DENV infection. The virus is transmitted by mosquitoes and is endemic in most tropical and sub-tropical countries.

Recommendation

- The STIKO recommends vaccination against dengue with the vaccine Qdenga as a travel vaccination (R) for individuals over the age of 4 years who have a **history of a prior laboratory-confirmed dengue virus infection** and who are travelling to a dengue-endemic region where they will have an increased risk of exposure (e.g.,

prolonged stay, current outbreak event). Prior to travel, a full vaccination series should be completed (i.e., 2 vaccine doses at a minimum interval of 3 months).

- The data for individuals who **have not previously had a dengue virus infection ("dengue-naïve")** are very limited at present. The STIKO therefore does not currently provide a general vaccine recommendation for dengue-naïve individuals.
  If, after a detailed medical consultation, vaccination is considered for a dengue-naïve individual in line with the licensure, the potential vaccinee should be informed that the risk of infection intensification in the event of a future infection cannot be ruled out. The currently available data for dengue-naïve individuals could not demonstrate any protection against DENV-3 and -4-associated disease following vaccination. If the vaccination nevertheless takes place, a full vaccination series (i.e., 2 vaccine doses at a minimum interval of 3 months) must be completed prior to departure.

- Individuals who have a **history of a laboratory-confirmed dengue virus infection** and who perform targeted activities with the dengue viruses outside endemic regions (e.g., in research institutions or laboratories), should receive a full vaccine series (i.e., 2 vaccine doses at a minimum interval of 3 months) as an occupationally indicated vaccination (B).

Vaccination against	Category	Indication	Application notes (observe package inserts/technical information)
Dengue	R	Individuals aged ≥ 4 years, who have a history of a laboratory-confirmed dengue virus infection and who are travelling to a dengue-endemic region where they will have an increased risk of exposure (e.g., prolonged stay, current outbreak event). For individuals who have not suffered a dengue virus infection in the past ("dengue-naïve"), the STIKO does not currently make a general recommendation for vaccination due to the currently limited data (see also the STIKO notes in the box in EpidBull 04/2023, page 7). For further notes, see the STIKO and DTG travel vaccination recommendations.	Primary immunisation with 2 vaccine doses of the tetravalent live attenuated vaccine Qdenga (minimum interval of 3 months between the vaccine doses). The full vaccine series (2 vaccine doses) should be completed prior to departure to a dengue-endemic region (endemic regions see also https://www.cdc.gov/dengue/areas-with-risk/?CDC_AAref_Val=https://www.cdc.gov/dengue/areaswithrisk/around-the-world.html). Booster vaccinations: at present, no statement can be made about the need for, or timing of, booster vaccinations since the corresponding studies have not yet been completed.
	B	Individuals who have a history of a laboratory-confirmed dengue virus infection and who perform targeted activities with dengue viruses outside endemic regions (e.g., in research institutes or laboratories).	

Extract from Table 2 | Recommendations for standard vaccination of adults as well as for indicated (occupational and travel immunisations) and booster vaccinations for all

Report of the Standing Committee
on Vaccination at the Robert Koch Institute
The STIKO recommendation on vaccination against dengue with the Qdenga vaccine

Table of contents

Table of abbreviations

Ae	*Aedes*
ADE	Antibody-dependent enhancement
AESI	Adverse events of special interest
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
DCAC	Dengue Case Adjudication Committee (Expert committee, which used a predefined list of criteria to classify the severity grade of hospitalised dengue cases)
DENV	Dengue-Virus
DHF	Dengue haemorrhagic fever
DSS	Dengue shock syndrome
DTG	*Deutsche Gesellschaft für Tropenmedizin, Reisemedizin und Globale Gesundheit e. V.* (German Society of Tropical Medicine, Travel Medicine, and Global Health)
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
ELISA	Enzyme-linked immunosorbent assay (antibody-based detection method)
EMA	European Medicines Agency
EU	European Union
FOI	Force of infection (*per capita* rate at which exposed individuals become infected)
GBA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
GMT	Geometric mean titre
IfSG	*Infektionsschutzgesetz* (Infection Prevention Act)
Ig	Immunoglobulin
JE	Japanese encephalitis
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
PFU	Plaque-forming units
RT-PCR	Reverse transcriptase polymerase chain reaction
RCT	Randomised controlled trial
RKI	Robert Koch Institute
RR	Risk ratio
SAE	Serious adverse events
SAGE	Strategic Advisory Group of Experts on Immunization
SR	Systematic review
SOP	Standard Operating Procedure
STIKO	Standing Committee on Vaccination
UAW	*Unerwünschte Arzneimittelwirkung* (Unwanted pharmacological effects)

USA	United States of America
VCD	Virologically confirmed dengue
VE	Vaccine effectiveness
WG	Working group
WHO	World Health Organisation
YF	Yellow fever

1. Introduction

Worldwide, the dengue virus (*Orthoflavivirus denguei,* DENV) is the most common human viral pathogen transmitted by mosquitoes. DENV, which for many decades was endemic predominantly in tropical and subtropical regions, and especially in the cities, has become more geographically widespread in recent years (1). DENV is now found both in the rural regions of already affected countries and also in countries which were previously non-endemic. DENV circulates in a primate-mosquito-primate cycle in which *Aedes (AE.) aegypti* is the most important vector. *Ae. albopictus* functions as a secondary vector, which possesses a lower vector capacity but can establish itself outside the tropics and subtropics, e.g., in North America and Europe (2). DENV is thus endemic in the tropical and subtropical regions of Central and South America, Africa, the Middle East, Asia, and the Pacific Islands, with the local transmission risk being influenced by climatic parameters as well as the local vector controls and social factors (1). The intensity of DENV transmission is influenced by such factors as the population density and ecological conditions such as temperature, precipitation, and altitude, and therefore varies widely between and within countries and over the course of the year. Global warming makes it easier for *Aedes* mosquitoes[1] to spread more widely and thus increases the risk that dengue epidemics will occur in temperate regions (3). The main drivers for the multiplication of the vectors and the rise in dengue incidence are, however, population growth and an increasing population density, migration from the land to the cities, unplanned urbanisation, the lack of a reliable water supply, and insufficiently financed mosquito control programmes (4). *Aedes* mosquitoes are also vectors for other arboviruses (e.g., Chikungunya, yellow fever and Zika viruses).

There are four serotypes of DENV (DENV-1, DENV-2, DENV-3, and DENV-4), each of which can cause dengue in infected humans. Dengue is mostly a febrile illness, which can be accompanied by bone and muscle pain and an exanthem. It is generally believed that recovering from an infection with a specific DENV serotype confers lifelong immunity to that serotype. Homotype reinfections, i.e., renewed infection with the same serotype, are rare, isolated cases (5-7). Cross immunity to the other serotypes following recovery is only partial and transient (8-13).

---

[1] The name *Stegomyia* indicates a subgenus within the genus *Aedes.*

Dengvaxia (Sanofi)

The first licensed vaccine against dengue was the tetravalent live attenuated vaccine Dengvaxia from the company Sanofi, which is based on the genetic backbone of the yellow fever vaccine strain YF-17D. It was approved by the European Commission in 2018 for use in individuals aged 9-45 years with prior laboratory-confirmed dengue living in European DENV-endemic regions. Since 2021 the minimum approval age has been reduced to 6 years. Primary immunisation consists of 3 vaccine doses of 0.5 ml, which are administered subcutaneously at intervals of 6 months. The vaccine showed varying efficacy depending on serotype, age group and severity of infection prevented (14). Initially, Dengvaxia was approved in some endemic countries independent of serostatus, since at that point there was not yet any evidence of possible negative effects following vaccination of immunologically naïve individuals.

However, analyses of the subsequently available long-term data from the clinical studies provided initial indications that vaccinated infants (age group 2-5 years) in particular, who were immunologically naïve (i.e., seronegative) at the time of vaccination, had an increased risk of hospitalisation in the event of a breakthrough infection compared to unvaccinated children.

As a result, all the data from the licensing studies, as well as further evaluations and follow-up investigations, were reanalysed in 2016 by the World Health Organisation, or rather its Strategic Advisory Group of Experts on Immunisation (SAGE), and the potential deployment of the vaccine in endemic countries was investigated with the help of modelling (15, 16). Since the disease burden is high in many endemic countries, particularly in the first years of life, but at the same time the number of people with no prior DENV infection is also high, two strategies were considered, namely either the fixing of an age limit of 9 years whilst simultaneously taking the local seroprevalence into account, or individual testing for DENV antibodies prior to vaccination. However, both strategies have practical difficulties in the context of a national vaccination programme. In addition, the acceptance of the vaccine was low due to the possible negative effects, so that this vaccine was little used in endemic regions. On the basis of the increasing data availability, the licensing authorities then also imposed corresponding restrictions on indications for use (14). This vaccine did not obtain approval in the EU for travellers from non-endemic regions.

Qdenga (Takeda)

Since the 5th December 2022, the tetravalent live attenuated vaccine Qdenga from the company Takeda has been approved by the European Commission from the age of ≥ 4 years (17). In accordance with the technical information, it can also be used with the appropriate indication in individuals who have not had a prior DENV infection. In contrast to Dengvaxia, its genetic backbone uses not the yellow fever vaccine strain YF-17D, but DENV-2. Primary immunisation with this vaccine consists of 2 vaccine doses of 0.5 ml, which are administered subcutaneously at intervals of 3 months. The vaccine has been available on the market in Germany since February 2023.

The efficacy and safety of the Qdenga vaccine was assessed in a systematic and evidence-based manner in accordance with the STIKO standard operating procedure (SOP) and the results were discussed in the working group (WG) for travel vaccinations, which consists of the members of the STIKO and the German Society for Tropical Medicine, Travel Medicine, and Global Health (DTG). The above-named recommendations were prepared in the STIKO-DTG WG and subsequently adopted by the STIKO, taking into account feedback from the commenting procedure.

2. Pathogens, vectors, and transmission

DENV, which belongs to the family of *Orthoflaviviridae* (18), occurs in four different serotypes (DENV-1, DENV-2, DENV-3, DENV-4), which are further divided into genotypes. Structurally, the virus resembles the yellow fever and Japanese encephalitis viruses. DENV is an enveloped virus possessing positive-strand RNA of about 11,000 nucleotides. The viral particle consists of a capsid protein (C-protein), a matrix protein (M-protein), and the envelope protein (E-protein). Seven additional proteins (so-called non-structural proteins, NS-proteins) have functions in the DENV reproductive cycle in the cell (19). The four serotypes differ in approx. 25-40% of their amino acids (2, 20).

DENV in humans is mainly transmitted through the bite of female mosquitoes. Rare modes of transmission include, for example, transfusion or transplantation of DENV-infected blood or organs, or viral contact during laboratory work, when the virus is absorbed through mucosal membranes as a result of inadequate protective measures, inoculation, or by virus-containing aerosols (21-24). The sexual transmission of DENV is still the subject of controversy, since

despite proven evidence of DENV in vaginal secretions or in male seminal fluid, transmission seems only to occur in exceptional cases (25). The most important DENV vector is the yellow fever mosquito *Ae. aegypti* which is mainly active in the daytime but also at night and is the mosquito type best adapted to humans. Other types including *Ae. albopictus a*nd *Ae. polynesiensis* can achieve great local significance (26, 27). With the proliferation of slums around cities and the increasing urbanisation of rural areas, and partly as a result of a central water supply, breeding sites for *Ae. aegypti* in the form of standing water accumulations are appearing in both urban and rural areas, which means that contact between vector and humans is becoming more common. As a result, dengue is no longer a mainly urban illness but is occurring increasingly in rural regions due to the spread of the vectors (28).

The effects of the climate crisis, with rising temperatures, more frequent heat waves and flooding events, enable both vector and virus to adapt to new environmental and climatic conditions outside the known tropical and subtropical endemic areas. In this way, *Ae. albopictus* has, in the last 10 years, been able to establish itself in 5 more countries in the EU or the European Economic Area (EEA), according to data from the European Centre for Prevention and Control of Diseases (ECDC) (2013: 8 countries; 2023: 13 countries). The number of regions in which *Ae. albopictus* has been found has more than doubled in the same time period (2013: 114 regions, 2023: 337 regions) (29).

Ae. aegypti predominantly resides in and around human habitation, tends to stay in one place and only flies relatively short distances of around 50 metres in the daytime.

Humans serve as an amplifying host. DENV replicates in humans, passes to the female mosquito in its blood meal and is then transmitted to other humans and/or animals. In Asia and Africa, non-human primates are also involved as amplifying hosts in sylvatic cycles (30). Viral transmission can originate both in individuals who are already sick with dengue, as well as from pre- and asymptomatic individuals. The likelihood of viral transmission is greatest in febrile individuals with high viraemic loads. Viruses can be transmitted up to 2 days before the development of symptoms and up to 2 days after the fever subsides (1). After 8 to 12 days (extrinsic incubation time), the mosquito is again capable of transmitting the DENV (31). High concentrations of DENV-specific antibodies in humans reduce the risk of infection by mosquitoes (32).

Cases of vertical DENV transmission, i.e., viral transmission from a pregnant woman to her unborn child, are described in the literature (33). The risk of vertical transmission appears to be linked to the point at which the DENV infection occurs in the pregnancy (34).

3. Clinical picture, diagnosis, and therapy

DENV infections are usually asymptomatic or mild in primary infection (approx. 75%) (4), though the ratio of asymptomatic to symptomatic infections in the same region can vary from year to year and in the context of outbreaks (10, 11). In a cohort study performed in Nicaragua over several years, the ratio of asymptomatic to symptomatic infections was 16.5:1 in the years 2006–2007 and 1.2:1 in the years 2009–2010 (35). Dengue and severe dengue, including dengue shock syndrome (DSS), develop in very rare cases with a first infection, but are more common with second infections. Third and fourth infections are normally associated again with a mild or asymptomatic course (9, 36).

The illness can have several phases, including a febrile, a critical, and a convalescent phase (see Fig. 1). After an average (intrinsic) incubation period of 5.9 days (in 95% of cases between 3-10 days) (31), non-specific symptoms can develop (headache, back and limb pains) which normally last for 2-7 days (1). Typically, the febrile phase consists of a very sudden and severe rise in temperature (up to 40°C) as well as severe headaches, retrobulbar pain, muscle and joint pains, nausea, vomiting and a maculo-papular or morbilliform rash (1). If at least 2 of these symptoms occur, dengue should be considered in the differential diagnosis. In most cases, the symptoms last for 1-2 weeks.
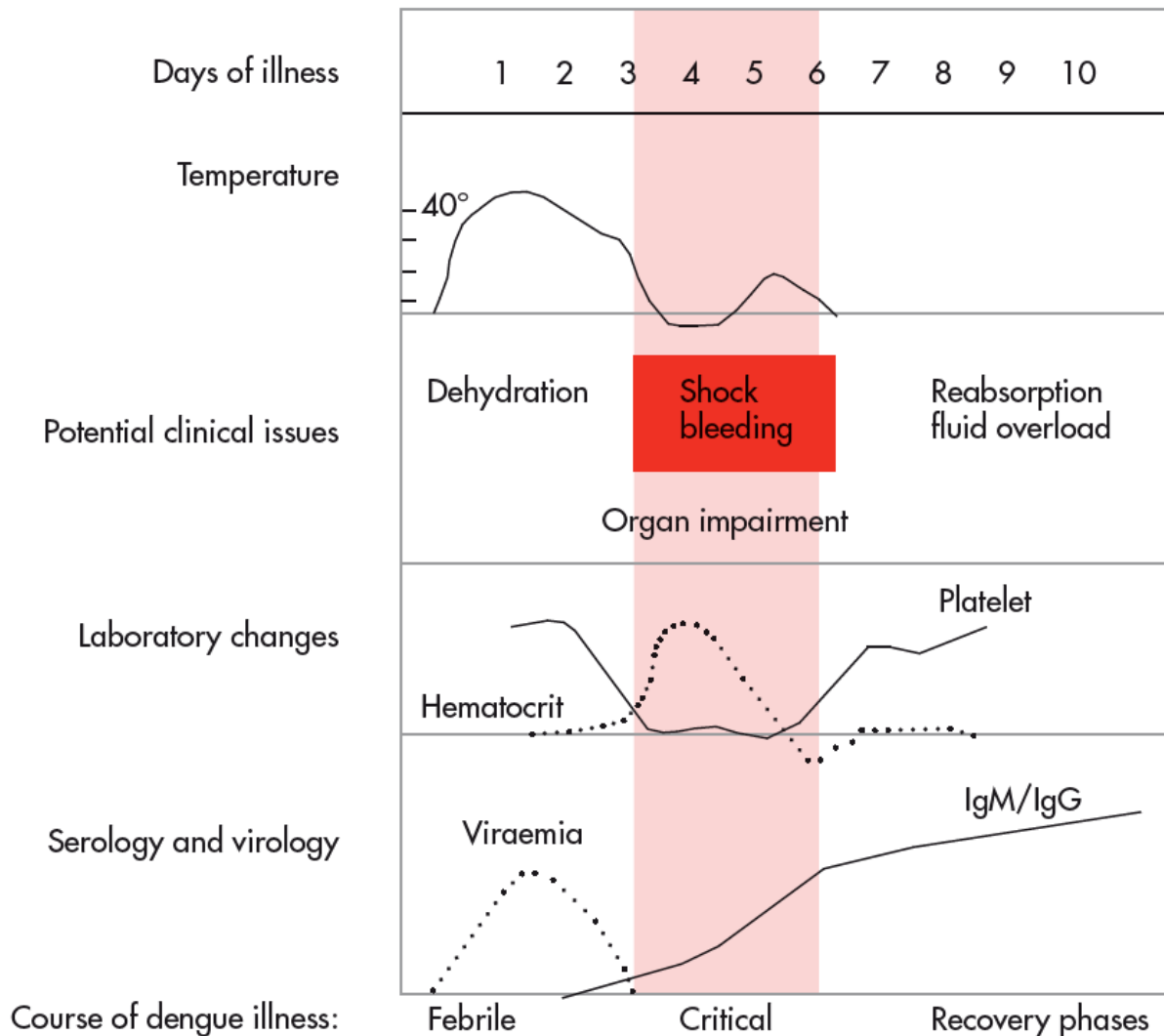
Figure 1: Clinical course of dengue compared to laboratory parameters and serology (37)

Approx. 3-7 days after the onset of symptoms, the fever usually subsides. Whilst most people improve clinically in this period, for some the so-called critical phase begins, in which the symptoms of severe dengue manifest. This is characterised by increased capillary permeability and fluid exudation from the vascular system, severe bleeding, and organ involvement. In severe dengue, the laboratory chemistry shows an increase in the haematocrit and a simultaneous significant drop in the leukocyte and thrombocyte counts. The serious fluid or plasma loss into the extravascular compartment can lead to symptoms of shock (DSS) and a potentially fatal outcome, with hypovolaemic (but usually not haemorrhagic) shock and multiple organ failure being the most common causes of death from dengue (38). Untreated, the mortality rate for dengue can be up to 13% (39), with frequent causes of death being unrecognised or long-lasting shock, unrecognised bleeding and secondary infections. With

early diagnosis and adequate clinical management, the mortality can be reduced to < 1% (37, 40). In epidemic years, the number of illnesses in travellers can be markedly elevated in comparison to non-epidemic years (41). In a study from Vietnam performed between 1996 and 2009, the case mortality rate in patients with DSS was 50-fold higher than in those without DSS (1.6% [153/9,784] versus 0.03% [28/92,683]) (42).

According to the WHO guideline from 2009 (37), the following criteria define severe dengue: 1. Severe plasma leakage, leading to shock or fluid collections with respiratory restriction or 2. Severe bleeding or 3. Severe organ involvement.

In addition to the liver, heart, and eyes, other organ systems may also be affected, such as the peripheral and central nervous system (43-49).

After the critical phase, the so-called convalescence phase begins, during which a gradual reabsorption of the fluid can occur.

Until 2009, the WHO had divided symptomatic dengue into three categories: undifferentiated fever, dengue fever and dengue haemorrhagic fever (DHF). DHF was divided into further severity grades, with grades III and IV defined as DSS.

With the geographical spread of severe dengue in Latin America in the 1970s and the increasing number of cases in young adults in Asia, the previous case definition was no longer applicable, so a revised case definition was introduced in 2009 under the leadership of WHO (37). This allowed severe cases to be better categorised as such and adequate therapy to be provided more quickly. Under this new classification, only 2 categories are now defined: dengue (with/without warning signs) and severe dengue, see Figure 2 (37).
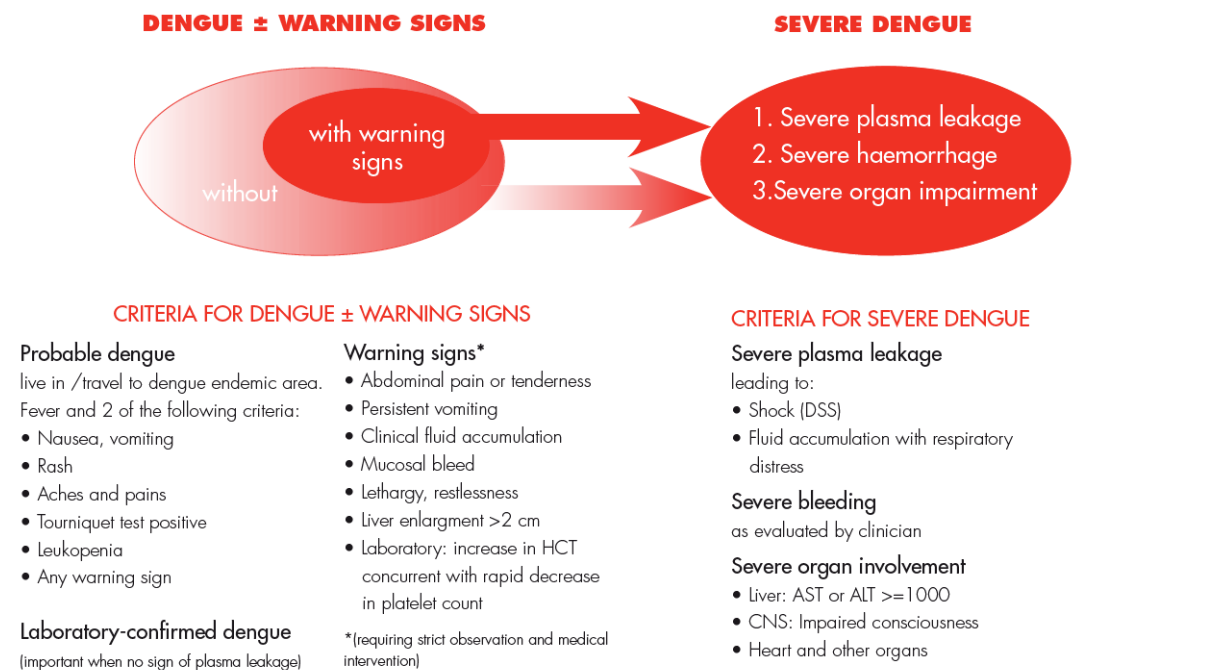
DENGUE ± WARNING SIGNS

SEVERE DENGUE

with warning signs

without

1. Severe plasma leakage
2. Severe haemorrhage
3. Severe organ impairment

CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue
live in /travel to dengue endemic area.
Fever and 2 of the following criteria:
• Nausea, vomiting
• Rash
• Aches and pains
• Tourniquet test positive
• Leukopenia
• Any warning sign

Laboratory-confirmed dengue
(important when no sign of plasma leakage)

Warning signs*
• Abdominal pain or tenderness
• Persistent vomiting
• Clinical fluid accumulation
• Mucosal bleed
• Lethargy, restlessness
• Liver enlargment >2 cm
• Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage
leading to:
• Shock (DSS)
• Fluid accumulation with respiratory distress

Severe bleeding
as evaluated by clinician

Severe organ involvement
• Liver: AST or ALT >=1000
• CNS: Impaired consciousness
• Heart and other organs

Figure 2: Dengue case classification according to WHO (37)

3.1 Secondary infection

The risk of severe dengue is higher with a second infection than with a first infection. A recent systematic review gave this elevated risk factor as 2.69 (50). In another systematic review, the relative risk (RR) of a severe clinical course in a secondary infection was given as 9.4 (95% confidence interval [CI]: 6.1-14.4) using modelling (51). This observation is explained by antibody-dependent enhancement (ADE): the antibodies formed during the initial infection are specifically directed against this serotype and cannot neutralise it in the event of a subsequent infection with another serotype. However, infectious immune complexes are formed during a secondary infection (consisting of the non-neutralising antibodies of the first infection and the DENV of the secondary infection), which are increasingly taken up by the mononuclear cells via Fc-receptors. This leads to an increased viral production and the formation of vasoactive mediators (36, 52) and then, due to an increase in the number of virus-infected cells and the viral biomass *in vivo*, to an increased risk of severe disease (53). By activating the immune system, the infection then leads to T-cell apoptosis, the release of cytokines and chemokines as well as to dysfunction and autophagy of the endothelial cells. The consequences observed in severe dengue are the increased capillary permeability with plasma leakage, reduction of intravascular volume and

ultimately shock and reduced perfusion of various organs, causing hypoxia in various organ systems.

In a study of children in Nicaragua, among the participants who found to have repeated DENV infections, those who had a shorter interval between the first and second infections (≤ 2 years) more frequently had occult second infections than those with longer intervals between the first and second infections (11). This may be important for the risk assessment of travellers, as unlike people in endemic countries, they are not exposed continuously, but usually over a longer time interval.

3.2 Diagnosis and protection following natural infection

Depending upon the infection phase, various laboratory methods can be used to diagnose a DENV infection. In principle, all 3 serological parameters - NS-1 antigen, immunoglobulin (Ig)M, IgG – should be checked simultaneously in the first 3 weeks after the start of the illness, in order to achieve the highest possible sensitivity and specificity (52). Samples taken in the first weeks of illness should be examined for the presence of viral nucleic acid using reverse transcriptase polymerase chain reaction (RT-PCR) and/or using the rapid test for the non-structural (NS)1 viral protein. The antigen rapid test is very specific, does not require specialised laboratory facilities, and can deliver a result after only approx. 20 minutes (1). Serological methods such as ELISA (enzyme-linked immunosorbent assay) can detect DENV antibodies, but the results must be interpreted alongside those from the RT-PCR or antigen rapid tests. IgM antibodies, which suggest a recent DENV infection, are detectable from week 1 after the infection until about 3 months after infection. IgG antibodies, indicating a past DENV infection, can only be detected later, but usually for several decades. An infection with one serotype provides, in most cases, lifelong persistent immunity against that serotype (**homotype protection**). However, in some studies it was possible to prove isolated cases of homotype reinfection (5-7). These few confirmed cases are currently limited to children in endemic countries. In addition, an infection with one serotype induces a transient cross-protection against the other serotypes (**heterotype protection**) (11, 54). Challenge studies have indicated the length of the cross protection as approx. 3 months, whilst epidemiological observations suggest that it may even persist for up to approx. 2 years (4). The decline in the cross protective antibodies may contribute to a severe clinical course during an infection with one of the other serotypes (see also the section *Secondary infection*).

Surviving a secondary infection appears to induce a broad neutralising antibody response (***multitypic immunity***) (36).

3.3 Therapy

There is no specific therapy for dengue. A mild case requires symptomatic treatment, such as rest, adequate fluid intake, measures to reduce fever, and pain relievers. Non-steroidal anti-inflammatory drugs (NSAIDs), particularly acetylsalicylic acid (aspirin), should be avoided due to their impairment of platelet function. Hospitalisation is generally not necessary in mild cases, though patients should be told about the above-named warning signs of a severe clinical course, with the advice that, should these develop, they should seek inpatient care without delay. In severe clinical courses, the mainstay of treatment is intravenous volume replacement which, along with close monitoring of vital signs and haematocrit, must continue for as long as the elevated vascular permeability persists. Even though severe dengue is a phenomenon produced by immunological processes, randomised controlled trials (RCT) have shown no effect of glucocorticoids on the clinical course (55). Prophylactic administration of thrombocytes is often neither indicated nor helpful (56).

4. Risk factors for a DENV infection or a severe clinical course

4.1 Risk factors for a DENV infection

4.1.1 Travel-dependent factors

The highest risk for a DENV infection derives from travel to tropical and subtropical dengue-endemic regions (57), which are predominantly found in Asia, but also in Latin America and Africa. Outside these regions, infections are rare but can occur, such as in a few European countries: In the year 2022, 65 autochthonous infections were recorded in France up to 21st October (see also Chapter 5. Epidemiology). This number exceeded the total number of autochthonous cases reported in France between 2010 and 2021 (58). Compared to travel to the tropical and subtropical endemic regions, the risk of infection within Europe remains, however, very low; 99% of the cases recorded in Europe are travel related (59). Sporadic outbreaks with local transmission also occur in the USA. Most recently, outbreaks have been reported in Texas (2013), Hawaii (2015), Florida (2013, 2020), and Arizona (2023) (60).

The risk of infection increases with the duration of travel. Thus, the frequency of a positive dengue ELISA test following travel from dengue non-endemic regions (USA) to dengue-endemic regions was 7% for journeys of 2 weeks up to < 1 year and 40% for stays > 1 year (61). The risk is also increased for journeys during the rainy season or during outbreaks or epidemics (36). The infection risk in tropical regions falls with increasing altitude, although *Ae. aegypti* has been found at altitudes of up to 1,700 m in Mexico, for example (62). Corresponding studies with the predominant vector in Europe, *Ae. albopictus,* showed that the vector occurs in Albania up to an altitude of 1,200 m (63).

The risk of transmission in individual cases also depends on knowledge regarding transmission modes, the protective measures adopted (repellents, long clothing) and the implementation of routine, sustainable vector control measures in the community. Good protection against mosquitoes or spending most of the time in air-conditioned rooms can markedly reduce the risk for the individual.

4.1.2 Working with DENV

Laboratory personnel in diagnostic and research departments may have an increased risk of exposure to DENV and thus a risk of a DENV infection. Non-vector associated transmissions of DENV have been reported in individuals in the healthcare sector (including 5 cases of percutaneous transmission by needlestick injury as well as a mucocutaneous transmission due to blood splashed onto the face (21, 23, 24)). In one case, a laboratory worker was found to have contracted the DENV laboratory strain via DENV-infected mosquitoes, although the exact mode of transmission could not be ascertained (22). These cases demonstrate the possibility of work-related DENV exposure outside endemic countries, which can just as well lead to a severe clinical course if there is a secondary infection.

4.2 Risk factors for a severe clinical course

According to multiple studies, the main factors associated with an increased risk of a severe clinical course are age and previous illnesses (64, 65).

4.2.1 Age

In southeast Asian countries, dengue has long been a disease of early childhood, while clinically manifest dengue in adults only occurred rarely. However, in recent years, there has

been a shift in the age groups of reported DENV infections towards more cases in people > 15 years of age (66, 67). Meanwhile, in some regions of Thailand, around 30-40% of cases now occur in adults (67, 68).

Severe clinical courses of DENV infections do occur in all age groups, but they are more common in adults. In a prospective study in Thailand, age > 40 years (Odds Ratio [OR]: 5.215, 95% CI: 1.538–17.689) was identified as an independent clinical factor for developing severe dengue (65).

The clinical manifestation of second infections differs between age groups: in children in endemic regions, second infections are more often accompanied by DSS, whereas in adults, it is associated more often with internal bleeding (4).

The highest lethality rate is seen in children with a second infection aged 3-14 years (14.5-times higher than in adolescents/young adults aged 15-39 years). The rate rises again slightly for those aged over 50 years (69). This age trend also persists in hospitalisations due to dengue and DHF (67).

4.2.2 Previous illnesses

The dataset on previous illnesses, which is a risk for a severe dengue course, is currently limited. Various prior illnesses have been studied in single surveys with respect to increased risk of a severe dengue course. Assessing these studies, and their at times differing results when studying the same prior illness, is made more difficult because the prior illnesses were not uniformly defined – mostly there is no assessment of the severity of the prior illness (50, 70, 71). It thus remained unclear whether the observed elevation of risk was independent of the individual stage of the previous illness or not. The issue of the effect of the severity of the illness is complicated by the fact that relevant immunosuppression can be a contraindication to the use of the vaccine.

4.2.3 Nutritional status

Isolated studies suggest that the nutritional status can influence the risk of a severe dengue course. Adiposity in children and hospitalised adults seems to be associated with a severe clinical course, whereas undernourished children rarely have a severe clinical course (72, 73). However, the influence of nutritional status is a matter of controversial discussion in one systematic review (74).

4.2.4 Pregnancy

Due to the physiological changes in pregnancy (such as e.g., hydraemia), abnormalities in laboratory results caused by dengue, such as thrombocytopaenia, leukocytopenia or elevated haematocrit, can be masked, making diagnosis more difficult. Pre-eclampsia or the HELLP syndrome can also produce symptoms and biochemical constellations similar to dengue.

The maternal mortality rate in case series of pregnant women with DENV infection varies between 6.6% in Sri Lanka (75) and 15.9% in India (76). The causes of the increased mortality are not clear (33).

4.2.5 Unborn children

Vertical transmission of DENV in maternal infection is possible at all stages of pregnancy, with a prospective study of laboratory-confirmed diagnoses of maternal transmission to the child showing that it occurred most commonly at the end of the 3rd trimester (15 days before delivery until 2 days *post partum*) (34). The risk of vertical transmission exists if there is insufficient time for the transfer of protective antibodies from mother to foetus (33). During the critical phase of organogenesis, or during late pregnancy, the foetus may be more vulnerable to DENV infection, even if the maternal infection is asymptomatic (33). The average time between maternal fever and symptoms in the newborn is said to be 7 days (range 5-13 days) (33).

A maternal DENV infection during pregnancy can lead to preterm birth, an increased rate of Caesarean section, and low birth weight in the neonate (77, 78).

The risk of miscarriage is increased in women who have had a DENV infection during pregnancy (76-78). Passive transmission of maternal anti-dengue IgG can increase the risk that a future heterotype infection will develop into a severe infection due to the presence of heterologous anti-dengue IgG (79).

4.2.6 Gender dependency

Several studies from the Southeast Asia region suggest a gender dependency for DENV infection and severe dengue. Studies in India, Bangladesh, Singapore, and Malaysia indicate a higher proportion of men being hospitalised with dengue or DHF cases in comparison to

women, whereas studies from Malaysia and India found a higher mortality rate in women compared to men (28).

It is uncertain whether these gender-specific differences are due to gender-specific pathogenesis/immune processes, reflect different exposure risks, or result from a difference in access to medical care in these countries. Further research into the background of the observed gender-specific differences is required to identify both biological and societal factors that determine the disease patterns in a community (28).

4.2.7 Secondary infection

The risk of a severe course of a DENV infection is highest with a secondary infection. For details see [Chapter 3. Clinical picture, diagnosis and therapy](), subsection "Secondary infection".

5. Epidemiology

5.1 Epidemiology in endemic countries

The earliest dengue epidemics were reported in the 17th and 18th centuries in Asia, Africa, and North America, which indicates that DENV and its mosquito vectors have been widespread in the tropics for over 200 years. During the dengue epidemics of the 17th, 18th, and 19th centuries, the DENV infection only caused mild, but not deadly clinical courses. It was only in the 1950s that DENV epidemics in the Philippines and then Thailand were accompanied by severe dengue courses (DHF). This was explained by the worldwide circulation of all four DENV serotypes, which carry a higher risk of severe illness with second infections.

DENV is mainly endemic in tropical and sub-tropical regions and causes epidemics every 3-4 years during the rainy season (May to November) (80). The most severely affected regions are Southeast Asia (approx. 75% of the disease burden), South and Central America and the Western Pacific regions (4), see also Figure 3 (82). Brady et al. estimate that approx. 3.9 billion people, or approx. 50% of humankind, are exposed to DENV (81).
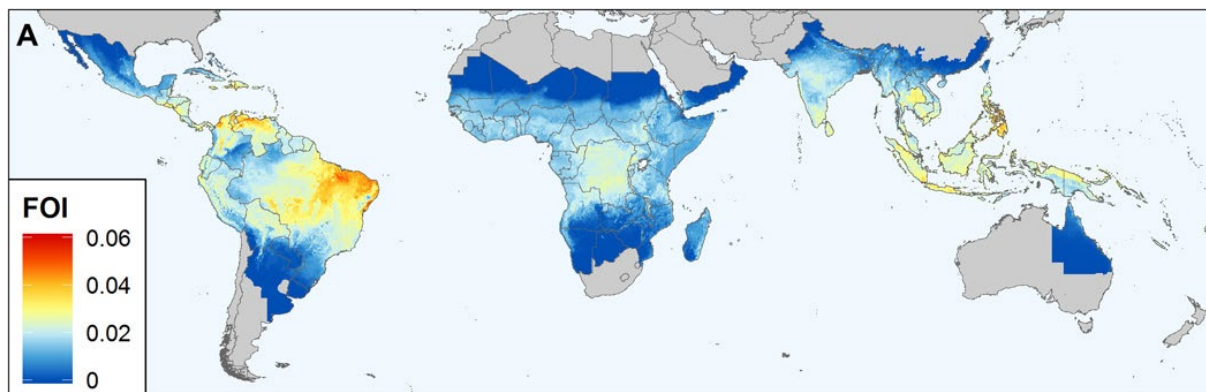
Figure 3: Estimated global risk of dengue: mean values of the estimated force of infection (FOI; *per capita* rate, at which exposed individuals become infected) in dengue-endemic countries. (82)

The number of dengue cases reported to the WHO has increased more than tenfold in the last two decades, from 505,430 cases in 2000 to 5.2 million in 2019 (1). Up to 23rd August 2023, a total of 3.7 million cases with more than 2,000 dengue-associated fatalities were reported (83).

As the majority of DENV infections are asymptomatic or mild, it can be assumed that the officially registered DENV infections only represent a fraction of the actual infections (84). Modelling estimates assume approx. 400 million DENV infections per year, of which approx. 100 million are clinically apparent (84, 85). For some years, there have also been autochthonous DENV infections in Europe, since the Asiatic tiger mosquito *Ae. albopictus* is widely distributed in most southern European countries. In the year 2022 alone, 65 autochthonous DENV infections were registered in France (86).

In DENV-endemic regions, about 10% of all febrile episodes in children aged between 2 and 16 years can be attributed to dengue, with Asia having 4.6 infections per 100 person years and Latin America 2.9 (87).

In a 2014 modelling study on species distribution, forecasts for worldwide distribution of dengue in the years 2020, 2050, and 2080 were made. It included the most extensive and geographically detailed compendium on the occurrence of dengue, socio-economic and ecological covariants, as well as the current and future distribution of *Aedes* mosquito vectors (88). It is estimated that by 2080 a further 2.25 billion people will be exposed to the risk of a DENV infection (60% of the global population) unless there are no improvements in vector control.

5.2 Epidemiology in travellers

Dengue is one of the main causes of febrile illness in travellers returning from Southeast Asia, Latin America, and the Caribbean and occurs more frequently than many other travel-associated, vaccine preventable illnesses such as Hepatitis A, Hepatitis B, rabies, Japanese encephalitis, or yellow fever (36).

Estimating the risk of travel-associated dengue is difficult due to the annual and seasonal fluctuations in incidence and travel patterns, as well as to incomplete surveillance, since a traveller's individual risk is dependent upon multiple factors: the geographical location of the travel destination, the season of travel, the local virus transmission rate at the time of the journey (e.g., elevated during an outbreak), the duration of exposure, individual risk behaviour (activities involving exposure to the vector, use of preventative measures), and not least the possibility of a prior antigen contact (infection or vaccination). It must be added that even a short stay in an endemic region is associated with some risk of infection (36).

The estimated incidence of symptomatic cases in travellers is 0.2-1.3% per travel month in non-immune individuals (89-91).

In a 2020 paper which analysed GeoSentinel-Surveillance data on international travellers from 1995-2020, it was shown that dengue was the commonest arboviral illness that occurred in the travellers studied, and that the trend had increased in the last two decades (41). The disadvantage of sentinel monitoring is the lack of a denominator, so that the absolute risk cannot be calculated. An increase in the number of cases in travellers could, for example, be due to increased travel activity in dengue endemic regions or alternatively to increased awareness and therefore more frequent laboratory testing for dengue (37).

According to ECDC, the age group with the highest sickness rate in Europe is 25- to 44-year-old travellers, with no gender difference observed (59).

DENV infections are rarely reported in travelling children, presumably because the majority of travellers are adults and a primary infection in children has a mostly mild or asymptomatic course and therefore often remains undiagnosed.

Dengue has been a notifiable disease in Germany since 2001. The number of clinically and laboratory confirmed dengue cases reported to the RKI among returning travellers in Germany had risen continuously in pre-pandemic years, most recently from 635 cases in the year 2017 to 1,176 cases in the year 2019. Due to the pandemic-related travel restrictions, this number

dropped to 205 in the year 2020 and 60 in the year 2021. Post pandemic, the number of cases has markedly increased again due to increasing travel activity (92).

The actual number of returning travellers who have had a DENV infection is presumably higher, not only because the majority of illnesses are asymptomatic: for longer durations of travel, and due to the relatively short incubation time, some illnesses occur in the destination country and are diagnosed and treated there. These cases then mostly do not appear in the Robert Koch Institute (RKI) statistics.

Severe dengue and fatalities due to dengue are very rare in travellers (36, 93-95). Since severe dengue is itself a rare event, studies to date have been unable to calculate the risk for travellers to various destination countries. Large prospective trials with tens of thousands of travellers in various geographic settings would be required for a valid assessment (36).

Travellers play a significant role in the global epidemiology of DENV infections, since viraemic travellers import DENV serotypes and strains into previously unaffected regions, where, if vectors are present, there can then be transmission. On the other hand, travellers can provide an early warning of developments in other parts of the world if they return from regions with limited diagnostic possibilities to their countries of origin and undergo diagnosis there. Therefore, once the serotype has been confirmed, a report should be sent back to the country of infection. Such internationally shared information could warn of the start of a possible epidemic in endemic countries. This is particularly important if geographical spread of virus serotypes and genotypes into new regions occurs, increasing the risk of severe dengue (37).

It is currently unclear whether vaccination of travellers would lead to a reduction in the likelihood of autochthonous transmission in Germany or Europe.

6. Goal of vaccination and public interest in the vaccination recommendation for Qdenga

The goal of vaccination against dengue with the tetravalent live attenuated vaccine Qdenga is to prevent disease and severe cases (including death) of dengue among travellers and individuals occupationally exposed.

Although dengue is one of the most common mosquito-borne viral infections among travellers, severe cases requiring hospitalisation are very rare. Dengue is thus not an illness

which leads to significant loss of work or to the burdening of the healthcare system. The interest in a vaccine against dengue primarily relates to travellers, including business travellers. There is also an interest on the part of employers to protect employees who are exposed to DENV outside endemic regions (e.g., in the context of laboratory work).

7. Qdenga dengue vaccine

7.1 Composition and application

On 8th December 2022, the European Commission approved the live attenuated vaccine against dengue for travellers over the age of 4 years. The vaccine, which was produced using recombinant DNA technology, is distributed by the firm Takeda under the trade name Qdenga and is based on a live attenuated DENV-2 virus, which forms the genetic "backbone" of the tetravalent vaccine. In contrast to the wild-type virus DENV-2, the attenuated DENV-2 is characterized by new properties, such as altered temperature sensitivity, lower replication capacity, lower neurovirulence, and higher genetic diversity (96).

Together with the attenuated DENV-2, the composition of the tetravalent live attenuated dengue vaccine Qdenga also includes 3 chimaeric, genetically modified viruses having the premembrane and envelope genes of DENV-1, DENV-3, and DENV-4 on the backbone of DENV-2 (96).

Preclinical studies have shown that the immune response to chimaeric DENV-3 and DENV-4 in the tetravalent vaccine was less than that seen when these were given as a monovalent vaccine. As a result, the 4 live attenuated DENV serotypes are present in varying concentrations in the tetravalent vaccine. According to the technical information, a dose of the tetravalent vaccine (0.5 ml) contains ≥ 3.3 log10 plaque-forming units (PFU) of DENV-1, ≥ 2.7 log10 PFU of DENV-2, ≥ 4.0 log10 PFU of DENV-3, and ≥ 4.5 log10 PFU of DENV-4.

In addition, the vaccine powder contains α,α-trehalose dihydrate, Poloxamer 407, human serum albumin, potassium hydrogen phosphate, disodium hydrogen phosphate, potassium chloride, and sodium chloride, and the solvent contains sodium chloride and water.

According to the technical information on Qdenga, individuals over the age of 4 years with the corresponding indications should obtain 2 vaccine doses of 0.5 ml at intervals of 3 months. It has not yet been demonstrated whether booster vaccinations are required.

The contents of the technical information are relevant to the doctor's discussion prior to the administration of the Qdenga vaccine. In the vaccine's technical information, under Section 4.3 "Contraindications", the following circumstances or groups of people are listed as contraindications to administration of the vaccine or individuals in whom vaccine delivery is contraindicated:

- Hypersensitivity to the active agents or other ingredients of the vaccine or hypersensitivity to a previous dose of Qdenga
- Individuals with congenital or acquired immunodeficiency, including individuals who have received immunosuppressive therapy such as chemotherapy or high dose systemic corticosteroids (e.g., 20 mg/day or 2 mg/kg body weight/day Prednisone for at least 2 weeks) during the 4 weeks prior to vaccination, as is the case for other live attenuated vaccines
- Individuals with symptomatic HIV infection or asymptomatic HIV infection with evidence of diminished immune function
- Pregnant women
- Breast feeding women

In Section 4.8. "Side effects" of the technical information, the possibility of developing vaccine viraemia is raised. In the days following delivery of the 1st vaccine dose, a study by Sirivichayakul et al. measured vaccine viraemia, i.e., evidence of viral RNA in vaccinated individuals, in 18 study participants (20%) on day 7 after the 1st vaccine dose, which was still detectable in 14 participants (15%) on day 14. The group of 1.5-to-5-year-old children was most affected (39% on day 7 and 15% on day 14). Following the 2nd vaccine dose, viraemia was only detectable in 2 individuals (day 97 and day 104 after the 1st vaccine dose) (97). According to the technical information, mild to moderate symptoms such as headache, arthralgia, myalgia, and rash developed at the time of the vaccine viraemia. Even if a vector is available, it cannot be presumed that the vaccinated individual is infectious, since almost no replication of the vaccine viruses occurs in the mosquitoes, making transmission of the dengue vaccine viruses by the tiger or yellow fever mosquito very unlikely (98).

7.2 Methodology of the literature review

According to the STIKO SOP, systematic reviews are performed in order to assess the efficacy and safety of a vaccine. With regard to efficacy, the following research question was defined as the core aspect of the review: **How effectively and safely do 2 doses of Qdenga vaccine, administered 3 months apart, protect individuals of any age group, independent of the underlying serostatus, against virologically confirmed dengue (VCD), severe dengue, and death?**

The 2009 WHO definition (see [Chapter 3](#)) was used to define severe dengue. Even though no serological correlate of protection is yet known, serological end points, i.e., the levels of the vaccine-specific antibodies (geometric mean titres, GMT), should be assessed in addition to clinical end points.

In order to answer the research question, a systematic literature search was first conducted for previously published reviews of Qdenga, or reviews which had been registered in the International Prospective Register of Systematic Reviews, Prospero. Two systematic reviews which deal with Qdenga were identified, of which one has not yet been definitively published and can only be read as a conference protocol (99, 100). A more detailed description of the systematic reviews can be found in the Appendix. The STIKO secretariat assessed the existing published review using Amstar 2 (101) and rated its quality as poor. The methodology of the conference proceedings cannot be conclusively assessed. Due to the methodological deficiencies of the available systematic reviews, and the publication in February 2023 of studies with longer follow-up periods (up to 3 years after vaccination), a new systematic literature search was carried out. The goal was, amongst other things, to identify possible post-marketing studies of efficacy and safety, which might have been carried out in those countries where the vaccine is already licensed (e.g., Indonesia or Brazil).

7.2.1 Systematic literature search

The STIKO secretariat developed the following PICO criteria for the systematic literature search together with the STIKO-DTG WG:

- ***Population:*** *male & female, all ages; irrespective of previous dengue infection; irrespective of endemic settings*
- ***Intervention:*** *TAK-003/Qdenga/Takeda tetravalent dengue vaccine/Denvax, complete dosing schedules (2 doses given 3 months apart)*

- **Comparator group:** *placebo, no vaccination, other vaccine (not directed against dengue), co-administration; vaccines for which cross-protection potential is considered (e.g., YF, JE)*
- **Effectiveness, efficacy, and immunogenicity outcomes:** *any immunogenicity data against dengue (assessment of vaccine-induced serotype-specific antibody GMT); virologically confirmed dengue (VCD) (confirmed by serotype-specific reverse PCR or NS1-Ag-test); severe dengue (confirmed by serotype-specific reverse PCR or NS-1-Ag-test) defined according to WHO classification (2009).*
- **Safety outcomes:** *local reactions; systemic events; serious adverse events (inc. death); adverse events of special interest (AESI): severe dengue according to WHO classification (2009) in dengue-naïve people*

On 6th February 2023, the STIKO secretariat performed a systematic literature search as defined in the PICO criteria for the Qdenga vaccine (study vaccine TAK-003, TDV) in 2 databanks (Embase, PubMed) (for search strategy, see Appendix). The search was limited to the years 2016-2023 since the efficacy data from Phase 2 and 3 studies were first published after 2016.

After removing duplicates, the title and abstract of 1,212 publications were screened independently by two STIKO secretariat employees, and 47 publications were included for full-text screening. Thirty-six studies which did not match the inclusion criteria were excluded (for inclusion and exclusion criteria, as well as a list of excluded studies including reasons for exclusion, see Appendix). In addition, the reference lists of relevant publications were checked for further publications that had not yet been included. With the inclusion of one additional publication which was published after completion of the literature search (102), and incorporating the Assessment Report of the European Medicines Agency (EMA) (103), which contains data on vaccine efficacy > 3 years after the 2nd vaccine dose that had not previously been published, data were extracted from a total of 13 publications (see Figure 4).

The 13 publications relate to a total of 6 randomised controlled clinical trials (RCTs) which were initiated or funded by the vaccine manufacturer (see Tab. 1). Post-marketing studies could not be identified.
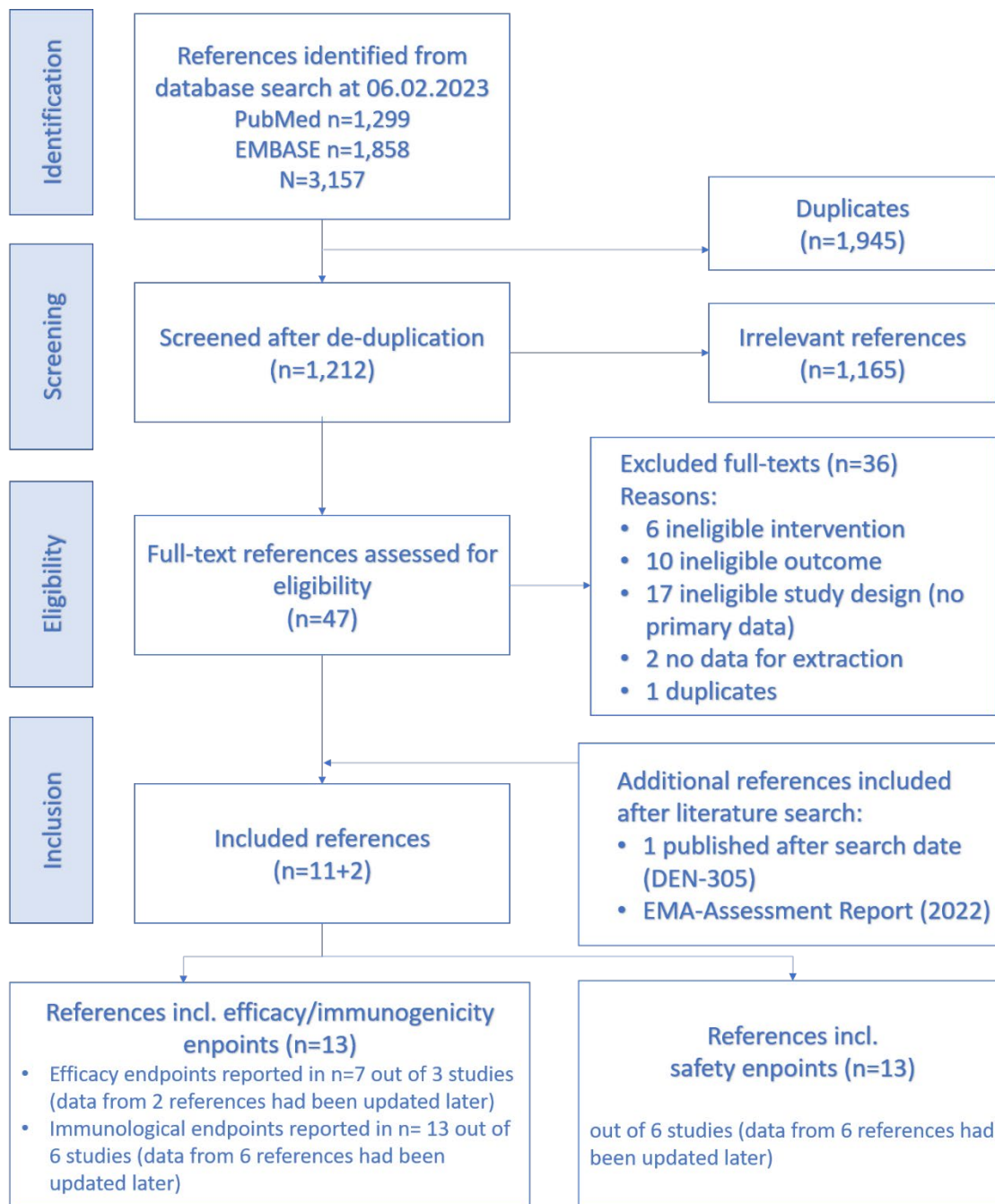
Figure 4: Prisma flowchart of the literature search on the efficacy and safety of Qdenga

Clinical efficacy data were reported in 7 publications, while immunogenicity and safety data were found in all 13 publications. If updated data were reported in subsequent publications, then only the data in the later publication were used. We did not perform a meta-analysis. On the one hand, the available studies differed with respect to the studied populations as well as the timing of the endpoint surveys (the study by Rivera et al. (104) included 4-16-year-olds with analysis after 1, 2, and 3 years; the study by Tricou et al. (105) included 2-17-year-olds with analysis after 48 months; the study by Sirivichayakul et al. (106) included 1.5-45-year-

olds with analysis after 36 months). On the other hand, the numbers of participants in the studies differed widely (Rivera et al. approx. 20,000 study participants versus 398 in Tricou et al. and 150 in Sirivichayakul et al.), so that a meta-analysis of these 3 studies would not permit any valid conclusions.

Study	Age of study pop. (years)	Study pop. total (approx.)	Performed in endemic region	Timing of analysis after 2nd vaccine dose	Data availability		
					VE	Immuno-genicity	Safety
DEN-301 (104, 107-109)	4-16	20,000	+	3 years	+	+	+
DEN-204 (105, 110, 111)	2-17	1,800*	+	3.75 years	+	+	+
DEN-203 (97, 106)	1.5-45	150	+	2.75 years	+	+	+
DEN-305 (Co-admin. YF-17D) (102)	18-60	900	-	9 months	-	+	+
DEN-314 (Co-admin. HAV) (112)	18-60	900	-	6 months	-	+	+
DEN-315 (113)	12-17	400	-	6 months	-	+	+
EMA-Assessment Report (103)	1.5-60	>27,000	+/-	6-54 months	+	+	+

Table 1: Included studies
* The 1,800 people were divided into 4 intervention groups: Group 1 (n= 201): 2 doses of TAK-003 at intervals of 3 months; Group 2 (n= 398): a dose of TAK-003 + a dose of placebo at intervals of 3 months; Group 3 (n= 1,002): a dose of TAK-003 + a dose of placebo at intervals of 3 months + a dose of TAK-003 at an interval of 12 months; Group 4 (n=199): 2 doses of placebo at intervals of 3 months + a further dose of placebo at an interval of 12 months
VE – vaccine efficacy; co-admin. YF-17D - study with co-administration of a yellow fever vaccine; co-admin. HAV – study with co-administration of a hepatitis A vaccine

The **TIDES study (DEN-301)** provided the majority of the data on efficacy, immunogenicity, and safety, due to the number of participants at approx. 20,000. The TIDES study is an ongoing double-blind placebo-controlled Phase 3 clinical trial in which 4-16-year-old individuals were randomised 2:1. The study has been conducted since September 2016 in 8 endemic countries

(Brazil, Colombia, the Dominican Republic, Nicaragua, Panama, the Philippines, Sri Lanka, and Thailand).

The primary end points of the TIDES study are the assessment of VE of 2 vaccine doses against VCD, defined as a febrile illness or illness with clinical suspicion of dengue with positive, serotype-specific quantitative real time-PCR, occurring beyond day 30 after the 2nd vaccine dose, regardless of the inducing serotype until the end of the first part of the study (12 months after the 2nd vaccine dose). The secondary efficacy end points include the VE of 2 vaccine doses from day 30 after the 2nd vaccine dose up to the end of the second part of the study against

 a) VCD independent of inducing serotype

 b) VCD dependent on the inducing serotype

 c) VCD independent of the inducing serotype in individuals who were seropositive prior to the vaccination

 d) VCD independent of the inducing serotype in individuals who were seronegative prior to the vaccination (dengue-naïve)

 e) Hospitalisation due to VCD independent of the inducing serotypes

 f) Severe dengue independent of the inducing serotypes

The study was divided into 5 parts. The participants were contacted weekly for the duration of the study and reminded that they should report any episode of fever, defined as temperature $\geq$ 38 °C on 2 of 3 sequential days. In Part 1 (up to 12 months after the 2nd vaccine dose) and Part 2 (up to 18 months after the 2nd vaccine dose), blood was taken from individuals with fever in the acute phase of the illness and tested for the presence of DENV using RT-PCR and ELISA for the dengue-NS-1 antigen, IgM, and IgG. Additional laboratory tests included the thrombocyte count, haematocrit, and liver function parameters, which were collected in both the acute and convalescent phases. From the third part of the study onwards, the above laboratory values were only checked in individuals whose fever symptoms led to hospitalisation (enhanced passive hospital-based surveillance). In all other individuals who were not hospitalised, an RT-PCR was only performed in the acute phase if no other differential diagnosis seemed more plausible.

Efficacy, immunogenicity, and safety data on a booster vaccination which will be given 48-54 months after the 2nd vaccine dose, will be surveyed in Parts 4 and 5 of the study. These data have not yet been published.

In total, 19,021 people – 6,317 placebo-vaccinated, 12,704 vaccinated with the study vaccine – have been included in the per protocol set of the study, of which 45% of the study participants came from the Asia-Pacific region and 55% from Latin America. The serostatus[2] of all included persons was determined before the administration of the 1st vaccine dose. 72% of the study participants were seropositive prior to delivery of the 1st vaccine dose, with a similar proportion in the placebo and treatment groups. The highest rate of seropositivity (84%) was in the 12-16-year-olds.

7.3 Immunogenicity of the vaccine and vaccine efficacy against virologically confirmed dengue (VCD)

VE data on the prevention of VCD at time points 1, 1.5, 2, and 3 years have been published in 4 original papers (Biswal et al., 2019 (107), Biswal et al., 2020 (108), Lopéz-Medina et al., 2022 (109), Rivera et al., 2022 (104)). The data obtained 4.5 years after vaccination are contained in the EMA-Assessment Report (103).

The VE in the publications for the 1st, 2nd, and 3rd years was only specified for individuals who had received 2 vaccine doses (the per-protocol set). This form of presentation reflects the VE for an individual to be vaccinated but is less suited to act as the basis for Public Health decisions[3]. This should be taken into account when reviewing the efficacy data given for the individual years in Table 2 and the efficacy data stratified by serostatus at the beginning of the study and by the disease-inducing serotype in Table 3. By contrast, the VE data over time (over 1.5, 2, and 3 years) were derived from the study population, which included both individuals who only received 1 vaccine dose and those who received both vaccine doses (the safety set as an approximator of an intention-to-treat analysis). Since these analyses correspond more closely to the real conditions, these estimates of efficacy were used to represent the efficacy over time.

In the **per-protocol analysis**, the VE against VCD of 2 vaccine doses given at an interval of 3 months fell off rapidly over time in the study population. Thus, the VE against VCD in the 1st

---

[2] The serostatus was defined as follows: seropositive = reciprocal neutralisation titre ≥ 10 for at least one dengue serotype; seronegative = reciprocal neutralisation titre < 10 for all dengue serotypes
[3] Effect estimates in the per-protocol set carry a certain risk of distortion, since individuals in whom the vaccine causes more side effects or who suffer an early infection may leave the study earlier and not obtain the 2nd vaccine dose.

year (survey period 30 days - 12 months after the 2nd vaccine dose) was 80.2% (95% CI: 73.3-85.3%), in the 2nd year (survey period 13-24 months after the 2nd vaccine dose) 56.2% (95% CI: 42.3-66.8%), and in the 3rd year (25-36 months after the 2nd vaccine dose) 44.7% (95% CI: 32.5-54.7%). The technical information for Qdenga contains additional VE data for the 4th year (37-48 months) after vaccination, but these have not yet been published elsewhere. According to this, the values were 62.8% (95% CI: 41.4-76.4%), see Tab. 2. The increase in the VE in the 4th year after the 2nd vaccine dose compared to the VE in year 2 and/or 3 cannot currently be explained (possibilities would include asymptomatic infections in the interim which led to fewer cases of VCD in vaccinated individuals, possible changes due to the occurrence of the COVID-19 pandemic between the 3rd and 4th years of the study, or withdrawal of a portion of the study participants before completion of the 4th year due to participation in the booster study) (103).

In the **intention-to-treat analysis**, the efficacy, reported over 1.5, 2, or 3 years, also dropped over time (see Tab. 3 and Fig. 5): The VE over 1.5 years (from the 1st vaccine dose to 18 months after the 2nd vaccine dose) was 80.2% (95% CI: 75.2-85.3%), over 2 and 3 years 72.7% (95% CI: 67.1-77.3%) and 62.0% (95% CI: 56.6-66.7%), respectively. Stratified by serostatus at the beginning of the study, variable efficacy was seen: the VE over 18 months, 2 years, and 3 years in individuals who tested seropositive at the start of the study was given as 81.9% (95% CI: 75.3-86.7%), 74.8% (95% CI: 68.6-79.8%), and 65.0% (95% CI: 58.9-70.1%), respectively. The corresponding VE over time for seronegative individuals was 78.5% (95% CI: 65.0-86.9%), 67.0% (95% CI: 53.6-76.5%), and 54.3% (95% CI: 41.9-64.1%), respectively.

Vaccine efficacy of Qdenga compared to placebo vaccination in people of any age

Bibliography: Biswal S, Reynales H, Saez-Llorens X, Lopez P, Borja-Tabora C, Kosalaraksa P, et al. Efficacy of a Tetravalent Dengue Vaccine in Healthy Children and Adolescents. N Engl J Med. 2019;381(21):2009-19;

López-Medina E, Biswal S, Saez-Llorens X, Borja-Tabora C, Bravo L, Sirivichayakul C, et al. Efficacy of a Dengue Vaccine Candidate (TAK-003) in Healthy Children and Adolescents 2 Years after Vaccination. Journal of Infectious Diseases. 2022;225(9):1521-32;

Rivera L, Biswal S, Sáez-Llorens X, Reynales H, López-Medina E, Borja-Tabora C, et al. Three-year Efficacy and Safety of Takeda's Dengue Vaccine Candidate (TAK-003). Clin Infect Dis. 2022;75(1):107-17.

Population: male & female, all ages, irrespective of endemic settings
Intervention: 2 doses of Qdenga vaccine given three months apart
Comparison: placebo vaccination
Outcome: virologically confirmed dengue (VCD) (serotype-specific reverse PCR or NS-1-Ag-test)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Vaccine effectiveness (95% CI)	Anticipated absolute effects	
							With Qdenga	With Placebo		Risk with Qdenga	Risk difference with Placebo

Virologically confirmed dengue, overall (intention-to-treat)

follow-up: up to 18 months after 2nd dose

20067 (1 RCT)	Some concerns	Not applicable[a]	Very serious[b1]	Not serious[d]	Not serious[c]	⊕⊕◯◯ Low	78/13380 (0.6%)	199/6687 (3.0%)	**80.2% (75.2 – 85.3)**	6 per 1000	24 more (18 to 34 more)

follow-up: up to 2 years after 2nd dose

20067 (1 RCT)	Some concerns	Not applicable[a,d]	Very serious[b1]	Serious[d]	Not serious[c]	⊕◯◯◯ Very low	175/13380 (1.31%)	310/6687 (4.64%)	**72.7% (67.1 – 77.3)**	13 per 1000	35 more (27 to 45 more)

follow-up: up to 3 years after 2nd dose

20067 (1 RCT)	Some concerns	Not applicable[a,d]	Very serious[b1]	Serious[d]	Not serious[c]	⊕◯◯◯ Very low	390/13380 (2.9%)	494/6687 (7.4%)	**62.0% (56.6 – 66.7)**	29 per 1000	48 more (38 more to 58 more)

Virologically confirmed dengue in people being seropositive at baseline (intention-to-treat)

follow-up: up to 18 months after 2nd dose

20067 (1 RCT)	Some concerns	Not applicable[a]	Serious[b2]	Not serious	Not serious[c]	⊕⊕⊕◯ Moderate	55/9661 (0.6%)	146/4852 (3.0%)	**81.9% (75.3- 86,7)**	6 per 1000	26 more (17 more to 37 more)

follow-up: up to 2 years after 2nd dose

20067 (1 RCT)	Some concerns	Not applicable[a,d]	Serious[b2]	Serious[d]	Not serious[c]	⊕⊕◯◯ Low	119/9663 (1.2%)	227/4854 (4,7%)	**74.8% (68.6-79.8)**	12 per 1000	37 more (27 more to 49 more)

follow-up: up to 3 years after 2nd dose

Vaccine efficacy of Qdenga compared to placebo vaccination in people of any age

Bibliography: Biswal S, Reynales H, Saez-Llorens X, Lopez P, Borja-Tabora C, Kosalaraksa P, et al. Efficacy of a Tetravalent Dengue Vaccine in Healthy Children and Adolescents. N Engl J Med. 2019;381(21):2009-19;

López-Medina E, Biswal S, Saez-Llorens X, Borja-Tabora C, Bravo L, Sirivichayakul C, et al. Efficacy of a Dengue Vaccine Candidate (TAK-003) in Healthy Children and Adolescents 2 Years after Vaccination. Journal of Infectious Diseases. 2022;225(9):1521-32;

Rivera L, Biswal S, Sáez-Llorens X, Reynales H, López-Medina E, Borja-Tabora C, et al. Three-year Efficacy and Safety of Takeda's Dengue Vaccine Candidate (TAK-003). Clin Infect Dis. 2022;75(1):107-17.

Population: male & female, all ages, irrespective of endemic settings
Intervention: 2 doses of Qdenga vaccine given three months apart
Comparison: placebo vaccination
Outcome: virologically confirmed dengue (VCD) (serotype-specific reverse PCR or NS-1-Ag-test)

Certainty assessment							Summary of findings				
20067 (1 RCT)	Some concerns	Not applicable[a,d]	Serious[b2]	Serious[d]	Not serious[c]	⊕⊕◯◯ Low	262/9663 (2.7%)	358/4854 (7.4%)	**65.0% (58.9–70.1)**	27 per 1000	50 more (39 more to 64 more)

Virologically confirmed dengue in people being seronegative at baseline (intention-to-treat)

follow-up: up to 18 months after 2nd dose

20067 (1 RCT)	Some concerns	Not applicable[a,d]	Serious[b2]	Serious[d]	Not serious[c]	⊕⊕◯◯ Low	23/3714 (0.6%)	53/1832 (2.9%)	**78.5% (65.0–86.9)**	6 per 1000	23 more (12 more to 41 more)

follow-up: up to 2 years after 2nd dose

20067 (1 RCT)	Some concerns	Not applicable[a,d]	Serious[b2]	Serious[d]	Not serious[c]	⊕⊕◯◯ Low	56/3714 (1.5%)	83/1832 (4.5%)	**67.0% (53.6–76.5)**	15 per 1000	31 more (17 more to 49 more)

follow-up: up to 3 years after 2nd dose

20067 (1 RCT)	Some concerns	Not applicable[a,d]	Serious[b2]	Serious[d]	Not serious[c]	⊕⊕◯◯ Low	128/3714 (3.4%)	136/1832 (7.4%)	**54.3% (41.9–64.1)**	34 per 1000	41 more (25 more to 62 more)

Figure 5: GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) evidence profile and "summary of findings"-Table for the end point "virologically confirmed dengue (VCD)"; CI: confidence interval

Explanations

a. Only one study available

b. Data only available for healthy children without comorbidities living in dengue-endemic countries. (b1) In the overall population, around three quarters of the children in the study population were seropositive at baseline and only one quarter were seronegative. This is a systematic deviation from the population (travellers from Germany), for which this recommendation is developed. In this population, the vast majority of travellers is likely seronegative. Therefore, the indirectness of the overall population is reduced by two levels. For the VE disaggregated by seronegative and seropositive status at baseline, certainty of evidence is reduced by one level.

c. According to studies registered in clinicaltrials.gov there are two completed studies (n=44 and n=80) for which data has not yet been published. Due to the low number of study participants, we do not assume that possible effects of these studies would have affected the overall effect.

d. The serotype specific VE estimates do not reveal VE (95% Confidence interval allows for the possibility of a null effect and of the vaccine increasing the risk if VCD), in particular against DENV-3 and DENV-4. Among the overall study population (including both participants classified as seronegative and seropositive at baseline), the VE against DENV-3 in year 2 was 32.8% (95% CI: -10.9 – 59.3) and could not be estimated for year 3. The VE against DENV-4 in year 1 was 63.2% (95% CI: -64.4 – 91.8), in year 2 41.2% (95% CI: -110.0 – 84.2), and could not be estimated for year 3.

Among the study population defined as seronegative at baseline, this includes the VE against DENV-1 for year 3 (VE: 17.2%; 95% CI: -31.8-47.9) and against DENV-2 in year 2 (VE: 70.5%; 95% CI: -23.4 – 93.0). The VE against DENV-3 for year 1 was -38.7% (95% CI: -335.7 – 55.8), for year 2 was -18.5% (95% CI: -236.2 – 58.3); and for year 3 was 9.5% (95% CI: -144.7 – 66.5). The VE against DENV-4 for year 1 could not be

estimated; for year 2 it was -47.6% (95% CI: -1319.1 – 84.6); and for year 3 it was -99.0% (95% CI: -1680.3 – 77.8). Therefore, we considered the provided overall estimate to be imprecise.

Vaccine efficacy (%) (95% confidence interval) of Qdenga against virologically confirmed dengue (VCD) – per-protocol set			
1st year	**2nd year**	**3rd year**	**4th year**
80.2% (73.3-85.3%)[1]	56.2% (42.3-66.8%)[1]	44.7% (32.5-54.7%)[1]	62.8% (41.4-76.4%)[2]

Table 2: Vaccine efficacy of Qdenga against virologically confirmed dengue (VCD) in the 1st, 2nd, 3rd, and 4th year after the 2nd vaccine dose
[1] DEN-301. Rivera L et al., 2022; López-Medina E et al. 2021; Biswal S et al. 2019;
[2] Technical information for Qdenga

Vaccine efficacy (%) (95% confidence interval) of Qdenga against virologically confirmed dengue (VCD) after the 1st vaccine dose over time – intention-to-treat analysis (safety set)[1]		
up to 1.5 years after 2nd vaccine dose	**up to 2 years after 2nd vaccine dose**	**up to 3 years after 2nd vaccine dose**
80.2% (75.2 – 85.3%) Seropositive: 81.9% (75.3-86.7%) Seronegative: 78.5% (65.0 – 86.9%)	72.7% (67.1 – 77.3%) Seropositive: 74.8% (68.6 – 79.8%) Seronegative: 67.0% (53.6 – 76.5%)	62.0% (56.6–66.7%) Seropositive: 65.0% (58.9–70.1%) Seronegative: 54.3% (41.9–64.1%)

Table 3: Vaccine efficacy of Qdenga against virologically confirmed dengue (VCD) after the 1st vaccine dose over time cumulated over 1.5, 2, and 3 years, respectively. The vaccine efficacy stratified by serostatus at the beginning of the study is added for each time point.
[1] DEN-301. Rivera L et al., 2022; López-Medina E et al. 2021; Biswal S et al. 2019

7.3.1 Efficacy against virologically confirmed dengue (VCD), stratified by serostatus before vaccination and dengue serotype

The efficacy data against VCD stratified by "serostatus at the beginning of the study" and "inducing serotype" were only reported for the per-protocol set in the studies, which exclusively included those individuals who had received 2 vaccine doses. The VE against VCD was markedly higher in individuals who were seropositive prior to the vaccination (i.e., who had suffered a prior DENV infection) than in seronegative individuals (i.e., dengue-naïves) (see Tab. 4). Thus, the VE after the 2nd vaccine dose was: in the 1st year in seropositives 82.2% (95% CI: 74.5-87.6%), in seronegatives 74.9% (95% CI: 57-85.4%); in the 2nd year 60.3% (95% CI: 44.7-71.5%) and 45.3% (95% CI: 9.9-66.8%), and in the 3rd year 48.3% (95% CI: 34.2-59.3%) and 35.5% (95% CI: 7.3-55.1%), respectively.

There were also differences in the VE of the vaccine in relation to the inducing DENV serotype. The VE against DENV-2 was greater than the VE against the other serotypes (see Tab. 4), which probably relates to the fact that DENV-2 forms the backbone of the vaccine viruses. The VE

against serotype DENV-1 in the first year was 73.7% (95% CI: 51.7-85.7%); against serotype DENV-3 it was 62.6% (95% CI: 43.3-75.4%). No significant VE against DENV-4 could be determined due to the very low number of DENV-4 associated VCD cases (VE 63.2% (95% CI: -64.4-91.8%)).

Further stratification of the data by serostatus prior to vaccination showed that in seropositives a VE could only be demonstrated up to year 3 inclusive, and only for serotypes DENV-1, -2, and -3. For DENV-4, the VE in seropositives in the 1st year was 63.8% (95% CI: -61.8-91.9%) and in the 2nd year 69% (95% CI: -85.7-94.8%) – but with a negative lower 95% CI in each case.

A significant VE In seronegatives was only found for DENV-1 and only over years 1 and 2. No efficacy could be demonstrated for the other serotypes (DENV-2, DENV-3, DENV-4) with the available data.

Vaccine efficacy (%) (95% confidence interval) against virologically confirmed dengue (VCD), stratified by serotype and serostatus at the end of the study					
Causal serotype	Serostatus	1st year	2nd year [1]	3rd year [1]	4th year [2,3]
Total		**80.2% (73,3-85.3%)**	**56.2% (42.3-66.8%)**	**44.7% (32.5-54.7%)**	**62.8% (41.4-76.4%)**
	Seropositive	82.2% (74.5-87.6%)	60.3% (44.7-71.5%)	48.3% (34.2-59.3%)	64.1% (37.4-79.4%)
	Seronegative	74.9% (57-85.4%)	45.3% (9.9-66.8%)	35.5% (7.3-55.1%)	60.2% (11.1-82.1%)
DENV-1		**73.7% (51.7-85.7%)**	**59.4% (38.5-73.2%)**	NA	NA
	Seropositive	79.8% (51.3-91.6%)	59.1% (31.1-75.7%)	45.4% (24.5-60.6%)	57.7% (17.0-78.4%)
	Seronegative	67.2% (23.2-86%)	60.7% (22.1-80.2%)	17.2% (-31.8-47.9%)	57.1% (-0.9-81.8%)
DENV-2		**97.7% (92.7-99.3%)**	**75% (52.3-86.9%)**	NA	NA
	Seropositive	96.5% (88.8-98.9%)	75.5% (49.5-88.1%)	72.1% (51.6-84%)	68.3% (-12.5-91.1%)
	Seronegative	100% (NE, NE)	70.5% (-23.4-93%)	84.9% (58.7-94.5%)	100% (NE, NE)

DENV-3		**62.6% (43.3-75.4%)**	**32.8% (-10.9-59.3%)**	NA	NA
	Seropositive	71.4% (54.3-82.1%)	44.9% (1.6-69.2%)	15.2% (-46.1-50.8%)	52.4% (-238.2-93.3%)
	Seronegative	-38.7% (-335.7-55.8%)	-18.5% (-236.2-58.3%)	9.5% (-144.7-66.5%)	100% (NE, NE)
DENV-4		**63.2% (-64.4-91.8%)**	**41.2% (-110-84.2%)**	NA	NA
	Seropositive	63.8% (-61.8-91.9%)	69% (-85.7-94.8%)	61.9% (-24.9-88.4%)	100% (NE, NE)
	Seronegative	NE	-47.6% (-1319.1-84.6%)	-99% (-1680.3-77.8%)	-999% (NE, NE)

Table 4: Vaccine efficacy of 2 Qdenga vaccine doses against virologically confirmed dengue (VCD) over time and in relation to the serostatus at the beginning of the study and the inducing serotype. The numbers in bold indicate the overall vaccine efficacy, i.e., not stratified by serostatus

NA not specified; NE not estimable

[1] DEN-301. Rivera L et al., 2022; López-Medina E et al. 2021; Biswal S et al. 2019
[2] Technical information on Qdenga
[3] EMA Assessment Report

7.3.2 Efficacy against virologically confirmed dengue (VCD) after 1 dose of vaccine

In the context of the TIDES study, the VE of a vaccine dose against VCD was recorded for the period between the 1st and 2nd vaccine dose. This resulted in a VE of 81% (95% CI: 64.1-90.0%) over the period of 3 months, which suggests a rapid onset of the protective effect after 1 vaccine dose. There are no data for the time beyond 3 months.

7.3.3 Immunogenicity of the vaccine

The immunogenicity of the vaccine was assessed in the TIDES study by means of seropositivity rates and the neutralising antibody levels (GMT), which were measured in the study prior to the 1st vaccine dose, 30 and 90 days after the 1st vaccine dose, prior to administration of the 2nd vaccine dose, 120, 270, and 450 days after the 1st vaccine dose and annually thereafter.

In addition to the efficacy data, the STIKO assessed the GMT of neutralising antibodies reported in the studies. Since, as mentioned at the beginning, there is no sero-immunological correlate of protection, these data can only be used to underpin the VE data. However, these data cannot be used to evaluate the protective effect or its duration.

The GMT over time reported by Rivera et al. (see Fig. 6) showed that their levels after 2 vaccine doses fell off in the first 6 months after the 2nd vaccine dose, but then stabilised at a level over

time. The GMT for DENV-2 were markedly above the GMT for the other serotypes over the entire period of 3 years.

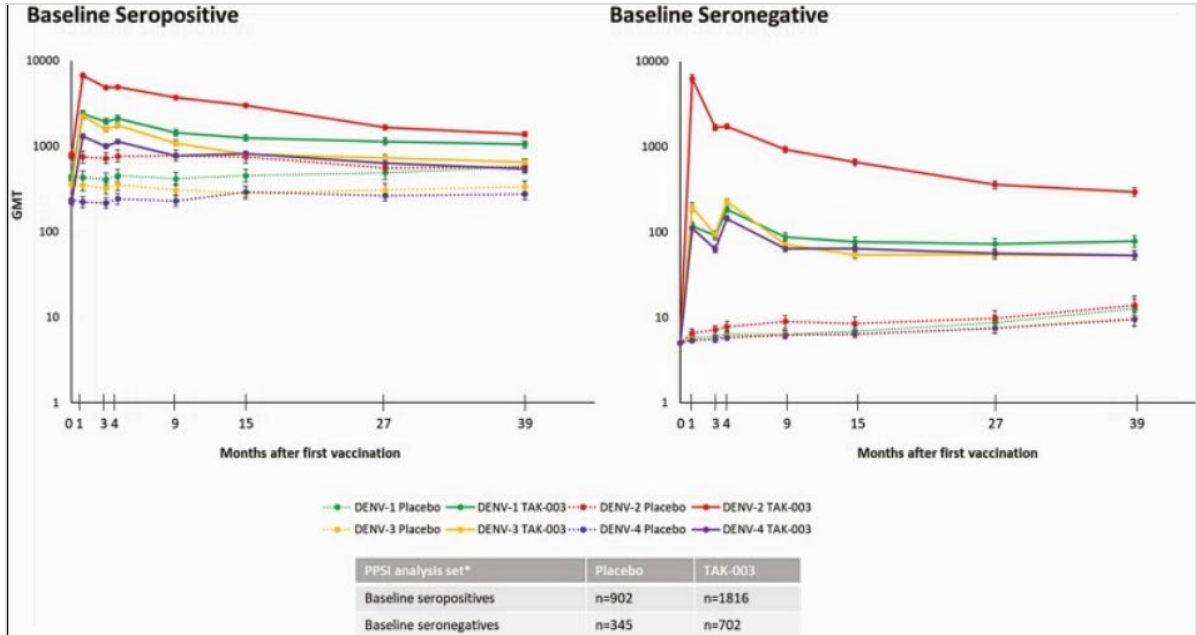The GMT were markedly higher for seropositives than for seronegatives.

Figure 6: Serotype-specific antibody values (geometric mean titres, GMT; 95% confidence interval) by serostatus at the start of the study (104)

7.3.4 Transferability of the study results from seronegative children from endemic countries to seronegative adults from non-endemic countries

In an immunobridging study, the immunogenicity parameters of 4-16-year-olds from endemic countries who were seronegative prior to vaccination (data from the TIDES study) were compared to those of seronegative 18-60-year-old adults from the USA, a non-endemic country. The GMT ratio between the two groups at the 6 month point after delivery of the 2nd vaccine dose was comparable, which supports the transferability of the immunogenicity data from seronegative children in endemic countries to seronegative adults in non-endemic countries (114).

7.3.5 Quality of the available evidence (GRADE)

The assessment of the VE of Qdenga against VCD is based on the multi-centre, triple blinded, randomised controlled **TIDES study**. Evaluation of the study showed no evidence of problems in the randomisation process (e.g., there was no relevant imbalance in the numbers of participants, nor evidence of unblinding). There was no evidence that the selection of the end points could have led to bias in the results. The rate of participants prematurely leaving the

study was comparable in the intervention and the control group with 1,036 of the 13,401 randomised individuals in the intervention group and 489 of 6,698 individuals in the control group (RR: 1.06; 95% CI: 0.95, 1.17). There was also no evidence of a selective choice of results, which could pose a relevant risk of systematic bias (see Fig. 7). It was, however, noticed that the results were not reported according to the random allocation to groups (the randomisation set) but rather according to the safety set (participants who had received at least 1 vaccine dose). This led to the exclusion of 11 people from the placebo group and 20 people from the intervention group as well as 1 person being moved from the intervention group to the control group.
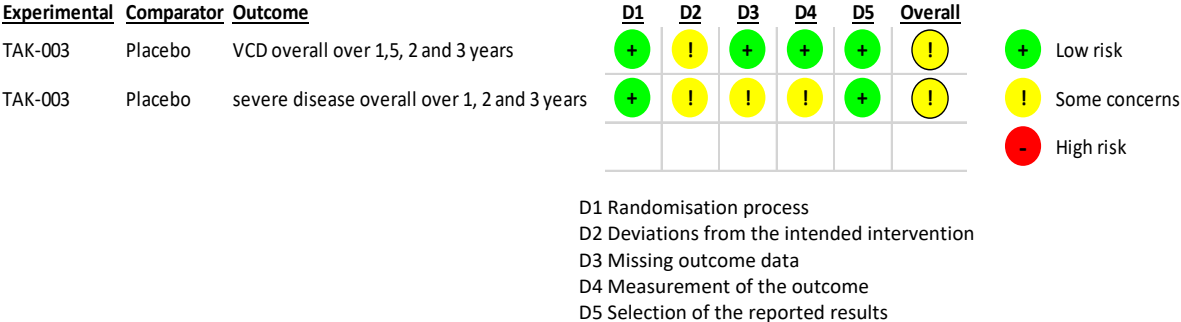
Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
TAK-003	Placebo	VCD overall over 1,5, 2 and 3 years	+	!	+	+	+	!
TAK-003	Placebo	severe disease overall over 1, 2 and 3 years	+	!	!	!	+	!

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended intervention
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported results

Figure 7: Risk of bias assessment for the TIDES study (DEN-301) for the end points virologically confirmed dengue (VCD) and severe dengue. As the data collection methods did not differ significantly in the different years, the two endpoints for the analysed endpoints were assessed together at 1.5 and 1 year, 2, and 3 years after vaccination.

Against this background, the certainty of evidence for the effectiveness of the vaccine (certainty of evidence according to GRADE) against VCD is reduced by one level (see also Fig. 5).

The study on which the evaluation of the reliability of the evidence relies only investigated the efficacy of the vaccine for healthy 4-17-year-olds with no previous illnesses living in dengue-endemic regions. Up to 3/4 of the study group consisted of children who were seropositive at the start of the study and only up to 1/4 were seronegative individuals. This represents a systematic deviation from the population in which the recommendations contained herein are supposed to apply (travellers from Germany). It can be assumed that the vast majority of travellers from a non-endemic country will be dengue-naïve. Therefore, the evidence derived from the study on the protective effect in the actual target population was assessed as highly indirect overall and reported separately for seropositive and seronegative individuals.

In addition, marked differences in efficacy were seen in regard to serotypes in the study: for the overall population, which contained both seropositive and seronegative individuals, the calculated 95% CI of VE against DENV-3 in years 2 and 3 and against DENV-4 in years 1, 2, and 3 allows the possibility of both a null effect and an increased risk due to vaccination. In the group of individuals who were seronegative at the start of the study, the 95% CI of the VE for DENV-1 in year 3, for DENV-2 in year 2, and for DENV-3 and DENV-4 in years 1, 2, and 3 allows equally for the possibility of a relevant benefit, harm, or a null effect. Therefore, the reliability of the evidence with respect to the efficacy estimators against VCD (overall) in the 1st year after vaccination was assessed as "low" and in the 2nd and 3rd years as "very low" (see Fig. 7).

7.4 Vaccine efficacy against severe dengue

In assessing the VE against severe dengue, the STIKO used the definition of severe dengue as laid out in the 2009 WHO definition. In the TIDES study, the severity of dengue was assessed by two methods:

1. Using comprehensive criteria from an expert committee (the Dengue Case Adjudication Committee, DCAC), which assessed all hospitalised dengue cases using a predefined list of criteria
2. Using the WHO definition for DHF from 1997

Since the DCAC list of criteria overlaps with the 2009 WHO classification for severe dengue, only those cases defined as severe dengue according to the DCAC were included as severe cases in the STIKO assessment.

The end point "Hospitalisation due to VCD" was deliberately not treated as a relevant end point by the STIKO. Hospitalisation may proceed differently depending upon the individual patient circumstances, country context, hospital setting, etc. Therefore, when evaluating the data, hospitalisation cannot be considered as being equivalent to a severe dengue diagnosis.

Vaccine efficacy of Qdenga compared to placebo vaccination in people of any age

Bibliography: López-Medina E, Biswal S, Saez-Llorens X, Borja-Tabora C, Bravo L, Sirivichayakul C, et al. Efficacy of a Dengue Vaccine Candidate (TAK-003) in Healthy Children and Adolescents 2 Years after Vaccination. Journal of Infectious Diseases. 2022;225(9):1521-32. Rivera L, Biswal S, Sáez-Llorens X, Reynales H, López-Medina E, Borja-Tabora C, et al. Three-year Efficacy and Safety of Takeda's Dengue Vaccine Candidate (TAK-003). Clin Infect Dis. 2022;75(1):107-17.

Population: Male & female, all ages, irrespective of endemic settings
Intervention: 2 doses of Qdenga vaccine given three months apart
Comparison: placebo vaccination
Outcome: severe dengue (serotype-specific reverse PCR or NS1-Ag-test) according to WHO classification from 2009

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Vaccine effectiveness (95% CI)	Anticipated absolute effects	
							With Qdenga	With Placebo		Risk with Qdenga	Risk difference with Placebo
Severe dengue, overall (intention-to-treat)											
Follow-up: up to 1 year after 2nd dose											
20067 (1 RCT)	Some concerns	Not applicable[a]	Very serious[b]	Serious[c]	Not serious[d]	⊕◯◯◯ very low	1/13380 (<0.1%)	1/6687 (<0.1%)	**50.2% (-696.1–96.9)**	7 per 100.000	7 more (234 more to 7 fewer)
Follow-up: up to 2 years after 2nd dose											
20067 (1 RCT)	Some concerns	Not applicable[a]	Very serious[b]	Serious[c]	Not serious[d]	⊕◯◯◯ very low	2/13380 (<0.1%)	3/6687 (<0.1%)	**66.9% (-97.8–94.5)**	15 per 100.000	30 more (257 more to 7 fewer)
Follow-up: up to 3 years after 2nd dose											
20067 (1 RCT)	Some concerns	Not applicable[a]	Very serious[b]	Serious[c]	Not serious[d]	⊕◯◯◯ very low	3/13380 (<0.1%)	5/6.687 (<0.1%)	**70.2% (-24.7–92.9)**	22 per 100.000	53 more (293 more to 4 fewer)

Figure 8: GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) evidence profile and "summary of findings" table for the end point severe dengue; CI: Confidence interval

Explanations

a. Only one study available

b. Data only available for healthy children without comorbidities living in dengue-endemic countries. In the overall population, around three quarters of the children in the study population were seropositive at baseline and only one quarter were seronegative. This is a systematic deviation from the population (travellers from Germany), for which this recommendation is developed. In this population, the vast majority of travellers is likely seronegative. Therefore, the indirectness of the overall population is reduced by two levels. For the VE disaggregated by seronegative and seropositive status at baseline, certainty of evidence is reduced by one level; severe dengue was not defined using the WHO criteria for severe dengue from 2009 but by the assessment of all hospitalised dengue cases by an expert committee (*Dengue Case Adjudication Committee*, DCAC) using a predefined set of criteria that are similar bot not equal to the WHO criteria

c. Only very few cases of severe dengue, wide and into the negative reaching confidence interval. Therefore, the evidence was downgraded by two levels.

d. According to studies registered in clinicaltrials.gov there are two completed studies (n=44 and n=80) for which data have not yet been published. Due to the low number of study participants, we do not assume that possible effects of these studies would have affected the overall effect.

The VE against severe dengue is reported in the publications for a study population which included both individuals who had only received 1 vaccine dose and for those who received both vaccine doses. It should be noted that in both cases the VE was reported over the period of 1, 2, or 3 years after administration of the 1st vaccine dose and not separately for each individual year. The reported VE in the 1st year after the 1st vaccine dose was 50.2% (95% CI: -696.1-96.9%). In the period of 15 months after the 1st vaccine dose, 1 case occurred in the intervention group and 1 case in the control group (107).

Over the period of 2 years and 3 months after the 1st vaccine dose, 2 cases of severe dengue occurred in the intervention group (n = 13,380) and 3 cases in the control group (n = 6,687), corresponding to a VE of 66.9% (95% CI: -97.8-94.5%) (109).

Over the period of 3 years from the 1st vaccine dose (up to 36 months after the 2nd vaccine dose), 3 cases of severe dengue occurred in the intervention group (n = 13,380) and 5 cases in the control group (n = 6,687), corresponding to a VE of 70.2% (95% CI: -24.7-92.9%) (104).

The respective wide CI include the possibility of a very high efficacy as well as a null effect or a severely increased risk from the vaccine. This is due, among other things, to the very small number of severe dengue cases in the study population.

Our own analysis of the relative risk of severe dengue stratified by serostatus gave the result that over the period of 3 years (up to 36 months after the 2nd vaccine dose) 2 cases of severe dengue (both induced by DENV-3) occurred in the intervention group (n = 3,714) and 0 cases occurred in the control group (n = 1,832) (see Fig. 9). This results in a relative risk of severe dengue in dengue-naïve individuals after vaccination of 2.47 (95% CI: 0.12-51.36), after imputation of 0.5 in both groups (115). The wide CI cannot be interpreted unambiguously. Whilst the point estimator suggests an increased risk of severe dengue in dengue-naïve individuals, the very wide CI allows the possibility of an increased relative risk in dengue-naïves as well as of a null effect or a high level of protection against severe dengue.
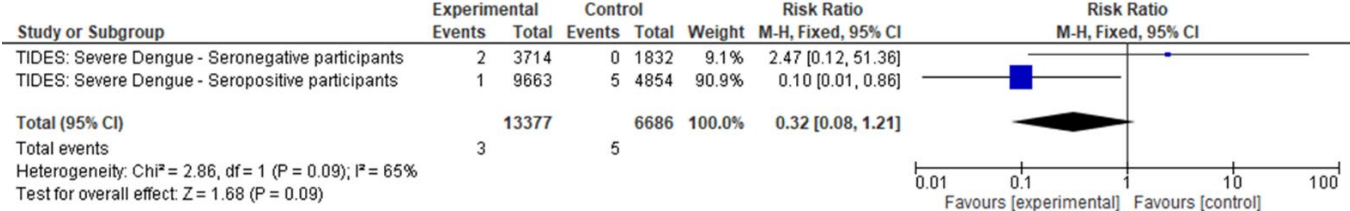

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
TIDES: Severe Dengue - Seronegative participants	2	3714	0	1832	9.1%	2.47 [0.12, 51.36]
TIDES: Severe Dengue - Seropositive participants	1	9663	5	4854	90.9%	0.10 [0.01, 0.86]
Total (95% CI)		13377		6686	100.0%	0.32 [0.08, 1.21]
Total events	3		5			
Heterogeneity: Chi² = 2.86, df = 1 (P = 0.09); I² = 65%						
Test for overall effect: Z = 1.68 (P = 0.09)						

Favours [experimental]   Favours [control]

Figure 9: Forest plot of relative risk for severe dengue stratified by dengue serostatus at the end of the study up to 3 years after vaccination (own analysis)

The evaluation of the study quality and the reliability of the evidence broadly corresponds with the assessment that was made of the efficacy against VCD. Due to the very small number of events and the resultant wide CI, the reliability of the evidence was downgraded by 2 levels. In addition, the data suggest a different efficacy of vaccination in individuals with seropositive and seronegative status. The reliability of the evidence was therefore reduced by 1 step (see Fig. 8).

7.5 Safety of the Qdenga vaccine

7.5.1 Local and systemic reactions

Local reactions < 7 days after the 1st or 2nd vaccine dose were reported by Biswal et al., 2019 (107) in the group of < 6-year-olds in 106/331 participants (32.02%). In the group of ≥ 6-year-olds, pain, reddening, and/or swelling occurred in 861/2,302 participants (37.40%). The corresponding data for the placebo groups can be found in Table 5. Also in Table 5 are the systemic reactions which occurred within 14 days. Because of the differing definitions of systemic reactions in children under and over 6 years, 2 data pairs are reported (systemic reactions < 6 years: irritability, sleepiness, loss of appetite; ≥ 6 years: headache, asthenia, malaise, muscle pain). Fever was recorded independently of the other systemic reactions, whereby it was noticeable that the symptom occurred almost as often in the < 6-year-olds in the placebo group as in the intervention group and was even observed slightly more frequently in the ≥ 6-year-olds in the placebo group. The data in Table 5 were not stratified by serostatus at the beginning of the study.

Safety of Qdenga compared to placebo vaccination in people of any age

Bibliography: TIDES study
Population: Male & female, all ages, irrespective of endemic settings
Intervention: 2 doses of Qdenga vaccine given three months apart
Comparison: placebo vaccination
Outcome: local reaction, serious adverse events (inc. death), adverse events of special interest (AESI): severe dengue according to WHO definition 2009 in sero-negatives

Certainty assessment							Summary of findings				
							Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Qdenga	With Placebo		Risk with Qdenga	Risk difference with Placebo

Local reactions (pain, redness, swelling) occurring up to 7 days after vaccination

All age-groups (4–16-year-olds)											
20067 (1 RCT)	Some concerns	Not applicable[a]	Serious[b]	Not serious	Not serious[c]	⊕⊕◯◯ Low	967/2633 (36.72%)	336/1317 (17.92%)	1.44 (1.30 – 1.60)	367 per 1000	188 fewer (164 fewer to 209 fewer)

Systemic reactions occurring up to 14 days after vaccination

All age-groups (4–16-year-olds)											
20067 (1 RCT)	Some concerns	Not applicable[a]	Serious[b]	Not serious	Not serious[c]	⊕⊕◯◯ Low	1029/2633 (39.08%)	457/1316 (34.73%)	1.13 (1.03 – 1.23)	391 per 1000	44 fewer (12 fewer to 73 fewer)

Fever occurring up to 14 days after vaccination

All age-groups (4–16-year-olds)											
20067 (1 RCT)	Some concerns	Not applicable[a]	serious[b]	serious[d]	not serious[c]	⊕◯◯◯ Very low	266/2606 (10.21%)	147/1303 (11.28%)	0.90 (0.75 – 1.09)	102 per 1000	11 more (34 more to 8 fewer)

Serious adverse events inc. death up to 3 years after vaccination

All age-groups (4–16-year-olds)											
20067 (1 RCT)	High[e]	Not applicable[a]	Serious[b]	Not serious	Not serious[c]	⊕◯◯◯ Very low	386/13380 (2.90%)	234/6687 (3.50%)	0.82 (0.70 – 0.97)	29 per 1000	6 more (12 more to 1 more)

Figure 10: "GRADE" (Grading of Recommendations, Assessment, Development, and Evaluations) evidence profile and "summary of findings" table for the safety end point; CI: Confidence interval.

[1] DEN-301. Rivera L et al., 2022; López-Medina E et al. 2021; Biswal S et al. 2019

Explanations

a. Only one study available

b. Data only available for healthy children without comorbidities living in dengue-endemic countries. In the overall population, around three quarters of the children in the study population were seropositive at baseline and only one quarter were seronegative. This is a systematic deviation from the population (travellers from Germany), for which this recommendation is developed. In this population, the vast majority of travellers is likely seronegative. Therefore, the indirectness of the overall population is reduced by two levels. c. According to studies registered in clinicaltrials.gov there are two completed studies (n=44 and n=80) for which data has not yet been published. Due to the low number of study participants, we do not assume that possible effects of these studies would have affected the overall effect.

d. Low number of events leads to a broad confidence interval, which allows for the possibility of relevant effects favouring the intervention, favouring the control, as well as a null effect.

e. High risk of bias due to potential misclassification of dengue cases as non-dengue serious adverse events; leading due to the protective effect of the vaccine against VCD to a relative reduction in the rate of SAE to the benefit of the intervention group.

Safety outcome	Observed period after each vaccine dose	Age group < 6 years Number of participants with reactions/analysis group (%)		Age group ≥ 6 years Number of participants with reactions/analysis group (%)	
		Intervention	Control	Intervention	Control
Local reactions (pain, reddening, swelling)	< 7d	106/331 (32.02%)	41/169 (25.44%)	861/2,302 (37.40%)	295/1,148 (25.70%)
Systemic reactions (apart from fever)	< 14d	88/331 (26.59%)	35/169 (20.71%)	941/2,302 (40.88%)	422/1,147 (36.79%)
Fever	< 14d	45/327 (13.76%)	23/169 (13.61%)	221/2,279 (9.70%)	124/1,134 (10.93%)

Table 5: Local and systemic reactions after each vaccine dose (107)

7.5.2 Serious adverse events including death

Serious adverse events (SAE) including death were reported up to the end of the study. The data available at the time of publication of the background paper from up to 3 years after the start of vaccination are presented in Table 6 (104). The data were obtained from the entire study population of the TIDES study (inclusion of 4-16-year-olds). The systemic symptoms included symptoms in various systems such as disorders of the gastrointestinal tract, the nervous system, the kidneys and urinary tract or infections and parasitic diseases. In part, these occurred more often in the placebo group than in the intervention group (for disorders of the gastrointestinal tract and for infections and parasitic diseases; data not shown). In total there were 7 fatalities during the TIDES trial, 5 in the intervention group and 2 in the placebo group. There has been a total of 21 fatalities in all the clinical TAK-003 studies, of which 14 occurred in placebo-controlled studies with similar incidences in the intervention and control groups (0.1%) (116). In the TAK-003 group there were 10 fatalities due to injuries (2 wounds, 2 traffic accidents, and 1 craniocerebral injury), one malignant ependymoma, suicide, asphyxia, cerebrovascular arteriovenous malformation, and a case of multiple organ failure. The 4 fatalities in the placebo group were due to a traumatic lung injury, an adenocarcinoma of the colon, a squamous carcinoma of the lung, and an aseptic meningitis (116).

According to the study leaders, there is no connection between the serious adverse events and fatalities and the use of vaccine or placebo.

Safety outcome	Observation period	Age group: 4-16 years Number of participants with reactions/analysis group (%)	
		Intervention	Control
Serious adverse events	Up to study end (3 years)	386/13,380 (2.90%)	234/6,687 (3.50%)
Death*	Up to study end (3 years)	5/13,380 (0.04%)	2/6,687 (0.03%)

Table 6: Severe adverse events (SAE) and deaths (104)
* Deaths in the intervention group: traffic accident, wound from sharp object, suicide, multiple organ dysfunction after attempted suicide, craniocerebral trauma. **Deaths in the control group:** adenocarcinoma of the colon, traumatic lung injury after drowning

7.5.3 Unexpected adverse events of special interest

Severe dengue as defined in the 2009 WHO classification when it occurred in vaccinated dengue-naïve individuals was classed as an unexpected adverse event of special interest (AESI) and interpreted as evidence of an ADE. Severe dengue was not reported stratified by serostatus in the included publications. The risk of an ADE is very difficult to determine in a study. The occurrence of severe illnesses after a vaccination can equally indicate a vaccine breakthrough with a severe course or a severe clinical course triggered by the vaccination.

As reported above in the analysis of the relative risk of severe dengue stratified by serostatus, a relative risk of severe dengue of 2.47 (95% CI: 0.12-41.36) was found in dengue-naïve individuals. The wide CI includes both the possibility of an increased relative risk in dengue-naïves and also a high level of protection against severe dengue. In any event, based on these data, it cannot be ruled out that the vaccination can trigger an ADE in dengue-naïve individuals.

7.5.4 Quality of the available evidence (GRADE)

The assessment of study quality and reliability of the evidence here largely corresponds to the assessment that was reached for efficacy against VCD and severe dengue (see Fig. 11).

It was not possible to conclusively assess whether there were differences between seropositive and seronegative individuals with respect to serious events based on the available data.

With respect to the SAE, the results for year 3 after the 2nd vaccine dose suggest that fewer events occurred in the intervention group (386/13,380; 2.90%) than in the control group (234/6,687; 3.50%), corresponding to a relative risk of 0.82 (95% CI: 0.70-0.97) (see Fig. 10). This was due primarily to differences in the infectious SAE ("infections and infestations"), with 248 (1.9%) events occurring in the intervention group and 169 (2.5%) in the control group (RR: 0.7; 95% CI: 0.6-0.9). If the SAE are ignored, the numbers of adverse events in the control and intervention groups were comparable (RR: 1.1; 95% CI: 0.8-1.4). These results can be interpreted as meaning that some of the VCD cases were incorrectly classified as SAE, and that the increased efficacy of the vaccine against VCD distorted the SAE to the disadvantage of the placebo group. With this background, the reliability of the evidence was downgraded by 2 levels, due to the risk of systematic distortion. Regarding the end point of all fatalities 36 months after the 2nd vaccine dose, the reliability was downgraded due to the very low numbers of events and the resultant wide CI (see Fig. 10).

Figure 11: Risk of bias assessment for the TIDES study (DEN-301) for the end points local and systemic reactions, serious adverse events including death.

7.5.5 Summary of efficacy and safety data on Qdenga

According to the available study data, the Qdenga vaccine shows good **VE against VCD** in the 1st and 2nd year after administration of 2 doses of vaccine at 3-month intervals in individuals who have had a DENV infection in the past. There was a serotype-specific VE in the 1st year

after vaccination against DENV-1, DENV-2, and DENV-3. A VE against DENV-4 could not be determined.

On the other hand, a VE against VCD in dengue-naïve individuals (serotype independent) could only be demonstrated in the 1st year after vaccination, though this related exclusively to an efficacy against DENV-1 and DENV-2. No efficacy against DENV-3 or DENV-4-associated VCD in seronegatives could be established.

The **VE against severe dengue** could not be determined due to the small numbers of cases of severe dengue that occurred in the studies.

On the basis of the available data, it is not possible to conclusively determine whether there is an increased risk of severe dengue, in the sense of an ADE, following vaccination in dengue-naïve individuals. Even if this is only a theoretical risk based on the current data, an ADE risk has already been observed with another live attenuated chimaeric dengue vaccine.

7.6 Immunogenicity of the vaccine and safety of co-administration with hepatitis A and yellow fever vaccines

At the time of data analysis, 2 studies on the co-administration of Qdenga have been published, 1 study on co-administration with a hepatitis A vaccine and 1 study on co-administration with a yellow fever vaccine.

The study on **co-administration with a hepatitis A** vaccine was performed on 900 seronegative participants aged 18-60 years in a non-endemic setting in the United Kingdom (112). The study investigated 3 groups, who received the hepatitis A vaccine and/or TAK-003 and/or placebo. On day 1 of the vaccine series, 2 doses of the vaccines were administered; 3 months later 1 vaccine dose of either TAK-003 or placebo (group 1: hepatitis A vaccine + placebo – placebo; group 2: TAK-003 + placebo – TAK-003, group 3: TAK-003 + hepatitis A vaccine – TAK-003). The co-administration of TAK-003 and a hepatitis A vaccine showed a non-inferiority with respect to the levels of the hepatitis A antibodies in comparison to single vaccination against hepatitis A and led in all DENV serotypes to similar or slightly higher GMT 1 month after the 2nd vaccine dose of TAK-003. The clinical relevance in the known absence of a cut-off for protection is unclear. The number of local and systemic reactions was comparable in the 3 groups. Pain at the injection site was reported most frequently (34.7-48.4% in all groups, for both vaccines). With few exceptions, all the local reactions were rated as mild. There were no clinically relevant differences in systemic reactions related to the placebo or the vaccine (41.9-49.5% in the 3 groups). Headache was reported most frequently (37.8%

regardless of vaccine administration). Most systemic reactions were rated as mild and occurred within 10 days. Serious reactions were observed in 0.7% in group 1, 2.7% in group 2, and 2.3% in group 3, unrelated to placebo or vaccine (112). There were no fatalities during the study.

The study on **co-administration with a yellow fever vaccine** was also carried out in a non-endemic setting (USA) in 900 seronegative participants aged 18-60 years (102). Here, too, 3 groups were studied in which the vaccines YF-17D (yellow fever vaccine) and/or TAK-003 and/or placebo were administered. On day 1 of the vaccination series, 2 of the vaccines were administered, at 3 and 6 months, 1 vaccine dose was administered (group 1: YF-17D + placebo – TAK-003 – TAK-003; group 2: TAK-003 + placebo – TAK-003 – YF-17D; group 3: TAK-003 + YF-17D – TAK-003 – placebo). The primary goal of the study was to demonstrate non-inferiority of the seroprotection rate of the yellow fever vaccination 1 month after the simultaneous administration of yellow fever vaccine and TAK-003, and secondary goals included the demonstration of the non-inferiority of the GMT after yellow fever vaccination and administration of TAK-003.

It was possible to demonstrate the non-inferiority of the seroprotection rate of the yellow fever vaccination. Co-administration of TAK-003 and the yellow fever vaccine resulted in slightly higher dengue GMT 1 month after the 2nd dose of TAK-003 (group 2: 3.078; 95% CI: 2.452 - 3.865, group 3: 4.322; 95% CI:3. 653-5,114) and 1 month after the 2nd dose of TAK-003 in a slightly lower GMT for DENV-1 compared to the GMT in group 2, which had only received 2 doses of TAK-003 by this time. Non-inferiority could be demonstrated in the study for DENV-2, DENV-3, and DENV-4, but not for DENV-1, the clinical relevance of which is unclear.

Most of the expected local and systemic side effects were transient and of mild to moderate severity. Local reactions were reported by 45.9%, 56.4%, and 60.3% of participants in groups 1, 2, and 3. The local reaction reported most frequently in all groups was pain at the injection site, with the rate depending markedly upon the vaccine administered (TAK-003: 24.9 – 42.2%, YF-17D: 10.4 – 24.1%; placebo: 9.7 – 16.5%). The systemic reactions occur with similar frequency in the 3 groups (55.2% in group 1, 59.2% in group 2, and 60.6% in group 3), with headache being the most common.

Unexpected side effects were reported by 20.3% (group 1), 25.3% (group 2), and 21.4% (group 3); a rash developed in 4 participants after administration of TAK-003 and in 1 participant after administration of a yellow fever vaccine.

Severe reactions were reported by 4.3% (group 1), 3.3% (group 2), and 2.3% (group 3) of the participants. No connection to the vaccination was seen for any of the severe reactions. Across all groups, 12 participants exhibited side effects that led to their withdrawal from the study, including 2 fatalities (diabetic ketoacidosis and drug abuse). Again, there was no relationship to the vaccines administered.

These data allow the conclusion that co-administration with hepatitis A or yellow fever vaccines does not significantly affect the immunogenicity or the safety of Qdenga.

7.7 Interval between a previous infection and vaccination

Following a laboratory-confirmed DENV infection, two aspects are relevant regarding the interval to a 1st vaccine dose:

1. Could too short an interval influence the efficacy of the live attenuated vaccine since the high levels of post-infectious antibodies present may prevent the replication of the attenuated vaccine viruses and thus reduce the antiviral immune response?

2. If the interval is too short, must we fear an increased reactogenicity of the vaccine because of the preexisting post-infectious immune response?

These questions were not evaluated systematically in the licensing studies for Qdenga. In a paper on the dengue vaccine Dengvaxia, it is discussed that the immune responses to a wild type infection should have no influence on the reactogenicity of the vaccine, but that a "refractory period with reduced efficacy [of the vaccine] might result after an infection" (117). To avoid both a reduced efficacy and an increased reactogenicity, the STIKO deemed an interval of 6 months between infection and vaccination to be sensible. This is in agreement with the recommendations of the US Centers for Disease Control and Prevention (CDC) on the usage of the dengue vaccine Dengvaxia (118). Since it can be assumed that a wild type infection generally induces at least a 6-month cross protection against the other 3 serotypes (8-11), the recommended interval is presumed to present no risk that a second infection could occur in this period.

8. Serological diagnostics

8.1 Notes on determination of serostatus

Most of the test procedures to detect antibodies against DENV have been developed and validated to diagnose acute or recent infections. The serological diagnosis of a prior DENV infection in order to determine the serostatus is becoming ever more difficult due to the increasing worldwide spread of various human pathogenic orthoflaviviruses (119). The orthoflaviviruses, which also include, in addition to DENV, the tick-borne encephalitis (TBE) virus, the Japanese encephalitis virus, and the yellow fever virus, are genetically related and have structural similarities, which means that IgG-antibodies, for example, that are formed in response to, e.g., a yellow fever infection or vaccination, can also produce a false positive reactivity in serological DENV tests (119). Serological DENV tests with higher specificity, such as the virus neutralisation tests or multiplex tests, whilst established, are not widely available for routine diagnostic use.

As a result, particularly in individuals from non-endemic regions, a reactive (positive) DENV antibody detection is not sufficient evidence of specific seropositivity for DENV. Even a non-reactive (negative) DENV antibody test is no certain proof that there has not been a prior DENV infection. This would require both known threshold values for DENV antibody concentrations, below which there is no increased risk of ADE, and test methods for which a sufficiently high sensitivity has been demonstrated. As this is not currently the case, the determination of serostatus does not appear to make sense at this stage.

8.2 Notes on laboratory diagnostics after vaccination

Unexpected pharmacological effects can occur in vaccinated individuals that are clinically similar to a DENV infection, see symptoms mentioned in chapter 7.5 Safety of the Qdenga vaccine. Since the Qdenga vaccine contains the NS-1 antigen (the target antigen for the usual DENV antigen test), the laboratory tests can show positive results in the first weeks after vaccination (both detecting DENV-specific IgG and IgM antibodies, and also a positive DENV antigen test for the NS-1 antigen), even though there is no wild-type DENV infection in the vaccinated individuals present. The occurrence of dengue-like symptoms after vaccination (occasionally also combined with positive results in the laboratory tests) can be termed "vaccine dengue".

If it is highly likely that the existing symptoms are due to "vaccine dengue" (development of symptoms 7-14 days after vaccination, wild virus infection unlikely due to lack of exposure to DENV), this symptom and laboratory constellation should not be classified as dengue. A case report to the responsible health authority is not necessary in the case of "vaccine dengue". Irrespective of this, a suspicion of damage to health exceeding the usual degree of a vaccine reaction must be reported by name in accordance with § 6 Para. 1 of the Infection Protection Act (IfSG).

9. Vaccine acceptance and feasibility of implementation

Since the vaccine became available to the market, it has been introduced in various endemic countries (latest data as of 23rd August 2023: Indonesia, Brazil, Argentina, Thailand). The vaccine was licensed for the European market by the European Commission on the 8th of December 2022. The recommendations for travellers differ from country to country in the EU: in Belgium, the Superior Health Council recommends vaccination against dengue with Qdenga for individuals over 4 years who are travelling for a period of > 4 weeks or who make frequent short trips and who fulfil all of the following criteria: 1. Prior dengue infection (medical history or laboratory confirmed), 2. Travel to a dengue-endemic region, 3. Receipt of both vaccine doses prior to departure (120).

In Sweden, the vaccine is only recommended for adults who have already had a prior DENV infection. In children aged 4-16 years it can be given independent of a prior infection (121).

9.1 Vaccine acceptance

Data on vaccine acceptance in endemic countries and/or in travellers from non-endemic countries are not available. The renewed post-pandemic increase in travel, especially in dengue endemic areas, suggests that vaccination against dengue would be accepted by travellers as long as it does not pose any significant risks.

9.2 Feasibility of implementation

The vaccination series consists of 2 vaccine doses which are given at a minimum interval of 3 months. Since advice about travel vaccination often occurs shortly before the start of the travel, completion of the vaccination series prior to the start of the travel cannot be

achieved in many cases. This vaccination schedule is not practical, especially for people travelling at short notice. Although the data indicate efficacy against DENV infection after 1 vaccine dose for up to 3 months after vaccination, there are currently no data regarding the period beyond 3 months. Departure after only 1 vaccine dose should especially not occur in dengue-naïve individuals.

Disclosure of a medical history of a laboratory-confirmed DENV infection is sufficient evidence of a prior DENV infection. Testing to find the DENV serostatus prior to vaccination is not recommended, see Chapter 8.1 Notes on determination of serostatus. The advice on travel vaccination should also contain information, and, if applicable, tips on additional preventative measures, such as adequate protection against mosquitoes, which can also protect travellers from other mosquito-borne diseases.

10. Summary

The present clinical efficacy data show that the vaccine can effectively prevent VCD in the 1st year, with higher efficacy in individuals who have had a prior DENV infection than in dengue-naïve individuals, which presumably includes the majority of travellers from Germany (VE against VCD in the 1st year after vaccination 82.2% versus 74.9%). The vaccine efficacy declines over time in both groups of individuals, with the decline shown in the studies being greater for seronegative individuals (VE against VCD in the 2nd year after vaccination: 60.3% versus 45.3%).

Regarding the serotype-specific protection rates against VCD, the efficacy patterns were heterogenous: due to the structure of the vaccine with a DENV-2 backbone, the greatest efficacy was seen against DENV-2-induced VCD (97.7% in the 1st year after vaccination). The efficacy against the other DENV serotypes is lower: the VE in the 1st year after vaccination against DENV-1 is 73.7%, against DENV-3 62.6%. The efficacy against DENV-4 could not be demonstrated due to the small number of VCD cases induced by DENV-4 in the licensing studies.

Protection against severe dengue could not be proven in the licensing studies due to the few cases of severe dengue which occurred.

Particularly in the light of experiences with the dengue vaccine Dengvaxia (Sanofi), which is only licensed for use in endemic countries, the requirements for future dengue vaccines

should be that they show efficacy against all 4 serotypes both in individuals with prior DENV infection as well as in dengue-naïves. Particularly for the latter group of individuals, this cannot be confirmed for Qdenga. The wide CI, which extend into the negative, do not permit definitive interpretation. In addition to a protective function, the vaccine might also harbour the risk that after the first DENV contact by means of vaccination, a second contact with DENV (e.g., infection during a later journey) might unleash an illness with a severe clinical course.

With regard to safety, no signals of a safety risk have been identified in the studies to date. Much of the available data are derived from an extensive study of 4-16-year-old children and adolescents in endemic countries, of which approx. 2/3 demonstrated antibodies against DENV in their serum at the beginning of the study. The transferability of these data to adults in non-endemic countries is only possible using immunogenicity parameters, and here the absence of antibody thresholds for protection limits the transferability.

According to Takeda, the first post-marketing studies in endemic countries are planned. The STIKO will discuss their results, along with results from studies on booster vaccination, with respect to possible changes in vaccine recommendation once they have been published.

The synthesis of the evidence assessed by the STIKO-DTG working group and STIKO can be found in the Evidence-to-Decision tables in the Appendix.

10.1 Vaccine recommendation for travellers with previous laboratory-confirmed DENV infection

The STIKO recommends vaccination against dengue with the Qdenga vaccine as a travel vaccine (R) for individuals who have a history of prior laboratory-confirmed DENV infection and who are travelling to a dengue-endemic region where they have an increased risk of exposure (e.g., longer stays, current outbreak event). A full vaccine series should be completed prior to departure (i.e., 2 vaccine doses at a minimum interval of 3 months).

A laboratory-confirmed DENV infection in the medical history means that proof of laboratory diagnostics carried out in the past does not necessarily have to be provided. However, a report of dengue-typical symptoms during or after an earlier stay in a dengue-endemic country is not sufficient without laboratory confirmation at the time of the acute symptoms due to the wide differential diagnosis. Laboratory testing for a prior DENV infection is not recommended, as explained in Section 8.1 Notes on determination of serostatus .

The vaccine is licensed from the age of ≥ 4 years, although there are currently no data on efficacy, immunogenicity, and safety for the age group > 60 years. The STIKO assumes that the risk-benefit ratio will also be positive in the age group > 60 years for individuals with a prior DENV infection.

10.2 Vaccine recommendation for travellers with no previous DENV infection

The data for individuals who have not had a prior DENV infection ("dengue-naïve") are very limited at present. The STIKO therefore does not currently provide a general vaccine recommendation for the dengue-naïve. If, after a detailed medical consultation, an individualised decision is made to vaccinate a dengue-naïve individual in line with the licensure, the individual to be vaccinated should be informed that the risk of infection intensification in the event of a future infection (e.g., during the next journey) cannot be ruled out. The currently available data for dengue-naïve individuals could not demonstrate any protection against DENV-3 and -4-associated disease following vaccination. If the decision is nevertheless made to vaccinate, a full vaccine series (i.e., 2 vaccine doses at a minimum interval of 3 months) must be completed prior to departure.

Serological testing to determine the serostatus is not recommended (see 8.1 Notes on determination of the serostatus).

10.3 Vaccine recommendation for occupational indication for vaccination against dengue

Individuals who have a history of a prior **laboratory-confirmed dengue virus infection** and who carry out targeted activities with dengue viruses outside endemic regions (e.g., in research institutes or diagnostic laboratories), should receive a complete vaccine series (i.e., 2 vaccine doses at a minimum interval of 3 months) as an occupationally indicated vaccination (B).

10.4 Notes on special groups (individuals with immune deficiency, pregnant and breast-feeding women)

The vaccine is **contraindicated** in individuals with congenital or acquired immune deficiency, as well as in pregnant or breast-feeding women.

10.5 Notes on booster vaccinations

At the present time, no statement can be made about the necessity or timing of a **booster vaccination**. Relevant studies have not yet been completed. As soon as results are available, the STIKO-DTG WG will assess them and determine whether this will lead to a change to, or extension of, the vaccine recommendation.

Authors

Dengue Working Group on Travel Vaccination of the Standing Committee on Vaccination (STIKO):
a) Dr. Kerstin Kling | a) Dr. Wiebe Külper-Schiek | b) Prof. Jonas Schmidt-Chanasit | a) Dr. Jan Stratil | c) Prof. Dr. Christian Bogdan | d) Prof. Michael Ramharter | e) Dr. Burkhard Rieke | a) PD Dr. Ole Wichmann | c) Prof. Dr. Gerd Burchard

a) Robert Koch Institute, Department 3 Infectious Disease Epidemiology, Group 33 Preventative Vaccination
b) Bernhard-Nocht Institute of Tropical Medicine, Department of Arbovirology and Entomology; Member of the DTG
c) Member of the STIKO
d) Bernhard-Nocht Institute of Tropical Medicine & 1st Medical Clinic, University Hospital Hamburg-Eppendorf; Member of the DTG
e) Tropical and Travel Medicine Practice, Düsseldorf; Member of the DTG

Corresponding author: klingk@rki.de

Conflict of interest
Jonas Schmidt-Chanasit: There may be potential conflicts of intertest with Takeda, GSK, Sanofi, Roche, DiaSorin, Euroimmun, Sonic Healthcare, and BASF which arise or have arisen due to an employment relationship, partnership, consultancy work or grants for research projects, lectures, or other activities.
All other authors declare that there is no conflict of interest.

10. References

1.   WHO. Dengue and severe dengue 2023 [updated 17.03.2023; cited 2023 20.05.2023]. Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.

2.   Guzman MG, Harris E. Dengue. Lancet. 2015;385(9966):453-65.

3.   Robert Koch Institute. Auswirkungen des Klimawandels auf Infektionskrankheiten und antimikrobielle Resistenzen – Teil 1 des Sachstandsberichts Klimawandel und Gesundheit 2023 2023 [cited 2023 05.09.2023]. Available from: https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsJ/JHealthMonit_2023_S3_Sachstandsbericht_Klimawandel_Gesundheit_Teil1.html.

4.   Wilder-Smith A, Ooi EE, Horstick O, Wills B. Dengue. Lancet. 2019;393(10169):350-63.

5.   Saez-Llorens X, Biswal S, Borja-Tabora C, Fernando L, Liu M, Wallace D, et al. Effect of the Tetravalent Dengue Vaccine TAK-003 on Sequential Episodes of Symptomatic Dengue. Am J Trop Med Hyg. 2023;108(4):722-6.

6.   Forshey BM, Stoddard ST, Morrison AC. Dengue Viruses and Lifelong Immunity: Reevaluating the Conventional Wisdom. J Infect Dis. 2016;214(7):979-81.

7.   Waggoner JJ, Balmaseda A, Gresh L, Sahoo MK, Montoya M, Wang C, et al. Homotypic Dengue Virus Reinfections in Nicaraguan Children. J Infect Dis. 2016;214(7):986-93.

8.   Anderson KB, Gibbons RV, Cummings DA, Nisalak A, Green S, Libraty DH, et al. A shorter time interval between first and second dengue infections is associated with protection from clinical illness in a school-based cohort in Thailand. J Infect Dis. 2014;209(3):360-8.

9.   Olkowski S, Forshey BM, Morrison AC, Rocha C, Vilcarromero S, Halsey ES, et al. Reduced risk of disease during postsecondary dengue virus infections. J Infect Dis. 2013;208(6):1026-33.

10.   Endy TP, Anderson KB, Nisalak A, Yoon IK, Green S, Rothman AL, et al. Determinants of inapparent and symptomatic dengue infection in a prospective study of primary school children in Kamphaeng Phet, Thailand. PLoS Negl Trop Dis. 2011;5(3):e975.

11.   Montoya M, Gresh L, Mercado JC, Williams KL, Vargas MJ, Gutierrez G, et al. Symptomatic versus inapparent outcome in repeat dengue virus infections is influenced by the time interval between infections and study year. PLoS Negl Trop Dis. 2013;7(8):e2357.

12.   Sabin AB. Research on dengue during World War II. Am J Trop Med Hyg. 1952;1(1):30-50.

13.   Snow GE, Haaland B, Ooi EE, Gubler DJ. Review article: Research on dengue during World War II revisited. Am J Trop Med Hyg. 2014;91(6):1203-17.

14.   SAGE. Background paper on dengue vaccines 2016 [Available from: https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Apr2016/10_session_dengue/Apr2016_session10_dengue_vaccines.pdf.

15.   Flasche S, Jit M, Rodriguez-Barraquer I, Coudeville L, Recker M, Koelle K, et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. PLoS Med. 2016;13(11):e1002181.

16.   Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. N Engl J Med. 2018;379(4):327-40.

17.   European Medicines Agency (EMA). Qdenga 2022 [updated 16.12.2022. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/qdenga.

18.   Postler TS, Beer M, Blitvich BJ, Bukh J, de Lamballerie X, Drexler JF, et al. Renaming of the genus Flavivirus to Orthoflavivirus and extension of binomial species names within the family Flaviviridae. Arch Virol. 2023;168(9):224.

19.   Henchal EA, Putnak JR. The dengue viruses. Clin Microbiol Rev. 1990;3(4):376-96.

20.   Lisova O, Belkadi L, Bedouelle H. Direct and indirect interactions in the recognition between a cross-neutralizing antibody and the four serotypes of dengue virus. J Mol Recognit. 2014;27(4):205-14.

21.   Lee C, Jang EJ, Kwon D, Choi H, Park JW, Bae GR. Laboratory-acquired dengue virus infection by needlestick injury: a case report, South Korea, 2014. Ann Occup Environ Med. 2016;28:16.

22.   Britton S, van den Hurk AF, Simmons RJ, Pyke AT, Northill JA, McCarthy J, McCormack J. Laboratory-acquired dengue virus infection--a case report. PLoS Negl Trop Dis. 2011;5(11):e1324.

23.   Sharp TM, Fisher TG, Long K, Coulson G, Medina FA, Herzig C, et al. Laboratory-Acquired Dengue Virus Infection, United States, 2018. Emerg Infect Dis. 2020;26(7):1534-7.

24.   Chen LH, Wilson ME. Update on non-vector transmission of dengue: relevant studies with Zika and other flaviviruses. Trop Dis Travel Med Vaccines. 2016;2:15.

25.   Wilder-Smith A. Can dengue virus be sexually transmitted? J Travel Med. 2019;26(3).

26.   Rakotonirina A, Pol M, Raharimalala FN, Ballan V, Kainiu M, Boyer S, et al. MALDI-TOF MS: An effective tool for a global surveillance of dengue vector species. PLoS One. 2022;17(10):e0276488.

27.   Calvez E, Pocquet N, Malau A, Kilama S, Taugamoa A, Labrousse D, et al. Assessing entomological risk factors for arboviral disease transmission in the French Territory of the Wallis and Futuna Islands. PLoS Negl Trop Dis. 2020;14(5):e0008250.

28.   Bhatia R, Dash AP, Sunyoto T. Changing epidemiology of dengue in South-East Asia. WHO South East Asia J Public Health. 2013;2(1):23-7.

29.   ECDC. Increasing risk of mosquito-borne diseases in EU/EEA following spread of Aedes species 2023 [updated 22.06.2023. Available from: https://www.ecdc.europa.eu/en/news-events/increasing-risk-mosquito-borne-diseases-eueea-following-spread-aedes-species.

30.   Braack L, Gouveia de Almeida AP, Cornel AJ, Swanepoel R, de Jager C. Mosquito-borne arboviruses of African origin: review of key viruses and vectors. Parasit Vectors. 2018;11(1):29.

31.   Chan M, Johansson MA. The incubation periods of Dengue viruses. PLoS One. 2012;7(11):e50972.

32.   Nguyet MN, Duong TH, Trung VT, Nguyen TH, Tran CN, Long VT, et al. Host and viral features of human dengue cases shape the population of infected and infectious Aedes aegypti mosquitoes. Proc Natl Acad Sci U S A. 2013;110(22):9072-7.

33.   Mulik V, Dad N, Buhmaid S. Dengue in pregnancy: Review article. Eur J Obstet Gynecol Reprod Biol. 2021;261:205-10.

34.   Basurko C, Matheus S, Hilderal H, Everhard S, Restrepo M, Cuadro-Alvarez E, et al. Estimating the Risk of Vertical Transmission of Dengue: A Prospective Study. Am J Trop Med Hyg. 2018;98(6):1826-32.

35.   Alexander LW, Ben-Shachar R, Katzelnick LC, Kuan G, Balmaseda A, Harris E, Boots M. Boosting can explain patterns of fluctuations of ratios of inapparent to symptomatic dengue virus infections. Proc Natl Acad Sci U S A. 2021;118(14).

36.   Halstead S, Wilder-Smith A. Severe dengue in travellers: pathogenesis, risk and clinical management. J Travel Med. 2019;26(7).

37.   WHO. Dengue guidelines for diagnosis, treatment, prevention and control - new edition 2009 [20.05.2023]. WHO Library Cataloguing-in-Publication Data]. Available from:

https://apps.who.int/iris/bitstream/handle/10665/44188/9789241547871_eng.pdf?sequence=1&isAllowed=y.

38.   Martina BE. Dengue pathogenesis: a disease driven by the host response. Sci Prog. 2014;97(Pt 3):197-214.

39.   CDC. Clinical Considerations for Dengue Virus Infection 2023 [updated 30.08.2022. Available from: https://emergency.cdc.gov/newsletters/coca/083022.htm.

40.   WHO. Dengue and severe dengue 2019 [updated 24.10.201928.08.2023]. Available from: https://www.who.int/news-room/questions-and-answers/item/dengue-and-severe-dengue.

41.   Osman S, Preet R. Dengue, chikungunya and Zika in GeoSentinel surveillance of international travellers: a literature review from 1995 to 2020. J Travel Med. 2020;27(8).

42.   Anders KL, Nguyet NM, Chau NV, Hung NT, Thuy TT, Lien le B, et al. Epidemiological factors associated with dengue shock syndrome and mortality in hospitalized dengue patients in Ho Chi Minh City, Vietnam. Am J Trop Med Hyg. 2011;84(1):127-34.

43.   Fernando S, Wijewickrama A, Gomes L, Punchihewa CT, Madusanka SD, Dissanayake H, et al. Patterns and causes of liver involvement in acute dengue infection. BMC Infect Dis. 2016;16:319.

44.   Wichmann D, Kularatne S, Ehrhardt S, Wijesinghe S, Brattig NW, Abel W, Burchard GD. Cardiac involvement in dengue virus infections during the 2004/2005 dengue fever season in Sri Lanka. Southeast Asian J Trop Med Public Health. 2009;40(4):727-30.

45.   Farrukh AM, Ganipineni VDP, Jindal U, Chaudhary A, Puar RK, Ghazarian K, et al. Unveiling the Dual Threat: Myocarditis in the Spectrum of Dengue Fever. Curr Probl Cardiol. 2023:102029.

46.   Yip VC, Sanjay S, Koh YT. Ophthalmic complications of dengue Fever: a systematic review. Ophthalmol Ther. 2012;1(1):2.

47.   Xie Cen A, Ng AWW, Rojas-Carabali W, Cifuentes-Gonzalez C, de-la-Torre A, Mahendradas P, Agrawal R. Dengue Uveitis - A Major Review. Ocul Immunol Inflamm. 2023:1-14.

48.   Trivedi S, Chakravarty A. Neurological Complications of Dengue Fever. Curr Neurol Neurosci Rep. 2022;22(8):515-29.

49.   Carod-Artal FJ, Wichmann O, Farrar J, Gascon J. Neurological complications of dengue virus infection. Lancet Neurol. 2013;12(9):906-19.

50.   Yuan K, Chen Y, Zhong M, Lin Y, Liu L. Risk and predictive factors for severe dengue infection: A systematic review and meta-analysis. PLoS One. 2022;17(4):e0267186.

51.   Mizumoto K, Ejima K, Yamamoto T, Nishiura H. On the risk of severe dengue during secondary infection: a systematic review coupled with mathematical modeling. J Vector Borne Dis. 2014;51(3):153-64.

52.   Halstead SB, Mahalingam S, Marovich MA, Ubol S, Mosser DM. Intrinsic antibody-dependent enhancement of microbial infection in macrophages: disease regulation by immune complexes. Lancet Infect Dis. 2010;10(10):712-22.

53.   Halstead SB. Neutralization and antibody-dependent enhancement of dengue viruses. Adv Virus Res. 2003;60:421-67.

54.   Reich NG, Shrestha S, King AA, Rohani P, Lessler J, Kalayanarooj S, et al. Interactions between serotypes of dengue highlight epidemiological impact of cross-immunity. J R Soc Interface. 2013;10(86):20130414.

55.   Tam DT, Ngoc TV, Tien NT, Kieu NT, Thuy TT, Thanh LT, et al. Effects of short-course oral corticosteroid therapy in early dengue infection in Vietnamese patients: a randomized, placebo-controlled trial. Clin Infect Dis. 2012;55(9):1216-24.

56.   Lye DC, Archuleta S, Syed-Omar SF, Low JG, Oh HM, Wei Y, et al. Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue

and thrombocytopenia: a multicentre, open-label, randomised, superiority trial. Lancet. 2017;389(10079):1611-8.

57.   CDC. Dengue Map 2023 [05.09.2023]. Available from: https://www.healthmap.org/dengue/en/.

58.   Cochet A, Calba C, Jourdain F, Grard G, Durand GA, Guinard A, et al. Autochthonous dengue in mainland France, 2022: geographical extension and incidence increase. Euro Surveill. 2022;27(44).

59.   The European Climate Adaptation Platform Climate-ADAPT. Dengue 2023 [updated April 202321.05.2023]. Available from: https://climate-adapt.eea.europa.eu/en/observatory/evidence/health-effects/vector-borne-diseases/dengue-factsheet.

60.   CDC. Dengue in the US States and Territories 2022 [21.05.2023]. Available from: https://www.cdc.gov/dengue/areaswithrisk/in-the-us.html.

61.   Sanchez-Vegas C, Hamer DH, Chen LH, Wilson ME, Benoit C, Hunsperger E, et al. Prevalence of dengue virus infection in US travelers who have lived in or traveled to dengue-endemic countries. J Travel Med. 2013;20(6):352-60.

62.   Lozano-Fuentes S, Hayden MH, Welsh-Rodriguez C, Ochoa-Martinez C, Tapia-Santos B, Kobylinski KC, et al. The dengue virus mosquito vector Aedes aegypti at high elevation in Mexico. Am J Trop Med Hyg. 2012;87(5):902-9.

63.   Mercier A, Obadia T, Carraretto D, Velo E, Gabiane G, Bino S, et al. Impact of temperature on dengue and chikungunya transmission by the mosquito Aedes albopictus. Sci Rep. 2022;12(1):6973.

64.   Temprasertrudee S, Thanachartwet V, Desakorn V, Keatkla J, Chantratita W, Kiertiburanakul S. A Multicenter Study of Clinical Presentations and Predictive Factors for Severe Manifestation of Dengue in Adults. Jpn J Infect Dis. 2018;71(3):239-43.

65.   Thanachartwet V, Oer-Areemitr N, Chamnanchanunt S, Sahassananda D, Jittmittraphap A, Suwannakudt P, et al. Identification of clinical factors associated with severe dengue among Thai adults: a prospective study. BMC Infect Dis. 2015;15:420.

66.   Limkittikul K, Brett J, L'Azou M. Epidemiological trends of dengue disease in Thailand (2000-2011): a systematic literature review. PLoS Negl Trop Dis. 2014;8(11):e3241.

67.   Tantawichien T. Dengue Fever and Dengue Hemorrhagic Fever in Adults. Southeast Asian J Trop Med Public Health. 2015;46 Suppl 1:79-98.

68.   Tantawichien T. Dengue fever and dengue haemorrhagic fever in adolescents and adults. Paediatr Int Child Health. 2012;32 Suppl 1(s1):22-7.

69.   Guzman MG, Kouri G, Bravo J, Valdes L, Vazquez S, Halstead SB. Effect of age on outcome of secondary dengue 2 infections. Int J Infect Dis. 2002;6(2):118-24.

70.   Sangkaew S, Ming D, Boonyasiri A, Honeyford K, Kalayanarooj S, Yacoub S, et al. Risk predictors of progression to severe disease during the febrile phase of dengue: a systematic review and meta-analysis. Lancet Infect Dis. 2021;21(7):1014-26.

71.   Tsheten T, Clements ACA, Gray DJ, Adhikary RK, Furuya-Kanamori L, Wangdi K. Clinical predictors of severe dengue: a systematic review and meta-analysis. Infect Dis Poverty. 2021;10(1):123.

72.   Chiu YY, Lin CY, Yu LS, Wang WH, Huang CH, Chen YH. The association of obesity and dengue severity in hospitalized adult patients. J Microbiol Immunol Infect. 2023;56(2):267-73.

73.   Maneerattanasak S, Suwanbamrung C. Impact of Nutritional Status on the Severity of Dengue Infection Among Pediatric Patients in Southern Thailand. Pediatr Infect Dis J. 2020;39(12):e410-e6.

74.   Trang NTH, Long NP, Hue TTM, Hung LP, Trung TD, Dinh DN, et al. Association between nutritional status and dengue infection: a systematic review and meta-analysis. BMC Infect Dis. 2016;16:172.

75.	Kariyawasam S, Senanayake H. Dengue infections during pregnancy: case series from a tertiary care hospital in Sri Lanka. J Infect Dev Ctries. 2010;4(11):767-75.

76.	Brar R, Sikka P, Suri V, Singh MP, Suri V, Mohindra R, Biswal M. Maternal and fetal outcomes of dengue fever in pregnancy: a large prospective and descriptive observational study. Arch Gynecol Obstet. 2021;304(1):91-100.

77.	Pouliot SH, Xiong X, Harville E, Paz-Soldan V, Tomashek KM, Breart G, Buekens P. Maternal dengue and pregnancy outcomes: a systematic review. Obstet Gynecol Surv. 2010;65(2):107-18.

78.	Paixao ES, Teixeira MG, Costa M, Rodrigues LC. Dengue during pregnancy and adverse fetal outcomes: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16(7):857-65.

79.	Kliks SC, Nimmanitya S, Nisalak A, Burke DS. Evidence that maternal dengue antibodies are important in the development of dengue hemorrhagic fever in infants. Am J Trop Med Hyg. 1988;38(2):411-9.

80.	WHO. Dengue vaccine: WHO position paper – September 2018. Weekly Epidemiological Record. 2018;93:457-76.

81.	Brady OJ, Gething PW, Bhatt S, Messina JP, Brownstein JS, Hoen AG, et al. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoS Negl Trop Dis. 2012;6(8):e1760.

82.	Cattarino L, Rodriguez-Barraquer I, Imai N, Cummings DAT, Ferguson NM. Mapping global variation in dengue transmission intensity. Sci Transl Med. 2020;12(528).

83.	ECDC. Dengue worldwide overview 2023 [updated 19.06.2023. Available from: https://www.ecdc.europa.eu/en/dengue-monthly.

84.	Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504-7.

85.	CDC. About Dengue: What You Need to Know 2023 [updated April 13, 2023. Available from: https://www.cdc.gov/dengue/about/index.html.

86.	ECDC. Communicable Disease Threats Report - Week 44, 30 - 5 November 2022 2022 [Available from: https://www.ecdc.europa.eu/sites/default/files/documents/2022-WCP-0044.pdf.

87.	L'Azou M, Moureau A, Sarti E, Nealon J, Zambrano B, Wartel TA, et al. Symptomatic Dengue in Children in 10 Asian and Latin American Countries. N Engl J Med. 2016;374(12):1155-66.

88.	Messina JP, Brady OJ, Golding N, Kraemer MUG, Wint GRW, Ray SE, et al. The current and future global distribution and population at risk of dengue. Nat Microbiol. 2019;4(9):1508-15.

89.	Olivero RM, Hamer DH, MacLeod WB, Benoit CM, Sanchez-Vegas C, Jentes ES, et al. Dengue Virus Seroconversion in Travelers to Dengue-Endemic Areas. Am J Trop Med Hyg. 2016;95(5):1130-6.

90.	Leder K, Mutsch M, Schlagenhauf P, Luxemburger C, Torresi J. Seroepidemiology of dengue in travellers: a paired sera analysis. Travel Med Infect Dis. 2013;11(4):210-3.

91.	Overbosch FW, Schinkel J, Stolte IG, Prins M, Sonder GJB. Dengue virus infection among long-term travelers from the Netherlands: A prospective study, 2008-2011. PLoS One. 2018;13(2):e0192193.

92.	Robert Koch Institute. Infektionsepidemiologisches Jahrbuch meldepflichtiger Krankheiten 2022 [updated September 202121.05.2023]. Available from: https://www.rki.de/DE/Content/Infekt/Jahrbuch/jahrbuch_node.html.

93.	Huits R, Schwartz E. Fatal outcomes of imported dengue fever in adult travelers from non-endemic areas are associated with primary infections. J Travel Med. 2021;28(5).

94.	Ujiie M. Deaths due to dengue in Japanese travellers. J Travel Med. 2021;28(5).

95.   Schmidt-Chanasit J, Tenner-Racz K, Poppert D, Emmerich P, Frank C, Dinges C, et al. Fatal dengue hemorrhagic fever imported into Germany. Infection. 2012;40(4):441-3.
96.   Hou J, Ye W, Chen J. Current Development and Challenges of Tetravalent Live-Attenuated Dengue Vaccines. Front Immunol. 2022;13:840104.
97.   Sirivichayakul C, Barranco-Santana EA, Esquilin-Rivera IDS, Oh HML, Raanan M, Sariol CA, et al. Safety and Immunogenicity of a Tetravalent Dengue Vaccine Candidate in Healthy Children and Adults in Dengue-Endemic Regions: A Randomized, Placebo-Controlled Phase 2 Study. Journal of Infectious Diseases. 2016;213(10):1562-72.
98.   Dietrich EA, Ong YT, Stovall JL, Dean H, Huang CY. Limited Transmission Potential of Takeda's Tetravalent Dengue Vaccine Candidate by Aedes albopictus. Am J Trop Med Hyg. 2017;97(5):1423-7.
99.   Foucambert P, Esbrand FD, Zafar S, Panthangi V, Cyril Kurupp AR, Raju A, et al. Efficacy of Dengue Vaccines in the Prevention of Severe Dengue in Children: A Systematic Review. Cureus. 2022;14(9):e28916.
100.   Kautsar A, Postma MJ, Suwantika AA. Systematic Review and Meta-Analysis of Randomized Trials: Efficacy, Immunogenicity, and Safety of Denvax Vaccine. ISPOR Europe 2022; Vienna2022.
101.   Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
102.   Tricou V, Essink B, Ervin JE, Turner M, Escudero I, Rauscher M, et al. Immunogenicity and safety of concomitant and sequential administration of yellow fever YF-17D vaccine and tetravalent dengue vaccine candidate TAK-003: A phase 3 randomized, controlled study. PLoS Negl Trop Dis. 2023;17(3):e0011124.
103.   European Medicines Agency (EMA). Assessment report - Qdenga 2022 [updated 13 October 202211.08.2023]. Procedure No. EMEA/H/C/005155/0000:[Available from: https://www.ema.europa.eu/en/documents/assessment-report/qdenga-epar-public-assessment-report_en.pdf.
104.   Rivera L, Biswal S, Sáez-Llorens X, Reynales H, López-Medina E, Borja-Tabora C, et al. Three-year Efficacy and Safety of Takeda's Dengue Vaccine Candidate (TAK-003). Clin Infect Dis. 2022;75(1):107-17.
105.   Tricou V, Sáez-Llorens X, Yu D, Rivera L, Jimeno J, Villarreal AC, et al. Safety and immunogenicity of a tetravalent dengue vaccine in children aged 2-17 years: a randomised, placebo-controlled, phase 2 trial. Lancet. 2020;395(10234):1434-43.
106.   Sirivichayakul C, Barranco-Santana EA, Rivera IE, Kilbury J, Raanan M, Borkowski A, et al. Long-term Safety and Immunogenicity of a Tetravalent Dengue Vaccine Candidate in Children and Adults: A Randomized, Placebo-Controlled, Phase 2 Study. Journal of Infectious Diseases. 2022;225(9):1513-20.
107.   Biswal S, Reynales H, Saez-Llorens X, Lopez P, Borja-Tabora C, Kosalaraksa P, et al. Efficacy of a Tetravalent Dengue Vaccine in Healthy Children and Adolescents. N Engl J Med. 2019;381(21):2009-19.
108.   Biswal S, Borja-Tabora C, Martinez Vargas L, Velásquez H, Theresa Alera M, Sierra V, et al. Efficacy of a tetravalent dengue vaccine in healthy children aged 4-16 years: a randomised, placebo-controlled, phase 3 trial. Lancet. 2020;395(10234):1423-33.
109.   López-Medina E, Biswal S, Saez-Llorens X, Borja-Tabora C, Bravo L, Sirivichayakul C, et al. Efficacy of a Dengue Vaccine Candidate (TAK-003) in Healthy Children and Adolescents 2 Years after Vaccination. Journal of Infectious Diseases. 2022;225(9):1521-32.
110.   Sáez-Llorens X, Tricou V, Yu D, Rivera L, Tuboi S, Garbes P, et al. Safety and immunogenicity of one versus two doses of Takeda's tetravalent dengue vaccine in children in Asia and Latin America: interim results from a phase 2, randomised, placebo-controlled study. The Lancet Infectious Diseases. 2017;17(6):615-25.

111.   Sáez-Llorens X, Tricou V, Yu D, Rivera L, Jimeno J, Villarreal AC, et al. Immunogenicity and safety of one versus two doses of tetravalent dengue vaccine in healthy children aged 2-17 years in Asia and Latin America: 18-month interim data from a phase 2, randomised, placebo-controlled study. Lancet Infect Dis. 2018;18(2):162-70.

112.   Tricou V, Eyre S, Ramjee M, Collini P, Mojares Z, Loeliger E, et al. A randomized phase 3 trial of the immunogenicity and safety of coadministration of a live-attenuated tetravalent dengue vaccine (TAK-003) and an inactivated hepatitis a (HAV) virus vaccine in a dengue non-endemic country. Vaccine. 2023.

113.   Biswal S, Mendez Galvan JF, Macias Parra M, Galan-Herrera JF, Carrascal Rodriguez MB, Rodriguez Bueno EP, et al. Immunogenicity and safety of a tetravalent dengue vaccine in dengue-naïve adolescents in Mexico City. Rev Panam Salud Publica. 2021;45:e67.

114.   LeFevre I, Bravo L, Folschweiller N, Medina EL, Moreira ED, Jr., Nordio F, et al. Bridging the immunogenicity of a tetravalent dengue vaccine (TAK-003) from children and adolescents to adults. NPJ Vaccines. 2023;8(1):75.

115.   Deeks JJ, Higgins JPT, Altman DGe. Chapter 10: Analysing data and undertaking meta-analyses. In: In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). editor. Cochrane Handbook for Systematic Reviews of Interventions version 63: Cochrane; 2022.

116.   Patel SS, Rauscher M, Kudela M, Pang H. Clinical Safety Experience of TAK-003 for Dengue Fever: a new Tetravalent Live Attenuated Vaccine Candidate. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2022.

117.   Guy B, Ooi EE, Ramos-Castaneda J, Thomas SJ. When Can One Vaccinate with a Live Vaccine after Wild-Type Dengue Infection? Vaccines (Basel). 2020;8(2).

118.   CDC. Vaccine Schedule & Dosing 2021 [updated December 16, 2021. Available from: https://www.cdc.gov/dengue/vaccine/hcp/schedule-dosing.html#:~:text=Vaccine%20Administration%20After%20Dengue%20Virus.

119.   Kasbergen LMR, Nieuwenhuijse DF, de Bruin E, Sikkema RS, Koopmans MPG. The increasing complexity of arbovirus serology: An in-depth systematic review on cross-reactivity. PLoS Negl Trop Dis. 2023;17(9):e0011651.

120.   Superior Health Counsil B. Vaccination against dengue 2023 [28.08.2023]. Available from: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/2023042 7_shc_9739_dengue_vaccination_vweb.pdf.

121.   Angelin M, Sjolin J, Kahn F, Ljunghill Hedberg A, Rosdahl A, Skorup P, et al. Qdenga(R) - A promising dengue fever vaccine; can it be recommended to non-immune travelers? Travel Med Infect Dis. 2023;54:102598.