

# **VACCINATION AGAINST DENGUE**

Dengue Vaccine

**APRIL 2023 SHC № 9739** 



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Federal Public Service Health, Food Chain Safety and Environment

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# ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9739

# **Vaccination against Dengue**

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides recommendations of vaccination against dengue for long-term or frequent travellers to endemic regions.

This version was validated by the Board on 05 April 2023<sup>1</sup>

#### I INTRODUCTION

Dengue is a mosquito-borne viral disease that has rapidly spread in recent years. Dengue virus is transmitted by female mosquitoes mainly of the species *Aedes aegypti* and, to a lesser extent, *Ae. albopictus*. These mosquitoes are also vectors of chikungunya, yellow fever and Zika viruses. Dengue is widespread throughout the tropics, with local variations in risk influenced by climate parameters as well as social and environmental factors (WHO, 2022).

Dengue is caused by a virus of the *Flaviviridae* family and there are four distinct, but closely related, serotypes of the virus that cause dengue (DENV-1, DENV-2, DENV-3 and DENV-4). Recovery from infection is believed to provide lifelong immunity against that serotype. However, cross-immunity to the other serotypes after recovery is only partial, and temporary. Subsequent infections (secondary infection) by other serotypes increase the risk of developing severe dengue (WHO, 2022).

The virus causes a wide spectrum of disease. This can range from subclinical disease (people may not even know they are infected) to severe flu-like symptoms in those infected. Although less common, some people develop severe dengue with severe bleeding, organ impairment and/or plasma leakage. Severe dengue has a higher risk of death when not managed appropriately. Severe dengue was first recognized in the 1950s during dengue epidemics in the Philippines and Thailand. Today, severe dengue occurs mainly in endemic countries, but is rare in travellers (WHO, 2022).

Dengue has distinct epidemiological patterns, associated with the four serotypes of the virus. These can co-circulate within a region, and indeed many countries are hyper-endemic for multiple serotypes. Dengue has an important impact on both human health and the global and national economies. DENV can be imported from one place to another by infected travellers; when susceptible vectors are present in these new areas, there might be a potential for local transmission.

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<sup>&</sup>lt;sup>1</sup> The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

## **Purposes of vaccination**

In endemic regions, a safe and efficacious vaccine is of major public health interest because:

- Dengue cases have increased in the past decades. Today, dengue is the most common and rapidly spreading mosquito-borne viral disease in the world.
- WHO has listed dengue as one of the ten threats to global health in 2019 and dengue is listed as High Priority Vaccine in the WHO vaccines prequalification priority list 2018-2020.
- Aggressive mosquito control efforts in endemic areas have been largely ineffective in preventing dengue outbreaks or in preventing further geographic spread of the disease.
- There is no specific treatment for dengue approved anywhere in the world.

For travellers from non-endemic countries, such as Belgium, vaccination against dengue has different goals:

- Protecting the individual traveller against :
  - Death.
  - Severe dengue infection, including dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS) and subsequently avoid hospitalisation abroad.
  - Symptomatic dengue infection.
- Avoid introduction of dengue and local transmission.

## **Dengue vaccines**

The only currently available dengue vaccine (Dengvaxia®) is licensed by the European Medicines Agency only for people aged 6–45 years with test-confirmed previous dengue infection. However, Dengvaxia® is not commercialised for use in Belgium.

On December 8, 2022 the European Commission (EC) granted marketing authorization for dengue vaccine Qdenga® (Dengue Tetravalent Vaccine [Live, Attenuated]) (TAK-003) for the prevention of dengue disease in individuals from four years of age in the European Union (EU). Qdenga® is on the Belgian market since March 2023.



## II CONCLUSIONS AND RECOMMENDATIONS

Dengue is common in Belgian travellers, but severe dengue, hospitalisation or death because of dengue is rare. All dengue cases are import cases. There has been no local transmission so far. Most dengue cases occur in long-term travellers (> 4 weeks) coming back from South-East Asia or Latin America. In Asia, DENV-3 is common.

Based on the low evidence and data currently available on Qdenga® several points need to be highlighted:

- There are **less data available on previously uninfected** (baseline seronegative) than on baseline seropositive individuals. Therefore, some questions about efficacy and safety remain unanswered for travellers, who have often not had dengue before (EPAR and ACIP meeting February 2023).
- The overall vaccine efficacy is **better in baseline seropositive** than in seronegative individuals and protects **better against hospitalisations** than against infection in general (EPAR).
- The vaccine efficacy (VE) varies for different serotypes, offering the best protection against DENV-2, followed by DENV-1 with immunity against DENV-1 declining more rapidly (EPAR).
- In baseline **seropositive individuals** the VE is also good for **DENV-3 infection** and **hospitalisation.**
- In baseline seronegative individuals there is no VE for DENV-3 infection or hospitalisation. More hospitalisations and more severe dengue were observed but this was not considered statistically significant due very small numbers. However, this signal should be monitored in the future (Rivera et al., 2022).
- There are **insufficient data for DENV-4** and therefore no conclusion can be drawn on efficacy and safety (Rivera et al., 2022).
- Safety data for Qdenga® are **limited to 57 months** after the first dose. There is no obvious pattern of increasing risk for hospitalisation in seronegative individuals over the years. But the overall numbers of hospitalisations are low, so caution is warranted as more severe disease has been observed in baseline seronegative children vaccinated with another dengue vaccine (Dengvaxia®) after three years. One can question if the follow-up is long enough to conclude that this is not a risk.
- There are no data on efficacy and safety when the second dose is not given.
- There are **no data in individuals older than 60 years**.

Since it is known that a subsequent natural infection with another serotype (secondary dengue) can cause antibody-enhanced disease, which can lead to severe dengue or death, travellers who have been previously exposed and who travel again to an endemic region, are the target group where the benefit of vaccination is the highest.



Based on the considerations above, the Superior Health Council (SHC) recommends vaccination against Dengue with Qdenga® for people residing for a period of more than 4 weeks, long-term travellers (> 4 weeks²) or frequent travellers from four years of age meeting all 3 of the following criteria:

- 1. Having had dengue before (based on history or laboratory confirmed<sup>3</sup>);
- 2. Travelling to a dengue endemic region; cfr map https://www.healthmap.org/dengue/en/
- 3. Receiving both priming doses before departure.

Considering the many uncertainties about favourable and unfavourable effects of the vaccine, it is important to discuss the expected benefits and secondary effects of the vaccine with the travellers.

Qdenga® should be administered as a 0.5 mL dose in a **two-dose (0 and 3 months) priming schedule.** The need for a booster dose has not been established yet, but is studied.

Qdenga® is currently not recommended for long-term or frequent travellers to endemic regions:

- Who did not have a previous dengue infection;
  - OR
- Who had dengue before and meet one (or more) of the 3 criteria below:
  - Cannot get two priming doses (day 0 month 3) before departure;
  - Leave for a short trip;
  - Who have a medical contra-indication for live attenuated vaccines (SHC 9158).

This recommendation will be revised when more long-term data are available, especially on safety data.

#### Keywords

Keywords	Sleutelwoorden	Mots clés	Schlüsselwörter
Dengue	Dengue	Dengue	Dengue-Fieber
Vaccines	Vaccin	Vaccins	Impfung
Travellers	Reizigers	Voyageurs	Reisenden
Prevention	Preventie	Prévention	Prävention

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<sup>&</sup>lt;sup>2</sup> 4 weeks is an arbitrary cut-off used also used for other vaccinations in travel medicine (to be coherent)

<sup>&</sup>lt;sup>3</sup> It is upon the clinician to evaluate whether the traveller has had dengue before, mainly based on history and potential exposure (visit to endemic region). Sometimes lab confirmation can help, but a general screening by serology is NOT recommended because of difficult interpretation due to cross reactions with other flaviviruses or vaccines. In case of doubt, please contact an infectious disease specialist.

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## IV METHODOLOGY

The Board and the Chair of the Vaccination Group identified the necessary fields of expertise. An *ad hoc* working group was set up which included experts in tropical medicine, infectiology, epidemiology and travel medicine.

The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed and non-peer-reviewed), as well as on the opinion of the experts.

Information and data used in the report were mainly extracted from EPAR and the ACIP meeting of February 2023.

- EMA: <a href="https://www.ema.europa.eu/en/documents/product-information/qdenga-epar-product-information">https://www.ema.europa.eu/en/documents/product-information/qdenga-epar-product-information en.pdf</a>
- EMA: <a href="https://www.ema.europa.eu/documents/assessment-report/qdenga-epar-public-assessment-report\_en.pdf">https://www.ema.europa.eu/documents/assessment-report/qdenga-epar-public-assessment-report\_en.pdf</a>
- ACIP: <a href="https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-23/Dengue-03-Paz-Bailey-508.pdf">https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-23/Dengue-03-Paz-Bailey-508.pdf</a>

Once the advisory report was approved by the ad hoc working group and Belgian NITAG, it was ultimately validated by the Board of the SHC.

## **V** ELABORATION AND ARGUMENTATION

## List of abbreviations used

ADE Antibody-Dependent Enhancement

DENV Dengue Virus

DENV-3 Dengue Virus Serotype 3
DENV-4 Dengue Virus Serotype 4
DHF Dengue Haemorrhangic Fever
DSS Dengue Shock Syndrome
EC European Commission

ECDC European Centre for Disease Prevention and Control

EPAR European public assessment report

EU European Union

ITM Institute of Tropical Medicine

NITAG National Immunization Technical Advisory Group

Qdenga® Dengue Tetravalent Vaccine Takeda

SHC Superior Health Council

SPC Summary of Product Characteristics VCD Virologically Confirmed Dengue

VE Vaccine efficacy

WHO World Health Organisation



## 1 Dengue

## 1.1 Symptoms and pathogenesis

# 1.1.1 Clinical presentation

Most of the dengue cases are asymptomatic (40-80% according to ECDC: <a href="https://www.ecdc.europa.eu/en/dengue-fever/facts">https://www.ecdc.europa.eu/en/dengue-fever/facts</a>).

After an incubation period of 4–10 days, symptoms occur including high fever, myalgia, headache and retro-orbital pain, arthralgia and a maculopapular rash. Symptoms usually last far a few days to a week, but complete recovery takes longer. A minority of the cases (<5%) evolve to severe dengue with dengue hemorrhagic fever or dengue shock syndrome, which can lead to dead.

## 1.1.2 Pathogenesis (WHO, 2018)

Dengue viruses are members of the genus *Flavivirus*, within the family *Flaviviridae*. There are four dengue virus serotypes (DENV-1, DENV-2, DENV-3 and DENV-4), all of which circulate globally, with most endemic countries reporting circulation of all four serotypes in recent years. *Flaviviruses* are lipid-enveloped, positive-sense, single-stranded RNA viruses. The structural premembrane and envelope proteins are embedded in the lipid envelope and are displayed on the surface of virions.

The four dengue serotypes are serologically and genetically distinct, although they share several of their structural antigens.

Following an infection with one DENV serotype, the antibodies induced are type specific but also cross-reactive with other DENV serotypes. After human inoculation via the bite of an infected female mosquito, the virus replicates in local dendritic cells. Subsequent entry into macrophages and activation of lymphocytes is followed by entry into the bloodstream. Dengue viruses primarily infect cells of the myeloid lineage, including macrophages, monocytes, and dendritic cells. Haematogenous spread is the likely mechanism for infection of peripheral organs.

## 1.1.3 Antibody-dependant enhancement of severe dengue disease

Severe dengue most commonly occurs among infants and patients with secondary dengue virus (DENV) infections (i.e., re-infection with a different serotype). The most widely cited hypothesis for this occurrence is antibody-dependent enhancement (ADE) of disease. ADE occurs when non-neutralizing anti-DENV antibodies bind to but do not neutralize an infecting DENV. This virus-antibody complex allows for enhanced viral entry into host cells, specifically dendritic cells and macrophages. Once inside the cell, the virus replicates and generates higher virus titers in the blood than when anti-DENV antibody is not present, which results in a "cytokine storm" and ultimately leading to more severe disease (CDC, 2018).

## 1.2 Epidemiology

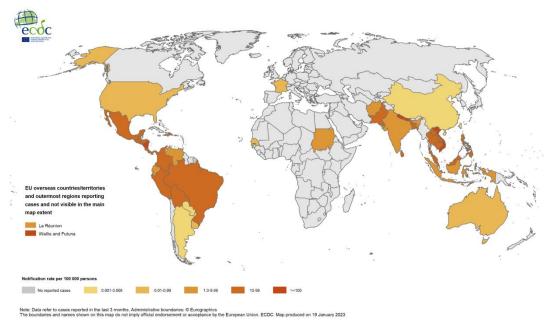
## 1.2.1 Worldwide

Worldwide, the incidence of dengue has increased dramatically over the past few decades. According to WHO, it was estimated for 2010 that 390 million dengue virus infections occur every year, of whom a quarter develop symptoms (with any severity of disease) (Bhatt et al., 2013). The disease is endemic in more than 100 countries, in Southeast Asia, Central and South America, the Western Pacific and Africa. The most significant dengue outbreaks in recent years have occurred in South-East Asia, the Americas and the Western Pacific (ECDC, 2023). In 2022, 4,110,465 cases of dengue and 4,099 deaths have been reported worldwide (ECDC, 2023). The majority of cases were reported from Brazil (2,363,490), Vietnam



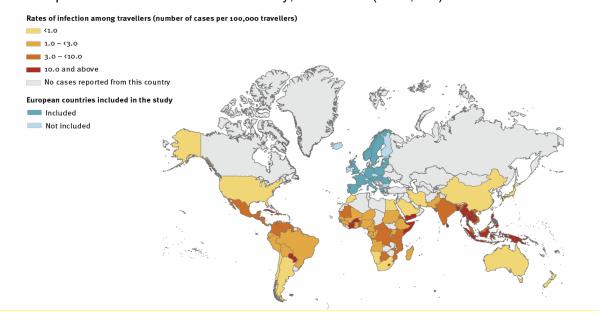
(367,729), the Philippines (220,705), Indonesia (125,888) and India (110,473). Figure 1 shows the countries with the highest notification rates during the period October-December 2022.

Figure 1. Three-month dengue virus disease case notification rate per 100 000 population, October-December 2022 (Source: ECDC)



In addition to the number of cases reported by the countries, data on travel-related dengue cases reported by European countries is also a useful source of information, to assess the risk of infection for travellers. Figure 2 presents the rates of infection among travellers for the period 2015 to 2019 (Gossner et al., 2022).

Figure 2: Rates of dengue virus infection among European travellers, per country of infection, and European countries included in the study, 2015-2019 (n=11,478)



For up-to-date information on areas where dengue has recently been reported, see also Dengue Map: <a href="https://www.healthmap.org/dengue/en/">https://www.healthmap.org/dengue/en/</a>



# 1.2.2 Europe

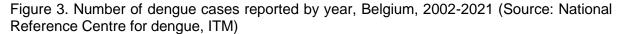
Transmission of dengue viruses in Europe depends on the presence of competent mosquito vectors. *Ae. albopictus*, known to be able to transmit dengue viruses, has been long established in several countries of southern Europe, with Albania and Italy being the first colonised countries in 1979 and 1990, respectively (Medlock et al., 2015). The progressive expansion of the mosquito from the Mediterranean basin to more Northern parts of Europe highlights the vulnerability of European countries to autochthonous transmission of dengue viruses (ECDC, 2021).

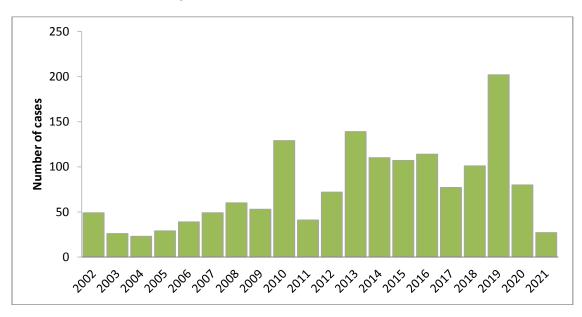
Since 2010 and until December 2021, autochthonous outbreaks of dengue have been reported in four European countries: Croatia, France, Italy and Spain (ECDC, 2023). In 2022, France faced an unusual situation of dengue transmission, with 65 autochthonous cases spread over nine transmission events, of which six occurred in departments that had never experienced autochthonous dengue transmission before (Cochet et al., 2022). The total number in 2022 exceeded the number of cases observed during the entire period 2010 to 2021.

# 1.2.3 Belgium

Between 2007 and 2021, mosquitoes and larvae of *Ae. albopictus* have sporadically been found in Belgium, following importation via lucky bamboo, used tyre trade and passive ground transport (Deblauwe et al., 2022). Monitoring results of exotic mosquitoes in 2022 in Belgium (through the <u>MEMO+ project</u>) indicate that the establishment of *Ae. albopictus* in the country is now in an early phase, most probably in a limited number of areas (Sciensano, 2022).

In this context, cases of dengue in Belgium are still all travel related. The number of dengue cases diagnosed in the country fluctuates from year to year, following the epidemiological situation of dengue in the endemic countries and the travel destinations chosen. The highest number of cases was registered in 2019 (n=202), which can be linked to outbreaks in South-East Asia (Thailand, Cambodia and the Philippines) (Figure 3). Globally, if information on travel is available, infections mostly occur in South-East Asia, followed by Latin America (Figure 4). The low number of infections in 2020 and 2021 is likely related to travel restrictions during the SARS-CoV-2 epidemic.







90 80 70 60 50 Number of cases 40 30 20 10 0 2015 2021 2016 2017 2018 2019 2020 ■ Southeast Asia Africa ■ South Asia America

Figure 4. Number of dengue cases reported by origin of infection Belgium, 2015-2021 (Source: National Reference Centre for dengue, ITM)

# 2 Qdenga®

Information and data here below were extracted from EPAR and the ACIP meeting of February 2023.

- <a href="https://www.ema.europa.eu/en/documents/product-information/qdenga-epar-product-information">https://www.ema.europa.eu/en/documents/product-information/qdenga-epar-product-information</a> en.pdf
- <a href="https://www.ema.europa.eu/documents/assessment-report/qdenga-epar-public-assessment-report\_en.pdf">https://www.ema.europa.eu/documents/assessment-report/qdenga-epar-public-assessment-report\_en.pdf</a>
- ACIP: <a href="https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-23/Dengue-03-Paz-Bailey-508.pdf">https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-23/Dengue-03-Paz-Bailey-508.pdf</a>

## 2.1 Type vaccine

Qdenga® is a live, attenuated virus consisting of four (tetravalent) components, each engineered to provoke an immune response to one serotype of the dengue virus. Each of the four virus components in the vaccine includes a DENV-2 backbone (TDV-2). Three of the vaccine strains (TDV-1, TDV-3, and TDV-4) are chimeras generated by replacing the E and prM sequences of TDV-2 with those from wild-type DENV-1, DENV-3, and DENV-4 strains.



## 2.2 Vaccine efficacy (VE)

## 2.2.1 VE for Virologically confirmed Dengue (VCD)

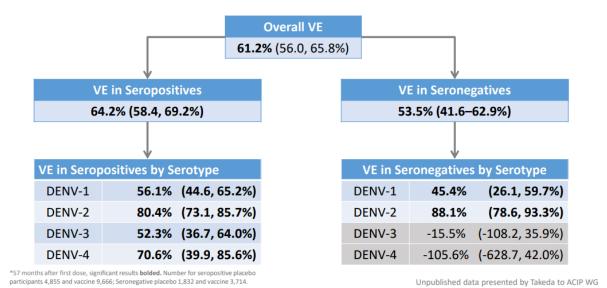


Table 1. VE for VCD presented at ACIP meeting February 2023.

Overall VE against VCD was 61.2%, with an overall better VE in seropositive than in seronegative individuals. The VE was best for DENV-2, remaining robust 57 months after the first vaccine. The VE for DENV-1 was lower and waned more rapidly. In seronegatives, no efficacy for DENV-3 was observed. There were insufficient data for DENV-4.

## 2.2.2 VE for hospitalisation

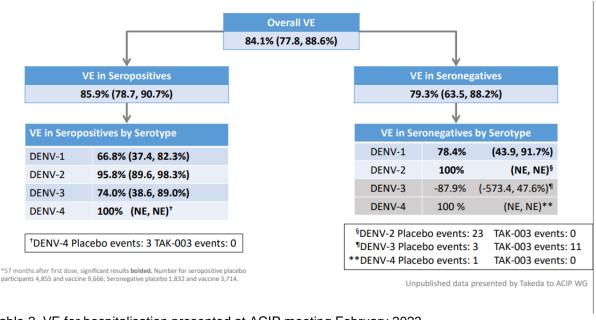
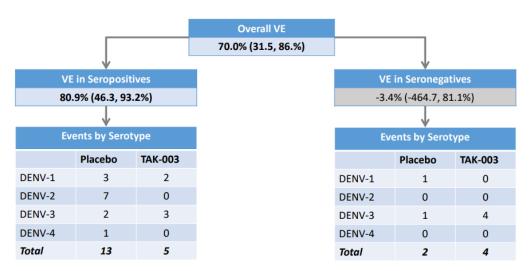


Table 2. VE for hospitalisation presented at ACIP meeting February 2023



Overall, VE against hospitalisation was 84.1% with a good VE against hospitalisation for DENV-1 and DENV-2. For DENV-3, more hospitalisations were observed in the seronegative individuals who were vaccinated. Because of the low number of cases, no conclusions could be drawn, but an increased risk of hospitalisation cannot be ruled out. Data for DENV-4 were insufficient to draw any conclusion.

# 2.2.3 VE for Severe dengue (Dengue Hemorrhagic Fever, 1997 definition)



\*57 months after first dose, significant results for vaccine efficacy **bolded**. Number for seropositive placebo participants 4,855 and vaccine 9,666; Seronegative placebo 1,832 and vaccine 3,714.

VE by serostatus from unpublished data from Takeda.

Table 3. VE for severe dengue presented at ACIP meeting February 2023

Qdenga® offered protection in seropositives for severe dengue. Due to small number of events, VE was difficult to stratify by serotype and no conclusions could be made in seronegatives.

## 2.3 Vaccination schedule and posology

## 2.3.1 Method of administration

After complete reconstitution of the lyophilised vaccine with the solvent, Qdenga® should be administered by subcutaneous injection preferably in the upper arm in the region of deltoid. Qdenga® must not be injected intravascularly, intradermally or intramuscularly

## 2.3.2 Schedule for individuals from 4 years of age

Qdenga® should be administered as a 0.5 mL dose in a **two-dose (0 and 3 months) priming** schedule.

The need for a booster dose has not been established yet, but is studied.



#### 2.4 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed here below or hypersensitivity to a previous dose of Qdenga®:
  - α,α-Trehalose dihydrate
  - Poloxamer 407
  - Human serum albumin
  - Potassium dihydrogen phosphate
  - Disodium hydrogen phosphate
  - Potassium chloride
  - Sodium chloride
  - Water for injections
- Individuals with congenital or acquired immune deficiency, including immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids (e.g. 20 mg/day or 2 mg/kg body weight/day of prednisone for two weeks or more) within four weeks prior to vaccination, as with other live attenuated vaccines (SHC 9158).
- Individuals with symptomatic **HIV** infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.
- Pregnant women: There is limited amount of data from the use of Qdenga® in pregnant women. These data are not sufficient to conclude on the absence of potential effects of Qdenga® on pregnancy, embryo-foetal development, parturition and post-natal development. Qdenga® is a live attenuated vaccine, therefore Qdenga® is contraindicated during pregnancy.
- **Breast-feeding women:** It is unknown whether Qdenga® is excreted in human milk. A risk to the newborns/infants cannot be excluded. Qdenga® is contraindicated during breast-feeding.
- **Women of childbearing potential:** Women of childbearing potential should avoid pregnancy for at least one month following vaccination. Women who intend to become pregnant should be advised to delay vaccination.
- The safety and efficacy of Qdenga® in **children aged less than 4 years** has not yet been established.

# 2.5 Coadministration (from SPC)

Qdenga® should not be administered to subjects receiving immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids within four weeks prior to vaccination

If Qdenga® is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

Qdenga® may be administered concomitantly with an hepatitis A vaccine. Coadministration has been studied in adults.

Qdenga® may be administered concomitantly with a yellow fever vaccine. In a clinical study involving approximately 300 adult subjects who received Qdenga® concomitantly with yellow



fever 17D vaccine, there was no effect on yellow fever seroprotection rate. Dengue antibody responses were decreased following concomitant administration of Qdenga and yellow fever 17D vaccine. The clinical significance of this finding is unknown.

#### 2.6 Adverse reactions

Most frequently reported reactions in subjects 4 to 60 years of age were injection site pain (50%), headache (35%), myalgia (31%), injection site erythema (27%), malaise (24%), asthenia (20%), and fever (11%). Very common reactions (≥1/10 of subjects) were: upper respiratory tract infection, decreased appetite, irritability, headache, somnolence, myalgia, injection site pain, injection site erythema, malaise, asthenia, fever. Common reactions (≥1/100 to <1/10) were: nasopharyngitis, pharyngotonsillitis, arthralgia, injection site swelling, injection site bruising, injection site pruritus, influenza like illness.

# 3 Therapeutic and preventive measures

Treatment of dengue fever is supportive, and based solely on the clinical signs and symptoms, with fluid replacement required for hemorrhagic or shock cases. A specific antiviral therapy for dengue virus infection is not available. Patient should be advised to stay well hydrated and to avoid aspirin and nonsteroidal anti-inflammatory drugs. Close observation in hospital is required for severe dengue.

Most of the current preventive measures that rely on mosquito control and individual protection are of limited efficacy, complex to implement, and questionable in terms of cost-effectiveness. While the malaria transmitting *Anopheles* mosquitoes predominantly feed during the night, the dengue transmitting *Aedes* mosquitoes feed predominantly at dusk and bed nets are therefore not effective. Dengue continues to spread despite the use of vector control measures.

## **Dengvaxia®**

In some endemic countries Dengvaxia® is used in children between 9 and 16 years old who were previously diagnosed with a dengue infection before. This vaccine is given subcutaneously, 3 doses with 6 months interval. Dengvaxia® has been linked with more severe dengue in children who had not had dengue before vaccination (GACVS, 2017).



## VI REFERENCES

- Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL et al. The global distribution and burden of dengue. Nature. 2013 Apr 25;496(7446):504-7. doi: 10.1038/nature12060
- 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 Nov;27(44):2200818. doi: 10.2807/1560-7917.
- CDC. Pathophysiology of Severe Dengue. https://www.cdc.gov/dengue/training/cme/ccm/Severe%20Disease%20in%20Infants F.pdf
- CDC. ACIP meeting February 2023. Work Group Summary and Interpretation of TAK-Interpretation of TAK-003 Efficacy, 003 Efficacy, Safety, and Immunogenicity Data. <a href="https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-23/Dengue-03-Paz-Bailey-508.pdf">https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-23/Dengue-03-Paz-Bailey-508.pdf</a>
- Deblauwe I, De Wolf K, De Witte J, Schneider A, Verlé I, Vanslembrouck A et al. From a long-distance threat to the invasion front: a review of the invasive Aedes mosquito species in Belgium between 2007 and 2020. Parasit Vectors. 2022 Jun 13;15(1):206. doi: 10.1186/s13071-022-05303-w.
- <a href="https://www.ema.europa.eu/en/documents/product-information/qdenga-epar-product-info
- <a href="https://www.ema.europa.eu/documents/assessment-report/qdenga-epar-public-assessment-report">https://www.ema.europa.eu/documents/assessment-report/qdenga-epar-public-assessment-report en.pdf</a>
- European Centre for Disease Prevention and Control and European Food Safety Authority. Mosquito maps [internet]. 2021. Available from: <a href="https://ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/mosquito-maps">https://ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/mosquito-maps</a>
- European Centre for Disease Prevention and Control (ECDC). Dengue worldwide overview. Situation overview 27 January 2023. https://www.ecdc.europa.eu/en/dengue-monthly
- European Centre for Disease Prevention and Control (ECDC). Autochthonous transmission of dengue virus in mainland EU/EEA, 2010-present. (update 6 february 2023) Available from: <a href="https://www.ecdc.europa.eu/en/all-topics-z/dengue/surveillance-and-disease-data/autochthonous-transmission-dengue-virus-eueea">https://www.ecdc.europa.eu/en/all-topics-z/dengue/surveillance-and-disease-data/autochthonous-transmission-dengue-virus-eueea</a>
- GACVS meeting 6-7 December 2017: https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/dengue-vaccines/safety-update
- Gossner CM, Fournet N, Frank C, Fernández-Martínez B, Del Manso M, Gomes DJ, de Valk H. Dengue virus infections among European travellers, 2015 to 2019. Euro Surveill. 2022;27(2):pii=2001937.
- Huits R, Schwartz E. Fatal outcomes of imported dengue fever in adult travellers from non-endemic areas are associated with primary infections. *J Travel Med.* 2021:1-6. doi:10.1093/jtm/taab020
- Medlock JM, Hansford KM, Versteirt V, Cull B, Kampen H, Fontenille D, et al. An entomological review of invasive mosquitoes in Europe. *Bull Entomol Res.* 2015;105(6):637-63. 10.1017/S0007485315000103
- Rivera L, Biswal S, Sáez-Llorens X, et al. Three-year Efficacy and Safety of Takeda's Dengue Vaccine Candidate (TAK-003). Clin Infect Dis. 2022;75(1):107-117. doi:10.1093/cid/ciab864
- SHC 9158: Vaccination of immunocompromised or chronically ill children and/or adults https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth\_theme\_file/2 0200212\_shc\_9158\_ic\_and\_vaccination\_vweb\_2.pdf
- Sciensano. Press release December 2022. An unexpected number of tiger mosquitoes found by citizens in Belgium. Available from: <a href="https://www.sciensano.be/en/press-corner/unexpected-number-tiger-mosquitoes-found-citizens-belgium">https://www.sciensano.be/en/press-corner/unexpected-number-tiger-mosquitoes-found-citizens-belgium</a>



- WHO. Dengue vaccines: position paper. 2018. WER No 36, 2018, 93, 457–476 WHO. Dengue and severe dengue (10 january 2022): <a href="https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue">https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue</a>



## VII COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group *in a private capacity*. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

The following experts were involved in drawing up and endorsing this advisory report. The ad hoc working group was chaired by **Ula MANIEWSKI-KELNER**; the scientific secretary was Veerle MERTENS.

HOYOUX Marie LERNOUT Tinne MANIEWSKI-Kelner Ula	Pediatrics, Travel Clinic, Infect Epidemiology, Tropical medicin Infectiology, Travel Clinic, medicine	ne Sciensano
MARTIN Charlotte	Infectiology, Internal Me Tropical medicine	edicine, CHU Saint-Pierre
MERTENS Rembert SOENTJENS Patrick	Infectiology, Internal Medicine Infectiology, Internal Medicine Tropical medicine	

The standing working group Vaccination (Belgian NITAG) has endorsed the advisory report. The standing working group was chaired by **David TUERLINCKX and Steven CALLENS**; the scientific secretary was Veerle MERTENS. The following experts approved the advisory report by mail on March 29, 2023.

BLUMENTAL Sophie BOIY Tine CALLENS Steven CARRILLO SANTISTEVE Paloma	Pediatric Infectious Disease Pediatrics Internal medicine, Infectiology Preventive medicine and public health, vaccinology	ULB UZA UZ Gent ONE
CHATZIS Olga	Pediatrics, vaccinology, infectiology	UCL
CORNELISSEN Laura	Epidemiology, Obstetrics, Gynaecology	Sciensano
DAELEMANS Siel	Pediatrics, Pneumology, Infectiology	UZ Brussel
DE LOOF Geert	General Medicine	BCFI
DE SCHEERDER Marie-	Internal medicine, Infectiology,	UZ Gent
Angélique	Travel clinic, HIV	
DE SCHRYVER Antoon	Occupational and environmental medicine	UAntwerpen
DESMET Stefanie	Clinical biology, microbiology,	KU Leuven
	vaccinology, pneumology	
DOGNE Jean Michel	Pharmacovigilance	UNamur, EMA
FRERE Julie	Pediatrics, Infectiology	CHR Citadelle
LEROUX-ROELS Isabel	Vaccinology, Infection prevention,	UZ Gent
	Microbiology	
MAERTENS Kirsten	Vaccinology, Maternal Immunization	UAntwerpen
MALFROOT Anne	Pediatrics, Infectiology	UZ Brussel
MANIEWSKI-KELNER	Infectiology, Travel Clinic, Tropical	ITG
Ula MICHIEL C Barbara	medicine	IIA a tura na ara
MICHIELS Barbara	General Medicine	UAntwerpen
PEETERMANS Willy	Internal medicine, infectiology and vaccinology	UZ Leuven



Infectiology, Vaccinology **PELEMAN Renaat** UZ Gent Clinical Evaluation, Epidemiology ROBERFROID KCE **Dominique ROSSI Camelia** Infectiology, HIV, Travel Medicine CHU Ambroise Paré SCHELSTRAETE Petra Pediatrics, Pneumology, Infectiology UZ Gent **SCHIRVEL Carole** Hospital Hygiene CHIREC Medicine. **SOENTJENS Patrick** Infectiology, Internal ITM

SPODEN Julie General medicine SSMG
SWENNEN Béatrice Epidemiology, Vaccinology ULB
TILMANNE Anne Pediatrics, Infectiology CHU TIVOLI

Tropical medicine

TUERLINCKX David Pediatrics, Infectiology CHU TVOLI

VAN DAMME Pierre Epidemiology, Vaccinology UAntwerpen

VAN DER LINDEN Pediatrics, Infectiology UCL

Dimitri

VAN LAETHEM YvesInfectiology, Vaccinology, Travel clinic,<br/>General MedicineCHU Saint-PierreVERHAEGEN JanMicrobiology, BacteriologyUZ LeuvenWAETERLOOSQuality of Vaccines and BloodSciensano

Geneviève Products

The following administrations and/or ministerial cabinets were heard:

DAEMS Joël Directorate Drugs RIZIV-INAMI THEETEN Heidi Vaccinology VAZG

WUILLAUME Francoise Vaccinovigilance AFMPS-FAGG

On November 17, 2022 the company TAKEDA was heard by the ad hoc working group.

On December 23, 2022 a joint meeting was organised between representatives and experts from the Superior Health Council of Belgium, Robert Koch Institute of Germany and Landelijk Coordinatiecentrum Reizigersadvisering of the Netherlands.







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