



National Institute for Public Health  
and the Environment  
*Ministry of Health, Welfare and Sport*

# Dengue (vaccination) in the Caribbean part of the Kingdom of the Netherlands

Background information for the Health Council of the Netherlands



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Background information for the Health Council of the Netherlands

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## Colophon

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This study was commissioned in order to enable the Dutch Health Council (Gezondheidsraad) to advise about programmatic vaccination against dengue virus in the Caribbean part of the Kingdom of the Netherlands (the special municipalities of the Caribbean Netherlands: Bonaire, Sint Eustatius, and Saba and the constituent countries: Curaçao, Aruba and Sint Maarten).

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## Synopsis

### **Dengue vaccination in the Caribbean part of the Kingdom of the Netherlands**

Background information for the Health Council of the Netherlands

Dengue is a viral disease transmitted by mosquitoes. There are four types of the virus. Many people who become infected have few or no symptoms, but some can become seriously ill. They may go into shock, which can result in organ damage. People who have been infected with a particular type of the virus are immune to that type for the rest of their lives – but if they become infected with another type, the risk of becoming seriously ill is greater.

Dengue is common in the tropics and may also occur in the Dutch Caribbean (Aruba, Bonaire, Curaçao, Saba, Sint Eustatius and Sint Maarten). The risk of infection is particularly high during the rainy season, when there are many mosquitoes. There are some years in which there are many cases of illness, and others in which there are virtually none. Between 2007 and 2024, the number of outbreaks on all islands varied.

Less than 1 percent of ill people die. Generally speaking, few people end up in hospital after an infection, but this varies significantly from island to island. In 2017, around two-thirds of people in the Caribbean Netherlands (Bonaire, Sint Eustatius, and Saba) turned out to have antibodies against dengue, which means they had been infected at some point.

Since 2023, a vaccine has been available (Qdenga®) that can help prevent serious illness and hospitalisation. This vaccine protects against two types of the virus. It is not yet known whether the virus also offers sufficient protection against the other two types. It is also still uncertain whether people are at greater risk of becoming seriously ill if they become infected naturally following vaccination.

This information and more is contained in RIVM's background document about dengue and vaccination in the Dutch Caribbean. The Health Council of the Netherlands uses this information to advise the Ministry of Health, Welfare and Sport on this vaccination.

Keywords: dengue, arbovirus, (sero-)epidemiology, vaccination



## Publiekssamenvatting

### **Denguevaccinatie in het Caribisch deel van het Koninkrijk der Nederlanden**

Achtergrondinformatie voor de Gezondheidsraad

Dengue is een virusziekte die wordt overgedragen door muggen. Er zijn vier typen van het virus. Veel mensen die besmet raken, merken er weinig tot niets van. Maar sommigen kunnen er heel ziek van worden. Zij kunnen in shock raken, waardoor hun organen kunnen worden beschadigd. Mensen die eenmaal besmet zijn geweest met één type van het virus, zijn daar hun hele leven immuun voor. Maar als ze daarna met een ander type besmet raken, is de kans juist groter om ernstiger ziek te worden.

Dengue komt veel voor in de tropen en soms in het Caribisch gebied, waaronder de eilanden (Aruba, Bonaire, Curaçao, Saba, Sint Eustatius en Sint Maarten). Vooral tijdens het regenseizoen kunnen veel mensen met het virus besmet worden, omdat er dan meer muggen zijn. Sommige jaren zijn er veel mensen ziek, andere jaren bijna niemand. Tussen 2007 en 2024 verschilde op alle eilanden het aantal uitbraken.

Minder dan 1 procent van de zieke mensen overlijdt. In het algemeen komen weinig mensen in het ziekenhuis terecht na een infectie, maar dat verschilt erg per eiland. In 2017 bleek dat ongeveer twee derde van de mensen op de Caribisch Nederlandse eilanden (Bonaire, Sint Eustatius en Saba) antistoffen tegen dengue hadden. Dat betekent dat ze ooit een infectie met dengue hadden.

Sinds 2023 is er een vaccin (Qdenga®) dat ernstige ziekte en ziekenhuisopnamen kan helpen voorkomen. Dit vaccin beschermt tegen twee typen van het virus. Het is nog niet bekend of het vaccin ook genoeg tegen de ander twee virustypen beschermt. Verder is het nog onzeker of mensen een grotere kans hebben om ernstig ziek te worden als ze na een vaccinatie op een natuurlijke manier worden besmet.

Dit en meer staat in het achtergronddocument van het RIVM over dengue en vaccinatie in het Nederlands Caribisch gebied. De Gezondheidsraad gebruikt deze informatie om het ministerie van VWS over deze vaccinatie te adviseren.

Kernwoorden: dengue, arbovirus, (sero-)epidemiologie, vaccinatie



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## Summary

Dengue is a mosquito-borne viral disease with four serotypes, common in the Caribbean region. Many infections are asymptomatic, but severe cases can result in shock and organ damage. Infection provides lifelong immunity to the same serotype, while a second infection with a different serotype increases the risk of severe illness.

Dengue incidence has surged globally over the past two decades. On the Caribbean islands of the Kingdom of the Netherlands, dengue is endemic, with outbreaks typically occurring during the rainy season when *Aedes aegypti* mosquito populations rise. The outbreaks can vary in intensity from one year to another, often occurring in intermittent cycles, with some years experiencing significant outbreaks and other years resulting in relatively few cases or none at all. From 2007 to 2024, all islands (Aruba, Bonaire, Curaçao, Sint Eustatius, Sint Maarten, and Saba) experienced outbreaks of varying sizes and impact. Hospitalisation rates were generally low, but relatively higher on smaller islands, probably due to small population sizes and possible reporting biases. Case fatality rates remained under 1%. Sero-epidemiological studies in 2017 found that about two-thirds of the Caribbean Netherlands population had dengue antibodies, with the highest seroprevalence on Bonaire and Sint Eustatius (about 70%), while seroprevalence was lower on Saba (38%). Seropositivity was higher among those of Latin American or Caribbean descent and increased with age and the number of years lived on the islands.

Dengue vaccination on the Caribbean islands offers several potential benefits but also presents challenges. One of the main advantages is that vaccination, particularly with Qdenga®, has been shown to effectively reduce severe dengue cases and hospitalisations, which are the primary targets of public health interventions. Efficacy decreases over time but remains substantial with regard to hospitalisations. On islands with high seroprevalence, vaccination could offer added protection to those previously exposed to the virus. However, the vaccine's effectiveness is lower against certain serotypes (DENV3 and DENV4), which may reduce overall protection. WHO advises vaccination among children aged between 6 and 16 years in areas with high Dengue transmission intensity (defined as a seroprevalence >60% at the age of 9 years). However, on small islands, such as the Dutch Caribbean, the Dengue epidemiology is characterised by intermittent cycles, with some years experiencing significant outbreaks and other years resulting in relatively few cases or none at all. Consequently, vaccination may actually increase the risk of severe disease because of a relatively large group (or even whole birth cohorts) of seronegative individuals. Resource and infrastructure limitations, including restricted laboratory and surveillance capacities on some islands, can complicate the monitoring and evaluation of vaccination programmes. The cost-effectiveness and real-world impact of dengue vaccination in small-island settings remain uncertain due to limited data. WHO recommends vaccination only as part of an integrated dengue control strategy (including vector control and case management) and suggests

considering age-specific seroprevalence and hospitalisation data before introducing vaccination programmes.

## 1 Background

### 1.1 Disease

Dengue virus (DENV), a mosquito-borne virus of the genus *Orthoflavivirus* in the family *Flaviviridae*, is the causative agent of dengue fever and severe dengue. Four serotypes of DENV can be distinguished (DENV1, DENV2, DENV3, and DENV4). All four serotypes circulate in the Region of the Americas. People become infected with DENV through a bite by an infected *Aedes aegypti* or *Aedes albopictus* mosquito. The incubation period for DENV infection ranges between 3 and 14 days, but usually between 4 and 7 days, following a bite by an infected mosquito (see Pathway of Infection). Viraemia reaches high titres on the day before the onset of symptoms. It is generally high enough to infect mosquitoes for the next 4 days. In addition, empirical findings and modelling analysis suggest that inapparent infections contribute significantly to DENV transmission. Moreover, a large proportion of human-to-mosquito transmission is silent; i.e. it takes place when there is no detectable illness. The substantial role that inapparent infections play during dengue epidemics may result in more rapid transmission and geographic spread and, consequently, in more widespread transmission prior to case-driven outbreak detection and onset of control efforts [1].

### 1.2 Symptoms

About 40-80% of infected individuals are asymptomatic. Non-severe or uncomplicated dengue begins as an acute febrile illness (up to 41 °C) with chills, headache (particularly retro-orbital), muscle, bone, and joint pains (particularly lumbosacral), and general malaise, often accompanied by a maculopapular exanthema on the first and second days of illness. A small percentage (<5%) shows a more serious course of illness, sometimes with the complication of dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), which can be life-threatening if left untreated. Severe dengue begins as an uncomplicated dengue, but after 2 to 5 days, the patient deteriorates rapidly with the appearance of an increased tendency to bleeding (petechiae or nosebleeds), severe plasma leakage resulting in shock and/or risk of serious damage to vital organs such as the brain, liver, or heart. If left untreated, the lethality for severe dengue is 10%. With proper treatment, this decreases to 1% [2,3].

### 1.3 Natural immunity

An infection with one of the serotypes is considered to give lifelong immunity to that serotype (homotypic immunity). Even though earlier estimates suggested that the first clinical attack most probably elicited cross-protective immunity to other serotypes, the length of cross-protection has since been estimated to last only 1 or 2 weeks, far shorter than previously believed [4]. The risk for severe dengue is greater during a second infection with a different serotype, a phenomenon called antibody-dependent enhancement [5].

## 1.4 Health systems in the Caribbean part of the Kingdom of the Netherlands

For an extended overview of the health systems on all individual islands within the Caribbean part of the Kingdom of the Netherlands, we refer to supplement 1: 'Current state of Infectious disease surveillance in the Dutch Caribbean region, a baseline assessment of actors, systems, legislation, and challenges involved with infectious disease surveillance on the islands of Aruba, Bonaire, Curaçao, Saba, Sint Eustatius and Sint Maarten'. In summary, the 4 countries within the Kingdom of the Netherlands are member of the World Health Organization (WHO) as one party, with the RIVM Centre for Infectious Disease Control (RIVM/CiB) designated as the International Health Regulations National Focal Point (IHR NFP). This was agreed upon in 2015 by the 4 countries in the mutual arrangement 'Onderlinge regeling samenwerking implementatie Internationale Gezondheidsregeling Nederland, Aruba, Curaçao en Sint Maarten'. This arrangement has been incorporated into national legislation as a law by the 4 countries. The Caribbean countries (Curaçao, Aruba and Sint Maarten: CAS), have their own laws, regulations, and responsibility for Public Health. The special municipalities (Bonaire, Sint Eustatius and Saba: BES) operate under the Public Health laws of the Netherlands. There has been a close cooperation between RIVM/CiB and the Public Health departments in the Caribbean countries and special municipalities. RIVM/CiB has a coordinating role and provides technical support and expert advice to the Caribbean islands in the context of communicable disease control, for tasks or expertise that cannot be achieved or maintained in a sustainable way within the limited possibilities of a (small) island setting. Health care in the Dutch Caribbean region is organised at country level.

### *Curaçao, Aruba, Sint Maarten*

Curaçao became a constituent country within the Kingdom of the Netherlands on 10 October 2010. Curaçao has a ministry of health, environment, and nature (Ministerie van GMN) and an executive organisation for public health (Geneeskunde en Gezondheidszaken acronym: GMN G&Gz). GMN G&Gz has tasks regarding health promotion, improving quality and accessibility of health care and particularly focusing on public health, youth healthcare, meat quality control, and prevention and control of infectious diseases, including mosquito control. GMN G&Gz has multiple departments: epidemiology and research, infectious disease control, youth healthcare, a prevention unit, and technical hygiene care.

On the island, there is one general hospital (Curaçao Medical Center, [CMC](#)), which provides second-line care on the island. Furthermore, there is a medical clinic ([Advent Hospital](#)), which provides eye care, gastro-intestinal care, surgery, and radiology. Primary care is provided by approximately 100 GPs, most of whom are united in the GP association of Curaçao (Curaçaose Huisartsen Vereniging, CHV). A sentinel group of GPs provides input for the GMN G&Gz-coordinated syndromic surveillance. On the island, there is also a GP clinic, which provides free primary care for undocumented inhabitants ([Salú pa Tur](#)). There are 3 private medical laboratories on the island. CMC has a contract with ADC laboratory. This institute also acts as the laboratory for public health.

There is a blood bank on the island operated by the RedCross in cooperation with ADC lab. Tests on doctors' prescriptions are performed at all 3 labs.

In 1986, Aruba was the first Caribbean island to become a constituent country within the Kingdom of the Netherlands. As of that year, Aruba has had a Ministry of Health and an executive organisation for public health (Directie Volksgezondheid, DVG). DVG has a task regarding: youth healthcare, infectious diseases control, hygiene inspection, social psychiatric care, veterinary inspection, mosquito control, and health promotion. The Epidemiology & Research Unit is a unit of the DVG in charge of surveillance.

On the island, there is one hospital (Horacio Oduber Hospital, [HOH](#)) with 187 beds, providing second-line care. Primary care is provided by 40 GPs, most of whom (but not all) are united in the GP association of Aruba (Huisartsen Vereniging Aruba, HAVA). Within this group of GPs, 12 act as a sentinel group for respiratory infections surveillance, sending weekly samples for analysis in cooperation with and funded by DVG. There are 3 locations where GPs 'cooperate under one roof' (Huisartsen onder een dak, acronym: HOED) these HOEDs are open during office hours and located near HOH, near ImSan and in the Paradera neighbourhood. In addition to HOH, there is a medical institute for hospital care on the island, specialised in the treatment and care of persons living with chronic non-communicable diseases (Instituto Medical San Nicolas, [ImSan](#)). There are 5 medical laboratories on the island. Four of these labs are privately owned and one lab is the HOH laboratory (LabHOH), which also includes a blood bank. Tests prescribed by GPs to the general public are performed at all medical laboratories, including LabHOH.

The Island of Sint Maarten is divided into a French and a Dutch part. The Dutch part of Sint Maarten became a constituent country within the Kingdom of the Netherlands on 10 October 2010. Since then, Sint Maarten has had a ministry of public health, social development, and labour (Ministerie van Volksgezondheid, Sociale ontwikkeling en Arbeid, acronym: VSA). The Ministry of VSA includes a policy department, the Department of Public Health (DPH) and an executing department for public health, the Collective Prevention Service (CPS).

CPS is tasked with the following: registration; prevention, tracing, and follow-up of communicable diseases; public health information and awareness; epidemiology of infectious diseases; youth health; the national immunisation programme (childhood vaccines); and COVID-19 vaccination. CPS has structured meetings and regular communications with their French counterparts on the island; surveillance reports from the French public health agency are distributed to the island via RIVM. On the Dutch part of the island, there is one hospital (Sint Maarten Medical Center, [SMMC](#)), which provides second-line care on the island as well as on the nearby islands of Saba and Sint Eustatius. Primary care is provided by 21 GPs. There is a GP association on Sint Maarten, but not all GPs are members. There are 2 medical laboratories on the island, namely Sint Maarten Laboratory Services (SLS) and the Health Care Laboratory Sint Maarten (HCLS). SLS has been appointed as the laboratory for public health for Sint Maarten, Saba, and Sint Eustatius, and also acts as the hospital laboratory for SMMC. Tests on doctors'

prescription are performed at both labs. Given that the island has a Dutch and a French part, inhabitants of the Dutch part of the island may seek healthcare on the French part. These circumstances complicate surveillance activities and may lead to underestimations of infectious diseases.

*Bonaire, Sint Eustatius, and Saba (Caribbean Netherlands)*

Since 10 October 2010, Bonaire, Saba, and Sint Eustatius have been 'public entities' (openbare lichamen) with the status of special municipalities of the Netherlands. The islands are referred to as the Caribbean Netherlands by the Netherlands government. This means that public health in the Caribbean Netherlands is organised according to the European Netherlands law on public health. Thus, in the Caribbean Netherlands all have a Public Health agency that has tasks regarding health promotion, infectious disease control (including mosquito control), policy, and research of health and health disaster management.

Bonaire has a hospital (Fundashon Mariadal, [FM](#)) on the island, which provides second-line care; third-line care patients are flown out to Colombia. Primary care is provided by 6 GP clinics that are united into the Primary Care Caribbean (PCC) group. There is 1 private medical laboratory on the island ([Bonlab](#)), which also acts as the default Public Health laboratory. FM also includes a medical laboratory that has the potential for medical microbiology testing. Tests on GP prescription are primarily performed by Bonlab.

Due to their small populations ( $n \sim 3200$ ,  $n \sim 2000$ , respectively), both Sint Eustatius and Saba each have a medical clinic on the island that provides GP care, has emergency room capacity and provides pregnancy care. Polyclinical services are provided by medical specialists from Sint Maarten at the island clinics on rotation.

On Sint Eustatius, Queen Beatrix Medical Centre (QBMC), which is operated by the Sint Eustatius Health care foundation ([SEHCF](#)), provides primary health care. On Saba, primary health care is provided by the [Saba Cares](#) medical clinic. Patients in need of second-line care are referred to Sint Maarten Medical Center and transported by helicopter in case of emergency (24/7), or by airplane in less urgent cases. QBMC on Sint Eustatius has a laboratory for clinical chemistry and limited PCR-based infectious disease testing (COVID-19, Flucovid, and dengue, there is a strong wish for more testing options). Saba Cares also has a laboratory for clinical chemistry and limited PCR-based infectious disease testing (COVID-19, influenza, and sexually transmitted infections testing). For more extensive medical microbiology diagnostics, the islands are depending on SLS on Sint Maarten.

The larger medical laboratories in the region (Curaçao: all labs; Aruba: labHOH; Bonaire: both labs; and Sint Maarten: SLS) are well equipped to perform serology testing for dengue. Possibilities for PCR testing are available but as there is often a delay between disease onset and testing, these tests are not performed often. Sint Eustatius has performed dengue testing since the outbreak in 2023-2024. These tests are PCR-based, using a GeneXpert© device [6]. Confirmational testing is occasionally performed at the RIVM reference laboratory for arboviruses.

## 2 Epidemiology

### 2.1 Global epidemiology

The global incidence of dengue has increased significantly over the past two decades. From 2000 to 2019, the World Health Organization (WHO) documented a ten-fold surge in reported cases worldwide, increasing from 500,000 to more than 5 million. The year 2019 marked an unprecedented peak, affecting populations across 129 countries. In 2023, an upsurge in dengue cases was observed globally, characterised by a significant increase in the number, scale, and simultaneous occurrence of multiple outbreaks, spreading into regions previously unaffected by dengue [7].

Since the beginning of 2023, the world has been facing an upsurge for dengue. In 2023, ongoing transmission, combined with an unexpected spike in dengue cases resulted in close to a historic high of over 5 million cases and more than 5000 dengue-related deaths reported in over 80 countries/territories and five WHO regions: Africa, Americas, South-East Asia, Western Pacific and Eastern Mediterranean Regions. Close to 80% of these cases, or 4.1 million, have been reported in the Region of the Americas. Dengue is the most widespread arbovirus and causes the highest number of reported arboviral disease cases in the Region of the Americas, with cyclic epidemics recurring every 3 to 5 years. However, these numbers are an underestimation of the true burden as a large portion of cases are not diagnosed and/or reported. In 2024, over 12 million dengue cases and over 8000 dengue-related deaths were reported from 86 countries/territories. Similarly to 2023, most cases worldwide have been reported from the WHO Region of the Americas. The more than 11 million cases reported by the Pan American Health Organization (PAHO) in 2024 are twice the number of cases reported throughout 2023. Brazil reported the most cases in 2024 (over 9 million) followed by Argentina, Paraguay, Peru and Colombia [8,9].

### 2.2 Incidence in the Caribbean part of the Kingdom

While dengue occurs sporadically all year round, epidemics occur during the rainy season. During this period, the *Aedes aegypti* mosquito reaches high population densities. In the 15 years before 2024, outbreaks of dengue fever occurred throughout the Caribbean part of the Kingdom, but differed in size and impact. Previous outbreaks were reported by Aruba (2008-2009, 2010-2011), Bonaire (2007-2008, 2011 and 2024), Curaçao (2008-2009, 2010-2011 and in 2024), Sint Eustatius (2013 and 2023-2024), Sint Maarten (2008, 2010, 2013 and 2023-2024) and Saba (2013 and 2024).

#### 2.2.1 *Confirmed and probable notified cases and syndromic surveillance 2007-2024*

##### *Background*

DENV has been prevalent in the Caribbean part of the Kingdom of the Netherlands for decades. In this chapter, we present registered laboratory-confirmed and probable cases over the period 2007-2024. This period has been selected because it covers an ongoing syndromic

surveillance for 'undifferentiated fever' in addition to laboratory outcomes for DENV. In 2007, volunteer general practitioners (GPs) on the former Dutch Antilles (Curaçao, Sint Maarten, Bonaire, Sint Eustatius and Saba) started registering 6 'syndromes' in their practices, which include: gastroenteritis, fever with respiratory symptoms, fever with rash, fever with neurological symptoms, fever with haemorrhagic symptoms, and undifferentiated fever [10,11]. The latter syndrome is used as a proxy for suspected arbovirus infections by GPs but may also be used to register other diseases that display undifferentiated fever as a symptom. Hence, registrations of undifferentiated fever are plotted in the figures directly below the laboratory diagnoses for dengue infections for confluence, but thus may be an overestimation.

#### *Case definitions applied in this study*

For the analyses below, we assessed historical laboratory outcomes for dengue diagnostics. We applied the case definitions that were agreed upon with the islands and confirmed by the 'Landelijke Overleg Infectieziekten' (LOI) on 24 September 2024 for the purpose of surveillance within the Kingdom of the Netherlands. These case definitions are:

- **Probable dengue**  
A patient with undifferentiated fever and/or two or more of the following symptoms:
  - Nausea/ vomiting
  - Rash
  - Myalgia/arthralgia
  - Headache, retro-orbital pain
  - Petechiae
  - Leukopenia
 And
  - A single serum sample IgM positive with or without IgG
 Or
  - During an outbreak (no lab test)
- **Confirmed dengue**  
A patient that meets the clinical criteria for probable dengue and/or adheres to one of the following test outcomes:
  - A clinical sample that tests NS1-antigen positive
  - A clinical sample that test RT-PCR positive
  - A paired serum sample with a 4x titer increase for IgM and/or IgG
  - A paired serum sample (14 day interval) with confirmed DENV antibody seroconversion

In summary, patients who tested positive for a single serum IgM were considered to be probable cases, as were patients for whom a paired serum sample was available with an antibody titre increase  $<4x$ . Patients who tested positive for NS1-antigen and patients with a paired serum sample with an antibody titre increase  $4x >$  were considered to be confirmed cases. Outcomes that adhered to these criteria were used to generate the figures and tables in this chapter.

#### *Completeness of data*

The data collected to generate the graphics and tables in this chapter was kindly provided by the Public Health agencies in the Dutch

Caribbean region. GMN G&Gz Curaçao played a specific role in procuring this data. The agency performs and performed a coordinating role within Public Health for the syndromic surveillance. Furthermore, the agency coordinated infectious disease surveillance until 10 October 2010 for the Netherlands Antilles islands. The majority of the historical data used in this chapter was available from Curaçao's repository. The data, however, is incomplete. This is an effect of the political changes that occurred in the period 2007-2024 and is also due to a combination of limited staff and additional and new tasks that needed to be performed by the Public Health agencies in the region.

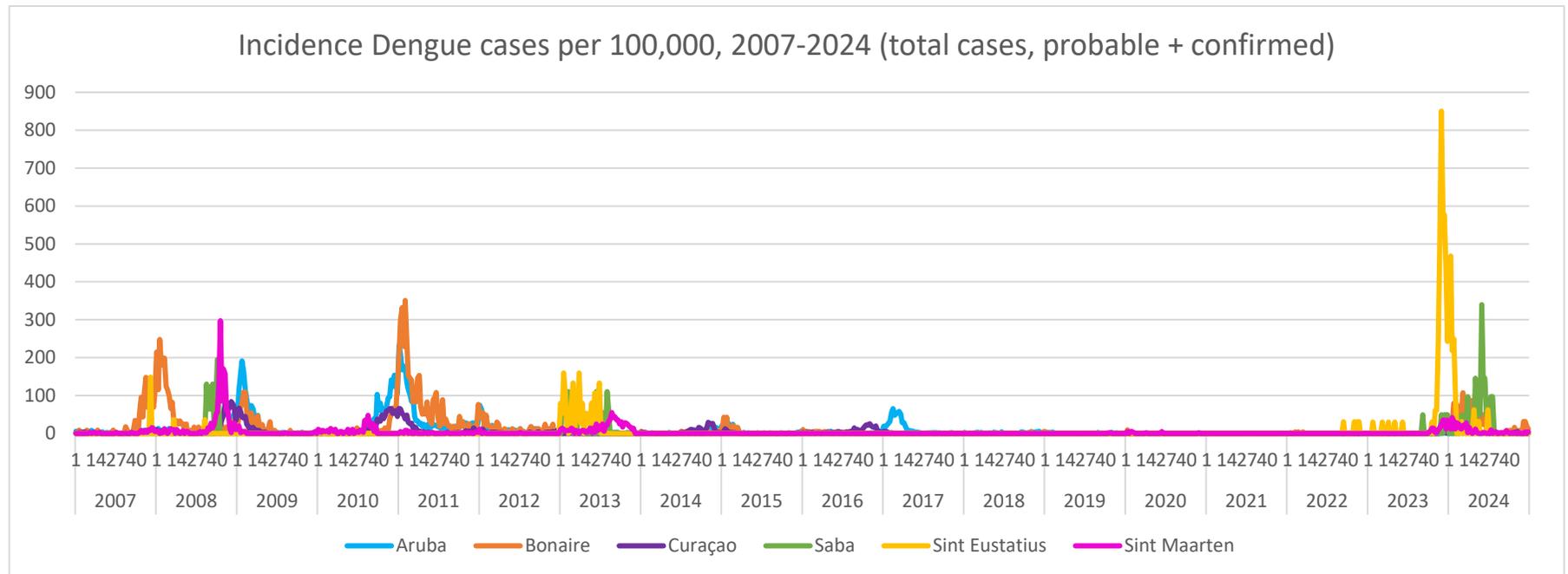
*Comparability of data between the islands*

Figure 1 gives a regional overview of dengue incidence (total cases: probable and confirmed cases) per 100,000 inhabitants. Please, bear in mind that due to the small population sizes, especially of Saba and Sint Eustatius, the number of cases is significantly higher in this overview than they are in the overviews of crude cases per island (Figures 2-7). Figures 2-7 represent the crude numbers of DENV infections or symptomology reports per island.

*Table 1 Recent population sizes for the Caribbean islands within the Kingdom of the Netherlands.*

<b>Island</b>	<b>Population size (rounded) (year)</b>	<b>Data source</b>
Aruba	108,000 (2024)	<a href="https://cbs.aw">cbs.aw</a>
Bonaire	25,000 (2024)	<a href="https://cbs.nl">cbs.nl</a>
Curaçao	156,000 (2023)	<a href="https://cbs.cw">cbs.cw</a>
Saba	2100 (2024)	<a href="https://cbs.nl">cbs.nl</a>
Sint Eustatius	3200 (2024)	<a href="https://cbs.nl">cbs.nl</a>
Sint Maarten (Dutch part of the island)	43,000 (2023)	<a href="https://stats.sintmaartengov.org">stats.sintmaartengov.org</a>

Figure 1 Total dengue notifications (confirmed + probable) per 100,000 inhabitants per week compared between all islands.



Note that the population sizes differ quite significantly across islands (Table 1). This results in the numbers of cases for Sint Eustatius and Saba being significantly higher in this graph, compared with the crude numbers of cases in the graphs below. Incidence was calculated using available census data. Please, see table in appendix 1 for an overview of used census data.

**Note:**

The plots below (Figures 2-7) show the crude case numbers per island and syndromic surveillance data per island. Please, bear in mind that the values on the y-axes of Figures 2-7 differ per island. The Y-axes for the laboratory-reported cases and syndromic surveillance are on the same scale for each individual island. The x-axes (individual years divided into quarters) are the same for all the figures in this chapter (Figures 1-7).

Figure 2 (top) Laboratory-confirmed and probable cases of dengue on Aruba 2007-2024, (bottom) syndromic surveillance: registrations of ICPC code A77 'other viral disease' for week 01 2023 through week 52 2024.

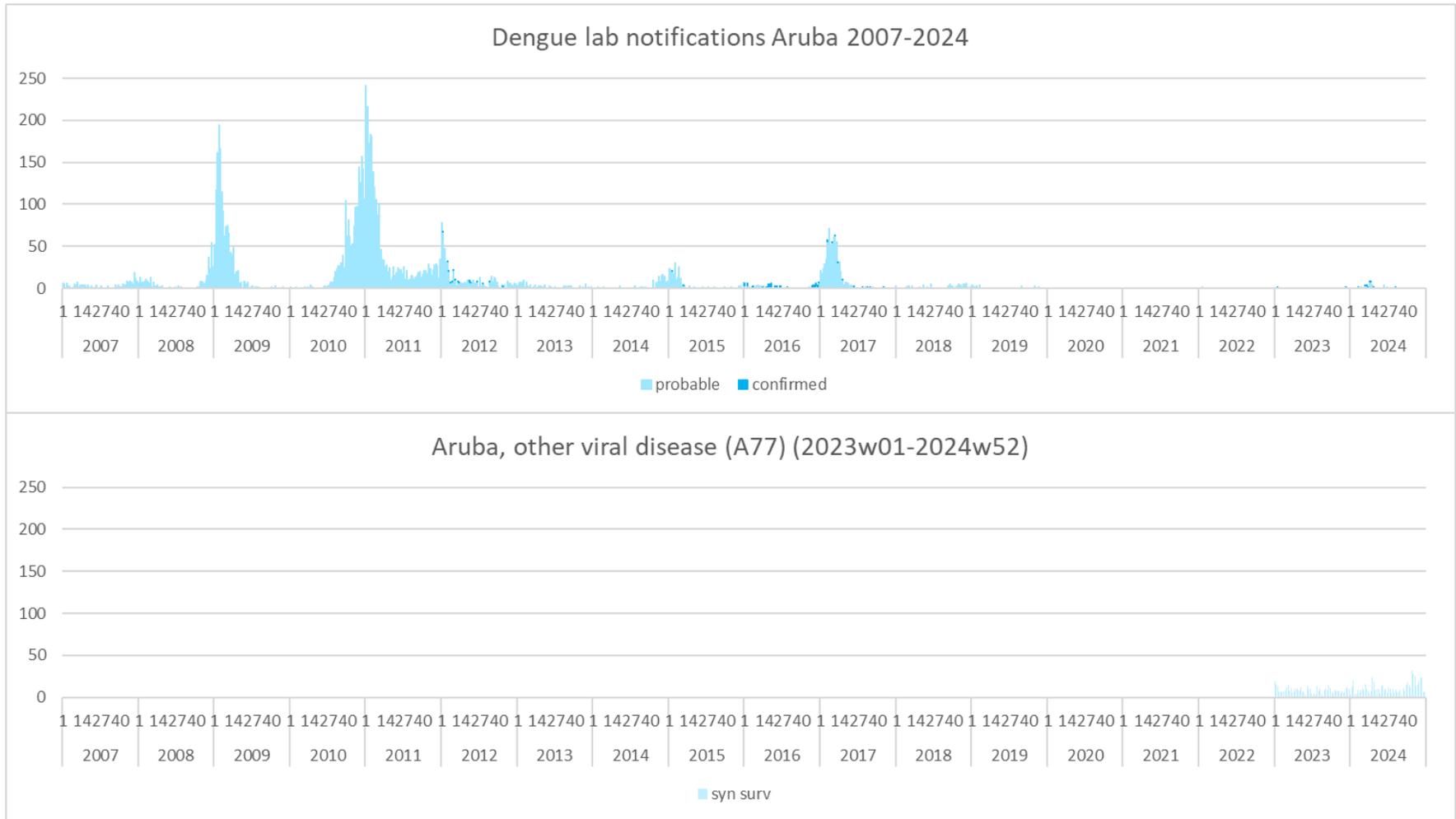


Figure 3 (top) Laboratory-confirmed and probable cases of dengue on Bonaire 2007-2024, (bottom) syndromic surveillance undifferentiated fever all ages until week 23, 2023 and registrations of ICPC code A77 'other viral disease' for week 24 2023 through week 44, 2024.

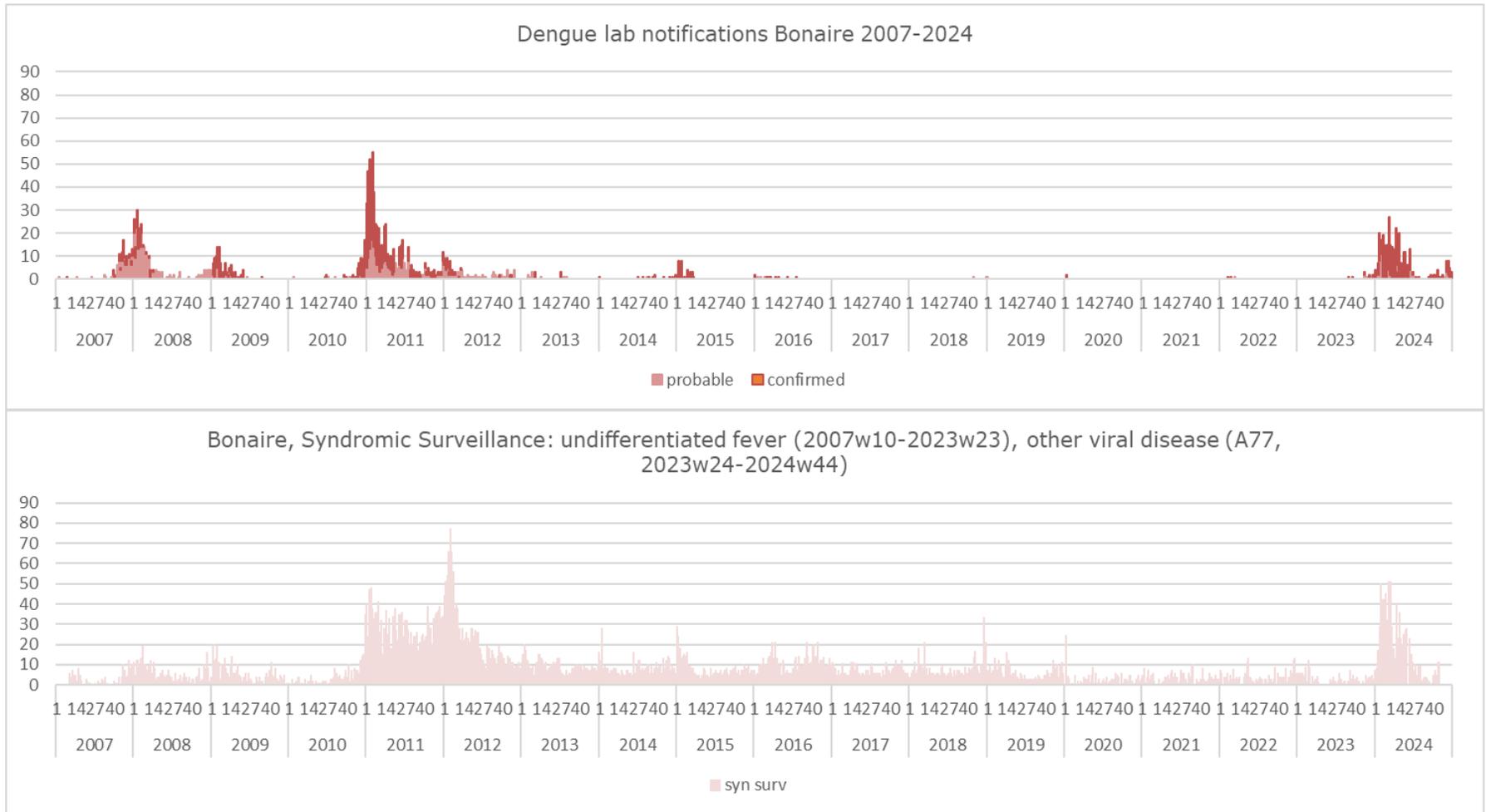


Figure 4 (top) Laboratory-confirmed and probable cases of dengue on Curaçao 2007-2024, (bottom) syndromic surveillance undifferentiated fever all ages for week 01 2007 through week 52 2023.

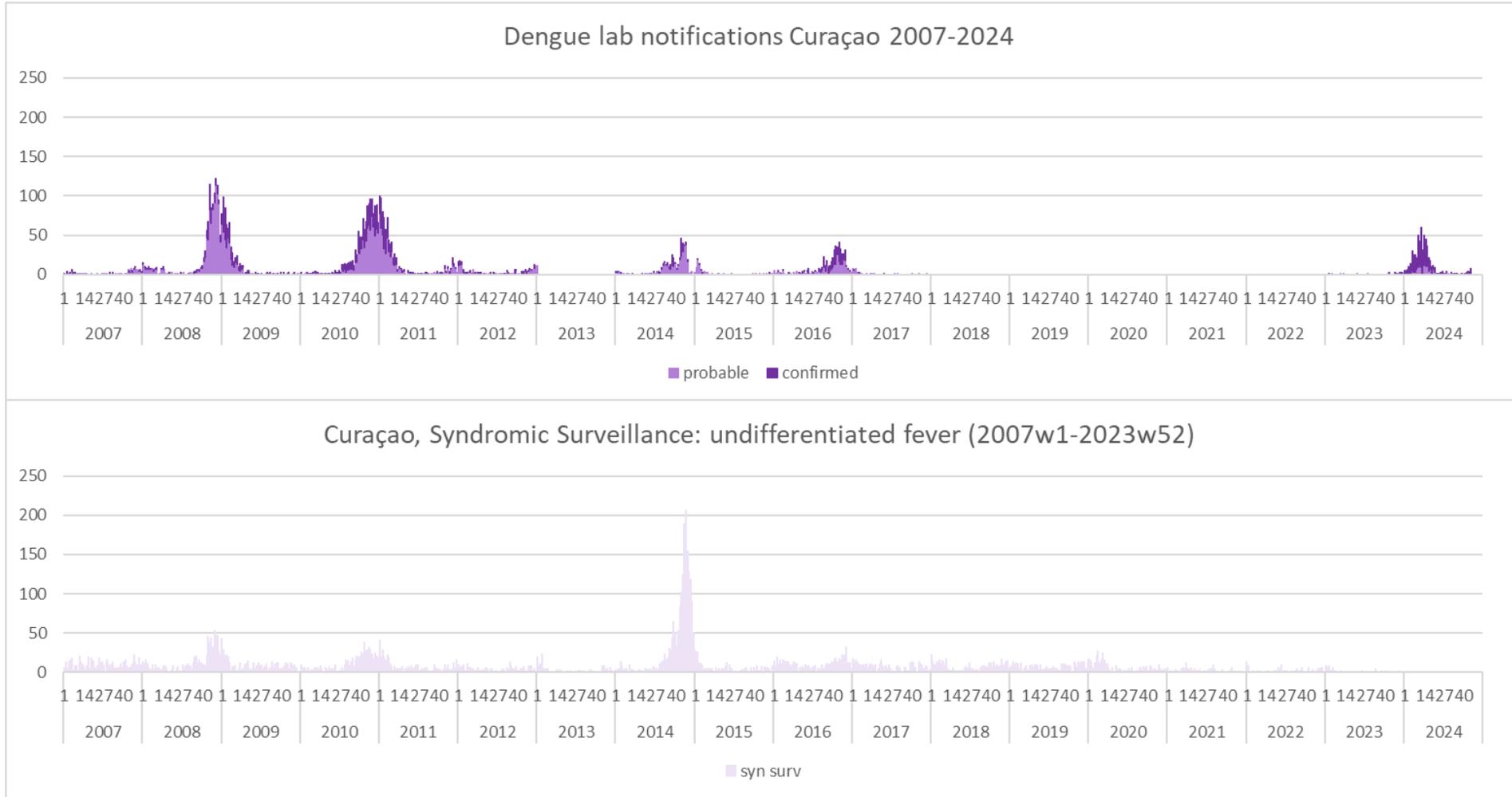
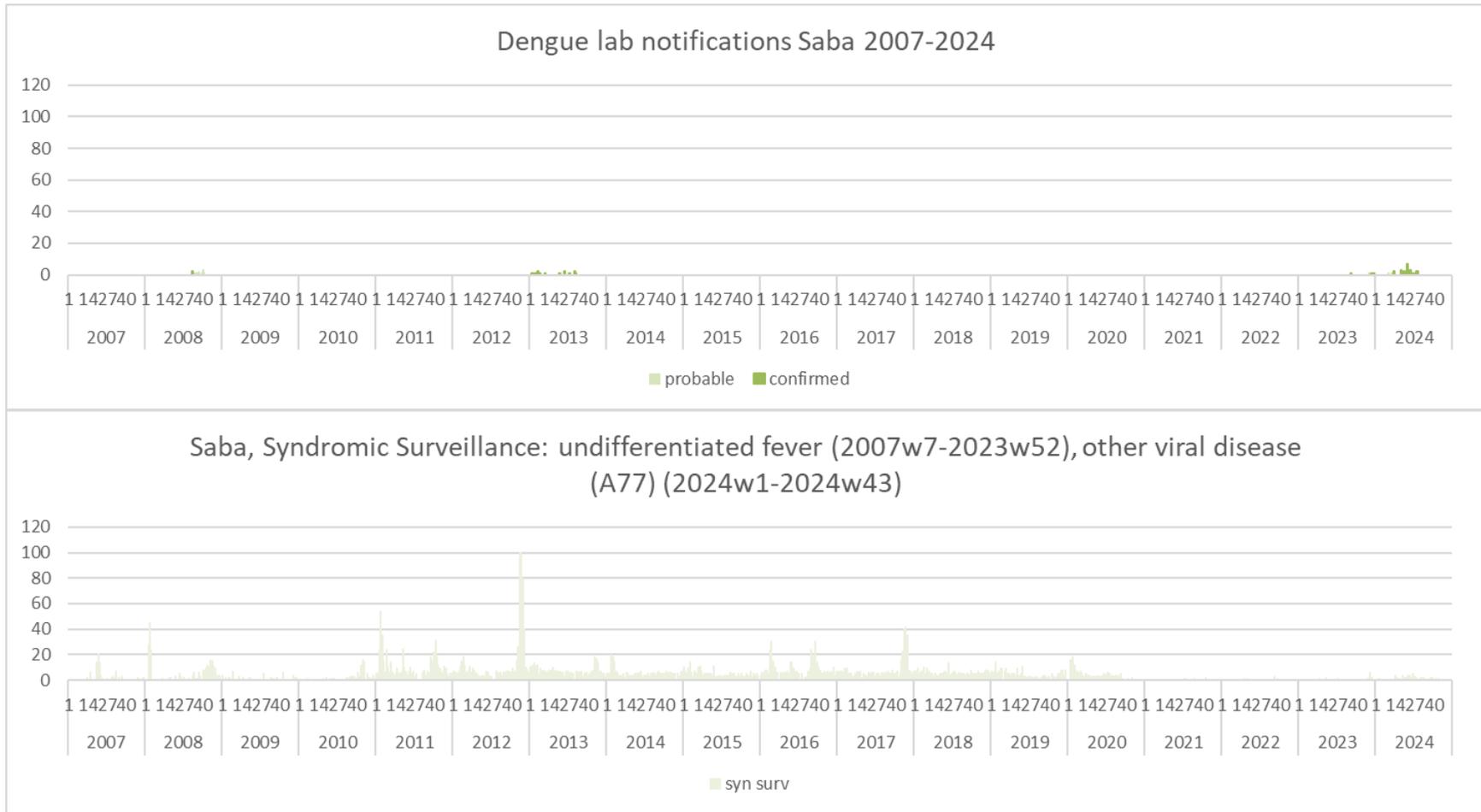


Figure 5 (top) Laboratory-confirmed and probable cases of dengue on Saba 2007-2024, (bottom) syndromic surveillance undifferentiated fever all ages for week 07 2007 through week 52 2023 and registrations of ICPC code A77 'other viral disease' for week 01 through week 43 2024.



Please note that the top graph only includes a fairly limited number of notified cases, this reflects the very small island population of Saba (N~2.100).

Figure 6 (top) Laboratory-confirmed and probable cases of dengue on Sint Eustatius 2007-2024, (bottom) syndromic surveillance undifferentiated fever all ages for week 10 2007 through week 52, 2023.

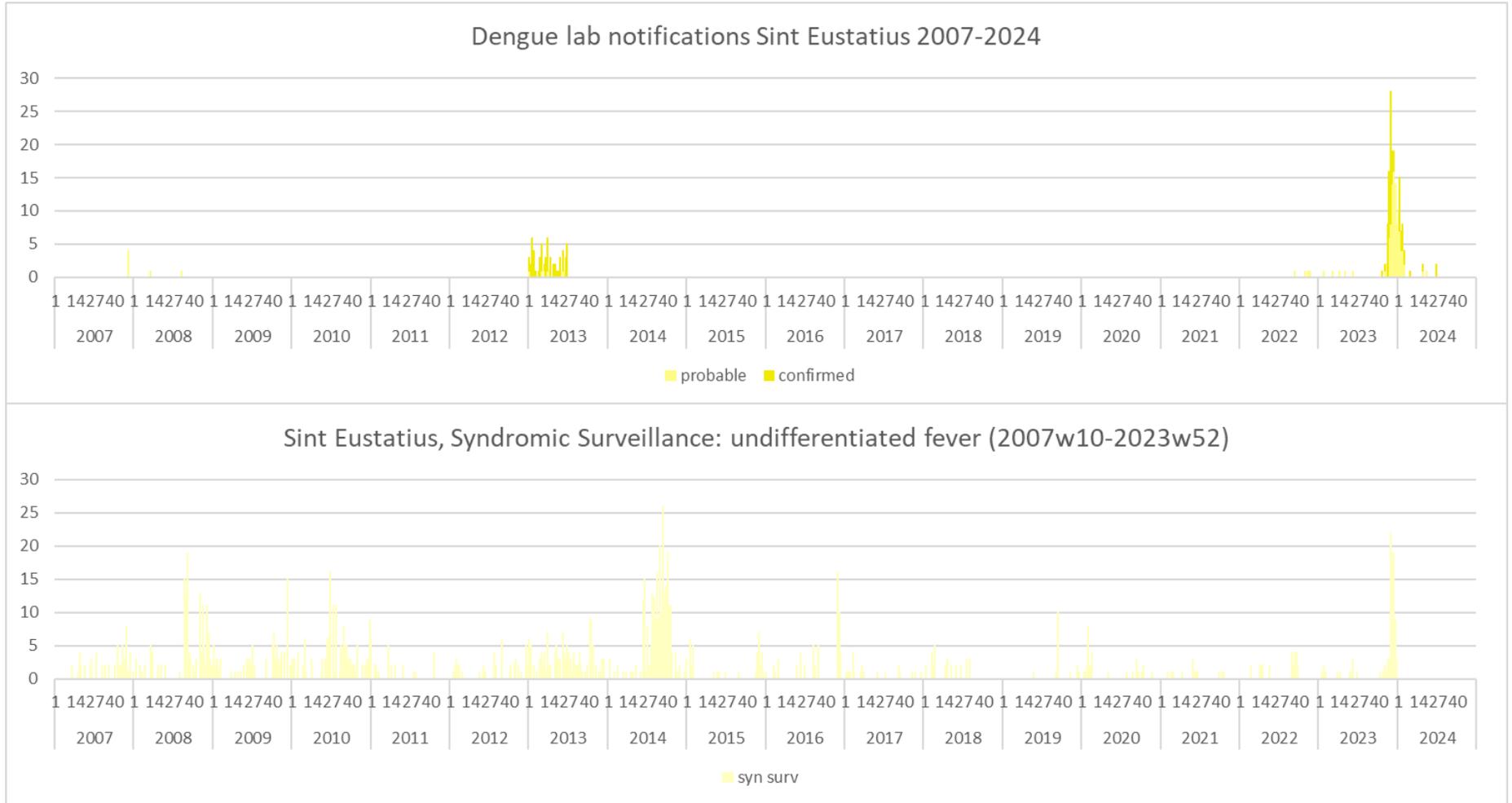


Figure 7 (top) Laboratory-confirmed and probable cases of dengue on Sint Maarten 2007-2024, (bottom) syndromic surveillance undifferentiated fever all ages for week 05 2008 through week 52 2023.

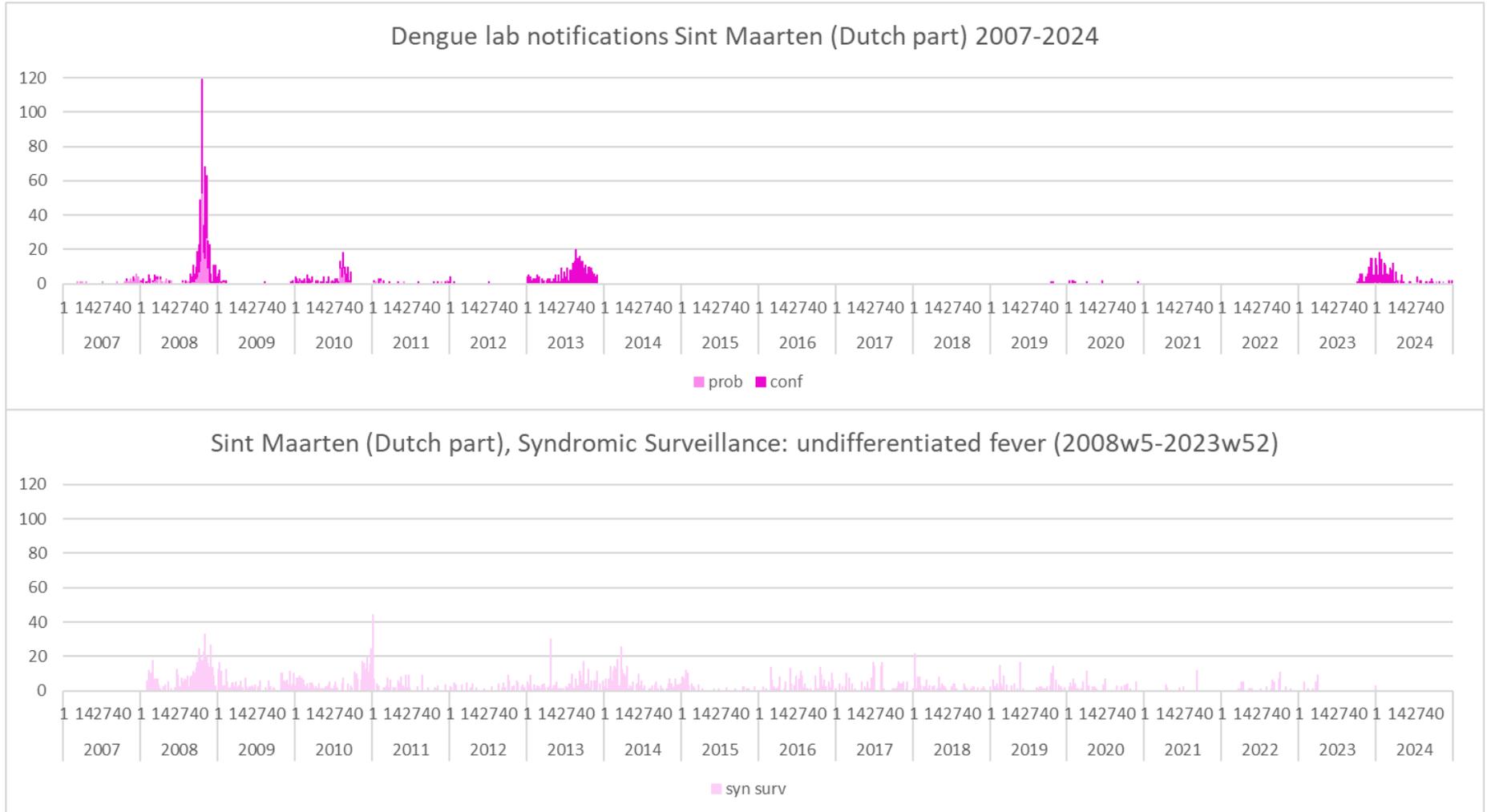


Table 2 Summary statistics of dengue in the Dutch Caribbean region.

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
<b>Aruba</b>																		
Lab-confirmed cases	0	0	0	0	0	16	0	0	2	47	14	0	2	1	0	0	8	9
Lab probable cases	195	324	1434	1614	2431	570	122	146	231	64	686	93	36	7	8	5	10	47
Syndromic surveillance A77#	n.a.	442	615															
Hospitalisations due to DENV infection	3	0	58	64	60	10	3	4	7	1	1	0	0	0	2	0	1	5
Mortality due to DENV infection	0	0	2	1	3	1	1	0	0	0	0	0	0	0	0	0	0	0
<b>Bonaire</b>																		
Lab-confirmed cases	34	47	75	45	384	24	5	12	32	10	0	0	0	2	0	2	5	262
Lab probable cases	91	214	31	25	257	81	11	1	0	3	0	2	1	0	0	1	9	79
Undifferentiated fever or A77*, #	134	324	306	225	1555	1238	493	458	435	589	386	438	335	164	199	225	160	803
Hospitalisations due to DENV infection	2	3	n.a.	n.a.	n.a.	n.a.	n.a.	0	0	0	0	1	0	0	0	0	0	2
Mortality due to dengue infection	0	0	n.a.	n.a.	n.a.	n.a.	n.a.	0	0	0	0	0	0	0	0	0	0	0

Table 2 Summary statistics of dengue in the Dutch Caribbean region (cont'd).

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
<b>Curaçao</b>																		
Lab-confirmed cases	23	188	276	493	317	69	0	104	6	233	4	n.a.	n.a.	n.a.	n.a.	n.a.	11	466
Lab probable cases	90	944	395	777	525	138	11	325	78	283	40	n.a.	n.a.	n.a.	n.a.	n.a.	11	113
Undifferentiated fever*	546	716	500	615	420	242	171	1778	304	578	396	420	412	350	140	131	65	n.a.
Hospitalisations due to DENV infection	4	5	0	26	7	1	0	2	0	n.a.	0	53						
Mortality due to dengue infection	0	0	0	0	1	0	0	0	0	n.a.	0	3						
<b>Saba</b>																		
Lab-confirmed cases	n.a.	2	n.a.	n.a.	n.a.	n.a.	13	n.a.	3	25								
Lab probable cases	n.a.	10	n.a.	n.a.	n.a.	n.a.	5	n.a.	2	5								
Undifferentiated fever or A77*, #	87	244	50	88	533	660	378	287	266	449	407	305	229	197	5	6	14	51
Hospitalisations due to DENV infection	n.a.	1	n.a.	n.a.	n.a.	n.a.	0	n.a.	0	10								
Mortality due to dengue infection	n.a.	0	n.a.	n.a.	n.a.	n.a.	0	n.a.	0	0								

Table 2 Summary statistics of dengue in the Dutch Caribbean region (cont'd).

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
<b>Sint Eustatius</b>																		
Lab-confirmed cases	0	0	n.a.	n.a.	n.a.	n.a.	55	n.a.	0	48	21							
Lab probable cases	4	2	n.a.	n.a.	n.a.	n.a.	8	n.a.	4	74	29							
Undifferentiated fever*	62	143	94	146	29	45	134	255	37	57	20	30	16	29	13	26	95	n.a.
Hospitalisations due to DENV infection	3	0	n.a.	n.a.	n.a.	n.a.	0	n.a.	0	2	2							
Mortality due to dengue infection	0	0	n.a.	n.a.	n.a.	n.a.	0	n.a.	0	0	0							
<b>Sint Maarten</b>																		
Lab-confirmed cases	3	365	22	97	14	6	292	n.a.	n.a.	n.a.	n.a.	n.a.	2	11	n.a.	n.a.	87	153
Lab probable cases	32	177	3	37	8	0	n.a.	1	5									
Undifferentiated fever*	n.a.	440	205	267	150	80	230	265	74	176	147	112	130	80	21	53	24	n.a.
Hospitalisations due to DENV infection	1	18	19	2	19	1	33	n.a.										
Mortality due to dengue infection	0	0	0	0	0	0	0	n.a.										

\* Data available from the manual syndromic surveillance coordinated by GMN G&amp;Gz Curaçao

# Data available from the automatic surveillance initiated by Nivel on Aruba and the BES-islands

### 2.2.2 *Hospitalisation* *Aruba*

The number of hospitalisations due to DENV infection on Aruba has been limited over the years. The general trend is that the crude number of hospitalisations is correlated with the extent of the ongoing outbreak. The case hospitalisation rate (number of hospitalisations divided by total number of reported probable and confirmed cases) never exceeded 8.9% in the years 2007-2024 (range: 0.9-8.9%), with the exception of 2021, during the COVID-19 pandemic when 2 persons were hospitalised with a DENV infection out of a total of 8 registered dengue cases that year.

#### *Bonaire*

The number of hospitalizations due to DENV infection on Bonaire has been limited over the years, with a maximum of 3 cases hospitalised in 2008. The case hospitalisation rate never exceeded 1.6% in the years 2007-2024 (range: 0.6-1.6%), except for 2018, when 1 out of 2 patients with a registered infection was hospitalised.

#### *Curaçao*

The trend in hospitalisations due to DENV infection on Curaçao is comparable to Aruba. The general trend is that the crude number of hospitalisations is correlated with the extent of the ongoing outbreak. The case hospitalisation rate never exceeded 10% in the years 2007-2024 (range: 0.4-9.2%), where 2024 stands out with the highest hospitalisation rate of 9.2% (n=53 patients hospitalised).

#### *Saba*

Compared to the larger islands, the number of hospitalisations due to a DENV infection on Saba is relatively high. In 2008, the case hospitalisation rate was 8.3% and in 2024, it was 33.3%. What this comes down to is that the proportion of patients seeking care for DENV infection-related complaints in these years increased from one out of twelve to ten out of thirty patients, respectively.

#### *Sint Eustatius*

Compared to the larger islands, the number of hospitalisations as a result of a DENV infection on Sint Eustatius is relatively high as well, with a case hospitalisation rate in 2007 of 75%, involving 3 out of 4 registered dengue patients. In the last 2 years, the hospitalisation rate was comparable to Aruba, Bonaire, and Curaçao, amounting to 1.6% in 2023 and to 4% in 2024.

#### *Sint Maarten (Dutch part of the island)*

The rate of hospitalisations on Sint Maarten due to DENV infections is in line with the rates on the other islands within the Kingdom. In 2013, the highest number of hospitalisations was reported (n=33). When considering case hospitalisation rates on Sint Maarten, a deviation can be observed compared to the other islands. The hospitalisation rate in the years 2007-2013 (the years for which hospitalisation data was available) ranged between 1.5 and 86.4%. An explanation for this high case hospitalisation rate on Sint Maarten could be a result of limited dengue testing on the island on prescription by GPs. If testing is predominantly performed on hospitalised patients and only to a limited

extent on GP prescription, this would bias hospitalisation rates, leading to an overestimate of dengue hospitalisation. A positive dengue test will not change the treatment possibilities for patients. Therefore, the willingness to get tested for dengue after a suspected infection diagnosed by a GP may be quite low.

### 2.2.3 Mortality

In the 2007-2024 period, few fatalities due to DENV infections occurred in the Caribbean part of the Kingdom of the Netherlands. The case fatality rate (number of deaths due to DENV infection divided by the total of registered probable and confirmed DENV cases per annum) never exceeded 1% (range: 0-0.82%). However, the prevalence of specific genetic characteristics in the Dutch Caribbean population, especially sickle cell anaemia, was previously described as an important risk factor that could result in mortality as an outcome of a dengue infection [12]. Given the relatively high prevalence of this genetic disease in the Caribbean region [13], this could pose an increased risk for severe dengue infection within the island populations. This effect was not directly shown in the epidemiological data in this chapter. However, the case reports of two fatal dengue infections during outbreaks in 2010-2011 indicate that this risk should be considered [12].

## 2.3 Sero-epidemiology

Sero-epidemiological studies investigate the presence of specific antibodies that are elicited by vaccination and/or infection. Such studies are of key importance to complementing other means of surveillance. This is particularly insightful for diseases that generally remain largely undetected, for instance because they are not notifiable, or due to the fact that a large part of cases is asymptomatic/mildly symptomatic, as is the case for dengue. As part of the PIENTER-3 study, a population-based sero-epidemiological study (Health Study Caribbean Netherlands; HSCN) was performed on Bonaire, Sint Eustatius and Saba in mid-2017 [14]. The primary aim of the study was to obtain insight into the protection against vaccine-preventable diseases, including an assessment of risk factors, as well as circulation and occurrence of local pathogens, such as dengue. Please note that results of the HSCN have previously been used as guidance for public health policy, for instance on optimisation of the vaccination policy regarding measles and varicella-zoster virus [15].

Participants in the HSCN have been randomly-selected from the population registry in an age-stratified manner (covering ages 0-90 years) and proportional to the population size of each island (see Table 1) – resulting in nearly one third of the total population receiving an invitation. Blood samples ( $n=1,829$ , dried blood spots) were collected, and questionnaires regarding general health, chronic diseases, and potential risk factors for (exposure to) infectious diseases were filled out. The fieldwork started on Bonaire ( $n=1,129$ ), directly followed by Sint Eustatius ( $n=477$ ) and Saba ( $n=223$ ). For the current study, samples were tested for IgG antibodies against a set of arboviruses using an in-house validated micro-array [16]. Exposure to orthoflaviviruses DENV1-4 is the focus for this report. Seropositivity per serotype was determined using the method by Frey *et al.* [17] (with

99% one-sided t-values based on  $n=40$  within-study assumed negative controls), a commonly used approach in the analysis of sero-surveillance data [18]. Due to potential cross-reactivity between DENV1-4 (and to a lesser extent with other flaviviruses), any valid distinction between the four serotypes is not possible. Hence, we report on the seropositivity to any of the four serotypes ('DENV seropositive'). Analyses were further stratified by relevant characteristics, such as island, ethnic background, and age, to detect potential trends. Estimates were weighted to match the general population on each island (as outlined in [15]).

Two-thirds of the Caribbean Netherlands population was DENV seropositive (66% (95% confidence interval (CI) 63-68%)) in 2017. However, large differences were noticeable between the islands. Overall DENV seropositivity was high on Bonaire and Sint Eustatius, both reaching 70% (Bonaire: 68% (95% CI 64-71%); Sint Eustatius: 70% (95% CI 64-75)), but lower on Saba, where nearly four out of ten inhabitants were seropositive (38% (95% CI 30-46%)). Dissimilarities between islands could be due to multiple factors, such as geography, population composition and density, environment/climate, vector control, etcetera. In addition, persons originating from Latin America (and other non-Western countries) were DENV seropositive the most: 82% (95% CI 76-88), followed by persons from Aruba, Curaçao, Sint Maarten, Caribbean Netherlands and Suriname (70% (95% CI 67-73)). The least seropositive were persons of Dutch and other Western descent (23% (95% CI 16-30)). This clear contrast between persons from different ethnic backgrounds is most likely to be due to their lifetime likelihood of past exposure.

Furthermore, with regard to DENV seropositivity a clear age pattern could be observed in the Caribbean Netherlands: a sharp increase in childhood was followed by a slower elevation into adulthood (Figure 8), reaching the highest seropositivity in the oldest ages. Yet, differences between islands and ethnic backgrounds were again apparent. On Bonaire and Sint Eustatius, 60% of adolescents and 70% of young adults were already seropositive, and this increased further to 80% in the older age groups (Figure 9). On Saba, seropositivity was low in children (<20%) and fluctuated between 40-50% in adults. Across all islands, 70% of adolescents from Latin-America were seropositive, compared to 50% among those from the Caribbean part of the Kingdom and Surinamese ethnic descent and 10% of Dutch origin (Figure 10). In the former two groups, seropositivity increased further with age up to 90% into adulthood, while reaching a maximum of 30% in the Dutch residents. This observed age pattern was also clearly reflected by the numbers of years lived on the islands (Figure 11). Around 60% of those who had been living on the islands for 10 years were seropositive. This increased further in a step-wise manner (by 10-year age groups), ultimately reaching nearly 100% in those who had been living on the islands for over 70 years.

Sensitivity analyses applying different cutoffs for seropositivity revealed that even the most conservative cutoff (highest specificity) provided an overall seroprevalence of >60% for Bonaire (64%) and Sint Eustatius (63%) and >30% for Saba (34%).

To conclude, reasonable differences in DENV seropositivity were noticeable within the Caribbean Netherlands population in 2017. Clear trends of higher seropositivity could be observed on Bonaire and Sint Eustatius, among those of non-Dutch ethnic descent, and in adults, adolescents and younger age groups. Please note that, even though we do not have data to directly confirm this, the relatively high DENV circulation in recent years may have concurrently increased the estimates provided in the current study.

Figure 8 Weighted seroprevalence (with 95% confidence intervals) against any of the DENV-1-4 serotypes in the Caribbean Netherlands, 2017, by age group.

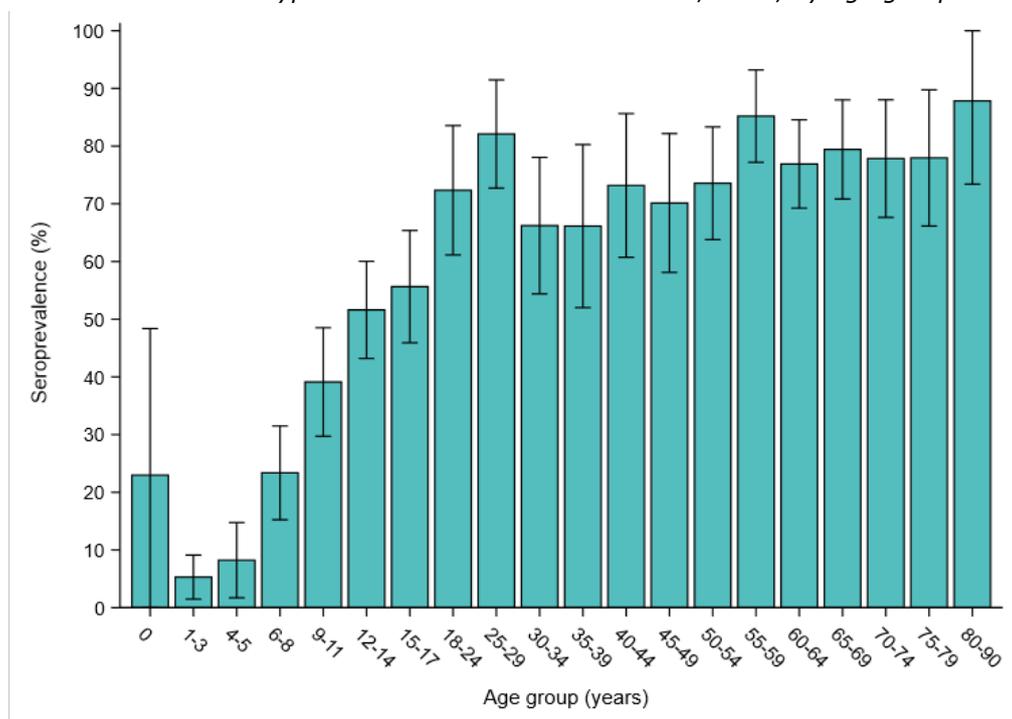


Figure 9 Weighted seroprevalence (with 95% confidence intervals) against any of the DENV-1-4 serotypes in the Caribbean Netherlands, 2017, by island and age group (years).

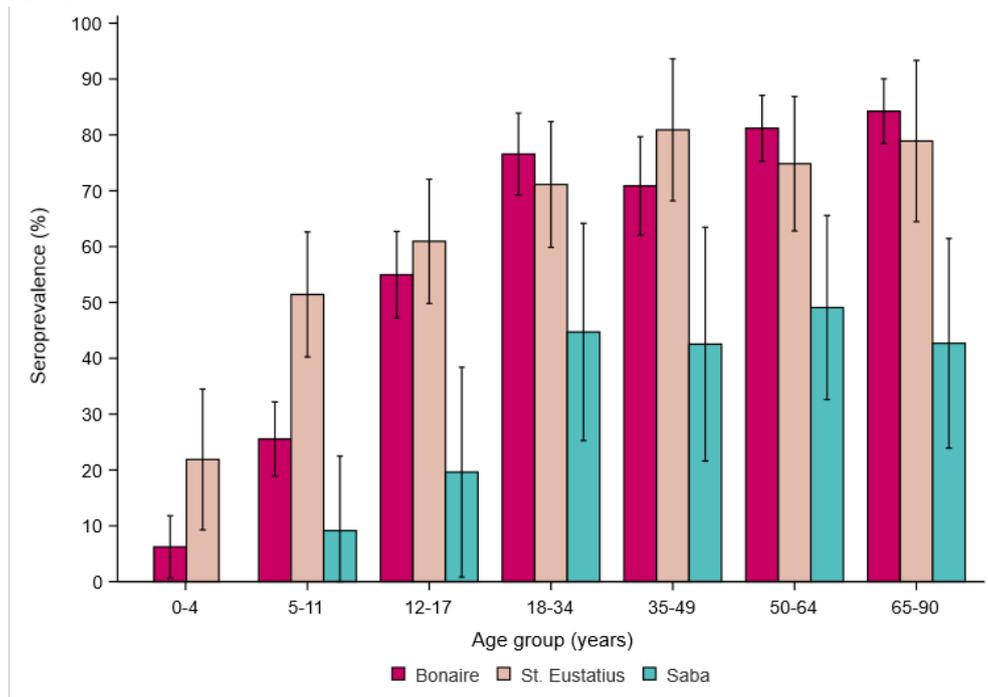
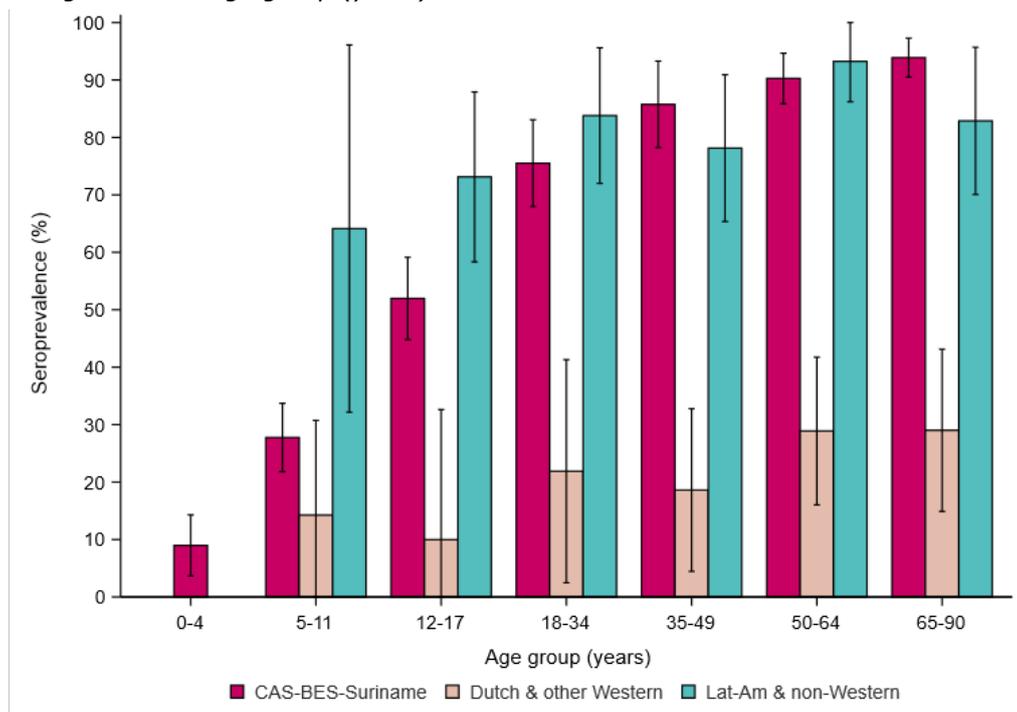
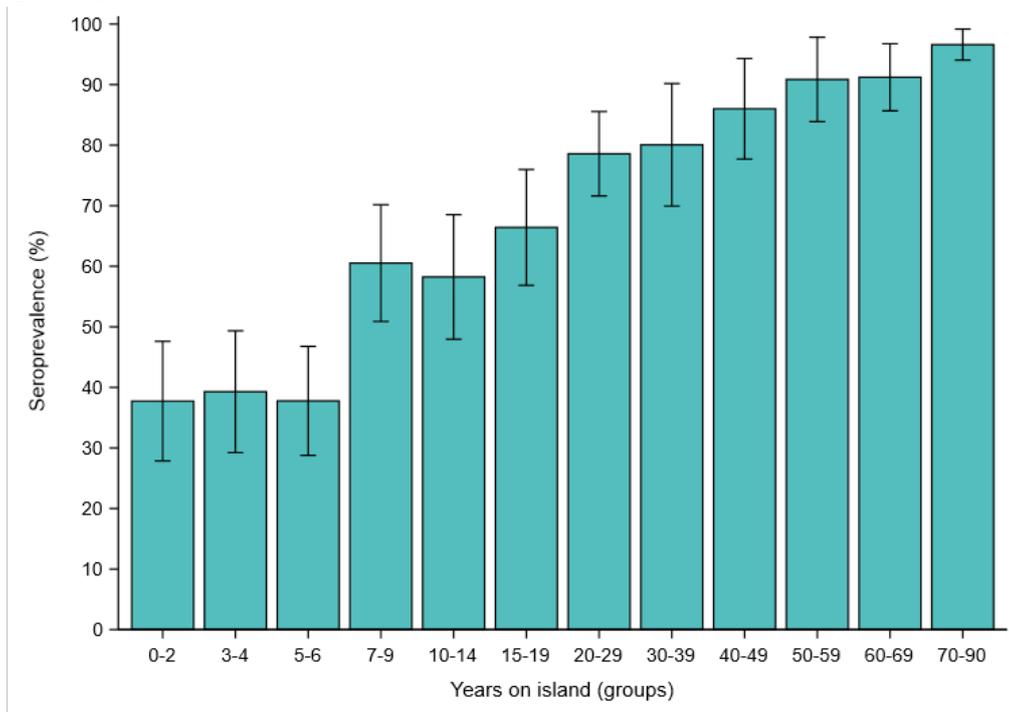


Figure 10 Weighted seroprevalence (with 95% confidence intervals) against any of the DENV-1-4 serotypes in the Caribbean Netherlands, 2017, by ethnic background and age group (years).



CAS-BES-Suriname=Aruba, Curaçao and Sint Maarten (CAS), Bonaire, Sint Eustatius, and Saba (BES) and Suriname; Lat-Am=other Latin American countries.

Figure 11 Weighted seroprevalence (with 95% confidence intervals) against any of the DENV-1-4 serotypes in the Caribbean Netherlands, 2017, by years (groups) lived on the islands.





### 3 Role of vector control

Dengue is a mosquito-borne disease; the presence of a mosquito vector species population is essential for virus transmission and spread. On the islands in the Caribbean part of the Kingdom, the vector species *Aedes aegypti* is present and poses a risk for autochthonous transmission. Vector control programmes are essentially based on source reduction, eliminating *Aedes aegypti* larval habitats from the domestic environment. The 'House Index' (HI), which represents the percentage of houses infested with *Aedes aegypti* larvae and/or pupae, has been widely used as an indicator for assessing vector control programmes and determining the risk of arboviral diseases such as dengue. Different thresholds have been proposed for minimising the risk of dengue transmission, often emphasising the need for HI to be below a specific percentage. These thresholds have been established by organisations such as WHO and PAHO, as well as through various research studies. Historically, the recommended threshold for HI has been below 5% [53] although, more recent studies suggest that transmission can still occur at even lower infestation levels. A HI threshold of 1% or less has been considered to prevent dengue transmission [54]. However, the reliability and sensitivity of the HI indices have been questioned because of a limited quantifiable association among vector indices, meteorological factors, and dengue transmission that could reliably be used for outbreak prediction [55,56].



## 4 Vaccination

### 4.1 Goal of vaccination

It is important to determine which primary outcome is being pursued with vaccination: prevention of hospitalisation, prevention of any clinical disease or reduction of circulation? This choice determines the vaccination strategy and the intended target groups.

### 4.2 Vaccines

There are currently two vaccines approved by the European Medicines Agency (EMA) to prevent Dengue infection: Dengvaxia (CYD-TDV)[47] and Qdenga (TAK-003)[49]. Both vaccines cover all four serotypes of Dengue virus (DENV1-4). There is, however, an increased risk of a clinically severe course of DENV infection after vaccination with Dengvaxia in individuals who have not previously been infected by a dengue virus. Therefore, the vaccine should be used with caution in populations with a low seroprevalence [19,47,48]. Given the epidemiological situation, and based on the recent WHO recommendations, this report will thus only consider the potential benefits and risks of the use of Qdenga® in the Dutch Caribbean region. Qdenga® was approved for use by the EMA on 8 December 2022 [49].

Qdenga® is the second vaccine approved on the European market against dengue virus, and a third vaccine is expected to become available in the near future. Qdenga® is based on DENV2, incorporating specific epitopes of DENV1, DENV3 and DENV4. Thus, the vaccine generates antibodies against the most antigenic areas (structural proteins) of all four serotypes and additionally offers a response against areas, partly conserved in all 4 serotypes, present in the DENV2 backbone. Qdenga® has a vaccination schedule of two doses, with an interval of three months, and is licensed for individuals aged 4 years and over.

### 4.3 Vaccine Efficacy

Vaccine efficacy measures the intrinsic capacity of the vaccine to confer protection after vaccination. This is generally established in prelicensure (placebo-controlled) comparative phase III clinical trials. Qdenga® was studied in one large placebo-controlled efficacy study in more than 20,000 children aged 4-16 years from Latin-America and Asia, primarily measuring protective vaccine efficacy (VE) up to 12 months after the second dose, defined against virologically confirmed dengue (VCD). VE following a booster dose administered 54 months after the second dose to all participants aged 4-11 years was also estimated. Overall vaccine efficacy was 80.2% (95% confidence interval [CI]: 73.3%, 85.3%) against virologically confirmed symptomatic dengue for children and adolescents aged 4-16 years over a 12-month period after the second dose [42]. The VE is, however, mainly driven by protection against virologically confirmed infections with DENV2 (VE 95.1%, 95% CI: 89.9-97.6%), followed by DENV1 (VE 69.8%, 95% CI: 54.8, 79.9) [42]. Protection against DENV3 and DENV4 infection was substantially lower, with particular concerns for DENV3 (49,51), i.e. 48.9% (95% CI:

27.2%, 64.1%) and case numbers were too small to estimate efficacy against DENV4. The same was observed for infections requiring hospitalisation. Overall efficacy against severe dengue and hospitalisations, especially in seropositive individuals, was 90.4% (95% CI: 82.6%, 94.7%) [40].

Vaccine-induced protection waned over time, such that after 54 months of follow-up, the overall vaccine efficacy of Qdenga® declined to 62.8% (95% CI: 41.4%, 76.4%), with a slight difference between subjects who were seropositive at baseline (64.1% (95% CI: 37.4%, 79.4%)), versus those who were seronegative at baseline (60.2% (95% CI 11.1%, 82.1%)). VE against hospitalisation due to dengue remained high at 94.0% (95% CI: (52.2%, 99.3%)) for the subjects who were seropositive at baseline; no data are available for the subjects who were seronegative at baseline (SMPC). Thus, it is likely that the impact of a vaccination programme will depend on geographical characteristics, the infecting serotypes, and the time since vaccination.

#### 4.4 Vaccine safety

Overall safety of Qdenga® is considered acceptable (SMPC, WHO position paper 2024), with mainly general and local reactogenicity in the clinical trials (headache, injection site pain, myalgia, injection site erythema, malaise, asthenia, and fever). These adverse reactions usually occurred within 2 days after the injection, were mild to moderate in severity, had a short duration (1 to 3 days) and were less frequent after the second injection of Qdenga® than after the first injection. Of clinical relevance is the observation of viremia, particularly following the first vaccine dose. Since Qdenga® is a live attenuated vaccine, viremia is to be expected. In the phase-III clinical trial, transient vaccine viremia, associated with mild clinical symptoms (for instance headache, arthralgia, myalgia, rash) in some of the vaccinees, was observed in 49% of Qdenga® vaccinees who were seronegative at baseline and in 16% who were seropositive at baseline, usually starting in the second week post-vaccination (SMPC). Please note that dengue diagnostic tests may be false positive in this period and cannot distinguish between vaccine-related viremia and wild-type dengue infection.

Although a tendency for more severe infection was observed for DENV3 in subjects who were seronegative at baseline, data was not conclusive. An increase in the risk of VCD requiring hospitalisation or severe dengue due to DENV3 in vaccinated seronegative subjects cannot be ruled out conclusively (WHO position paper 2024).

This was also recently concluded in the SAGE position on the safety of Qdenga®, but the possible lack of efficacy against DENV3 in baseline seronegative subjects is reported as a possible concern, and the possibility of enhanced disease due to infections with DENV3 or DENV4 in seronegative vaccinated individuals cannot be ruled out [51].

#### 4.5 Post-marketing experience

Although extensive clinical trials were conducted with Qdenga®, including a placebo-controlled efficacy study [42], no documented post-licensure field experience study has been published so far. Particularly, no clinical efficacy or effectiveness has been evaluated in individuals over the age of 16 years, nor is there any experience with the vaccine in

the Caribbean regional context. This is important, given the current question at hand and the specific Caribbean circumstances concerning the exposure history (including frequency, virus genetics, and orthoflavivirus vaccination history) and genetic and demographic backgrounds among Caribbean populations.

## 4.6 Effectivity

Primary infection with a DENV can result in long-lasting immunity against that specific DENV serotype, as well as in temporary cross-reactive immunity against other DENV serotypes. Secondary DENV infections with another serotype of the virus were shown to cause symptomatic infections [19] and posed an increased risk for severe disease [20, 21]

While many modelling studies of dengue transmission have been performed in the past decades [22-24], many models exclude the effects of vaccination, due to the relatively recent introduction of vaccines against dengue viruses. Whereas, some modelling studies have looked at the impact of vaccination, most focus on dengue-endemic settings [25-28] in heavily populated continental areas (such as Brazil [29] or Thailand [30]) or in densely populated island nations (such as the Philippines [31]). There are few studies that focus on dengue transmission in small-island settings [32-34] or the role of vaccination in these settings.

There are only a very limited number of studies on the impact of Qdenga® on dengue transmission dynamics, particularly within small-island settings. Therefore, the majority of the literature included in this review will be based on studies using the characteristics of the Dengvaxia vaccine. The discussion will, however, focus on how benefits and risks may differ for Qdenga® when compared to Dengvaxia.

We focus on how prior modelling work can answer three questions:

1. Is there a difference between the impact of vaccination on small islands versus large continental areas? (Section 4.6.1)
2. What is the expected quantitative impact of vaccination against Dengue? (Section 4.6.2)
3. Is there a risk of aggravating the severity of Dengue epidemics by (programmatically) vaccinating the population? (Section 4.6.3)

In the final section (Section 4.6.4) we will discuss gaps in the literature and areas for future research.

### 4.6.1 *Impact of vaccination on small islands versus large continental areas* *Transmission dynamics*

The impact of a vaccination programme depends on the transmission dynamics of a disease within the population where the vaccination programme is to be implemented. Small islands often have limited population sizes, unique ecological conditions, and isolated communities, which can result in more geographically isolated, less frequent, but more intense outbreaks, depending on control measures. The transmission settings in isolated geographic areas, such as small Caribbean islands,

may have more predictable transmission patterns [36] compared to larger continental areas, such as Brazil, where variable socioeconomic conditions, differing public health infrastructure, and diverse environmental contexts can cause variable, and more unpredictable, outbreak patterns [37,38]. Additionally, due to higher urbanisation rates, large-scale movement of population, and greater mosquito habitat diversity, large continental areas can experience year-round transmission. By contrast, dengue transmission in isolated areas may be governed by seasonal variation [34] and by introduction of cases into the population. A modelling study on Madeira, Portugal, showed that outbreaks on the island were driven by the arrival of infected individuals on the island [32].

#### *Transmission setting*

Differences in transmission settings (high transmission versus low transmission) can also have an effect on the impact of vaccination campaigns against dengue [25–27]. The BES and CAS islands are not currently classified as high-transmission settings for dengue, unlike regions in South America, such as Brazil. Due to the tropical climate, warm temperatures, and seasonal rainfall on the BES and CAS islands, they are considered high-risk zones for dengue transmission but are currently considered low-transmission settings.

In the context of implementing a vaccination programme, these demographic, geographic, and environmental factors play a large role. Modelling studies suggest that the smaller population sizes and reduced mobility on small islands can result in more localised outbreaks [39]. Thus, targeted vaccination efforts may be more effective on small islands. Targeted vaccination campaigns are much more difficult in larger continental areas, particularly with sustained transmission, due to logistical challenges, such as large-scale distribution, and coordination with other control methods, such as vector management.

#### 4.6.2 *Expected quantitative impact of vaccination against Dengue? Vaccine Impact*

A study that evaluated the results of 10 mathematical models with respect to the long-term safety, public health impact, and cost-effectiveness of routine vaccination with Dengvaxia found that the burden of dengue disease would be reduced by 6%-25% in moderate to high dengue transmission settings (defined as a seroprevalence in 9-year-olds >50%)[27]. However, in settings with low transmission intensity (seroprevalence in 9-year-olds  $\leq$  30%), the models predicted that vaccination could result in a substantial increase in hospitalisation because of dengue. Additionally, the impact of vaccination scaled approximately linearly with the number of people vaccinated. This study also looked at the optimal age of vaccination and found that targeting older children could increase the net benefit of vaccination in settings with moderate transmission intensity [27]. This study did not consider small island populations and how the impact of vaccination might vary depending on the unique conditions among these populations.

A recent paper by Daniels et al. modelled the impact of vaccination in children with a Qdenga-like vaccine in different settings [26]. The study found that in moderate- to high-transmission settings (defined as

seroprevalence in 9-year-olds >60%), vaccination of children aged over six years could reduce the burden of hospitalisation due to dengue by 10-22% on average over ten years. The study found some evidence of a risk of vaccine-induced disease enhancement in seronegative vaccine recipients for DENV3 and DENV4, especially for children under the age of 6 years. Therefore, the study concluded that in lower-transmission settings, the benefits of vaccination are more uncertain [26]. This study has not yet been peer-reviewed.

#### *Cost Effectiveness*

The list price of dengue vaccine Qdenga® is 82 euros per vaccine [43]. The burden of disease due to non-fatal dengue infections, expressed in disability-adjusted life years lost (DALYs) per person, is 0.01–0.03 DALYs per case [52]. A detailed cost-effectiveness analysis would be difficult, due to the paucity of data. Cost-effectiveness modelling studies in the literature have shown that vaccination with Dengvaxia would be cost effective in most endemic settings, provided that effectiveness is sufficiently high and vaccine cost is sufficiently low [27,29,31]. A cost-effect study in Brazil found that routine dengue vaccination of 9-year-olds would be cost-effective when the cost of vaccination per individual is less than \$262 [29]. A similar study found that there is no cost-effective modelling on Qdenga® in non-endemic settings.

#### 4.6.3 *Risk of aggravating the severity of epidemics by vaccinating the population*

##### *Antibody-Dependent Enhancement*

Antibody-Dependent Enhancement (ADE) is one of the major concerns following vaccination against dengue viruses. ADE is a phenomenon where, rather than neutralising the virus, some antibodies enhance viral entry into cells, potentially worsening the disease during subsequent infections with other serotypes of the virus. In individuals who have not been previously infected with DENV (seronegative), vaccination acts as their first exposure and could lead to more severe outcomes because the vaccine can mimic the effect of a prior infection, predisposing these individuals to more severe dengue disease if they are later infected with another DENV serotype. However, the formulation of the new vaccine against dengue, Qdenga®, mitigates the risk of ADE and unlike prior vaccine products (Dengvaxia), Qdenga® is recommended regardless of infection history [44].

Modelling studies have shown that in the short term, large-scale vaccination campaigns in endemic regions can lead to large transient spikes in disease [45] and an increase in hospitalisations, particularly in those who have not had a prior infection [7,10]. Despite these short-term increases in dengue disease, these studies showed an overall decrease in dengue disease in the long term (>10 years) [25,28,45]. These studies were conducted, assuming the characteristics of the Dengvaxia vaccine and in endemic settings with large populations. Therefore, their application to small island population settings is limited. One study also considered low-transmission settings and found that the vaccine's effects might be marginal [25]. The Qdenga® vaccine mitigates the risk of severe disease in seronegative individuals; therefore, a reduced risk of hospitalisations in seronegative individuals following vaccine introduction, can be expected. However, due to the

risk of vaccine-induced disease enhancement in seronegative vaccine recipients for DENV3 and DENV4, especially for children aged under 6 years, one study (not yet peer-reviewed) concluded that in lower transmission settings, the benefits of Qdenga® vaccination are more uncertain [26].

#### 4.6.4 *Discussion on cost-effectiveness*

There is a lack of modelling studies on the impact of vaccination against dengue in small-island populations, particularly with regard to the newly approved Qdenga® vaccine. Prior modelling work using the vaccine characteristics of Dengvaxia found that the impact of a vaccination programme depended on the serostatus prior to vaccination, infecting serotype, age, and disease outcome of interest [25-27,46]. A consensus among modelling studies is that in low-transmission settings, the benefits of a vaccination campaign are uncertain [25-27], and it is currently not the recommendation of the WHO to vaccinate against dengue in low-transmission settings [44]. However, all of these studies were performed assuming the transmission dynamics of large, densely populated areas, such as Brazil and the Philippines. There is not sufficient evidence within the literature to determine the impact of a vaccine campaign against dengue in small-island settings, such as on the islands of the Caribbean part of the Kingdom of the Netherlands.

#### 4.7 **WHO position on programmatic vaccination**

According to WHO ([WHO position paper on dengue vaccines, May 2024](#)), *'vaccination against dengue should be viewed as part of an integrated strategy to control the disease, including vector control, proper case management, community education, and community engagement. Vaccination does not prevent all cases of dengue. Comprehensive vector control must remain a critical component of dengue control programmes. Furthermore, the mosquito vectors of dengue transmit other important viruses, including yellow fever, chikungunya, and Zika viruses. To determine the extent of dengue transmission intensity, countries should consider data on age-specific seroprevalence and/or age-specific dengue hospital admissions. There is no precise age-specific seroprevalence threshold above which vaccination is indicated; the benefit of vaccination will increase with increasing seroprevalence, with better vaccine performance being expected in seropositive persons. Threshold cut-offs for minimal seroprevalence to initiate vaccination should be decided by countries; typically, an SP9 of >60% could be considered an indicator of high dengue transmission. In addition, a mean age of peak dengue-associated hospitalizations of <16 years could be considered an indicator of high dengue transmission.'*

## 5 Conclusions

Dengue vaccination on the Caribbean islands offers several potential benefits but also presents challenges. One of the main advantages is that vaccination, particularly with Qdenga®, has been shown to effectively reduce severe dengue cases and hospitalisations, which are the primary targets of public health interventions. Vaccination can complement ongoing vector control efforts, providing an extra layer of protection during outbreaks, especially when *Aedes aegypti* mosquito populations are high. In areas such as Bonaire and Sint Eustatius, where seroprevalence is around 70%, introducing vaccination could give added protection to those already exposed to the virus.

However, there are also several drawbacks to consider. The vaccine's effectiveness is lower against certain serotypes (DENV3 and DENV4), which may reduce overall protection against severe disease. WHO advises vaccination among children aged between 6-16 years in areas with high dengue transmission intensity (defined as a seroprevalence >60% among at the age of 9 years). However, on small islands, such as in the Dutch Caribbean region, the dengue epidemiology is characterised by intermittent cycles, with some years experiencing significant outbreaks and other years having relatively few cases or none at all. Consequently, vaccination may actually increase the risk of severe disease because of a relatively large group (or even whole birth cohorts) of seronegative individuals. The cost-effectiveness and real-world impact of dengue vaccination in small-island settings remain uncertain due to limited data. Finally, the World Health Organization advises that dengue vaccination should only be considered in areas with high seroprevalence and as part of an integrated dengue control strategy, rather than as a stand-alone intervention.



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## Appendix 1 Census data

Table Census data per year and island used to calculated dengue incidence

	Aruba <sup>a</sup>	Bonaire <sup>b,1</sup>	Curaçao <sup>c</sup>	Saba <sup>b,2</sup>	Sint Eustatius <sup>b,3</sup>	Sint Maarten <sup>d,4</sup>
<b>2007</b>	100,428	11,515	142,902	1,522	2,694	38,927
<b>2008</b>	101,406	12,093	145,220	1,537	2,739	40,009
<b>2009</b>	101,801	12,877	146,543	1,597	2,845	40,915
<b>2010</b>	101,874	13,389	147,122	1,737	2,886	37,429
<b>2011</b>	103,307	15,679	150,563	1,797	3,611	37,055*
<b>2012</b>	104,912	16,463*	151,378	1,806*	3,683*	36,684*
<b>2013</b>	106,438	17,286*	152,798	1,815*	3,757*	36,090
<b>2014</b>	107,176	18,150*	154,846	1,824*	3,832*	37,132
<b>2015</b>	108,635	18,905	156,971	1,811	3,877	38,247
<b>2016</b>	108,818	19,283*	158,989	1,829*	3,683*	39,411
<b>2017</b>	108,651	19,669*	160,338	1,847*	3,499*	40,535
<b>2018</b>	109,164	20,062*	160,012	1,866*	3,324*	40,614
<b>2019</b>	109,241	20,463*	158,659	1,885*	3,158*	41,177
<b>2020</b>	107,932	20,915	156,223	1,933	3,139	42,044
<b>2021</b>	107,468	21,961*	153,671	1,952*	3,202*	42,577
<b>2022</b>	107,152	22,573	151,066	1,911	3,242	42,759
<b>2023</b>	107,566	24,090	155,826	2,035	3,293	42,938
<b>2024</b>	108,027	25,133	155,826	2,060	3,204	42,938

Note: Numbers with \* indicate population estimates; these were generated by:

1. 2012-2014; estimate based on 2008-2010 trend, 2016-2019; estimate based on growth between 2015-2020, 2021; estimate based on 2022-2024 trend  
2012-2014 estimate based on 2008-2011 trend, 2016-2019; estimate based on growth between 2015-2020, 2021; estimate based on 2022-2024 trend
2. 2012-2014; estimate based on 2008-2010 trend, 2016-2019; estimate based on contraction between 2015-2020, 2021; estimate based on 2022-2024 trend
3. 2011-2012; estimate based on contraction between 2010-2013

a: source: cbs.aw

b: sources: cbs.cw statistical year book 2010 and cbs.nl

c: source: cbs.cw historical data

d: source: [Department of Statistics Sint Maarten](#) and [cbs.cw statistical year book 2010](#)

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