POSITION PAPER ON

DENGUE VACCINATION

A recommendation by
Dengue Prevention Advocacy Malaysia

An initiative by

Dengue Prevention Advocacy Malaysia

Malaysian Paediatric Association
PERSATUAN PEDIATRIK MALAYSIA

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ADDENDUM

Purpose

This supplementary document provides clarifications and updates to the DPAM Dengue Position Paper as new scientific evidence on the conditionally approved TAK-003 dengue vaccine becomes available. Recognising that TAK-003 is currently undergoing post-licensure clinical evaluations, additional data on its real-world safety and effectiveness will continue to emerge over time. These surveillance activities are conducted in line with the World Health Organisation (WHO) guidelines to ensure that the vaccine remains safe and effective for the population.[1] It is important to note that this gold-standard practice should not be perceived as a lack of safety data, but rather as a commitment to continuous safety monitoring and public health assurance.

Important notes

1. This addendum is supplementary to the DPAM Dengue Vaccine Position Paper and should be read together with the main document to ensure full comprehension.
2. These updates do not change the overall recommendations regarding dengue vaccination outlined in the main document but provide additional information on safety, administration, and pharmacovigilance.
3. Healthcare professionals (HCPs) should refer to the updated information in this addendum before clinical application.

Disclaimer

All clarifications and updates in this addendum have been reviewed and approved by the DPAM Dengue Vaccine Position Paper expert panel. This addendum is intended for healthcare professional use only and should not be distributed to the public without appropriate context and guidance.

Addendum number: 1
Date issued: July 2025

Reasons
DPAM Dengue Vaccine Position Paper was originally developed based on the TAK-003 package insert dated November 2022 (refer to Appendix, page 39–53). An updated package insert was later issued in June 2025, incorporating post-authorisation findings. Scan the QR code to access the updated package insert.[2]

[1]World Health Organisation (2017). Guidelines on clinical evaluation of vaccines: regulatory expectations. https://www.who.int/publications/m/item/WHO-TRS-1004-web-annex-9
[2]National Pharmaceutical Regulatory Agency (2025). Package insert - QDENGA. Last revision in June 2025. https://quest3plus.bpfk.gov.my/pmo2/detail.php?type=product&id=MAL24026010A

Updates

A) Diagnostic implications following TAK-003 administration

Section 4.1 – Indication and Administration (page 21)

Original entry:
Based on the approved package insert by NPRA released in November 2022 (please refer to the appendix for the full document), TAK-003 is indicated for the prevention of dengue disease in individuals from 4 years of age. It should be administered as a 0.5 mL dose in two separate doses, 3 months apart, regardless of age (NPRA, 2022). If the second dose is delayed, it is not necessary to restart the series, and the second dose should be administered at the first available opportunity (WHO, 2024b).

The need for booster dose(s) has not been established. The vaccine requires complete reconstitution of the lyophilised vaccine with the solvent. It should then be administered through subcutaneous injection, preferably in the upper arm in the deltoid region. It should not be injected intravascularly, intradermally, or intramuscularly (NPRA, 2022).

Added information:
Healthcare professionals (HCPs) should be aware that dengue diagnostic tests including IgG, IgM, NS1 antigen detection and viral RNA detection using real-time quantitative polymerase chain reaction (RT-qPCR) may be positive during vaccine viraemia, which can occur for up to 30 days after vaccination (common after the first dose, but rarely detected after the second dose).[3] These tests cannot distinguish between vaccine-induced viraemia and a natural dengue infection and therefore, cannot be used to confirm a dengue diagnosis in suspected cases with symptom onset within 30 days after vaccination.

According to the Pan American Health Organisation (PAHO), the most reliable way to differentiate between vaccine-derived and wild-type dengue virus infections in such cases is through advanced genome sequencing (refer **Figure Ad1**).[3] However, standardised and validated protocols for this purpose are not yet available. This method can also be costly and time-consuming, potentially limiting its practicality for timely medical decisions. Therefore, in suspected dengue cases with symptom onset within 30 days after dengue vaccination, diagnosis and management will primarily rely on the HCP's clinical evaluation and judgement.

After 30 days post-vaccination, vaccine-induced viraemia is unlikely. Although there are no specific diagnostic guidelines for suspected dengue cases with symptom onset occurring more than 30 days after vaccination, NS1 antigen detection as well as viral RNA detection using RT-qPCR testing (higher sensitivity) can be used to confirm or rule out dengue infection. These tests should be performed within 5 days of symptom onset for optimal accuracy. Additionally, as serological detection of dengue-specific IgG and IgM antibodies may be influenced by prior vaccination or exposure to other flaviviruses, these tests are less reliable for diagnosis in such cases.[4]

[3]Pan American Health Organisation (2024). Technical note: Detection and differentiation of dengue virus in the context of dengue vaccine administration. https://www.paho.org/en/documents/technical-note-detection-and-differentiation-dengue-virus-context-dengue-vaccine
[4]Frazer, J. L., & Norton, R. (2024). Dengue: A review of laboratory diagnostics in the vaccine age. Journal of medical microbiology, 73(5), 10.1099/jmm.0.001833. https://doi.org/10.1099/jmm.0.001833

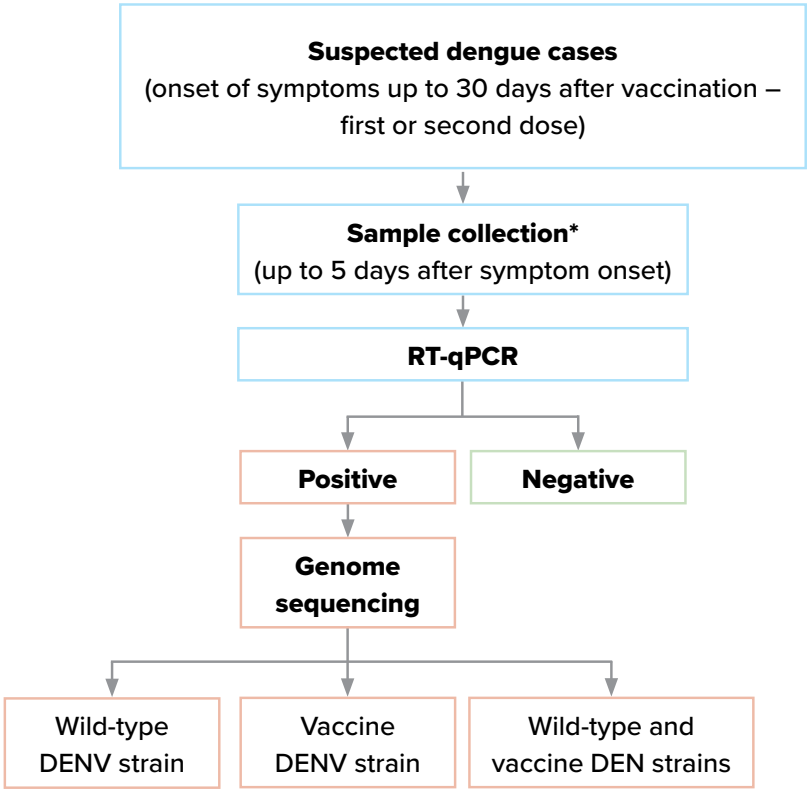

Figure Ad1. *PAHO diagnostic recommendation of suspected dengue cases with symptom onset within 30 days after dengue vaccination.*

In cases where vaccinated individuals (> 30 days post-vaccination) present late (>5 days after symptom onset), NS1 antigen detection and viral RNA detection using RT-qPCR may yield negative results, while IgM and IgG results remain unreliable due to prior vaccination. Therefore, management of such cases should primarily rely on clinical evaluation, epidemiological risk assessment, and clinical judgement.

Overall, it is crucial for all HCPs to recognise these diagnostic limitations and to include dengue vaccination history in their routine assessment of suspected dengue cases. This diagnostic gap underscores the urgent need to develop more specific antigen-, molecular-, and serology-based tests that can accurately differentiate between vaccine-derived and natural dengue infections, thereby ensuring accurate dengue diagnosis in the era of dengue vaccination.[5]

B) Time to avoid vaccination after immunosuppressive treatments

Section 4.3 - Interaction with Other Medications (page 22)

Original entry:
For individuals receiving treatment with immunoglobulins or blood products containing immunoglobulins, it is recommended to wait for at least six weeks, and preferably for three months, following the end of treatment before administering TAK-003. This is to avoid neutralisation of

[5]Low, J. G., Oh, H. M., Leo, Y. S., Kalimuddin, S., Wijaya, L., Pang, J., Lee, T. H., Moss, K. J., Brose, M., & Tricou, V. (2024). IgG, IgM, and Nonstructural Protein 1 Response Profiles after Receipt of Tetravalent Dengue Vaccine TAK-003 in a Phase 2 Randomized Controlled Trial. The American journal of tropical medicine and hygiene, 111(1), 102–106. https://doi.org/10.4269/ajtmh.23-0549

the attenuated viruses contained in the vaccine. The vaccine should not be given to individuals who have received immunosuppressive treatments, like chemotherapy, in the four weeks before getting vaccinated (NPRA, 2022).

Added information:
The time to avoid vaccination after immunosuppressive treatment should be considered on an individual basis.[7]

C) Co-administration with HPV vaccine

Section 4.4 – Co-administration with Other Vaccines (page 22)

Original entry:
TAK-003 may be co-administered at different injection sites, with hepatitis A or yellow fever vaccines (NPRA, 2022). Co-administration with other vaccines, such as the HPV vaccine, has been studied. However, an update to the regulatory label is still pending (Clinicaltrials.gov, 2024).

Added information:
TAK-003 may be co-administered at different injection sites, with hepatitis A, yellow fever or human papillomavirus (HPV) vaccines.[6,7]

In study DEN-308 involving approximately 300 subjects aged 9 to 14 years who received TAK-003 concomitantly with a 9-valent HPV vaccine, there was no effect on the immune response to the HPV vaccine. The study only tested co-administration of the first doses of TAK-003 and the 9-valent HPV vaccine. Non-inferiority of the TAK-003 immune response, when TAK-003 and the 9-valent HPV vaccine were co-administered, has not been directly assessed in the study. In the dengue seronegative study population, dengue antibody responses after co-administration were in the same range as those observed in the Phase 3 study (DEN-301) where efficacy against virologically confirmed dengue (VCD) and hospitalised VCD was shown.[7]

D) Updated reporting on adverse effects following immunisation

Section 4.9 – Side effects (page 25)

Added information:
Cases of thrombocytopenia, anaphylactic reactions (including anaphylactic shock), eye pain, and petechiae have been reported during post-authorisation use. Please refer to Table 4 on page 25 for the complete list of adverse reactions observed in both clinical studies and post-authorisation experience.

For any further clarification or enquiries, kindly contact DPAM Secretariat at:
secretariat@dpam.org.m

[6]National Pharmaceutical Regulatory Agency (NPRA). (2022). Qdenga Package Insert. Last revision in November 2022. https://quest3plus.bpfk.gov.my/front-end/attachment/19386/pharma/539089/539089_20221207_105812_.pdf
[7]National Pharmaceutical Regulatory Agency (2025). Package insert - QDENGA. Last revision in June 2025. https://quest3plus.bpfk.gov.my/pmo2/detail.php?type=product&id=MAL24026010A

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ABOUT DPAM

Dengue Prevention Advocacy Malaysia (DPAM) constitutes a multidisciplinary group of medical and non-medical experts dedicated to making a significant impact in reducing the dengue burden in Malaysia.

Our Vision

To reduce the dengue burden in Malaysia.

Our Mission

To advocate for the strengthening of dengue prevention, management, and control in Malaysia.

Our Aspirations

DPAM supports the national and global dengue targets as highlighted in:

Ministry of Health Malaysia's *"Pelan Strategik Pencegahan dan Kawalan Denggi Kebangsaan 2022-2026"*:

- To reduce national dengue cases by 5% annually
- To maintain the national dengue case-fatality rate below 0.2% every year

World Health Organization's (WHO) "2021-2030 Roadmap for Neglected Tropical Diseases":

- To reduce global dengue incidence and burden by 25% by 2030
- To reduce dengue preventable death to 0% by 2030

Our Scope

The group will focus its efforts on the following areas of WHO's proposed integrated management strategy for dengue prevention and control:

- Epidemiology
- Integrated Vector Management
- Laboratory
- Patient Care
- Environment
- Vaccines

Our Approaches

DPAM aims to achieve its goals through:

- Healthcare professionals' education & communication
- Public education & communication
- Guidelines recommendations
- Research
- Policy recommendations

FOREWORD

BY DPAM CHAIRMAN

Dengue remains a significant public health challenge in Malaysia, where it is hyperendemic and continues to impact lives and healthcare resources. In 2024, dengue cases decreased slightly by 0.58%, but the number of deaths rose by 17%, leading to an increase in the case fatality rate (CFR) from 0.08% in 2023 to 0.10% in 2024. These figures underscore the urgent need to strengthen our efforts to combat this preventable disease.

The World Health Organization (WHO) aims to reduce the global dengue case fatality rate to 0% by 2030, while the Ministry of Health Malaysia (MOH) targets a 5% reduction in dengue cases annually and maintaining a case fatality rate of less than 0.2% each year. Achieving these goals requires a multi-faceted approach, including robust clinical management, effective vector control, and the introduction of vaccination as an important preventive tool.

With the conditional approval of the TAK-003 dengue vaccine by Malaysia's Drug Control Authority (DCA) in 2024, we are now able to recommend and administer vaccination as part of our effort to prevent severe dengue and reduce hospitalisations. As such, DPAM has developed this position paper to serve as a guide for medical professionals to familiarise themselves with the approved dengue vaccine and confidently advocate for its uptake in their clinical practice.

This position paper was developed by a multidisciplinary expert panel comprising infectious disease physicians, paediatricians, consultant microbiologists, health economists, virologists, and public health medicine specialists. It provides evidence-based expert opinions on vaccine safety and efficacy, recommendations for vaccine administration and priority groups, as well as strategies to effectively communicate with patients to enhance vaccine acceptance.

I would like to thank the expert panel members and secretariat for their effort and dedication in developing this position paper. It is my hope that this guideline will empower and encourage healthcare professionals to advocate for vaccination as part of an effort to reduce dengue burden in Malaysia.

Together, let us work towards achieving the goal of zero dengue preventable deaths by 2030 and a future where dengue no longer poses a threat to our communities.

Professor Datuk Dr Zulkifli Ismail
Chairman, DPAM
Advisor, DPAM Position Paper on Dengue Vaccination Expert Panel

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Malaysian Medical Association Public Health Society

Malaysian Paediatric Association

Malaysian Society of Infection Control and Infectious Diseases

Malaysian Society of Infectious Diseases and Chemotherapy

Malaysian Society of Occupational Health Doctors

Malaysian Thoracic Society

Malaysian Urological Association

National Cancer Society Malaysia

List of Abbreviations

ADE — Antibody-Dependent Enhancement
Ae. aegypti — Aedes aegypti
Ae. albopictus — Aedes albopictus
AEs — Adverse Events
ANVISA — National Health Surveillance Agency
AS — Active Surveillance
ATAGI — Australian Technical Advisory Group on Immunisation
CDC — Centre for Disease Control
CI — Confidence Interval
COMBI — Communication for Behavioural Impact
COVID-19 — Coronavirus Disease 2019
CPG — Clinical Practice Guidelines
CPI — Consumer Price Index
CYD-TDV — Chimeric Yellow Fever Virus-DENV Tetravalent Dengue Vaccine
DALY — Disability-Adjusted Life Years
DCA — Drug Control Authority
DENV — Dengue Virus
DHF — Dengue Haemorrhagic Fever
DOSM — Department of Statistics Malaysia
DPAM — Dengue Prevention Advocacy Malaysia
DSS — Dengue Shock Syndrome
EC — European Commission
ECDC — European Centre for Disease Control
EMA — European Medicines Agency
GDP — Gross Domestic Product
HCP — Healthcare Professional
GMR — Geometric Mean Ratio
HIV — Human Immunodeficiency Virus
HLA — Human Leukocytes Antigen
ICER — Incremental Cost-Effectiveness Ratio
IgE — Immunoglobulin Type E
IL — Interleukin
IMS-Dengue — Integrated Management System Dengue
IVM — Integrated Vector Management
JAK — Janus Kinase
MCO — Movement Control Order
MHRA — United Kingdom Medicines and Healthcare Products Regulatory Agency
MOH — Ministry of Health
MSA — Malaysia Specific Annex
nAbs – Neutralising Antibodies
NPRA — National Pharmaceutical Regulatory Agency
NS1 — Non-Structural Protein 1
PAHO — Pan American Health Organization
RMP — Risk Management Plan
SAGE — Strategic Advisory Group of Experts on Immunization
TAP — Transporter Associated with Antigen Processing
TDV — Takeda Dengue Vaccine
TIDES — Phase III Tetravalent Immunization against Dengue Efficacy Study
TNF — Tumor Necrosis Factor
VCD — Virologically-Confirmed Dengue
VE — Vaccine Efficacy
VHR — Vaccine Hesitancy and Refusal
WHO — World Health Organization

Executive Summary

Dengue remains a significant global health threat, with its incidence rising dramatically over the last two decades. Malaysia, being a hyperendemic region, has faced recurrent dengue outbreaks, with 123,133 cases reported in 2023 alone. Despite rigorous public health measures, including vector control and community engagement, the resurgence of dengue cases underscores the need for more robust prevention strategies.

The ongoing transmission of dengue, exacerbated by factors like climate change and international travel, has led to the spread of the disease to previously unaffected areas.In Malaysia, the worst outbreak occurred in 2019 with over 130,000 cases, and though cases declined during the Coronavirus Disease 2019 (COVID-19) pandemic, they have since rebounded. By the first week of November 2024, 112,833 cases and 104 deaths had already been reported. This is an increase of 9.2% in cases and 30% in deaths when compared to the same period in the year 2023.

While clinical management of dengue is primarily supportive, focusing on the early recognition of signs of dengue and judicious fluid management, vaccination has emerged as a crucial tool in preventing severe cases and reducing mortality. In 2024, Malaysia's Drug Control Authority (DCA) conditionally approved the TAK-003 dengue vaccine for individuals age four years and older, recognising its potential to reduce the burden of severe dengue and death, especially in high-risk areas.

The TAK-003 vaccine's introduction is part of a broader integrated management strategy, complementing existing vector and environmental control initiatives. Its efficacy, particularly strong against DENV-2, has been demonstrated in clinical trials, with the vaccine showing a high level of protection against hospitalisations and severe dengue cases over a 4.5-year follow-up period.

The economic burden of dengue in Malaysia is significant, with the costs associated with vector control and dengue illness management amounting to millions of US dollars annually. Prevention efforts, including vaccination, offer a cost-effective solution that can alleviate this burden, reducing both direct healthcare costs and the broader socioeconomic impact of the disease.

DPAM's position and recommendations on the dengue vaccine are as follows:

1) All relevant healthcare professionals (HCPs) should recommend the uptake of the dengue vaccine as per the approved indication.
2) HCPs should view each patient visit as an opportunity to recommend dengue vaccination to all individuals age 4 years and above.
3) Dengue vaccine recommendation is especially crucial if the individual falls into one of the following categories, which increases their risk of getting dengue or developing severe dengue:
    a) Individuals with comorbidities (eg. diabetes, cardiac disorders etc.).
    b) Individuals residing or working in outbreak/hotspot areas.
    c) Individuals residing or working in densely populated areas with poor drainage and waste management.
    d) Individuals at risk of secondary dengue infection (this statement does not necessitate pre-screening)

4) HCPs should be aware of the contraindications as well as precautionary measures as stated in the approved product insert (https://www.npra.gov.my/index.php/my/consumers-2/maklumat/carian-produk-berdaftar-bernotifikasi.html)
5) HCPs are to comply with the mandatory listing of all vaccinees in the dengue registry (HCP Registration for Takeda - Act2Care Registry) as per DCA's requirement.
6) HCPs are to practice effective communication including communicating in a simple and relatable manner with the goal of enhancing and optimising vaccine acceptance among patients and the public.

Point 4:
NPRA website

Point 5:
Act2Care Registry

In conclusion, vaccination, alongside other measures, like vector control, improved clinical management and community empowerment, play a crucial role in reducing the incidence and severity of dengue. Malaysia's efforts to combat dengue must continue to focus on integrated prevention, management and control strategies, all of which will contribute to the country's public health goals of reducing cases and eliminating preventable deaths by 2030.

1.0 Disease and Economic Burden

1.1 Dengue

Dengue is a mosquito-transmitted viral infection and is the leading cause of arthropod-borne viral disease worldwide (Schaefer et al., 2024). It was declared as one of the top ten threats to global health by the World Health Organization (WHO) in 2019. Over the past two decades, the incidence of dengue has surged dramatically, increasing more than tenfold from 505,430 cases in the year 2000 to a historic high of over 6.5 million infections in 2023 (WHO, 2024a; WHO 2019). More concerning, the disease is spreading into previously unaffected areas, including in Europe, due to climate change and international travel from endemic countries (European Centre for Disease Prevention and Control, 2024).

Dengue is considered hyperendemic in Malaysia (Ng et al., 2023; Cheah et al., 2014). The outbreak of dengue in the country exhibits a 4-to-5-year cyclical pattern, following the shift in circulating dengue virus serotypes (DENV-1, 2, 3 and 4) (Suppiah et al., 2023). The worst outbreak was recorded in 2019 with 130,101 cases nationwide, followed by a sharp decline in the number of cases during the COVID-19 pandemic. The decline has been attributed to reduced reporting during the period and enforcement of the Movement Control Order (MCO) (Md Iderus et al., 2023).

However, dengue cases have since resurged, culminating in 123,133 cases in 2023 and, as of epidemiology week 45 (November 3–9, 2024), the Ministry of Health (MOH) has reported 112,833 cases and 104 deaths. This marks a 9.2% increase in cases and a 30% increase in deaths compared with the same period last year (MOH, 2024a). Despite the rising cases, Malaysia has, thus far, managed to keep its case-fatality rate below 0.2%, reflecting clinicians' competencies in managing severe dengue cases. Figure 1 shows the trend of dengue cases and mortality rate in Malaysia from 2014 to 2024 (MOH, 2025; MOH, 2022). Nonetheless, our national target is to achieve a 5% reduction in cases annually and 0% preventable deaths by 2030 (WHO, 2021a; MOH 2022b).

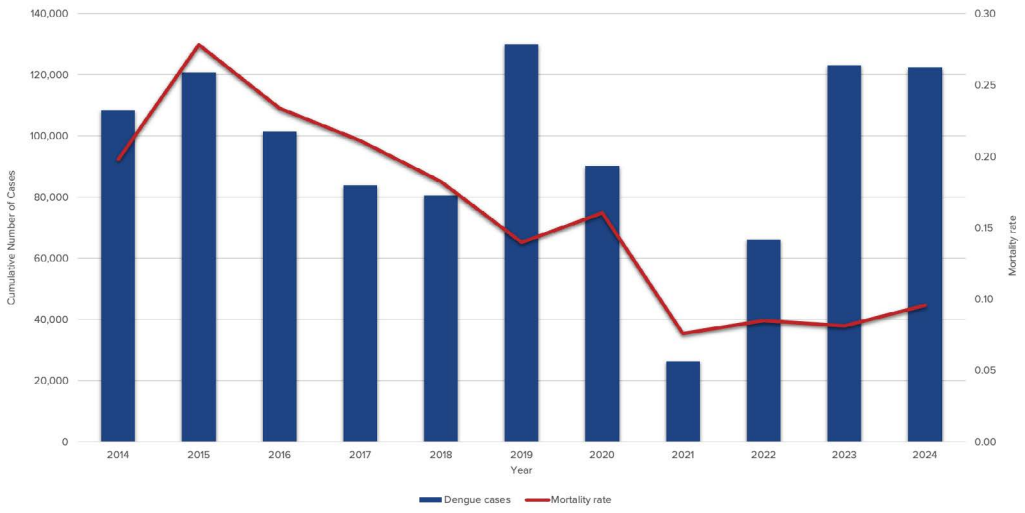

Figure 1. Cumulative dengue cases (n) and mortality rate (%) in Malaysia from 2014 – 2024.

Most dengue infections are asymptomatic or cause mild symptoms, however, they can also lead to severe illness resulting in death (WHO, 2024a). Unfortunately, there is currently no definitive curative treatment, and no antiviral is available for dengue (WHO, 2024a; Tayal et al., 2022). Clinical management of dengue is mainly supportive and resolving symptoms (WHO, 2024a; Tayal et al., 2022). In addition, individuals who are infected for the second time are at greater risk of severe dengue which can be deadly (WHO, 2024a). This amplifies the importance of implementing effective prevention and control measures to combat the disease.

Vaccination is a component of an Integrated Management Strategy for the Prevention and Control of Dengue (IMS-Dengue) (PAHO, 2018). It is an important preventive tool that will complement existing and ongoing integrated vector management (IVM) and communication for behavioural impact (COMBI) initiatives. Such a comprehensive approach to conducting dengue preventive measures will help Malaysia to achieve its targets by 2030 (MOH, 2022b).

On February 8, 2024, the DCA, MOH Malaysia, gave conditional approval for the use of the TAK-003 dengue vaccine to prevent dengue fever in individuals age four years and older (MOH, 2024b). It is currently the only dengue vaccine available for use in Malaysia. Although the vaccine is not a standalone solution for reducing the dengue burden, it has the potential to significantly lower virologically confirmed cases, severe dengue, hospitalisation, and related deaths, especially in high-burden areas.

1.2 Dengue Incidence

Annually, dengue cases are reported throughout Malaysia and in every state. In 2023, the incidence is higher in Selangor, Wilayah Persekutuan, Pulau Pinang, Negeri Sembilan, Perlis, Johor, Kedah and Sabah (MOH, 2024c). Selangor's notably higher incidence rate suggests a significant dengue burden in this state compared to others. It is also worth noting that dengue incidence is higher in densely populated areas especially if it is compounded by drainage issues, poor waste management, and water supply shortages (Chaudhary et al., 2024).

Monitoring circulating DENV serotypes is important because it could help predict dengue outbreaks. It is also important because it has been reported that different dengue serotypes could be associated with different complications and levels of severity (Vincente et al., 2016). However, more studies and scientific evidence are required to confirm the association.

From the perspective of vaccination practice, it is also important to ensure that the vaccine use is efficacious against circulating serotypes in the country. Being a hyperendemic country, all four dengue serotypes can be isolated in Malaysia at any point of time (Cheah et al., 2014). However, the predominant serotypes appear to shift every few years. Most recently, between 2021 to 2022 the predominant serotype was DENV-4, it has since shifted to DENV-2 in the following year (MOH, 2024d).

Table 1 below shows the number of cases and the incidence rate of dengue in each state in Malaysia in 2023 (MOH, 2024c):

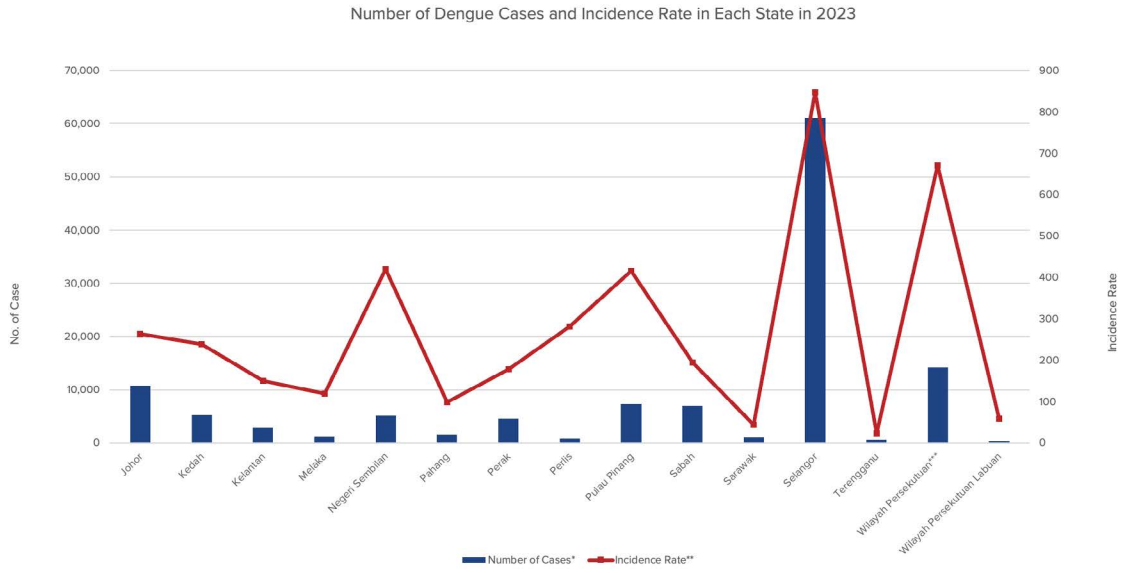

Figure 2. The number of cases and incidence rate of dengue in each state in Malaysia in 2023.
* Including dengue haemorrhagic fever
** Incidence rate per 100, 000 population
***Includes WP Putrajaya

1.3 Economic Burden

It is estimated that globally, dengue resulted in 2.4 million (95% CI: 0.8 million -3.3 million) disability-adjusted life years and 36, 055 deaths (95%CI: 9176–44 468) in 2019, with an estimated cost of US$ 8.9 billion (95% CI: US$ 3.7 billion–19.7 billion), based on direct medical and nonmedical costs as well as costs from illness, care or death (WHO, 2024b).

In Malaysia, Shepard et al. (2012) estimated the economic burden of dengue illness to be US$56 million (MYR196 million) per year, which is approximately US$2.03 (MYR7.14) per capita. It is important to note that this estimation does not include costs associated with dengue prevention and control, dengue surveillance, and long-term sequelae of dengue. The direct and indirect costs per case were estimated at US$555.19 (hospitalised) and US$247.00 (ambulatory) in the private sector and US$518.07 (hospitalised) and US$269.48 (ambulatory) in the public sector. The total aggregated annual national cost of dengue illness was estimated at US$68.9 million, with the private sector accounting for 45.1% and the public sector 54.9%. Furthermore, direct costs represented 33% of the total cost, and indirect costs represented 67%.

Packierisamy et al. (2015) studied the overall economic impact of dengue prevention in Malaysia and its estimated cost. The study examined expenses and resource consumption in 2010 for activities such as inspecting premises for mosquito breeding sites, fogging to eliminate adult mosquitoes, and larviciding potential breeding areas. In 2010, Malaysia allocated approximately US$73.5 million (95% CI = US$62.0–US$86.3 million) to its national dengue vector control programme. The estimated cost per reported dengue case was US$1,591 (95% CI = US$1,343–US$1,870), while the per capita cost was US$2.68 (95% CI = US$2.26–US$3.15). Around 92.2% of these expenditures were concentrated at the district level, primarily covering fogging operations and inspections of premises for mosquito breeding sites. Based on the current Consumer Price Index (CPI), the costs of vector control in 2023 are estimated to have increased to US$95.3 million, while the estimated cost per reported dengue case and the per capita cost are now at US$2,062.64 and US$3.47 respectively.

2.0 Clinical Manifestations

Dengue is an acute febrile illness, caused by infection with any of the four (4) serotypes of dengue virus 1, 2, 3, or 4 (DENV1-4). It is transmitted primarily through the bite of infected *Aedes aegypti (Ae. aegypti)* and *Aedes albopictus (Ae. albopictus)* mosquitoes. (Bhatt et al., 2021). Bloodborne transmission is possible through exposure to infected blood, organs, or other tissues including bone marrow because of the approximately 7-day viremia in humans (CDC, 2024).

Perinatal transmission of DENV may also occur if the mother is infected close to the time of birth. The transmission from mother to newborn can occur via microtransfusions as the placenta detaches or through mucosal contact with maternal blood during labour. Several case studies reported that vertical transmission could be a potential mode of dengue infection (Gupta et al., 2022; Yin et al., 2016). Fever is the most common manifestation of congenital dengue. Breastfeeding has been proposed as a route for vertical transmission of dengue virus (Barthel et al., 2013).

Dengue haemorrhagic fever/ dengue shock syndrome (DHF/DSS) can occur in infants under 1 year old, who are among the high-risk groups for severe dengue. The waning of passively transferred maternal antibodies from mothers with prior dengue infections can enhance the severity of infant's primary dengue infection, potentially leading to severe symptoms (Ranjan et al., 2016; Kliks et al., 1988). Sexual transmission, while considered rare, has been reported (ECDC, 2019; Lee & Lee, 2018; Wilder-Smith, 2013).

Most dengue infections are mild or asymptomatic. However, some people (approximately 5% of cases) can develop severe dengue that will lead to hospitalisation or death (WHO, 2024a; Rathore et al., 2020; St John & Rathore, 2019). For clinical triage, the WHO classifies dengue illness as (WHO, 2024b):

1) dengue without warning signs for progression towards severe dengue
2) dengue with warning signs for progression towards severe dengue
3) severe dengue

Warning signs of severe dengue include persistent vomiting, abdominal pain or tenderness, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement of >2cm, or an increase in haematocrit concurrent with a rapid decrease in platelet count. Severe dengue criteria include any sign of severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment.

While it is not fully understood why only some patients develop severe dengue, there are several host-associated risk factors that have been identified to influence the likelihood of developing complications and/or severe disease (Rathore et al., 2020): 1) prior exposure to DENV due to antibody-dependant enhancement effect, where weakly neutralising antibodies can either enhance virus infection and/or enhance release of pro-inflammatory mediators from immune cells; 2) pre-existing conditions such as diabetes, hypertension, obesity, and cardiac disorders; and 3) genetic predisposition such as polymorphisms in Class-I HLA types, B*48 and B*51, TNF, IL-10, JAK-1 and TAP alleles. Based on pooled data from six seroprevalence studies conducted in Malaysia, it is estimated that more than half of adults age 30 years and above were seropositive, indicating a prior DENV infection and therefore at higher risk of developing severe dengue (Chew et al., 2016).

3.0 Dengue Vaccine as a Tool to Complement Other Preventive Measures

Integrated Vector Management (IVM) is a key strategy recommended by the World Health Organization (WHO) and Pan American Health Organization (PAHO) for controlling mosquito-borne diseases like dengue (WHO, 2022; PAHO, 2019). It is also one of the key strategic pillars in Malaysia's National Dengue Strategic Plan 2022-2026 (MOH, 2022b). IVM involves the coordinated use of various methods to reduce the population of disease-carrying mosquitoes, combining chemical, biological, environmental, and mechanical strategies. This includes habitat modification, use of larvicides and insecticides, introduction of natural predators, and community engagement (Sarimin et al., 2020; WHO, 2009). The aim is to use resources efficiently while minimising environmental and human health risks. While IVM remains a cornerstone in dengue prevention, it is not sufficient on its own (Sarimin et al., 2020).

The WHO's Global Strategic Plan and PAHO's Integrated Management Strategy (IMS) for dengue prevention and control (refer to Figure 3) highlight the importance of other intervention strategies, such as patient care, community involvement and vaccination to effectively address dengue (PAHO, 2019; WHO, 2024d). By combining these efforts, countries can achieve better outcomes in reducing dengue transmission and mitigating its impact on public health. The Ministry of Health Malaysia's (MOH) Clinical Practice Guidelines (CPG) for paediatric dengue management suggested that vaccination is essential for preventing dengue (Abdul Hadi et al., 2020). Vaccination, in combination with mosquito control and public education, should be employed to create a collective impact in reducing severe dengue cases and fatalities in Malaysia.

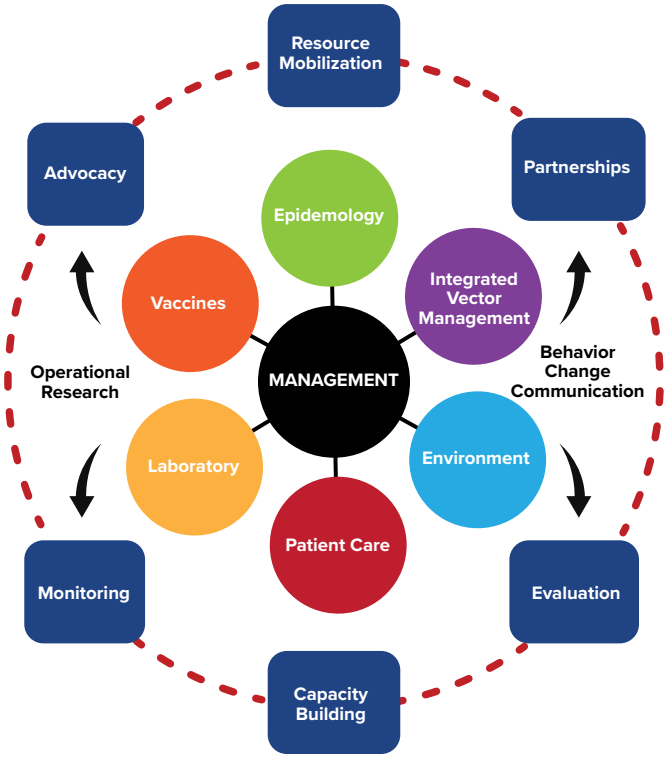

Figure 3. Integrated management strategy for dengue prevention and control.

Currently, there are two dengue vaccines available for use globally, Chimeric Yellow Fever Virus-DENV Tetravalent Dengue Vaccine (CYD-TDV) and TAK-003. However, only TAK-003 has been licensed for use in Malaysia (WHO, 2024c). The World Health Organization (WHO) recommends that countries where there is a high transmission intensity of dengue leading to significant public health problem to consider introducing TAK-003 into their routine immunisation programme (WHO, 2024b). However, it should be viewed as part of an IMS-dengue strategy because vaccination is potentially important in reducing risk of severe dengue but does not prevent all dengue cases. In addition, the integrated vector management (IVM) should remain a critical component of dengue control programmes (WHO, 2024b).

3.1 TAK-003 Approval in Other Countries

Other countries, and regional and global agencies that have also approved the use of the TAK-003 vaccine are as listed in table 1 (this list is non-exhaustive) (Takeda, 2024).

Table 1. List of regulatory agencies, countries and organisations that have approved TAK-003 use.

No.	Country / Agency / Organisation	Approval date	Approved indication
1	Indonesia National Agency for Drug and Food Control (Takagi, 2022)	August 19, 2022	6–45 years
2	European Commission (EC) (EMA, 2022)	December 5, 2022	4 years and above
3	United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) (Vasundhara, 2023)	January 26, 2023	4 years and above
4	National Health Surveillance Agency (ANVISA) Brazil (Vaidya, 2023)	March 2, 2023	4–60 years
5	Argentina (Buenos Aires Herald, 2023)	April 26, 2023	4 years and above
6	Thailand Medicines Regulation Division (Ministry of Public Health of Thailand, 2024)	May 8, 2023	4–60 years
7	Malaysian Drug Control Authority, MOH (MOH, 2024b)	February 8, 2024	4 years and above
8	World Health Organisation (WHO, 2024e)	May 9, 2024	6 years and above
9	Vietnam Drug Administration, MoH (Daklak, 2024)	May 14, 2024	4 years and above
10	Switzerland Swissmedic (Eperon et al., 2024)	July 29, 2024	4 years and above

3.2 Experience with the Use of TAK-003 in Other Dengue Hyperendemic Countries

Indonesia

The TAK-003 vaccine was approved for use in individuals between ages 6 and 45, by the Indonesia National Agency for Drug and Food Control (Takeda, 2022). The approval was granted in August 2022. Since then, the vaccine has been used throughout the country including on a cohort of 9,800

school children between ages 9 and 12 in Balikpapan, East Kalimantan (Angelina, 2024). The TAK-003 vaccines were offered at school and acceptance of the vaccine was high for the first dose (80%). Administration is ongoing for the second dose (20%). Owing to the success of the roll-out in Balikpapan, a second roll-out is planned for 2,750 children in neighbouring Samarinda, the capital city of East Kalimantan (Sapos, 2024). Thus far, there have been no safety alarms reported throughout the implementation of the immunisation programme.

Brazil

The National Health Surveillance Agency (ANVISA) Brazil granted approval for TAK-003 use in individuals between ages 4 and 60 in March 2023 (ANVISA, 2024). Since then, the vaccine has been widely used in Brazil and has been introduced into their National Immunisation Programme by Sistema Único de Saúde (Unified Health System) (Setoh, 2024). The targeted cohort, since the beginning of the immunisation programme in February 2024, is 3.3 million children between ages 10 and 14. This age group was selected as it has the second-highest number of dengue-related hospitalisation, after the elderly. A total of 522 cities with high dengue incidence were selected for this programme. Among the vaccinees mentioned earlier, 16 cases of anaphylaxis have been reported. Beyond these, no other safety concerns have arisen during the programme's implementation.

3.3 Recommendation on the Use of TAK-003 in Non-endemic Countries

The WHO does not recommend pre-vaccination screening strategy to limit vaccination in settings with high dengue transmission (WHO, 2024). However, in countries where dengue is non-endemic, the recommendation may differ. For example, in the United Kingdom (UK), the objective of its immunisation programme is primarily to protect those who are at risk of dengue and have already experienced dengue infection in the past, from a secondary (potentially more severe) infection (UKHSA, 2024). Therefore, the UK Joint Committee on Vaccination and Immunisation (JCVI) recommended that the TAK-003 vaccine be considered for individuals age 4 years and older with likely history of previous dengue infection in the past and are either: 1) planning to travel to areas where dengue infection risk is present or 2) exposed to the dengue virus through work (eg. laboratory staff working with the virus) (UKHSA, 2024).

3.4 Mechanism of Action

The TAK-003 is a live-attenuated vaccine with a DENV-2 strain (TDV-2) providing the genomic backbone of the vaccine. The three other vaccine recombinant strains: TDV-1, TDV-3, and TDV-4 were generated by replacing the E and prM genes of TDV-2 with those from wild-type DENV-1, DENV-2, and DENV-4 strains, respectively (EMA, 2022). The primary mechanism of action is to replicate locally and elicit humoral and cellular immune responses against the four dengue virus serotypes (Takeda, 2023).

In other words, the vaccine triggers a wide range of immune responses, including the production of neutralising antibodies (nAbs) against all four dengue virus serotypes, measured using a plaque reduction neutralisation test that shows a 50% reduction in the virus. It also generates cross-reactive antibodies that inhibit the NS1 protein and induces type-specific memory B cells for all four serotypes. Additionally, the vaccine stimulates CD4+ and CD8+ T-cell responses, promoting the release of T-cells

that produce interferon-γ, tumour necrosis factor α, and interleukin-2 (Tricou et al., 2024).

Based on findings from its phase III clinical trials, the vaccine stimulates a robust immune system response without causing illness. The components of immune response were, activated neutralising antibodies (nAbs), cell-mediated immunity and antibodies to the non-structural protein 1 (NS1) (WHO, 2024b; Jamaluddin, 2020).

3.5 Efficacy

In general, the WHO indicated that for a vaccine to be approved, it must have a high efficacy rate of 50% and above (WHO, 2021b). Vaccine efficacy is measured in controlled clinical trials. The vaccine efficacy (VE) data and information for the TAK-003 vaccine was provided through its Phase III Tetravalent Immunization against Dengue Efficacy Study (TIDES), a double-blind, randomised, placebo-controlled trial conducted among 20,099 participants between ages 4 and 16 years in 8 dengue-endemic countries (Biswal et al., 2019a). As illustrated in Figure 4, the findings were then supplemented with a 4.5-year follow-up at 12, 18, 24, 36, and 54 months (Biswal et al., 2019b; Biswal et al., 2020; López-Medina et al., 2022; Rivera at al., 2022; Tricou et al., 2024).

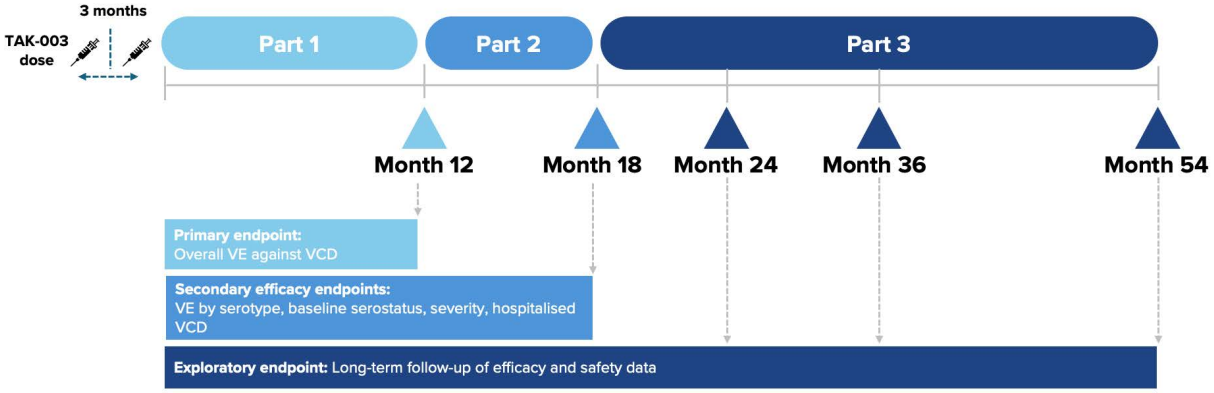

Figure 4. Summary of the phase 3 pivotal trial (TIDES) study design

The summary and conclusion of VE findings for TAK-003 against virologically confirmed dengue (VCD) and hospitalised VCD in seropositive as well as seronegative individuals at months 12, 18 and 54 are as depicted in table 3 (Biswal et al., 2019; Biswal et al., 2020; Tricou et al., 2024). It was observed that while there was some waning of the vaccine efficacy, the overall efficacy against VCD and hospitalised VCD remained good (>50%) over the 4.5-year period.

Table 2. Summary of VE against VCD and hospitalised VCD by baseline serostatus in individuals age 4–16 years old at month 12, 18 and 54, after the second dose.

VE	Against VCD			Against hospitalised VCD		
Duration after 2nd dose	12 months	18 months	54 months	12 months	18 months	54 months
Overall	**80.2%** (73.3 – 85.3)	**73.3%** (66·5 – 78·8)	**61.2%** (56·0 – 65·8)	**95.4%** (88.4 – 98.2)	**90.4%** (82·6 – 94·7)	**84.1%** (77·8 – 88·6)
Seropositive	**82.2%** (74.5 – 87.6)	**76.1%** (68·5 – 81·9)	**64.2%** (58·4 – 69·2)	**94.4%** (84.3 – 98.0)	**91.4%** (81·7 – 95·9)	**85.9%** (78·7 – 90·7)
Seronegative	**74.9%** (57.0 – 85.4)	**66.2%** (49·1 – 77·5)	**53.5%** (41·6 – 62·9)	**97.2%** (79.1 – 99.6)	**88.1%** (68·5 – 95·5)	**79.3%** (63·5 – 88·2)
Remarks	Good efficacy	Good efficacy	Good efficacy	Good efficacy	Good efficacy	Good efficacy
Conclusion	**1)** TAK-003 showed good overall efficacy against confirmed dengue cases and hospitalised dengue cases up to 54 months in individuals between ages 4 and 16 years with seropositive and seronegative at baseline. **2)** Some waning of vaccine efficacy (VE) against the confirmed dengue cases was observed over the 4.5-year trial period. However, VE against hospitalisation remained high. Additional studies are underway to determine the use of a booster dose and its optimal timing (Clinicaltrials.gov, 2024).					

Based on the VEs obtained 12 months after the second dose, it can be concluded that:

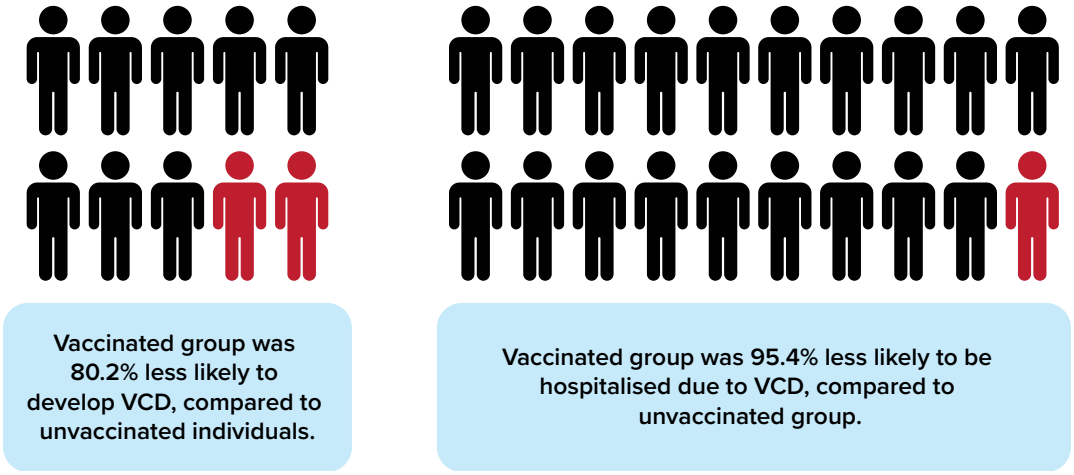

Figure 5. Vaccine Efficacies obtained 12 months after the second dose

Dengue cases have traditionally been more common among children and adolescents. However, the mean age of infection is increasing in certain regions, such as Bangladesh, Thailand, and Malaysia, with a significant proportion of cases now occurring in adults (Ashraf et al., 2023; Pang et al., 2017; Jalil, 2023). This shift underscores the importance of evaluating vaccine efficacy in the adult population.

While a study to evaluate immunogenicity and safety in adults between ages 46 and 79 years old, including individuals with comorbidities, is still in progress (Takeda, 2024), the vaccine developer has already completed an immunobridging study to compare vaccine immunogenicity between seronegative paediatric (4 – 16 years old) and adult (18 – 60 years old) populations (LeFevre et al., 2023). The summary of key findings from the immunobridging study is depicted in Table 3 below.

Table 3. Summary and conclusion from immunobridging study comparing the immunogenicity between baseline seronegative individuals from paediatric population (ages 4 – 16 years old) and adult population (18 – 60 years old). Non-inferiority of the immune response was concluded if the upper bound of the GMR 95% CI between the two age groups was <2.0
CI: confidence interval

Time point	Month 4			Month 9		
Parameters	**Adjusted GMR (95% CI)**	**Lower bound**	**Upper bound**	**Adjusted GMR (95% CI)**	**Lower bound**	**Upper bound**
DENV1	0.69	0.58	0.82	0.62	0.51	0.76
DENV2	0.59	0.52	0.66	0.66	0.57	0.76
DENV3	1.77	1.53	2.04	0.98	0.84	1.14
DENV4	1.05	0.92	1.20	1.01	0.86	1.18
Conclusion	**1)** Non-inferiority of immunogenicity was concluded for all serotype between both age groups at month 9. **2)** TAK-003 produces a biologically comparable immune response in seronegative adults as it does in children, suggesting that its protective effects may be similar in both adult and paediatric populations.					

GMR: geometric mean ratio (between studied age groups)

Unlike vaccine efficacy data, which is obtained through clinical trials, the measure of vaccine effectiveness can only be obtained by establishing how well the vaccine works in the real world WHO, 2021b). There are no known TAK-003 vaccine effectiveness study findings that have been published at the time of writing this document.

3.6 Safety

Overall, during the clinical trials, the vaccine was well tolerated. Solicited adverse events (AEs) occurred more frequently in the vaccine group. However, the frequency of unsolicited AEs reporting was found to be similar between vaccine and placebo groups (WHO, 2024b).

For non-dengue adverse events, solicited adverse events were more common in the vaccine group, while unsolicited events were reported at similar rates in both the vaccine and control groups. The most frequent unsolicited adverse events related to the TAK-003 vaccine were injection site itching (0.7%), bruising (0.6%), and fever (0.2%). Overall, the vaccine was well-tolerated (SAGE, 2023). Although animal studies have not shown any direct or indirect harmful effects of TAK-003 related to developmental or reproductive toxicity, the vaccine has not been specifically studied in pregnant women during clinical trials. Data on pregnancy outcomes are limited in cases where the vaccine was unintentionally given to women who were pregnant or became pregnant shortly after vaccination (SAGE, 2023).

Safety data approximately 22 to 57 months after the first dose show that its safety profile was favourable, regardless of baseline serostatus. There was no evidence of an increase in disease severity, no increased risk of hospitalisation, no severe adverse events were considered related to TAK-003 or placebo, and most importantly no deaths related to TAK-003 (Tricou et al., 2024).

It is important to note that a higher number of DENV-3 infections were reported among baseline seronegative children in the TAK-003 group, although the difference is not statistically significant. Similarly, there was an observed increase in severe dengue and dengue hemorrhagic fever cases among seronegative vaccine recipients, all linked to DENV-3, but this difference is also not statistically significant. Nonetheless, an increase in the risk of VCD requiring hospitalisation or severe dengue due to DENV3 among seronegative subjects cannot be ruled out (WHO, 2024b).

During the clinical trial, no cases of anaphylaxis were observed. However, following the use of TAK-003 in Brazil, between March 1, 2023, and March 11, 2024, it was reported that there were 24 cases of anaphylaxis (63.1 cases per million) out of the 380,358 doses administered. No deaths related to anaphylaxis were reported (Percio et al., 2024). WHO and DCA (MOH), in their approved packaged insert for TAK-003, state precautionary measures to mitigate the risk of anaphylaxis (WHO, 2024b; NPRA, 2022).

3.7 Cost-effectiveness

In addition to that, the TIDES exploratory analyses revealed that over the 4.5-year study follow-up, TAK-003 effectively prevented 84% of hospitalised dengue cases and 61% of virologically confirmed dengue in the overall population, encompassing both seropositive and seronegative individuals (Tricou et al., 2024). Milder forms of dengue significantly add to the overall public health burden. Preventing these less severe cases would not only lower morbidity but also reduce the economic and opportunity costs associated with missed work or school (Thomas, 2023). Moreover, a vaccine that primarily prevents hospitalisation or severe dengue can still have a significant public health impact, especially during high-transmission outbreaks. This is particularly important in low- and middle-income countries where resources for critical care are limited or where there is a lack of experience in treating severe dengue cases. Additionally, freeing up hospital beds that would otherwise be used for dengue patients allows those resources to be redirected toward other public health challenges.
A study by Azzeri et al. (2024) reported significant public health benefits from various TAK-003 vaccination strategies in Malaysia. The most notable impact was achieved through routine vaccination starting at age 7, which led to a 32% reduction in infections and substantial cost savings over a 30-

year period. Adding a catch-up cohort (ages 8 to 11) resulted in an additional 3-4% reduction in infections and further cost savings. Routine vaccination of 7-year-olds at 85.9% coverage resulted in estimated reductions of 39% in symptomatic dengue cases and 43% in hospitalised cases. The DALYs averted totalled 64,680. The vaccination strategy was cost-saving compared to payer (-USD205M) and societal (-USD719M) perspectives, with a vaccine price of USD25.

A study by Shen et. al. (2023) reported that administering the TAK-003 vaccine routinely at age 11 in Thailand prevented 41% of symptomatic dengue cases and 50% of hospitalisations, which equated to 138,783 disability-adjusted life years (DALY) being averted. When routine vaccination was combined with catch-up campaigns targeting 5, 10, and 20 age cohorts, symptomatic cases were reduced by 46%, 49%, and 55%, respectively, while hospitalisations decreased by 57%, 62%, and 69%, respectively. All vaccination strategies proved to be cost saving compared to no vaccination, potentially resulting in cost savings ranging from $1.9 million to $1.6 billion over 20 years, considering both medical expenses and patients' out-of-pocket costs and productivity losses, with vaccine prices ranging between $25 and $60 per dose.

Additionally, Zeng et al. (2018) assessed the cost-effectiveness of dengue vaccination in populations similar to those at the trial sites in various Latin American and Asian countries. Their primary scenarios, involving a 30-year time frame and 80% coverage, included administering a 3-dose routine vaccination at a cost of US$20 per dose starting at age 9, potentially accompanied by catch-up programmes targeting 4- or 8-year cohorts. They derived illness costs per case, dengue mortality, vaccine wastage, and administration costs from existing literature. The study estimated that routine vaccination would lower annual direct and indirect illness costs per capita by 22% (from US$10.51 to US$8.17) in Latin American countries and by 23% (from US$5.78 to US$4.44) in Asian countries.

From a health system perspective, the study showed incremental cost-effectiveness ratio (ICER) averaged US$4,216 per DALY averted across five Latin American countries (ranging from US$666 per DALY in Puerto Rico to US$5,865 per DALY in Mexico). In five Asian countries, the ICER averaged US$3,751 per DALY (ranging from US$1,935 per DALY in Malaysia to US$5,101 per DALY in the Philippines). The vaccine was deemed highly cost-effective (with an ICER below the per capita GDP) in seven countries and cost-effective (with an ICER 1–3 times the per capita GDP) in the remaining three countries. From a societal perspective, routine vaccination was cost-saving in three countries, namely Brazil, Malaysia, and Puerto Rico (Zeng et al, 2018).

4.0 Approval and Indication for Use in Malaysia

The DCA of Malaysia has granted a conditional registration for the TAK-003 tetravalent dengue vaccine (live, attenuated) on February 8, 2024, for use in individuals age 4 years and above without having to conduct a prior seroprevalence test (NPRA, 2024). This makes it possible for individuals in the country to get vaccinated against dengue. The registration conditions set by DCA to the product registration holder, Takeda (M) Sdn Bhd include: 1) to conduct a local post-approval observational study derived from a QDENGA registry involving all QDENGA recipients in the country; 2) to include Malaysia as one of the sites in DEN-401 study, subject to confirmation of study feasibility; 3) to implement Risk Management Plan (RMP) according to the Malaysia Specific Annex (MSA) upon product registration (NPRA, 2024b).

4.1 Indication and Administration

Based on the approved package insert by NPRA released in November 2022 (please refer to the appendix for the full document), TAK-003 is indicated for the prevention of dengue disease in individuals from 4 years of age. It should be administered as a 0.5 mL dose in two separate doses, 3 months apart, regardless of age (NPRA, 2022). If the second dose is delayed, it is not necessary to restart the series and the second dose should be administered at the first available opportunity (WHO, 2024b).

The need for booster dose(s) has not been established. The vaccine requires complete reconstitution of the lyophilised vaccine with the solvent. It should then be administered through subcutaneous injection, preferably in the upper arm in the region of deltoid. It should not be injected intravascularly, intradermally, or intramuscularly (NPRA, 2022).

4.2 Contraindications

The vaccine is contraindicated for individuals with one or more of the following conditions (NPRA, 2022):

1) Hypersensitivity to any of the active substance in the vaccine or a previous dose of TAK-003.
2) 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 before vaccination, as with other live attenuated vaccines.
3) Symptomatic HIV infection or with asymptomatic HIV infection when there is evidence of impaired immune function.
4) Pregnant women.
5) Breastfeeding women.

4.3 Interactions with Other Medications

For individuals receiving treatment with immunoglobulins or blood products containing immunoglobulins, it is recommended to wait for at least six weeks, and preferably for three months, following the end of treatment before administering TAK-003. This is to avoid neutralisation of the attenuated viruses contained in the vaccine. The vaccine should not be given to individuals who have received immunosuppressive treatments, like chemotherapy, in the four weeks before getting vaccinated (NPRA, 2022).

4.4 Co-administration with Other Vaccines

TAK-003 may be co-administered at different injection sites, with hepatitis A or yellow fever vaccines (NPRA, 2022). Co-administration with other vaccines, such as the HPV vaccine, has been studied. However, an update to the regulatory label is still pending (Clinicaltrials.gov, 2024).

4.5 Handling and Storage

This tetravalent-live attenuated vaccine is stable at 2°C–8°C storage and away from light. The shelf life of the vaccine is 18 months. After reconstitution with the solvent provided, it should be used immediately. If not used immediately, the vaccine must be used within two hours. Chemical and physical in-use stability has been demonstrated for two hours at room temperature (up to 32.5°C) from the time of reconstitution of the vaccine vial. After this time period, the vaccine must be discarded (NPRA, 2022).

4.6 Dengue Vaccine Registry

All individuals who have received TAK-003 vaccine will be mandatorily enrolled in the dengue vaccine registry as part of the service to keep track of vaccine recipients and the overall vaccine coverage in Malaysia as per conditions stipulated by DCA. The objective is to establish a systematic method for collecting and maintaining essential data on vaccine recipients who receive the TAK-003 vaccine in Malaysia. It is not intended for research purposes (Sekawi & Dapari, 2024).

The following data that are collected as part of routine clinical practice will be included in the registry (refer to Figure 6):

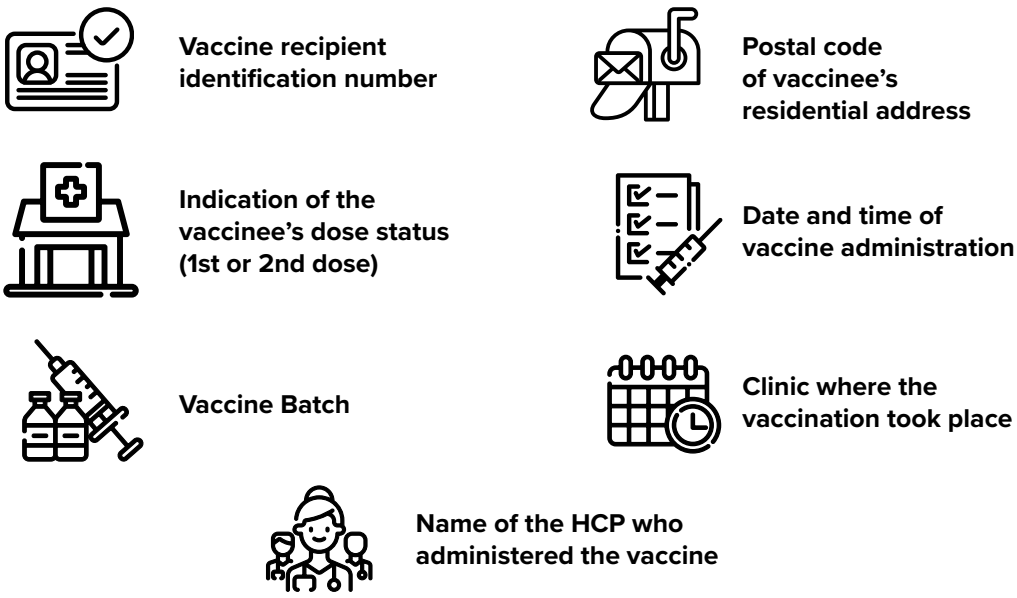

Figure 6. Data collected as part of the clinical practice that will be included in the registry

Vaccine recipients will not be followed up over time and data collection will stop upon entering data on the latest vaccine injection. Data within the registry will be collected and maintained ensuring privacy protection and data security.

4.7 Reporting of Side Effects through Passive and Active Surveillance

Monitoring of vaccine safety in Malaysia is typically done through passive surveillance, whereby there is no follow-up on vaccinees and reports of any Adverse Events Following Immunisation (AEFI) made to the regulatory agency are made independently by the vaccinees themselves, HCPs or vaccine manufacturers. In Malaysia, such AEFI reports can be made by healthcare professionals to the NPRA through its official website: https://www.npra.gov.my/index.php/en/health-professionals/reporting-adr.html

AEFI reporting

However, during this roll-out period of the TAK-003 vaccine, healthcare professionals (HCP) are encouraged to ask vaccine recipients to take part in the active surveillance (AS) initiative, in line with DCA requirements. This initiative allows researchers to follow-up with dengue vaccine recipients to proactively identify any AEs and hospitalisation due to severe dengue cases among vaccinees in Malaysia.

4.8 Participation in Active Surveillance

All vaccine recipients should be offered by their respective physicians to voluntarily participate in the TAK-003 vaccine AS initiative. It is a non-interventional prospective cohort vaccine surveillance study and involves the collection of data from TAK-003 vaccine recipients through survey questionnaires, complemented by other data sources (e.g., discharge summaries) where applicable (Sekawi & Dapari, 2024).

Upon providing consent, enrolled vaccinees will be asked to answer a short baseline e-survey (5-10 minutes in length). The baseline survey will capture information such as demographics, vaccination information (i.e., vaccination clinic, vaccine dose), and contact details. Subsequently, participants will be required to complete four short follow-up surveys (5–10-minutes-long each) via accessing e-survey links within fifteen months after vaccination at the following time points (refer to Figure 7):

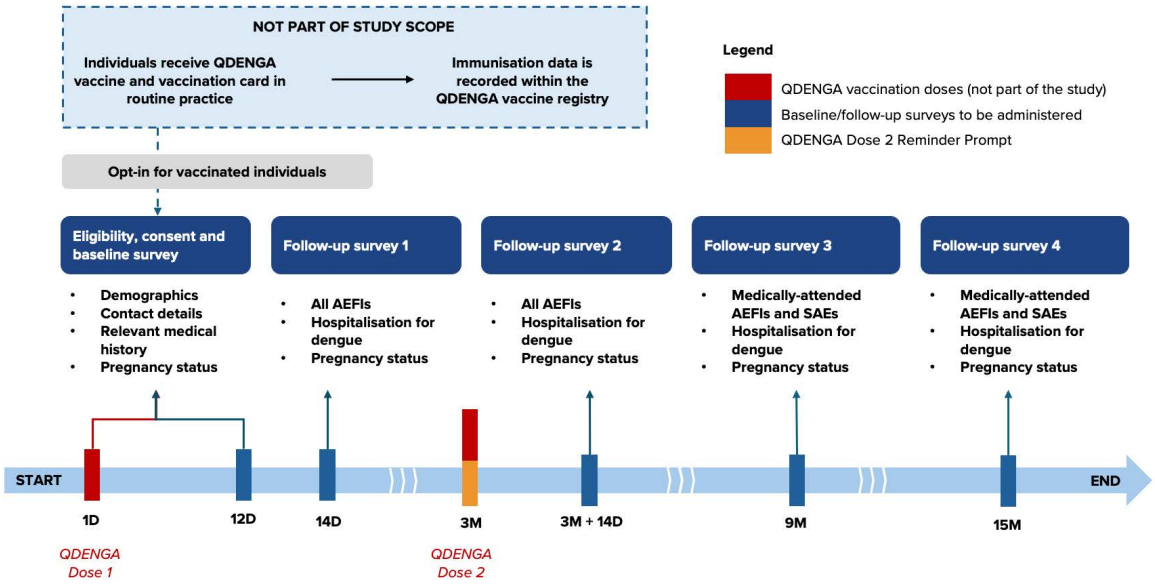

Figure 7. The time points of the four short follow-up surveys following immunisation

4.9 Side Effects

Risk of Antibody-Dependent Enhancement

A major challenge in the development of a DENV vaccine is antibody-dependent enhancement (ADE). ADE occurs if a secondary infection is caused by a heterotypic serotype. It can cause a higher risk of severe disease by enhancing the entry and replication of viruses. ADE is mediated by non-neutralising antibodies generated after the primary DENV infection (Chen et al., 2023). TAK-003 has been generally well tolerated, with no evidence of antibody enhancement in vaccine recipients, and no important safety risks identified, to date (MSIDC, 2023; Takeda, 2022a). TAK-003 is a live-attenuated tetravalent DENV-2-based (PDK-53) recombinant vaccine that elicits neutralising antibodies to DENV structural proteins of all four serotypes and cross-reactive humoral immune responses against DENV NS1 and cross-reactive, cell-mediated immune responses directed against DENV NS proteins. There has been no indication of increased risk of disease severity in dengue-naive participants following TAK-003 vaccination (Tricou et al., 2024).

Allergy and Anaphylaxis

Immediate hypersensitivity reactions to vaccines, with anaphylaxis being the most serious, are rare events, happening in less than one in a million doses given (Stone et al., 2023). Hypersensitivity reactions following vaccination may be triggered by various components of the vaccine, including pathogen-related antigens and excipients like adjuvants, stabilisers, preservatives, emulsifiers,

residual antibiotics, and contaminants from cell cultures (Mahler & Junker, 2022).

During the clinical trial, no instances of anaphylaxis were observed. However, due to the reported anaphylaxis cases in Brazil as mentioned earlier, the currently approved package inserts for TAK-003 outlines precautionary measures to reduce the risk of anaphylaxis, and steps have been taken to include anaphylaxis as a potential adverse reaction. A comprehensive evaluation of the cases from the Brazil national immunisation programme is ongoing (WHO, 2024b).

However, it is noted that occasional cases of anaphylaxis have been reported even among recipients of vaccines with well-established safety profiles, such as the influenza vaccine (Kim et al., 2020). Even though, immediate hypersensitivity reactions, including anaphylaxis, have been reported among TAK-003 recipients, the incidence is low, and no deaths have been reported. Nonetheless, precautionary measures remain critical to ensure patient safety. Therefore, it is encouraged to monitor the vaccinees in the clinic for at least 15 minutes after vaccination (ATAGI, 2022).

Other Adverse Events

The table below summarises the adverse reactions associated with TAK-003, as observed from clinical studies and post-authorisation experience. The safety profile is derived from a pooled analysis of 14,627 study participants age 4–60 years (including 13,839 children and 788 adults) who received the TAK-003 vaccine. Among these participants, 3,830 (3,042 children and 788 adults) were included in a reactogenicity subset for detailed safety evaluation (NPRA, 2022 ; NPRA, 2025).

Table 4. Adverse reactions observed in clinical studies (age 4 to 60 years) and post-authorisation experience (age 4 years and older)

MedDRA System Organ Class	Frequency*	Adverse Reactions
Infections and infestations	Very common	Upper respiratory tract infection (a)
	Common	Nasopharyngitis Pharyngotonsillitis (b)
	Uncommon	Bronchitis Rhinitis
Blood and lymphatic system disorder	Very rare	Thrombocytopenia (c)
Immune system diorders	Not known	Anaphylactic reaction, including anaphylactic shock (c)
Metabolism and nutrition disorders	Very common	Decreased appetite (d)
Psychiatric disorders	Very common	Irritability (d)
Nervous system disorders	Very common	Headache Somnolence (d)
	Uncommon	Dizziness
Eye disorders	Not known	Eye pain (c)
Gastrointestinal disorders	Uncommon	Diarrhoea Nausea Abdominal pain Vomiting

MedDRA System Organ Class	Frequency*	Adverse Reactions
Skin and subcutaneous tissue disorders	Uncommon	Rash (e) Pruritus (f) Urticaria
	Rare	Petechiae (c)
	Very rare	Angioedema
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Common	Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Injection site erythema Malaise Asthenia Fever
	Common	Injection site swelling Injection site bruising (f) Injection site pruritus (f) Influenza-like illness
	Uncommon	Injection site haemorrhage (f) Fatigue(f) Injection site discolouration (f)

*Adverse reactions are categorized by the following frequency classifications: **Very common**: ≥1/10; **Common**: ≥1/100 to <1/10; **Uncommon**: ≥1/1,000 to <1/100; **Rare**: ≥1/10,000 to <1/1,000; **Very rare**: <1/10,000; **Not known**: cannot be estimated from the available data
a Includes upper respiratory tract infection and viral upper respiratory tract infection
b Includes pharyngotonsillitis and tonsillitis
c Adverse reaction observed post-authorisation
d Collected in children below 6 years of age in clinical studies
e Includes rash, viral rash, rash maculopapular, rash pruritic
f Reported in adults in clinical studies

Clinicians play a vital role in safeguarding patient health, not only by prescribing appropriate treatments but also by ensuring that any adverse effects are promptly identified and managed. It is essential for clinicians to actively encourage their patients to report any side effects they may experience during or after treatment. This open line of communication is crucial for timely intervention and improvement of drug safety.

5.0 Effective Communication Strategy to Enhance Vaccine Acceptance

Vaccines are effective only when administered to individuals who need them. The responsibility of communicating the benefits and safety of the dengue vaccine rests with frontline healthcare professionals. Effective communication between HCPs and patients is essential, especially when discussing vaccines. Communication that is clear, empathetic, and grounded in evidence can greatly impact patients' comprehension and acceptance of vaccines, building trust and supporting informed decisions. This section provides three practical strategies for HCPs to promote vaccine confidence and improve uptake among patients and the public.

Tip 1: Avoid prematurely rejecting vaccination on patient's behalf.

Recommendations from HCPs is one of the most influential factors in a patient's decision to get vaccinated. However, sometimes these recommendations were not communicated to patients because the HCPs had preconceived notion that patients will not want to be vaccinated. Some HCPs might assume that patients will reject either because they generally have negative attitudes to vaccines post-pandemic, cannot afford the vaccine or will not trust their recommendations (Hurley, 2014; Su et al., 2022).

While some of these assumptions may be true on a case-by-case basis, HCPs should not take away patients' autonomy or their rights to self-determination in making informed decision about potentially life-saving preventive measures such as vaccinations. Instead, take a positive "presumptive communication" approach where you assume that the patient is ready to accept vaccination because this has been shown to be effective in clinical practice (Opel, 2015; CDC, 2024). For example, you can start your conversation about the vaccine by saying "I think you need the dengue vaccine, because you live in a dengue hotspot area".

Tip 2: Build and strengthen trust through knowledge and transparency

Healthcare providers play a crucial role in influencing a person's decision to get vaccinated against dengue. A cross-sectional study on knowledge, attitudes, and practices related to dengue fever, vector control, and vaccine acceptance found that 90%, 52%, and 44% of Malaysian respondents trusted doctors, pharmacists, and nurses/paramedics, respectively, as their most reliable sources of health-related information (Shafie et al., 2023).

However, this trust must be maintained and strengthened. To do so, healthcare providers must ensure they are well-informed about the vaccines they recommend. It is equally important to be transparent about potential side effects, especially if patients inquire or express concerns. Patients often seek clear and consistent information about vaccines, and it's not uncommon for them to verify what they've been told by doctors with other credible sources available online.

Tip 3: Take an empathetic approach during consultation

Effective communication necessitates an empathetic approach from the healthcare provider. They should understand patients' beliefs and concerns about vaccines and tailor their counselling to align with their perspective and sociocultural context (Maurici et al., 2019). Empathy and communication skills are shaped by the characteristics and experience of HCPs (Maurici et al., 2019). Communicating with empathy involves three main components (Olson, 2019) :

- Actively listening to the person you're communicating with.
- Recognising their level of scientific literacy.
- Striving to understand their concerns without dismissing their emotions.

Tip 4: Provide tailored communication for different patient profiles

Each patient may have varying levels of knowledge and different attitudes toward the dengue vaccine. Tailoring communication strategies to align with each patient's profile is essential for effective engagement. Vaccine acceptance, hesitancy, and refusal exist on a continuum, as shown in Figure 8 (Meerpohl et al., 2014; Ismail et al., 2021).

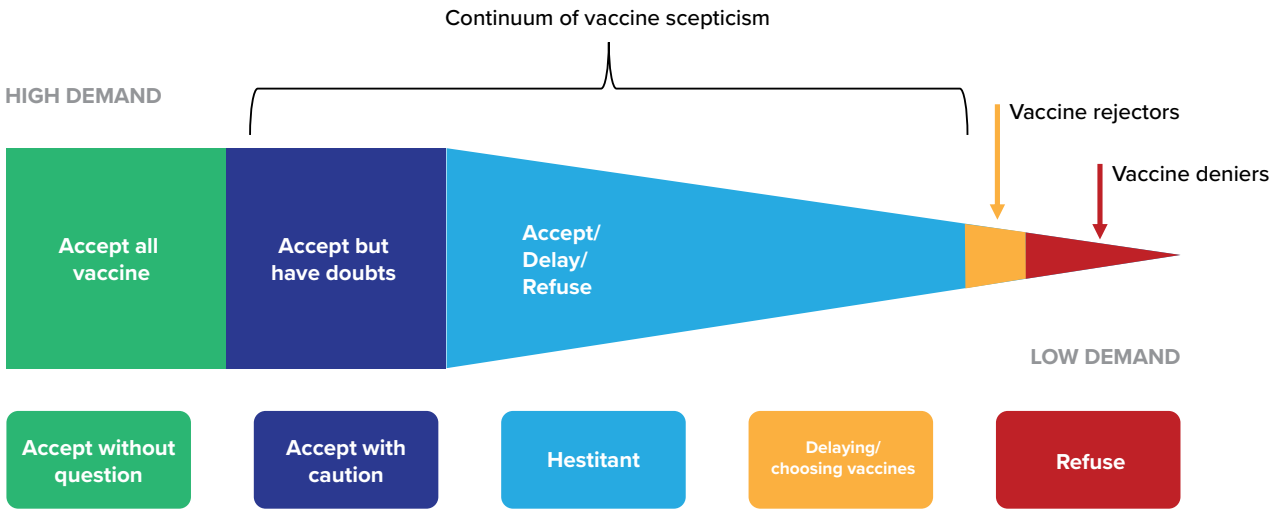

Figure 8. The spectrum of vaccine acceptance, skepticism and rejection among individuals

It is important for HCPs to identify which category their patients fall into to tailor communication techniques effectively. If a patient falls under the continuum of vaccine scepticism or hesitancy, identify their main cause of concern, be it religious, safety, or cost before addressing them accordingly. Avoid mentioning common misinformation about the vaccine that the patient did not ask about, as it might be counterproductive (Ismail et al., 2021; Goje & Kapoor, 2024).

Tip 5: Communicate information in a simple and relatable manner

Several studies have explored how healthcare providers' communication skills may influence clinical outcomes, including patients' adherence to medical recommendations. These studies consistently indicate that effective communication involves minimising jargon and simplifying the message (King & Hoppe, 2013).

Apart from avoiding using complex medical terms, utilising analogies can make information easier to understand, and sharing personal vaccination experiences may make things more relatable to patient. The selected analogy should be familiar to the listener and maintain the same level of abstraction, ensuring it is clear and free of any confusing or contradictory elements. (Innamuri & Ramaswamy, 2020). For instance, getting vaccinated can be compared to wearing a seatbelt or helmet — both are preventive measures that offer protection against serious injury in the event of an accident. Similarly, when discussing vaccine side effects, it may be helpful to liken them to trying new cosmetics or skincare products, despite the potential risk of side effects like an allergic reaction.

In summary, it is crucial for healthcare professionals to effectively address patient concerns and misconceptions, fostering a well-informed and trusting relationship. By actively listening, personalising communication, and offering accurate information in the most simple and relatable manner, HCPs can guide patients towards making informed decisions about immunisation, ultimately contributing to improved public health outcomes.

6.0 DPAM Position and Recommendations

Dengue is hyperendemic in Malaysia, with the number of cases increasing significantly each year. Despite existing public health measures such as vector control and community education initiatives, the problem of dengue continues to grow, highlighting the need for more comprehensive strategies. Vaccination plays a crucial role in bridging the gap in dengue prevention, not only by reducing virologically confirmed cases but, more importantly, by decreasing the incidence of severe dengue and associated deaths. The dengue vaccine is efficacious and safe to be used for individuals age 4 years and above — as per the indication approved by the DCA of Malaysia. DPAM's position and recommendations on the dengue vaccine are as follows:

1) All relevant healthcare professionals (HCPs) should recommend the uptake of the dengue vaccine as per the approved indication.
2) HCPs should view each patient visit as an opportunity to recommend dengue vaccination to all individuals age 4 years and above.
3) Dengue vaccine recommendation is especially crucial if the individual falls into one of the following categories which increases their risk of getting dengue or developing severe dengue:
   a) Individuals with comorbidities (eg. diabetes, cardiac disorders etc.).
   b) Individuals residing or working in outbreak/hotspot areas.
   c) Individuals residing or working in densely populated areas with poor drainage and waste management.
   d) Individuals at risk of secondary dengue infection (this statement does not necessitate pre-screening).
4) HCPs should be aware of the contraindications as well as precautionary measures as stated in the approved product insert (https://www.npra.gov.my/index.php/my/consumers-2/maklumat/carian-produk-berdaftar-bernotifikasi.html).
5) HCPs should comply with the mandatory listing of all vaccinees in the dengue registry (HCP Registration for Takeda - Act2Care Registry) as per DCA's requirement.
6) HCPs should practise effective communication that will enhance and optimise vaccine acceptance among patients and public by avoiding prematurely deciding against vaccination on patient's behalf; building and strengthening trust; taking an empathetic approach; tailoring communication based on patient's profile, as well as communicating in a simple and relatable manner.

Point 4:
NPRA website

Point 5:
Act2Care Registry

In conclusion, the rising incidence of dengue in Malaysia underscores the urgent need for enhanced preventive measures. While current strategies such as vector control and community education remain essential, they have not sufficiently reduced dengue cases and deaths. Vaccination serves as an additional tool to protect the Malaysian population against severe dengue, supporting the country's goal of significantly reducing severe dengue cases and achieving zero preventable dengue deaths by 2030.

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APPENDIX

1. NAME OF THE MEDICINAL PRODUCT

Qdenga (Dengue tetravalent vaccine (live, attenuated))

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 mL) contains:
Dengue virus serotype 1 (live, attenuated)*: ≥ 3.3 log10 PFU**/dose
Dengue virus serotype 2 (live, attenuated)#: ≥ 2.7 log10 PFU**/dose
Dengue virus serotype 3 (live, attenuated)*: ≥ 4.0 log10 PFU**/dose
Dengue virus serotype 4 (live, attenuated)*: ≥ 4.5 log10 PFU**/dose

*Produced in Vero cells by recombinant DNA technology. Genes of serotype-specific surface proteins engineered into dengue type 2 backbone. This product contains genetically modified organisms (GMOs).
#Produced in Vero cells by recombinant DNA technology
**PFU = Plaque-forming units

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Prior to reconstitution, the vaccine is a white to off-white coloured freeze-dried powder (compact cake).

The solvent is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Qdenga is indicated for the prevention of dengue disease in individuals from 4 years of age.

The use of Qdenga should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals from 4 years of age

Qdenga should be administered as a 0.5 mL dose at a two-dose (0 and 3 months) schedule.

The need for a booster dose has not been established.

Other paediatric population (children <4 years of age)

The safety and efficacy of Qdenga in children aged less than 4 years has not yet been established. Currently available data are described in section 4.8 but no recommendation on a posology can be made.

Elderly

No dose adjustment is required in elderly individuals ≥60 years of age. See section 4.4.

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.

The vaccine should not be mixed in the same syringe with any vaccines or other parenteral medicinal products.

For instructions on reconstitution of Qdenga before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or hypersensitivity to a previous dose of Qdenga.
- Individuals with congenital or acquired immune deficiency, including immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids (e.g. 20 mg/day or 2 mg/kg body weight/day of prednisone for 2 weeks or more) within 4 weeks prior to vaccination, as with other live attenuated vaccines.
- Individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.
- Pregnant women (see section 4.6).
- Breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use

General recommendations

Anaphylaxis
As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in the event of a rare anaphylactic reaction following administration of the vaccine.

Review of medical history
Vaccination should be preceded by a review of the individual's medical history (especially with regard to previous vaccination and possible hypersensitivity reactions which occurred after vaccination).

Concurrent illness
Vaccination with Qdenga should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in a deferral of vaccination.

Limitations of vaccine effectiveness
A protective immune response with Qdenga may not be elicited in all vaccinees against all serotypes of dengue virus and may decline over time (see section 5.1). It is currently unknown whether a lack of protection could result in an increased severity of dengue. It is recommended to continue personal protection measures against mosquito bites after vaccination. Individuals should seek medical care if they develop dengue symptoms or dengue warning signs.

There are no data on the use of Qdenga in subjects above 60 years of age and limited data in patients with chronic medical conditions.

Anxiety-related reactions
Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions may occur in association with vaccination as a psychogenic response to the needle injection. It is important that precautions are in place to avoid injury from fainting.

Women of childbearing potential
As with other live attenuated vaccines, women of childbearing potential should avoid pregnancy for at least one month following vaccination (see sections 4.6 and 4.3).

Other
Qdenga must not be administered by intravascular, intradermal or intramuscular injection.

4.5 Interaction with other medicinal products and other forms of interaction

For patients receiving treatment with immunoglobulins or blood products containing immunoglobulins, such as blood or plasma, it is recommended to wait for at least 6 weeks, and preferably for 3 months, following the end of treatment before administering Qdenga, in order to avoid neutralisation of the attenuated viruses contained in the vaccine.

Qdenga should not be administered to subjects receiving immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids within 4 weeks prior to vaccination (see section 4.3).

Use with other vaccines

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.

4.6 Fertility, pregnancy and lactation

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 (see sections 4.4 and 4.3).

Pregnancy

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

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 (see section 4.3).

Breast-feeding

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 (see section 4.3).

Fertility

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
No specific studies have been performed on fertility in humans.

4.7 Effects on ability to drive and use machines

Qdenga has minor influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies, the 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%).

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.

Vaccine viremia

In clinical study DEN-205, transient vaccine viremia was observed after vaccination with Qdenga in 49% of study participants who had not been infected with dengue before and in 16% of study participants who had been infected with dengue before. Vaccine viremia usually started in the second week after the first injection and had a mean duration of 4 days. Vaccine viremia was associated with transient, mild to moderate symptoms, such as headache, arthralgia, myalgia and rash in some subjects. Vaccine viraemia was rarely detected after the second dose.

Tabulated list of adverse reactions

Adverse reactions associated with Qdenga obtained from clinical studies are tabulated below (**Table 1**).

The safety profile presented below is based on a pooled analysis including 14,627 study participants aged 4 to 60 years (13,839 children and 788 adults) who have been vaccinated with Qdenga. This included a reactogenicity subset of 3,830 participants (3,042 children and 788 adults).

Adverse reactions are listed according to the following frequency categories:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000

Table 1: Adverse reactions from Clinical Studies (Age 4 to 60 years)

MedDRA System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Very common	Upper respiratory tract infection[a]
	Common	Nasopharyngitis Pharyngotonsillitis[b]
	Uncommon	Bronchitis Rhinitis
Metabolism and nutrition disorders	Very common	Decreased appetite[c]
Psychiatric disorders	Very common	Irritability[c]
Nervous system disorders	Very common	Headache Somnolence[c]
	Uncommon	Dizziness
Gastrointestinal disorders	Uncommon	Diarrhoea Nausea Abdominal pain Vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash[d] Pruritus[e] Urticaria
	Very rare	Angioedema
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Common	Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Injection site erythema Malaise Asthenia Fever
	Common	Injection site swelling Injection site bruising[e] Injection site pruritus[e] Influenza like illness
	Uncommon	Injection site haemorrhage[e] Fatigue[e] Injection site discolouration[e]

[a] Includes upper respiratory tract infection and viral upper respiratory tract infection
[b] Includes pharyngotonsillitis and tonsillitis
[c] Collected in children below 6 years of age in clinical studies
[d] Includes rash, viral rash, rash maculopapular, rash pruritic
[e] Reported in adults in clinical studies

Paediatric population

Paediatric data in subjects 4 to 17 years of age

Pooled safety data from clinical trials are available for 13839 children (9210 aged 4 to 11 years and 4629 aged 12 to 17 years). This includes reactogenicity data collected in 3042 children (1865 aged 4 to 11 years and 1177 aged 12 to 17 years).

Frequency, type and severity of adverse reactions in children were largely consistent with those in adults. Adverse reactions reported more commonly in children than in adults were fever (11% versus 3%), upper respiratory tract infection (11% versus 3%), nasopharyngitis (6% versus 0.6%), pharyngotonsillitis (2% versus 0.3%), and influenza like illness (1% versus 0.1%). Adverse reactions reported less commonly in children than adults were injection site erythema (2% versus 27%), nausea (0.03% versus 0.8%) and arthralgia (0.03% versus 1%).

The following reactions were collected in 357 children below 6 years of age vaccinated with Qdenga:

decreased appetite (17%), somnolence (13%) and irritability (12%).

Paediatric data in subjects below 4 years of age, i.e. outside the age indication

Reactogenicity in subjects below 4 years of age was assessed in 78 subjects who received at least one dose of Qdenga of which 13 subjects received the indicated 2-dose regimen. Reactions reported with very common frequency were irritability (25%), fever (17%), injection site pain (17%) and loss of appetite (15%). Somnolence (8%) and injection site erythema (3%) were reported with common frequency. Injection site swelling was not observed in subjects below 4 years of age.

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Viral vaccines, ATC code: J07BX04

Mechanism of action

Qdenga contains live attenuated dengue viruses. The primary mechanism of action of Qdenga is to replicate locally and elicit humoral and cellular immune responses against the four dengue virus serotypes.

Clinical efficacy

The clinical efficacy of Qdenga was assessed in study DEN-301, a pivotal Phase 3, double-blind, randomized, placebo-controlled study conducted across 5 countries in Latin America (Brazil, Colombia, Dominican Republic, Nicaragua, Panama) and 3 countries in Asia (Sri Lanka, Thailand, the Philippines). A total of 20,099 children aged between 4 and 16 years were randomized (2:1 ratio) to receive Qdenga or placebo, regardless of previous dengue infection.

Efficacy was assessed using active surveillance across the entire study duration. Any subject with febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) was required to visit the study site for dengue fever evaluation by the investigator. Subjects/guardians were reminded of this requirement at least weekly to maximize the detection of all symptomatic virologically confirmed dengue (VCD) cases. Febrile episodes were confirmed by a validated, quantitative dengue RT-PCR to detect specific dengue serotypes.

Clinical efficacy data for subjects 4 to 16 years of age

The Vaccine Efficacy (VE) results, according to the primary endpoint (VCD fever occurring from 30 days to 12 months after the second vaccination) are shown in **Table 2**. The mean age of the per protocol trial population was 9.6 years (standard deviation of 3.5 years) with 12.7% subjects in the 4-5 years, 55.2% in the 6-11 years and 32.1% in the 12-16 years age-groups. Of these, 46.5% were in Asia and 53.5% were in Latin America, 49.5% were females and 50.5% were males. The dengue serostatus at baseline (before the first injection) was assessed in all subjects by microneutralisation test (MNT_{50}) to allow Vaccine Efficacy (VE) assessment by baseline serostatus. The baseline dengue seronegativity rate for the overall per protocol population was 27.7%.

Table 2: **Vaccine efficacy in preventing VCD fever caused by any serotype from 30 days to 12 months post second vaccination in study DEN-301 (Per Protocol Set)[a]**

	Qdenga N = 12,700[b]	Placebo N = 6316[b]
VCD fever, n (%)	61 (0.5)	149 (2.4)
Vaccine efficacy (95% CI) (%)	80.2 (73.3, 85.3)	
p-value	<0.001	

CI: confidence interval; n: number of subjects with fever; VCD: virologically confirmed dengue
[a] The primary analysis of efficacy data were based on the Per Protocol Set, which consisted of all randomized subjects who did not have any major protocol violations, including not receiving both doses of the correct assignment of Qdenga or placebo
[b] Number of subjects evaluated

VE results according to the secondary endpoints, preventing hospitalisation due to VCD fever, preventing VCD fever by serostatus, by serotype and preventing severe VCD fever are shown in **Table 3**. For severe VCD fever, two types of endpoints were considered: clinically severe VCD cases and VCD cases that met the 1997 WHO criteria for Dengue Haemorrhagic Fever (DHF). The criteria used in Trial DEN-301 for the assessment of VCD severity by an independent "Dengue Case severity Adjudication Committee" (DCAC) were based on the WHO 2009 guidelines. The DCAC assessed all cases of hospitalisation due to VCD utilizing predefined criteria which included an assessment of bleeding abnormality, plasma leakage, liver function, renal function, cardiac function, the central nervous system, and shock. In Trial DEN-301 VCD cases meeting the WHO 1997 criteria for DHF were identified using a programmed algorithm, i.e., without applying medical judgment. Broadly, the criteria included presence of fever lasting 2 to 7 days, haemorrhagic tendencies, thrombocytopenia, and evidence of plasma leakage.

Table 3: Vaccine efficacy in preventing hospitalisation due to VCD fever, VCD fever by dengue serotype, VCD fever by baseline dengue serostatus, and severe forms of dengue from 30 days to 18 months post second vaccination in study DEN-301 (Per Protocol Set)

	Qdenga N=12,700[a]	Placebo N=6316[a]	VE (95% CI)
VE in preventing hospitalisations due to VCD fever[b], n (%)			
Hospitalisations due to VCD fever[c]	13 (0.1)	66 (1.0)	90.4 (82.6, 94.7)[d]
VE in preventing VCD fever by dengue serotype, n (%)			
VCD fever caused by DENV-1	38 (0.3)	62 (1.0)	69.8 (54.8, 79.9)
VCD fever caused by DENV-2	8 (<0.1)	80 (1.3)	95.1 (89.9, 97.6)
VCD fever caused by DENV-3	63 (0.5)	60 (0.9)	48.9 (27.2, 64.1)
VCD fever caused by DENV-4	5 (<0.1)	5 (<0.1)	51.0 (-69.4, 85.8)
VE in preventing VCD fever by baseline dengue serostatus, n (%)			
VCD fever in all subjects	114 (0.9)	206 (3.3)	73.3 (66.5, 78.8)
VCD fever in baseline seropositive subjects	75 (0.8)	150 (3.3)	76.1 (68.5, 81.9)
VCD fever in baseline seronegative subjects	39 (1.1)	56 (3.2)	66.2 (49.1, 77.5)
VE in preventing DHF induced by any dengue serotype, n (%)			
Overall	2 (<0.1)	7 (0.1)	85.9 (31.9, 97.1)
VE in preventing severe dengue induced by any dengue serotype, n (%)			
Overall	2 (<0.1)	1 (<0.1)	2.3 (-977.5, 91.1)

VE: vaccine efficacy; CI: confidence interval; n: number of subjects; VCD: virologically confirmed dengue; DENV: dengue virus serotype
[a] Number of subjects evaluated
[b] key secondary endpoint
[c] Most of the cases observed were due to DENV-2 (0 cases in Qdenga arm and 46 cases in Placebo arm)
[d] p-value <0.001

Early onset of protection was seen with an exploratory VE of 81.1% (95% CI: 64.1%, 90.0%) against

VCD fever caused by all serotypes combined from first vaccination until second vaccination.

Long term protection

In study DEN-301, a number of exploratory analyses were conducted to estimate long term protection from first dose up to 4.5 years after the second dose (**Table 4**).

Table 4: Vaccine efficacy in preventing VCD fever and hospitalisation overall, by baseline dengue serostatus, and against individual serotypes by baseline serostatus from first dose to 54 months post second dose in study DEN-301 (Safety Set)

	Qdenga n/N	Placebo n/N	VE (95% CI) in preventing VCD Fever[a]	Qdenga n/N	Placebo n/N	VE (95% CI) in preventing Hospitalisation due to VCD Fever[a]
Overall	442/13380	547/6687	61.2 (56.0, 65.8)	46/13380	142/6687	84.1 (77.8, 88.6)
Baseline Seronegative, N=5,546						
Any serotype	147/3714	153/1832	53.5 (41.6, 62.9)	17/3714	41/1832	79.3 (63.5, 88.2)
DENV-1	89/3714	79/1832	45.4 (26.1, 59.7)	6/3714	14/1832	78.4 (43.9, 91.7)
DENV-2	14/3714	58/1832	88.1 (78.6, 93.3)	0/3714	23/1832	100 (88.5, 100)[b]
DENV-3	36/3714	16/1832	-15.5 (-108.2, 35.9)	11/3714	3/1832	-87.9 (-573.4, 47.6)
DENV-4	12/3714	3/1832	-105.6 (-628.7, 42.0)	0/3714	1/1832	NP[c]
Baseline Seropositive, N=14,517						
Any serotype	295/9663	394/4854	64.2 (58.4,69.2)	29/9663	101/4854	85.9 (78.7, 90.7)
DENV-1	133/9663	151/4854	56.1 (44.6, 65.2)	16/9663	24/4854	66.8 (37.4, 82.3)
DENV-2	54/9663	135/4854	80.4 (73.1, 85.7)	5/9663	59/4854	95.8 (89.6, 98.3)
DENV-3	96/9663	97/4854	52.3 (36.7, 64.0)	8/9663	15/4854	74.0 (38.6, 89.0)
DENV-4	12/9663	20/4854	70.6 (39.9, 85.6)	0/9663	3/4854	NP[c]

VE: vaccine efficacy, CI: confidence interval, VCD: virologically confirmed dengue, n: number of subjects, N: number of subjects evaluated, NP: not provided

[a] Exploratory analyses; the study was neither powered nor designed to demonstrate a difference between the vaccine and the placebo group

[b] Approximated using a one-sided 95% CI

[c] VE estimate not provided since fewer than 6 cases, for both TDV and placebo, were observed

Additionally, VE in preventing DHF caused by any serotype was 70.0% (95% CI: 31.5%, 86.9%) and in preventing clinically severe VCD cases caused by any serotype was 70.2% (95% CI: -24.7%, 92.9%).

In year-by-year analysis until four and a half years after the second dose, VE in preventing VCD was shown for all four serotypes in baseline dengue seropositive subjects. In baseline seronegative subjects, VE was shown for DENV-1 and DENV-2, but not suggested for DENV-3 and could not be shown for DENV-4 due to lower incidence of cases (**Table 5**).

Table 5: Vaccine efficacy in preventing VCD fever and hospitalisation overall and by baseline dengue serostatus in yearly intervals 30 days post second dose in study DEN-301 (Per Protocol Set)

		VE (95% CI) in preventing VCD Fever N[a] = 19,021	VE (95% CI) in preventing Hospitalisation due to VCD Fever N[a] = 19,021
Year 1[b]	Overall	80.2 (73.3, 85.3)	95.4 (88.4, 98.2)
	By baseline dengue serostatus		
	Seropositive	82.2 (74.5, 87.6)	94.4 (84.4, 98.0)
	Seronegative	74.9 (57.0, 85.4)	97.2 (79.1, 99.6)
Year 2[c]	Overall	56.2 (42.3, 66.8)	76.2 (50.8, 88.4)
	By baseline dengue serostatus		
	Seropositive	60.3 (44.7, 71.5)	85.2 (59.6, 94.6)
	Seronegative	45.3 (9.9, 66.8)	51.4 (-50.7, 84.3)
Year 3[d]	Overall	45.0 (32.9, 55.0)	70.8 (49.6, 83.0)
	By baseline dengue serostatus		
	Seropositive	48.7 (34.8, 59.6)	78.4 (57.1, 89.1)
	Seronegative	35.5 (7.4, 55.1)	45.0 (-42.6, 78.8)
Year 4[e]	Overall	62.8 (41.4, 76.4)	96.4 (72.2, 99.5)
	By baseline dengue serostatus		
	Seropositive	64.1 (37.4, 79.4)	94.0 (52.2, 99.3)
	Seronegative	60.2 (11.1, 82.1)	NP[f]

VE: vaccine efficacy, CI: confidence interval, VCD: virologically confirmed dengue, NP: not provided, N: total number of subjects in the per analysis set, [a] number of subjects evaluated in each year is different.
[b] Year 1 refers to 11 months starting 30 days after second dose.
[c] Year 2 refers to 13 to 24 months after second dose.
[d] Year 3 refers to 25 to 36 months after second dose.
[e] Year 4 refers to 37 to 48 months after second dose.
[f] VE estimate not provided since fewer than 6 cases, for both TDV and placebo, were observed.

Clinical efficacy for subjects from 17 years of age

No clinical efficacy study has been conducted in subjects from 17 years of age. The efficacy of Qdenga in subjects from 17 years of age is inferred from the clinical efficacy in 4 to 16 years of age by bridging of immunogenicity data (see below).

Immunogenicity

In the absence of correlates of protection for Dengue, the clinical relevance of immunogenicity data remains to be fully understood.

Immunogenicity data for subjects 4 to 16 years of age in endemic areas

The GMTs by baseline dengue serostatus in subjects 4 to 16 years of age in study DEN-301 are shown in **Table 6**.

Table 6: Immunogenicity by baseline dengue serostatus in study DEN-301 (Per Protocol Set for Immunogenicity)[a]

	Baseline Seropositive		Baseline Seronegative	
	Pre-Vaccination N=1816*	1 month Post-Dose 2 N=1621	Pre-Vaccination N=702	1 month Post-Dose 2 N=641
DENV-1				
GMT	411.3	2115.2	5.0	184.2
95% CI	(366.0, 462.2)	(1957.0, 2286.3)	NE**	(168.6, 201.3)
DENV-2				
GMT	753.1	4897.4	5.0	1729.9
95% CI	(681.0, 832.8)	(4645.8, 5162.5)	NE**	(1613.7, 1854.6)
DENV-3				
GMT	357.7	1761.0	5.0	228.0
95% CI	(321.3, 398.3)	(1645.9, 1884.1)	NE**	(211.6, 245.7)
DENV-4				
GMT	218.4	1129.4	5.0	143.9
95% CI	(198.1, 240.8)	(1066.3, 1196.2)	NE**	(133.6, 155.1)

N: number of subjects evaluated; DENV: Dengue virus; GMT: Geometric Mean Titre; CI: confidence interval; NE: not estimated

[a] The immunogenicity subset was a randomly selected subset of subjects, and the Per Protocol Set for Immunogenicity was the collection of subjects from that subset who also belong to the Per Protocol Set

* For DENV-2 and DENV-3: N= 1815

** All subjects had GMT values below LLOD (10), hence were reported as 5 with no CI values

Immunogenicity data for subjects 18 to 60 years of age in non-endemic areas

The immunogenicity of Qdenga in adults 18 to 60 years of age was assessed in DEN-304, a Phase 3 double-blind, randomized, placebo-controlled study in a non-endemic country (US). The post-dose 2 GMTs are shown in **Table 7**.

Table 7: GMTs of dengue neutralising antibodies in study DEN-304 (Per Protocol Set)

	Baseline Seropositive*		Baseline Seronegative*	
	Pre-Vaccination N=68	1 month Post-Dose 2 N=67	Pre-Vaccination N=379	1 month Post-Dose 2 N=367
DENV-1				
GMT	13.9	365.1	5.0	268.1
95% CI	(9.5, 20.4)	(233.0, 572.1)	NE**	(226.3, 317.8)
DENV-2				
GMT	31.8	3098.0	5.0	2956.9
95% CI	(22.5, 44.8)	(2233.4, 4297.2)	NE**	(2635.9, 3316.9)
DENV-3				
GMT	7.4	185.7	5.0	128.9
95% CI	(5.7, 9.6)	(129.0, 267.1)	NE**	(112.4, 147.8)
DENV-4				
GMT	7.4	229.6	5.0	137.4
95% CI	(5.5, 9.9	(150.0, 351.3)	NE**	(121.9, 155.0)

N: number of subjects evaluated; DENV: Dengue virus; GMT: Geometric Mean Titre; CI: confidence interval; NE: not estimated

* Pooled data from Dengue tetravalent vaccine Lots 1, 2 and 3

** All subjects had GMT values below LLOD (10), hence were reported as 5 with no CI values

The bridging of efficacy is based on immunogenicity data and results from a non-inferiority analysis, comparing post-vaccination GMTs in the baseline dengue seronegative populations of DEN-301 and DEN-304 **(Table 8)**. Protection against dengue disease is expected in adults although the actual magnitude of efficacy relative to that observed in children and adolescents is unknown.

Table 8: GMT ratios between baseline dengue seronegative subjects in studies DEN-301 (4-16 years) and DEN-304 (18-60 years) (Per Protocol Set for Immunogenicity)

GMT Ratio* (95% CI)	DENV-1	DENV-2	DENV-3	DENV-4
1m post-2nd dose	0.69 (0.58, 0.82)	0.59 (0.52, 0.66)	1.77 (1.53, 2.04)	1.05 (0.92, 1.20)
6m post-2nd dose	0.62 (0.51, 0.76)	0.66 (0.57, 0.76)	0.98 (0.84, 1.14)	1.01 (0.86, 1.18)

DENV: Dengue virus; GMT: Geometric Mean Titre; CI: confidence interval; m: month(s)
*Non-inferiority: upper bound of the 95% CI less than 2.0.

Long-term persistence of antibodies

The long-term persistence of neutralising antibodies was shown in study DEN-301, with titres remaining well above the pre-vaccination levels for all four serotypes, up to 51 months after the first dose.

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed with Qdenga.

5.3 Preclinical safety data

Non-clinical safety data revealed no special hazard for humans based on conventional studies of single dose, local tolerance, repeated dose toxicity, and toxicity to reproduction and development. In a distribution and shedding study, there was no shedding of Qdenga RNA in faeces and urine, confirming a low risk for vaccine shedding to the environment or transmission from vaccinees. A neurovirulence study shows that Qdenga is not neurotoxic.
Although no relevant hazard was identified, the relevance of the reproductive toxicity studies is limited, since rabbits are not permissive for dengue virus infection.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
α,α-Trehalose dihydrate
Poloxamer 407
Human serum albumin
Potassium dihydrogen phosphate
Disodium hydrogen phosphate
Potassium chloride
Sodium chloride

Solvent:
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other vaccine or medicinal products except for the solvent provided.

6.3 Shelf life

The expiry date is indicated on the label and packaging.

After reconstitution with the solvent provided, Qdenga should be used immediately.

If not used immediately, Qdenga must be used within 2 hours.

Chemical and physical in-use stability have been demonstrated for 2 hours at room temperature (up to 32.5°C) from the time of reconstitution of the vaccine vial. After this time period, the vaccine must be discarded. Do not return it to the refrigerator.

From a microbiological point of view Qdenga should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze.
Store in the original package.

For storage conditions after reconstitution of Qdenga, see section 6.3.

6.5 Nature and contents of container

Qdenga powder and solvent for solution for injection:

- Powder (1 dose) in glass vial (Type-I glass), with a stopper (butyl rubber) and aluminium seal with green flip-off plastic cap + 0.5 mL solvent (1 dose) in glass vial (Type-I glass), with a stopper (bromobutyl rubber) and aluminium seal with purple flip-off plastic cap

  Pack size of 1 or 10.

Qdenga powder and solvent for solution for injection in pre-filled syringe:

- Powder (1 dose) in vial (Type-I glass), with a stopper (butyl rubber) and aluminium seal with green flip-off plastic cap + 0.5 mL solvent (1 dose) in pre-filled syringe (Type-I glass), with a plunger stopper (bromobutyl) and a tip cap (polypropylene), with 2 separate needles

  Pack size of 1 or 5.

- Powder (1 dose) in vial (Type-I glass), with a stopper (butyl rubber) and aluminium seal with green flip-off plastic cap + 0.5 mL solvent (1 dose) in pre-filled syringe (Type-I glass), with a plunger stopper (bromobutyl) and a tip cap (polypropylene), without needles

  Pack size of 1 or 5.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

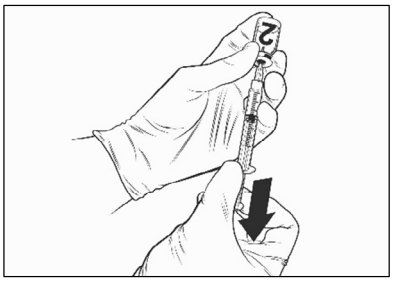
Instructions for reconstitution of the vaccine with the solvent presented in vial

Qdenga is a 2-component vaccine that consists of a vial containing lyophilised vaccine and a vial containing solvent. The lyophilised vaccine must be reconstituted with solvent prior to administration.

Use only sterile syringes for reconstitution and injection of Qdenga. Qdenga should not be mixed with other vaccines in the same syringe.

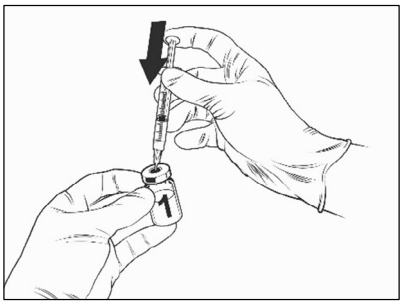
To reconstitute Qdenga, use only the solvent (0.22% sodium chloride solution) supplied with the vaccine since it is free of preservatives or other anti-viral substances. Contact with preservatives, antiseptics, detergents, and other anti-viral substances is to be avoided since they may inactivate the vaccine.

Remove the vaccine and solvent vials from the refrigerator and place at room temperature for approximately 15 minutes.



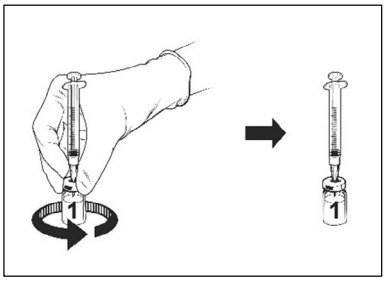
Solvent vial

- Remove the caps from both vials and clean the surface of stoppers on top of the vials using an alcohol wipe.
- Attach a sterile needle to a sterile 1 mL syringe and insert the needle into the solvent vial. The recommended needle is 23G.
- Slowly press the plunger completely down.
- Turn the vial upside down, withdraw the entire contents of the vial and continue to pull plunger out to 0.75 mL. A bubble should be seen inside of the syringe.
- Invert the syringe to bring the bubble back to the plunger.



Lyophilised vaccine vial

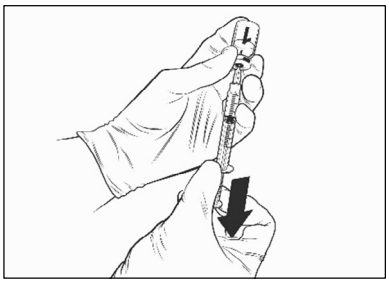
- Insert the needle of the syringe assembly into the lyophilised vaccine vial.
- Direct the flow of the solvent toward the side of the vial while slowly depressing the plunger to reduce the chance of forming bubbles.



Reconstituted vaccine

- Release your finger from the plunger and, holding the assembly on a flat surface, gently swirl the vial in both directions with the needle syringe assembly attached.
- DO NOT SHAKE. Foam and bubbles may form in the reconstituted product.
- Let the vial and syringe assembly sit for a while until the solution becomes clear. This takes about 30-60 seconds.

Following reconstitution, the resulting solution should be clear, colourless to pale yellow, and essentially free of foreign particulates. Discard the vaccine if particulates are present and/or if it appears discoloured.



Reconstituted vaccine

- Withdraw the entire volume of the reconstituted Qdenga solution with the same syringe until an air bubble appears in the syringe.
- Remove the needle syringe assembly from the vial.
- Hold the syringe with the needle pointing upwards, tap the side of the syringe to bring the air bubble to the top, discard the attached needle and replace with a new sterile needle, expel the air bubble until a small drop of the liquid forms at the top of the needle. The recommended needle is 25G 16 mm.
- Qdenga is ready to be administered by subcutaneous injection.

Qdenga should be administered immediately after reconstitution. Chemical and physical in-use stability have been demonstrated for 2 hours at room temperature (up to 32.5°C) from the time of reconstitution of the vaccine vial. After this time period, the vaccine must be discarded. Do not return it to the refrigerator. From a microbiological point of view Qdenga should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

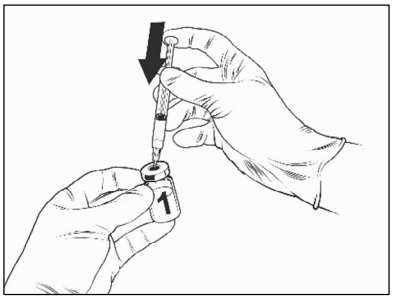
Instructions for reconstitution of the vaccine with solvent presented in pre-filled syringe

Qdenga is a 2-component vaccine that consists of a vial containing lyophilised vaccine and solvent provided in the pre-filled syringe. The lyophilised vaccine must be reconstituted with solvent prior to administration.

Qdenga should not be mixed with other vaccines in the same syringe.

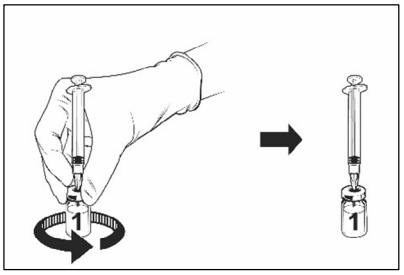
To reconstitute Qdenga, use only the solvent (0.22% sodium chloride solution) in the pre-filled syringe supplied with the vaccine since it is free of preservatives or other anti-viral substances. Contact with preservatives, antiseptics, detergents, and other anti-viral substances is to be avoided since they may inactivate the vaccine.

Remove the vaccine vial and pre-filled syringe solvent from the refrigerator and place at room temperature for approximately 15 minutes.



Lyophilised vaccine vial

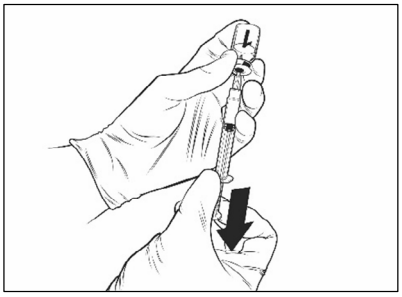
- Remove the cap from the vaccine vial and clean the surface of stopper on top of the vial using an alcohol wipe.
- Attach a sterile needle to the pre-filled syringe and insert the needle into the vaccine vial. The recommended needle is 23G.
- Direct the flow of the solvent toward the side of the vial while slowly depressing the plunger to reduce the chance of forming bubbles.



Reconstituted vaccine

- Release your finger from the plunger and, holding the assembly on a flat surface, gently swirl the vial in both directions with the needle syringe assembly attached.
- DO NOT SHAKE. Foam and bubbles may form in the reconstituted product.
- Let the vial and syringe assembly sit for a while until the solution becomes clear. This takes about 30-60 seconds.

Following reconstitution, the resulting solution should be clear, colourless to pale yellow, and essentially free of foreign particulates. Discard the vaccine if particulates are present and/or if it appears discoloured.



Reconstituted vaccine

- Withdraw the entire volume of the reconstituted Qdenga solution with the same syringe until an air bubble appears in the syringe.
- Remove the needle syringe assembly from the vial. Hold the syringe with the needle pointing upwards, tap the side of the syringe to bring the air bubble to the top, discard the attached needle and replace with a new sterile needle, expel the air bubble until a small drop of the liquid forms at the top of the needle. The recommended needle is 25G 16 mm.
- Qdenga is ready to be administered by subcutaneous injection.

Qdenga should be administered immediately after reconstitution. Chemical and physical in-use stability have been demonstrated for 2 hours at room temperature (up to 32.5°C) from the time of reconstitution of the vaccine vial. After this time period, the vaccine must be discarded. Do not return it to the refrigerator. From a microbiological point of view Qdenga should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Product Registration Holder

Takeda Malaysia Sdn Bhd
Unit TB-L13-1, Level 13, Tower B,
Plaza 33, No. 1, Jalan Kemajuan,
Seksyen 13, Petaling Jaya, 46200
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8. Date of Revision

Version: 1
Reference: EU SmPC
Date of Local Revision: 28 November 2022

Dengue Prevention Advocacy Malaysia