QDENGA: TRANSFORMING DENGUE PREVENTION

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President, Global Portfolio Division

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Guest Speaker:
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Professor, Programme in Emerging Infectious Diseases,
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Better Health, Brighter Future

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TODAY'S SPEAKERS

Presenting

Ramona Sequeira
President,
Global Portfolio Division

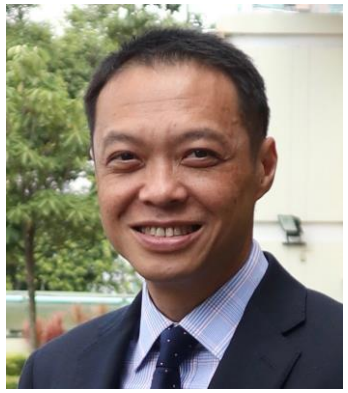
Derek Wallace
Vice President,
Head of Dengue Global Program

Q&A

Gary Dubin
President,
Global Vaccines Business Unit

Renata Campos
President,
Growth and Emerging Markets Business Unit

Joined by Special Guest



Eng Eong Ooi
Professor,
Programme in Emerging Infectious Diseases,
Duke-NUS Medical School

DENGUE – TOP 10 THREAT TO GLOBAL PUBLIC HEALTH

Ramona Sequeira – President, Global Portfolio Division

DENGUE IS LISTED BY THE WORLD HEALTH ORGANIZATION AS ONE OF TEN THREATS TO GLOBAL HEALTH[1]

>3.9 Billion

people are at risk of dengue infection globally[2]

>125

Endemic in over 125 countries; 70% of the burden in Asia[2]

390M

390M estimated infections and **500,000 hospitalizations each year,** with an estimated **death rate of 20-25,000 per year, primarily in children**[2,4,5]

Growing prevalence

Global **incidence rates have increased 30-fold** over the last 50 years due to urbanization, travel and climate change[6]

Urgent need for a safe and effective vaccine for endemic and travel markets

Severe dengue is a **leading cause of hospitalization** and death in children and adults of all ages in endemic regions,[2] resulting in a high burden on healthcare systems

Significant **economic burden of disease**; families in endemic regions may spend 15-23% of monthly household income for hospitalizations[7,8]

Dengue is a **leading cause of fever among travelers** returning from Latin America, the Caribbean & Southeast Asia
More than **90 million arrivals** from the United States, Canada and Europe to dengue endemic countries in 2018[3]

1 .World Health Organization. Ten threats to global health in 2019. Retrieved October 2022.
2. World Health Organization. Fact Sheet. Dengue and Severe Dengue. January 2022. Retrieved October 2022.
3. Bulugahapitiya, U., Siyambalapitiya, S., Seneviratne, S. L., & Fernando, D. 3. J. (2007). Dengue fever in travellers: A challenge for European physicians. European journal of internal medicine, 18(3), 185–192. https://doi.org/10.1016/j.ejim.2006.12.002
4. Guzman MG, Halstead SB, Artsob H, et al. Dengue: a continuing global threat. Nat Rev Microbiol. 2010;8(12 Suppl):S7-S16. doi:10.1038/nrmicro2460.
5. Schaefer T, Panda P, Wolford R. Dengue Fever. April 2022. Retrieved October 2022.
6. Ebi KL, Nealon J. Dengue in a changing climate. Environmental Research. 2016;151:115-123. doi:10.1016/j.envres.2016.07.026
7. Tozan Y, Ratanawong P, Sewe MO, Wilder-Smith A, Kittayapong P. Household costs of hospitalized dengue illness in semi-rural Thailand. PLoS Negl Trop Dis. 2017;11(9):e0005961
8. Senanayake MP, Jayasinghe SSK, Wijesundera DS, Manamperi M. Economic cost of hospitalized non-fatal Paediatric Dengue at the Lady Ridgeway Hospital for Children in Sri Lanka. Sri Lanka Journal of Child Health. 2014;43(4):205. doi:10.4038/sljch.v43i4.7762

QDENGA STRATEGIC LAUNCH IMPERATIVES

Create awareness of the health and economic risks associated with dengue for consumers living or traveling to endemic regions

Build confidence with regulators, recommending bodies, HCPs and consumers by leveraging strong clinical profile

Establish rapid and broad access at an individual- and population-level

Ensure launch preparedness through increased manufacturing capacity, established supply network and proven global commercial capabilities

TODAY'S AGENDA

Dengue Burden and Control – Eng Eong Ooi BMBS, PhD, FRCPath Professor Programme in Emerging Infectious Diseases, Duke NUS Medical School. Singapore

QDENGA Program and Clinical Results – Derek Wallace

QDENGA Commercial Outlook – Ramona Sequeira

Q&A – Ramona Sequeira, Derek Wallace, Gary Dubin, Renata Campos and Eng Eong Ooi

Dengue burden and control

Why the world needs a vaccine

Eng Eong Ooi BMBS, PhD, FRCPath
Professor
Programme in Emerging Infectious Diseases

THE GLOBAL BURDEN OF DENGUE

- **More than 4 billion people are at risk and estimated 390 million infections per year[1]**

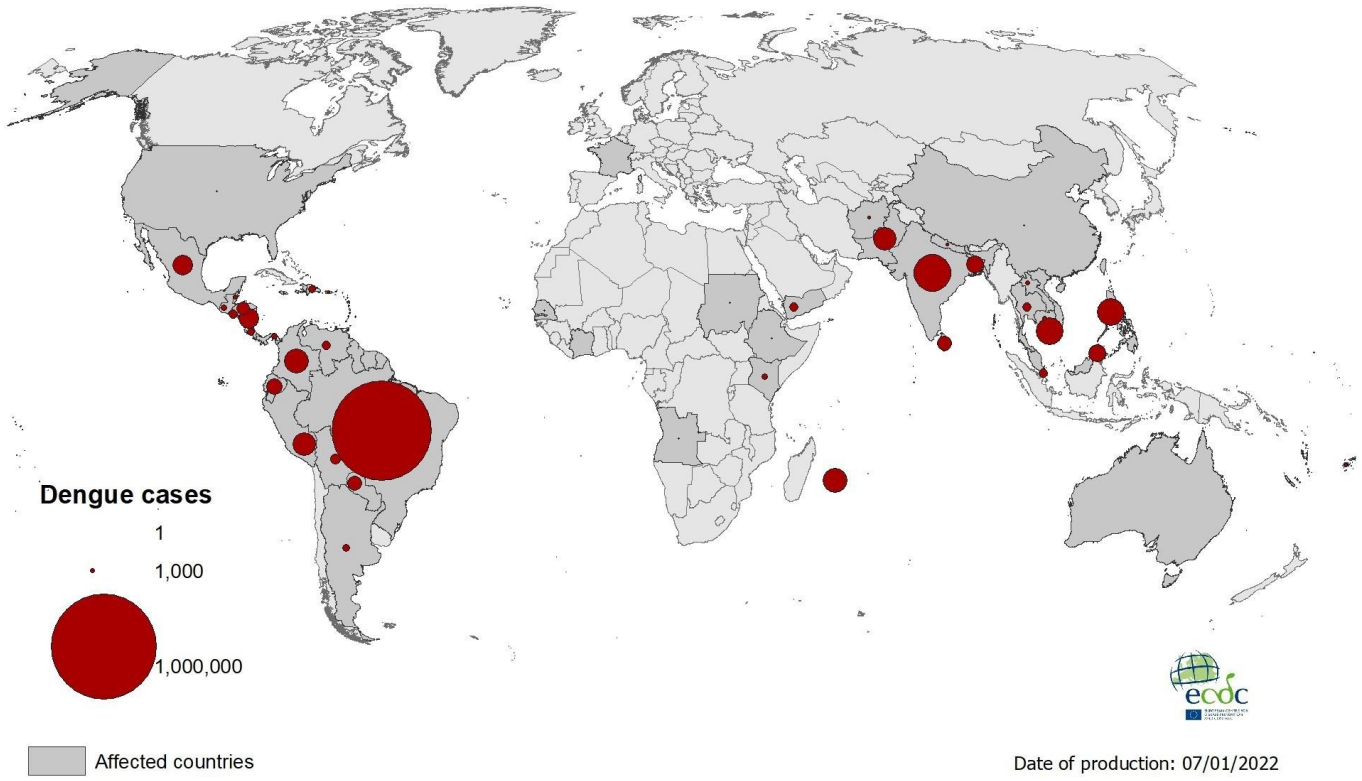
- **30 times increase in disease over the past 50 years[2]**

  Driven by
  - Urbanization
  - Global warming
  - Increased global travel

  More mosquitos
  More mosquito / people contact

- **By 2080, more than 6 billion people are estimated to be at risk[3]**

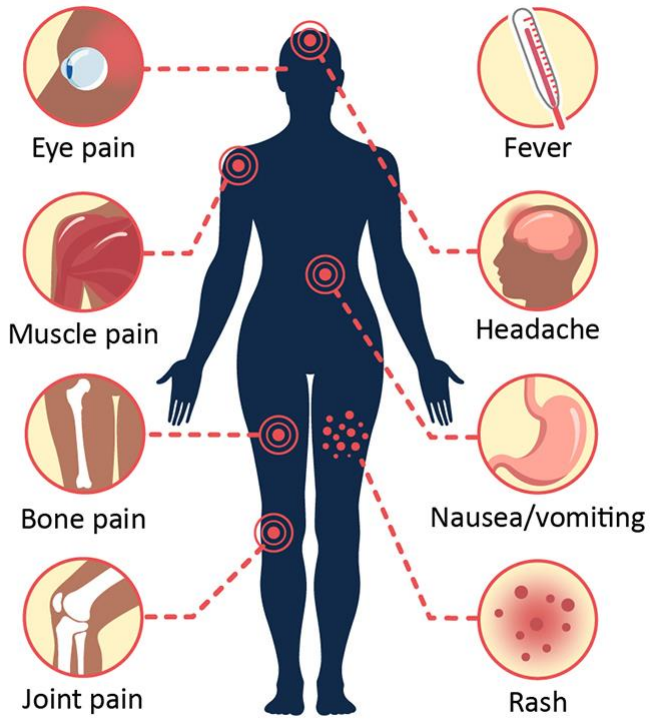
Geographical distribution of dengue cases reported worldwide, 2021[4]



1. World Health Organization. Fact Sheet. Dengue and Severe Dengue. January 2022. Retrieved October 2022.
2. WHO. Global Strategy for Dengue Prevention and Control 2012–2020. Available at: www.who.int/ denguecontrol/9789241504034/en/
3. Messina, J.P., Brady, O.J., Golding, N. *et al.* The current and future global distribution and population at risk of dengue. *Nat Microbiol* 4, 1508–1515 (2019). https://doi.org/10.1038/s41564-019-0476-8.
4. European Centre for Disease Prevention and Control, https://www.ecdc.europa.eu/en/publications-data/geographical-distribution-dengue-cases-reported-worldwide-2021

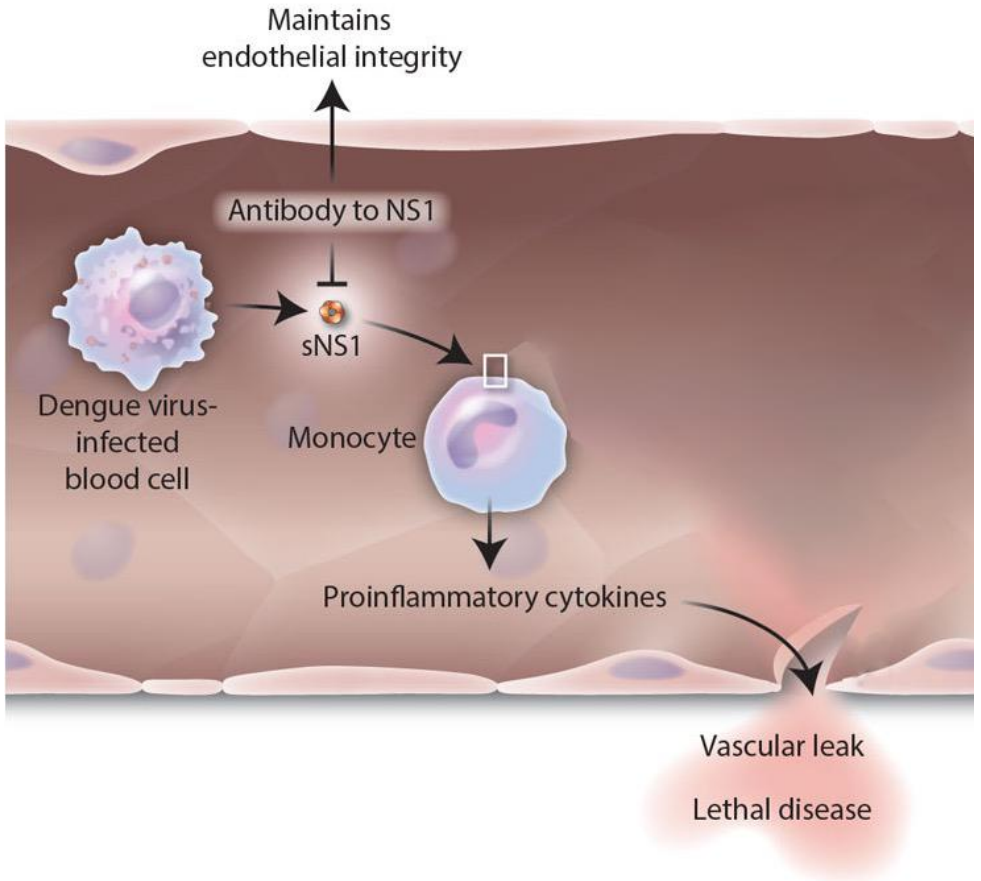
DENGUE SYMPTOMS AND PRESENTION VARIES

Most dengue infections are asymptomatic or lead to mild illness with flu-like symptoms[1]



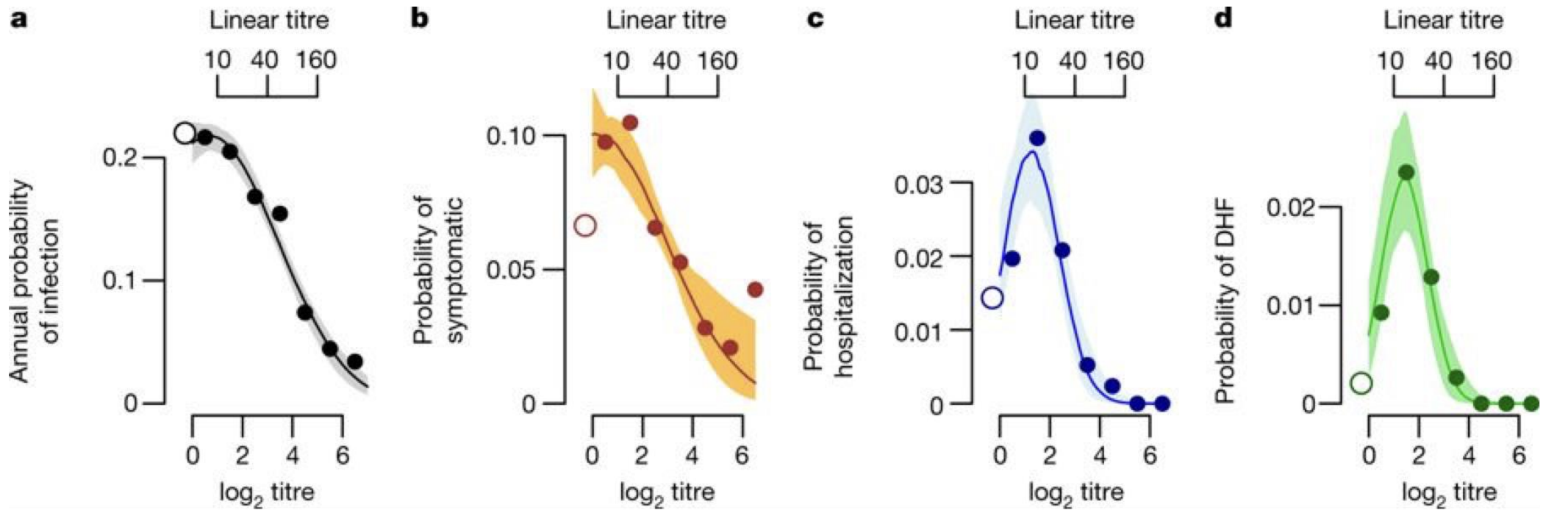
CDC image

Severe dengue is present in 5% of cases[2,3]. High plasma viral load and NS1 levels have been associated with plasma leakage, a hallmark of severe dengue[4]



1. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
2. CDC. Travelers' Health- Yellow book. New York: Oxford University Press; 2020.
3. Wilder-Smith A. Current Infectious Disease Reports. 2018;20:50
4. *Clinical Infectious Diseases*, Volume 72, Issue 12, 15 June 2021, Pages e1074–e1083, https://doi.org/10.1093/cid/ciaa1840

RISK OF SEVERE DENGUE PEAKS WITHIN A NARROW RANGE OF PRE-INFECTION ANTIBODY LEVELS[1]



1. Salje et al, Nature 2018

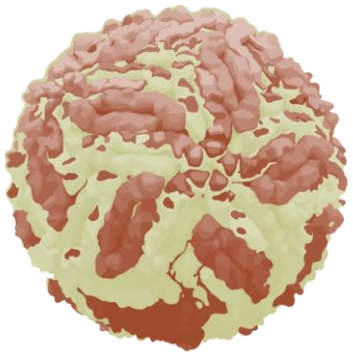
DENGUE TYPES 1 AND 2 CAUSE MAJORITY OF OUTBREAKS

Four strains of the dengue virus (DENV) 1-4 are spread by the *Aedes aegypti* and *Aedes albopictus* mosquitos worldwide

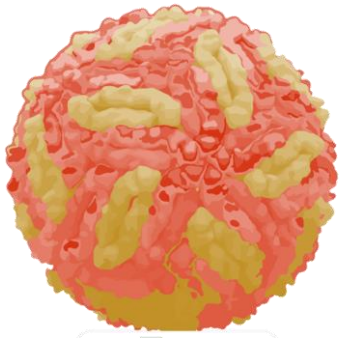
In recent years, **DENV-1 and DENV-2 have emerged as the most prominent strains associated with known outbreaks**[1]

- According to empirical data, the highest pooled mortality rate has been reported during DENV-2 outbreaks[1]

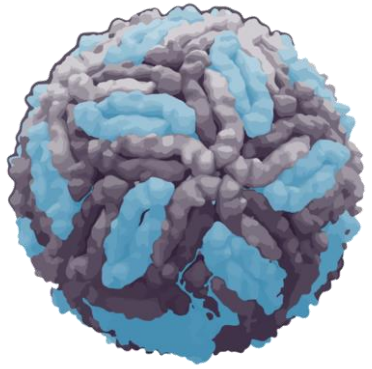
- Studies have also shown that DENV-2 causes more severe secondary infections than other serotypes[1]



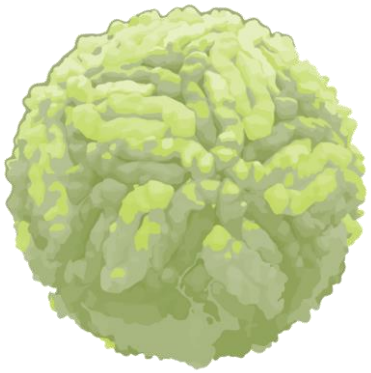
DENV-1



DENV-2



DENV-3



DENV-4

1. Yenamandra, S.P., Koo, C., Chiang, S. *et al.* Evolution, heterogeneity and global dispersal of cosmopolitan genotype of Dengue virus type
2. *Sci Rep* **11**, 13496 (2021). https://doi.org/10.1038/s41598-021-92783-y

Dengue outbreaks occur every few years[1]

Hospitals can become overwhelmed with the spike in cases[2]

1. Clin Epidemiol. 2013; 5: 299–309.
Published online 2013 Aug 20. doi: 10.2147/CLEP.S34440
2. PLOS. Neglected Tropical Disease. Societal impact of dengue outbreaks: Stakeholder perceptions and related implications. A qualitative study in Brazil, 2015.

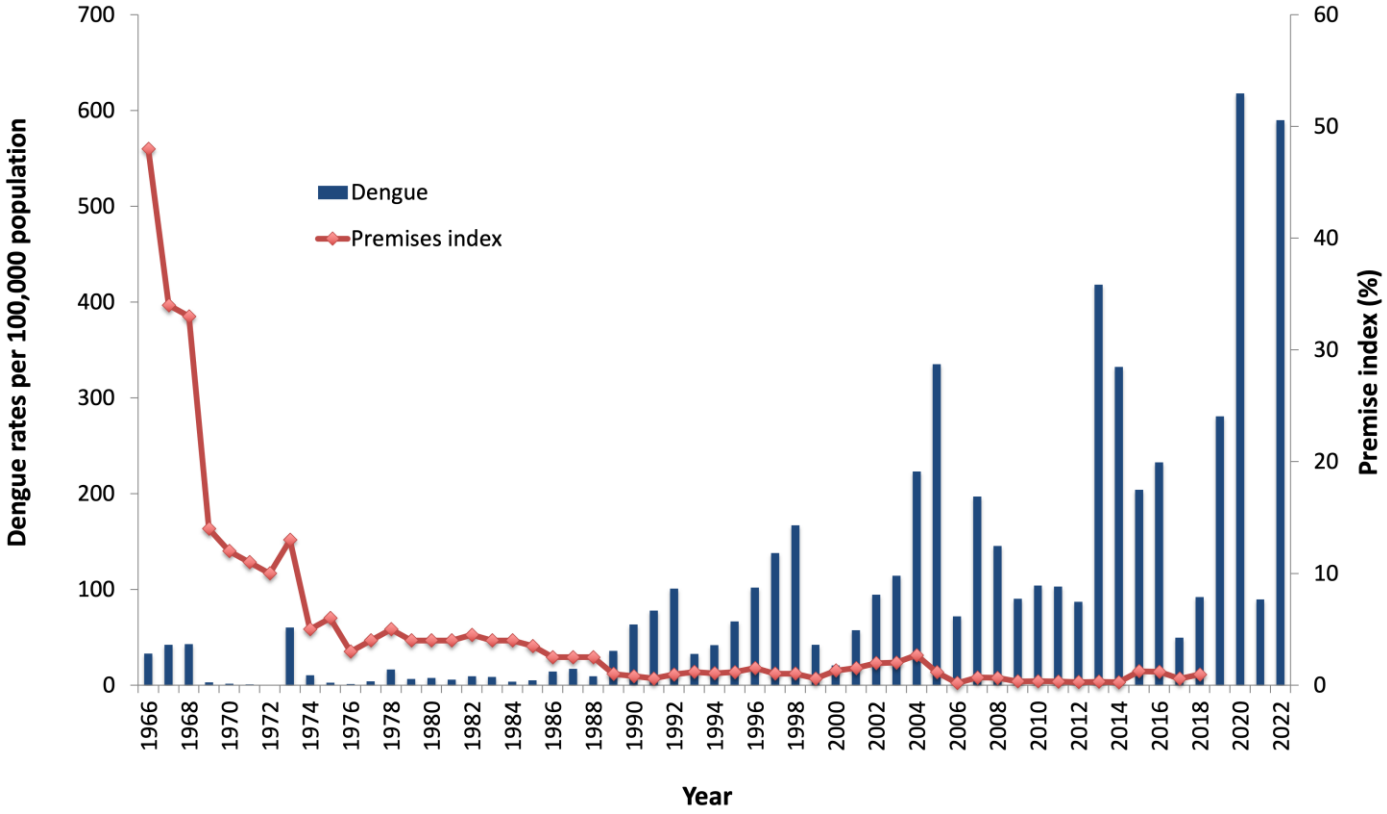
WITHOUT VACCINATION, DENGUE CONTROL LACKS SUSTAINABILITY

Current efforts for dengue control are directed at reducing infection rate through vector control methods

In the medium to long term, this could cause lower population immunity and make them more susceptible to dengue outbreaks

Elevating immunity levels with vaccination is the missing link in integrated dengue control

Dengue and Aedes population density in Singapore – 1966 to 2022[1]



1. Data from Ministry of Health, Singapore
Adapted from Ooi et al, Emerg Infect Dis 2006

DEVELOPING SAFE AND EFFECTIVE VACCINE FOR A BROAD POPULATION

Derek Wallace, MBBS – Head of Dengue Global Program

DENGUE VIRUS INFECTIONS HAVE A DISTINCT PATHOPHYSIOLOGY

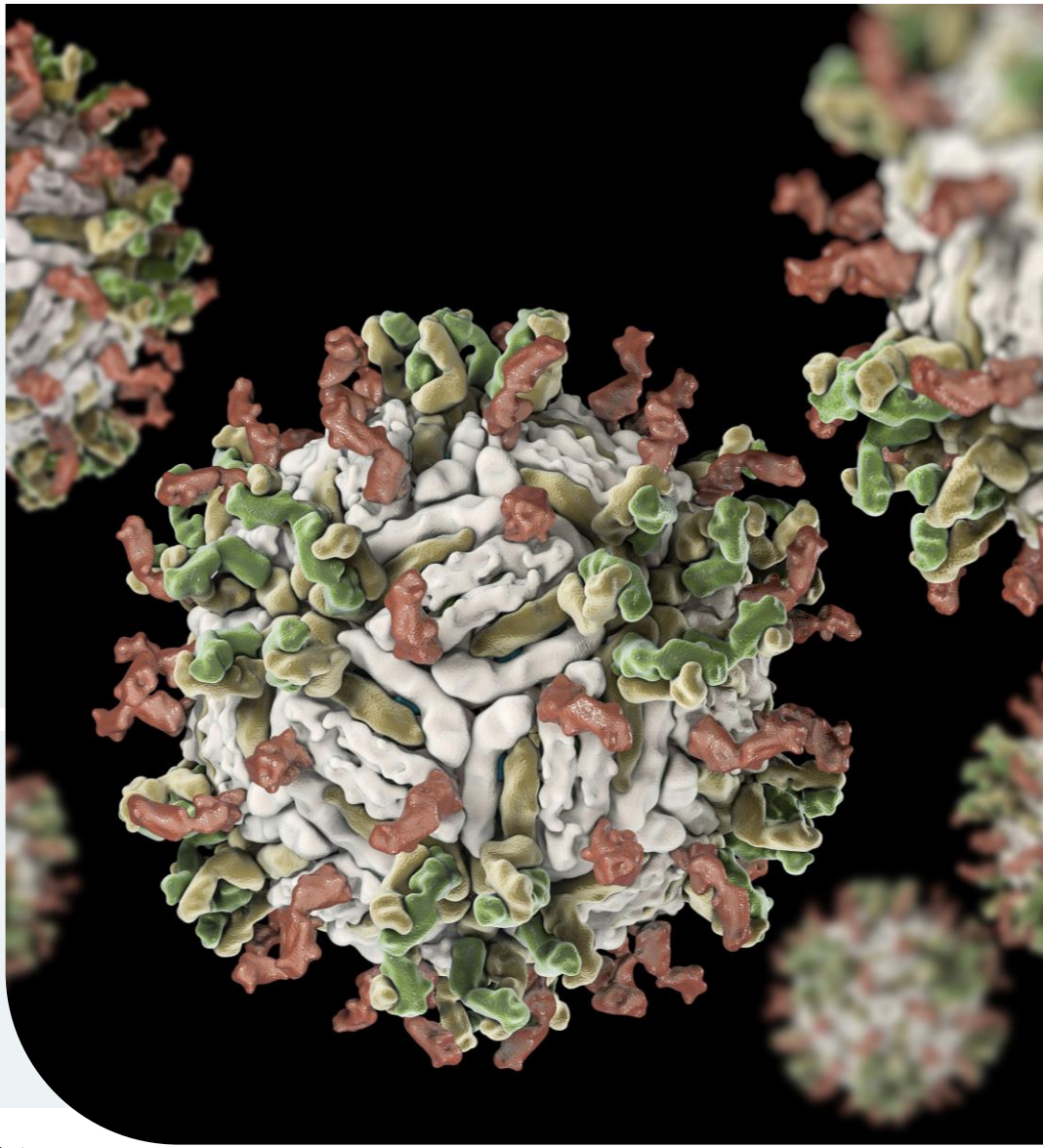
Severe disease, although rare, is unpredictable and typically affects children[1,2]

Severe dengue infections are characterized by vascular leakage associated with a high risk of hospitalization and mortality[2]

- Dengue virus non-structural (NS) protein 1 can trigger vascular leakage
- NS1 protein is highly conserved across the four dengue serotypes
- No specific treatment options exist to manage vascular leakage

Potential for disease enhancement[2]

- After an initial infection, a subsequent infection with a different serotype can lead to more severe outcomes
- There is no method of predicting or preventing disease enhancement in patients



1. An estimated 1 in 4 dengue virus infections are symptomatic. Symptomatic dengue virus infection most commonly presents as a mild to moderate, nonspecific, acute febrile illness. Approximately 1 in 20 patients with dengue virus disease progress to develop severe, life-threatening disease called severe dengue.

2. Guzman, M., Gubler, D., Izquierdo, A. *et al.* Dengue infection. *Nat Rev Dis Primers* 2, 16055 (2016). https://doi.org/10.1038/nrdp.2016.55

QDENGA: ENGINEERED TO ELICIT A BROAD AND LASTING IMMUNE RESPONSE AGAINST ALL DENGUE SEROTYPES

Tetravalent QDENGA was engineered:

1. **To contain the structural genes of serotypes 1 to 4**
2. **Built on a dengue virus serotype 2 backbone containing dengue virus non-structural genes, including NS-1 protein**

QDENGA VACCINATION HYPOTHESIS

Activation of….	**Antibodies against structural proteins for serotypes 1-4**	**Antibodies against NS proteins cross-reactive against all NS serotypes**	**T- and B-cells reactive against dengue antigens**
With the objective of….	Efficiently blocking infection with wildtype virus of all serotypes	Reducing risk for severe dengue by preventing vascular leakage induced by NS1 protein	Support long-term immunity against dengue infections with different serotypes
WITH THE GOAL TO DEMONSTRATE….	Reduction in Symptomatic Dengue	Reduction in Hospitalizations	Sustained Protection Against All Serotypes

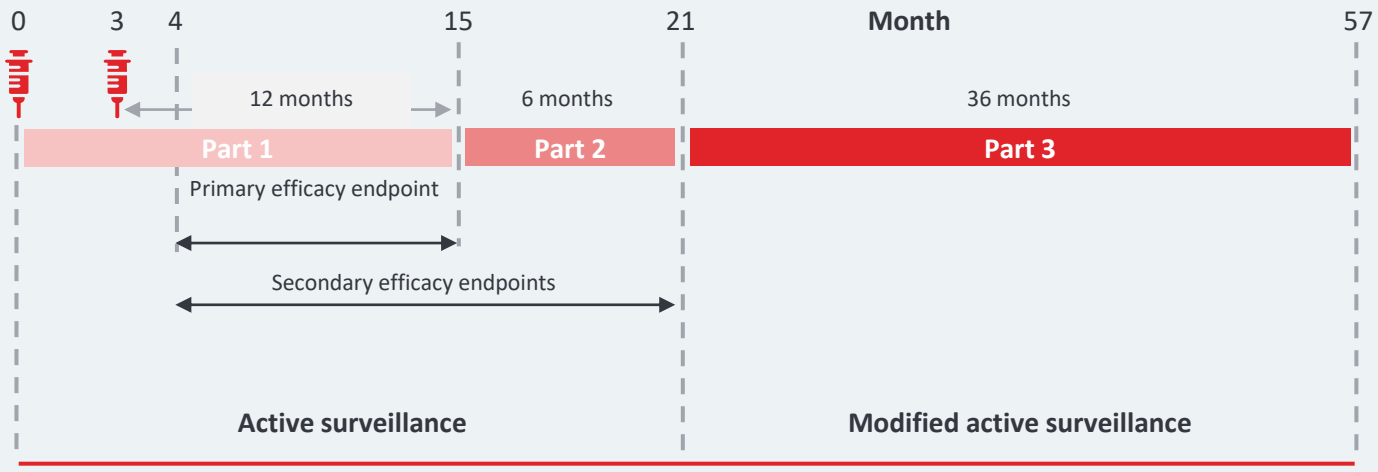
PHASE 3 TIDES TRIAL DESIGNED TO ASSESS THE SAFETY AND EFFICACY OF TAK-003 IN BROAD POPULATION

Trial design met WHO recommendations for a second-generation dengue vaccine – 3-5 years of follow-up prior to licensure

Broad Population

- **20,000** children & adolescents
- **8** endemic countries
- **4/4** Includes all four serotypes
- **Both** Sero-positive & Sero-negative[2]

Ph 3 TIDES Trial



Participants followed for up to 57 months

Participants stratified by serostatus[1]

Primary endpoint – prevention of symptomatic dengue cases @ 12mo

Key secondary endpoint – reduction in hospitalizations @ 18mo

Exploratory endpoint – sustained preventions of symptomatic dengue and reduction in hospitalization @ 4.5yrs

1. Serostatus – is whether a patient has had a prior infection or not.
2. Sero-positive (earlier exposure to dengue) and sero-negatives (not exposed before)

SUSTAINED PROTECTION AGAINST ALL DENGUE SEROTYPES & LOWER RISK OF HOSPITALIZATION REGARDLESS OF PREVIOUS EXPOSURE

Strong efficacy across all endpoints

Reduction in symptomatic VCD & hospitalizations regardless of previous exposure

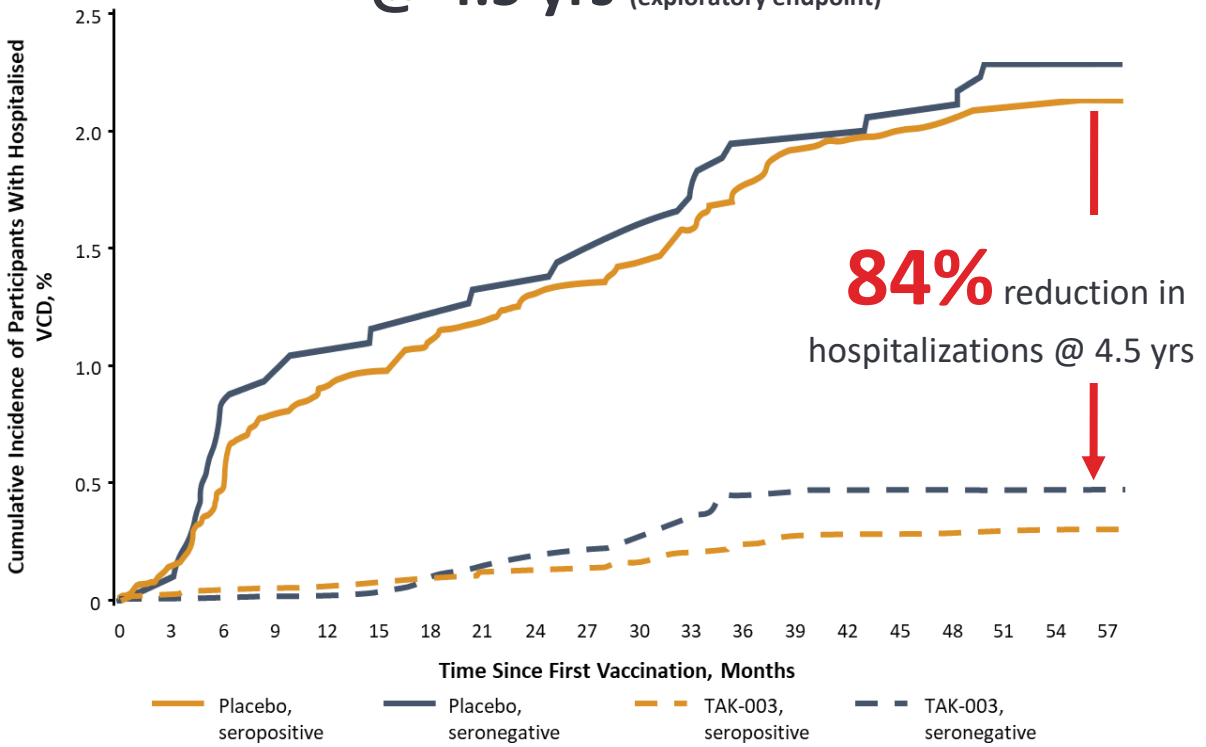
80.2%
reduction in symptomatic VCD @ 12mo (primary endpoint)[1]

90.4%
reduction in hospitalizations @ 18mos (secondary endpoint)[2]

No important identified safety risks[3]

- No evidence of disease enhancement
- Well tolerated
- Most frequently reported reactions were common to vaccines, including injection site pain, headache, myalgia, injection site erythema, malaise, asthenia and fever

Durable Reduction in Hospitalizations @ 4.5 yrs (exploratory endpoint)[3]



1 Biswal S, et al. Efficacy of a tetravalent dengue vaccine in healthy children and adolescents. N Engl J Med. 2019; 2019;381:2009-2019
2 Biswal S, et al. Efficacy of a tetravalent dengue vaccine in healthy children aged 4-16 years: a randomized, placebo controlled, phase 3 trial. Lancet. 2020. 2020;395:1423-1433.
3 Tricou, V. Efficacy and Safety of Takeda's Tetravalent Dengue Vaccine Candidate (TAK-003) After 4.5 Years of Follow-Up. Presented at the 8th Northern European Conference of Travel Medicine; June 2022
VCD – Virologically confirmed dengue

SIGNIFICANT REGULATORY MOMENTUM: QDENGA APPROVED WITH BROAD LABEL REGARDLESS OF SEROSTATUS

August 2022

Approved in Indonesia[1] for ages 6-45

October 2022

EU-M4all application receives Positive CHMP opinion

November 2022

US FDA accepts filing

December 2022

Approved in EU[2] for ages 4 and up

2023

Approved in Brazil for ages 4 - 60[3]

Ongoing regulatory reviews in several endemic countries & travel markets

1. Indonesia National Agency for Drug and Food Control, Badan Pengawas Obat dan Makanan (BPOM) https://www.takeda.com/4a410b/siteassets/system/what-we-do/areas-of-focus/vaccines/pdf/acc_qdenga_smpc.pdf
2. European Medicines Agency https://www.ema.europa.eu/en/medicines/human/EPAR/qdenga
3 Anvisa approval https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2023/anvisa-aprova-nova-vacina-para-a-dengue

QDENGA is approved in Indonesia, EU, UK, Norway, Iceland, Lichtenstein, Brazil

EU-M4all The European Medicines Agency. **Medicines for use outside the EU — EU-M4all**. July 2020. Retrieved March 2021.

QDENGA COMMERCIAL OUTLOOK

Ramona Sequeira – President, Global Portfolio Division

QDENGA STRATEGIC LAUNCH IMPERATIVES

Create awareness of the health and economic risks associated with dengue for consumers living or traveling to endemic regions

Build confidence with regulators, recommending bodies, HCPs and consumers by leveraging strong clinical profile

Establish rapid and broad access at an individual- and population-level

Ensure launch preparedness through increased manufacturing capacity, established supply network and proven global commercial capabilities

COUNTRY-LEVEL ACTIVATION OF STRATEGIC IMPERATIVES INITIATED AHEAD OF EXPECTED APPROVALS

Driving consumer awareness of dengue risk and prevalence *in THAILAND*

70M+ people in country

Public Education Partnerships

- Partnering with 11 entities to raise public awareness
- Ing-Ma virtual human video campaign launched: >35 million views
- Partnership with Kao Thailand, top consumer brand

Establishing trust in dengue prevention *in BRAZIL*

200M+ people in country

Consumer Engagement Initiatives

- UNICEF partnership to educate 90,000 people to reduce the transmission of water and vector borne infectious diseases
- Dengue prevention social media campaign

Building a dengue travel business *in NON-ENDEMIC COUNTRIES*

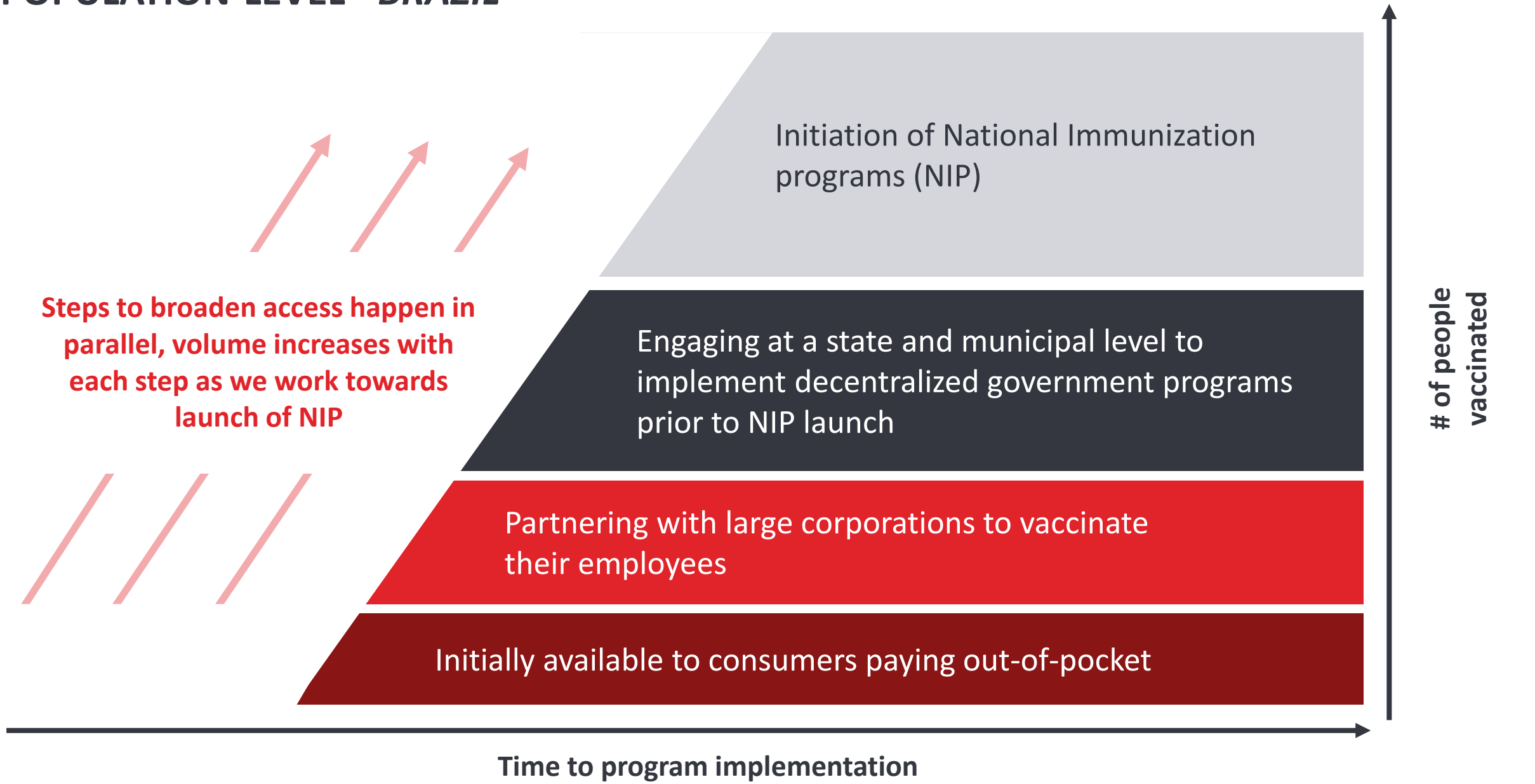
90M+ arrivals from the US, CA & EU*

Critical External Engagements

- Partnership with leading travel immunization clinics and HCPs
- Ongoing engagements with CDC ACIP dengue working group

* Bulugahapitiya, U., Siyambalapitiya, S., Seneviratne, S. L., & Fernando, D. 3. J. (2007). Dengue fever in travellers: A challenge for European physicians. European journal of internal medicine, 18(3), 185–192. https://doi.org/10.1016/j.ejim.2006.12.002

ESTABLISH RAPID AND BROAD ACCESS AT AN INDIVIDUAL- AND POPULATION-LEVEL - *BRAZIL*



VARIABLE PRICING APPROACH TO MEET THE NEEDS OF INDIVIDUAL COUNTRIES & MARKET SEGMENTS

We aim to make **QDENGA available to all who are eligible for vaccination** in the countries where approved

PRIVATE ENDEMIC

- Pricing at or below the average price for other innovative vaccines
- Tiered pricing corridors based on factors such as GDP & sophistication of healthcare system.

Maximum retail price for **Indonesia is $40 USD[6] per dose[1], $26 USD[6] ex-factory**

Average price for innovative vaccines in Indonesia is $73 USD[6] per dose[2,3]

PUBLIC ENDEMIC

- Aim to price lower than average for innovative vaccines.
- One pricing corridor and a discount matrix.

Ensures affordability for all.

TRAVEL

- Pricing similar to other innovative travel vaccines in their respective countries.

Retail price in Germany **$115 USD[7] per dose[1], $80 USD[7] ex-factory**

Average price for innovative vaccines in Germany is $119 USD[7] per dose[2,4]

Implementation of QDENGA has the potential to create **significant cost savings** for individuals and governments taking into account economic factors such as: cost of care, missed work, lost tourism, etc[5]

1. Two-dose series
2. Dosing regimens vary by vaccine
3. The average retail price obtained based on market survey (printed price on the box) and validated with IQVIA / IPMA data
4. Basket of licensed innovative vaccines in travel markets (unweighted average used for comparison)
5. Shen J, Kharitonova E, Biswal S, Sharma M, Aballea S, Tytula A et al. Disease impact of a new dengue vaccine (TAK-003) in Thailand, International Congress on Infectious Diseases; 17–20 November 2022; Kuala Lumpur, Conference abstract and poster
6. 15117.87 IDR/USD
7. 1.0199 EUR/USD

LAUNCH READY: ESTABLISHED MANUFACTURING & SUPPLY CHAIN AND LEVERAGING BROAD GLOBAL FOOTPRINT

Manufacturing capacity in place for launch and investing to expand for growth

- **Early investments to established in-house manufacturing for launch**
- Aim to achieve **100 mill doses per year** through in-house and strategic CMO partnerships

Well-established distribution network

- **Cold chain distribution partner** has broad global network.
- **Existing distribution networks and commercial infrastructure** in the initial launch markets

Proven track record In Growth & Emerging Markets (GEM)

- **150** successful **commercial launches** since 2019
- **14.5%** FY2022 Q3YTD revenue growth YoY at CER

CMO: Contract Manufacturing Organization

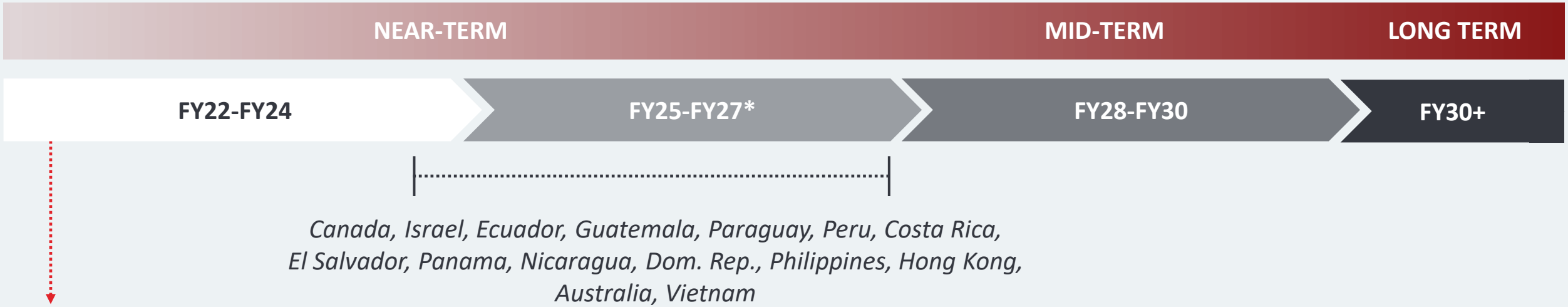
GLOBAL EXPANSION THROUGH THE END OF THE DECADE

Target launches in >20 countries by 2025, representing 55% of eligible at-risk population

Leveraging EU-M4all review process to potentially accelerate approvals in participating endemic markets

Indonesia, Malaysia, Thailand, Colombia, Brazil, Mexico, Singapore, Sri Lanka, Argentina, US, EU

*China, India, Cuba, Honduras, Venezuela, additional PAHO countries, GAVI***



Canada, Israel, Ecuador, Guatemala, Paraguay, Peru, Costa Rica, El Salvador, Panama, Nicaragua, Dom. Rep., Philippines, Hong Kong, Australia, Vietnam

- Significant regulatory progress
- Initiating launches where approved

*Anticipated access via PAHO
**assuming dengue is incorporated in Gavi Vaccine Investment Strategy

GAVI: Global Alliance for Vaccines and Immunization PAHO Pan American Health Organization

STEADY REVENUE GROWTH THROUGH THE END OF THE DECADE

Strong Clinical Profile - 4.5-yr data demonstrating durable reduction in hospitalization and no important safety signals consistent with 1° & 2 ° endpoints

Momentum with regulators – Brazil, Indonesia & EU approvals with **broad labels, regardless of serostatus**

Expanding manufacturing capacity with aim to achieve annual output 100M+ doses

- Continuing to add to in-house capacity and manufacturing efficiencies
- Contracting for additional capacity with CMOs; actively exploring potential partners in India and other large endemic markets

Previous peak sales estimate of $700M - $1.6B was based on:

24-month data – prior to the 4.5-year data readout

Manufacturing assumptions of 50M+ doses annually

SUMMARY OF QDENGA COMMERCIAL OUTLOOK

Near-term:
Drive Early Adoption

- Launch into key endemic and travel markets – **leveraging strong clinical profile**
- **Establish rapid access** – Private segment/local partnerships
- **Ensure affordability** through variable pricing approach

Mid-term:
Accelerate Volume Growth

- Initiation of **national vaccination** programs will **drive volume**
- Recognize **economies of scale** to reduce CoGS **as volume grows**

Long-term:
Durable Sales Post Peak

- **Continued global expansion** into the next decade
- Ensure **new generations** are being vaccinated
- **Durable sales post peak** – Vaccines face **limited generic threats** due to high barriers to entry

QDENGA – ADDRESSING THE URGENT NEED FOR A SAFE AND EFFECTIVE DENGUE VACCINE

Significant, Growing Global Burden

- >3.9 billion people at risk of infection[1]
- Growing prevalence – increasing 30-fold over the last 50yrs[2]
- Significant economic burden of disease both at the government, healthcare systems and patient level[3,4]

Differentiated Clinical Profile[5]

- Demonstrated strong safety and efficacy against all dengue serotypes regardless of previous exposure
- Durable reduction in hospitalizations – 84% reduction @ 4.5yrs
- No important safety risks identified

Delivering Steady Revenue Growth Through the End of the Decade

- Peak sales expected to grow to $1.6 - 2.0B USD
- Innovative access strategy to drive rapid and broad access
- Established manufacturing, supply chain and global footprint to ensure launch readiness

1. World Health Organization. Fact Sheet. Dengue and Severe Dengue. January 2022. Retrieved October 2022.
2. Ebi KL, Nealon J. Dengue in a changing climate. Environmental Research. 2016;151:115-123. doi:10.1016/j.envres.2016.07.026
3. Tozan Y, Ratanawong P, Sewe MO, Wilder-Smith A, Kittayapong P. Household costs of hospitalized dengue illness in semi-rural Thailand. PLoS Negl Trop Dis. 2017;11(9):e0005961
4. Senanayake MP, Jayasinghe SSK, Wijesundera DS, Manamperi M. Economic cost of hospitalized non-fatal Paediatric Dengue at the Lady Ridgeway Hospital for Children in Sri Lanka. Sri Lanka Journal of Child Health. 2014;43(4):205. doi:10.4038/sljch.v43i4.7762
5. QDENGA was assessed across a clinical development program that included 19 Phase 1, Phase 2 and Phase 3 trials, and more than 28,000 participants, including Takeda's pivotal Tetravalent Immunization against Dengue Efficacy Study (TIDES) trial. The TIDES trial met its **primary endpoint** of overall vaccine efficacy (VE) against virologically-confirmed dengue (VCD) with 80.2% efficacy at 12-months follow-up. The trial also met all **secondary endpoints** for which there were a sufficient number of dengue cases at 18-months follow-up. The VE result in preventing hospitalization due to VCD fever was 90.4%. Through four and a half years (54 months after the second dose), QDENGA demonstrated continued overall protection, with sustained overall VE of 61.2% and 84.1% VE against hospitalized dengue. Observations of VE varies by serotype and remained consistent with previously reported results. QDENGA has been generally well tolerated, with no evidence of disease enhancement in vaccine recipients, and no important safety risks have been identified in the TIDES trial, to date.

THANK YOU

Better Health, Brighter Future