Vaccinating Against Dengue

A viable reality for the first time in history

What and who is this information packet for?

- **Dengue is becoming an increasingly pressing global health issue**, one that until recently, we could only take limited action against
- **The development of a vaccine, for the first time, that is safe for all – regardless of prior infection status – is groundbreaking**
- Therefore, GDAC has created this information packet as **a basic primer on dengue and the new vaccines, for doctors, scientists, healthcare workers, and government regulators** who are not specialists in the field
- There is still much we are learning about dengue, and many complexities are not discussed here, but this packet summarises the key things that are important to know
- This packet is **accompanied by a simpler handout** that can be distributed to the general public
- **We now have an option that can save countless lives – please consider urgently taking action in your communities**

Glossary of terms

- ”Dengue-naïve” → people who have not yet been infected with dengue
- “Dengue-recoverees” → people who have had a dengue infection
- “Neutralising antibodies (nAbs)” → antibodies that disarm pathogens to prevent infection
- “Primary infection” → the first dengue infection a patient experiences
- “Secondary infection” → the second dengue infection a patient experiences
- “Serotype” → one of the four dengue viruses, i.e. DENV-1, -2, -3 or -4
- “T-cell” → a type of white blood cell that is part of our immune defence against pathogens
- ”Tetravalent vaccine” → a vaccine containing all four dengue strains
- “Vaccinees” → people receiving vaccination
- “Viremia” → the presence of viruses in the blood

Dengue: Understanding the Basics

Why is it so urgent yet difficult to address?

Dengue is spreading fast – and it will get worse

- **Infects hundreds of millions** yearly (est. 96 million requiring care) in **120 countries**
- **Kills as many as 40,000** people yearly, many of whom are children
- **Worldwide incidence has increased 8x in 20 years**, driven by climate change and urbanization, which creates environments the *Aedes* mosquito flourishes in
- With globalization and warming climates, it is **no longer just a "tropical disease"**: local transmission seen in traditionally non-endemic areas, including Western Europe and the US – and this will grow
- By 2080, it is estimated that dengue will afflict **60% of the world's population**, over 6 billion people

Dengue is painful, dangerous, and can cripple hospital systems

- Dengue is a **serious, painful disease**, which can cause plasma leakage, hemorrhagic fevers and death – especially in children
  - Hence its colloquial name: "**break-bone fever**"; the fever that feels like it's breaking your bones
- Because dengue occurs in **epidemic waves**, it can **paralyze hospital systems** in cities
- **Serious dengue infections require close monitoring and complex care**, sometimes for long periods – which many medical institutions lack capability or resources for
- There are **no licensed antiviral treatments** currently: building immunity is the only way to protect people from the disease

What can we do about it?

- Vector control (reducing the mosquito population) can only do so much
  - Costly to sustain
  - Limited in long-term effect: reduction in dengue transmission can reduce population immunity and make it more susceptible to epidemics (Singapore's example)
- **The only way to beat dengue is to combine vector control with durable, high levels of population immunity** – finally achievable through vaccination
- But, **dengue vaccines take many months to grow** – they cannot be deployed at short notice; **populations must be inoculated ahead of time**

Understanding a common misconception about dengue

- What we consider ‘dengue’ is not a single disease: it comprises **4 genetically distinct viruses**
  - DENV-1, -2, -3, and -4 (“serotypes”)
- Because these 4 viruses are so distinct, **infection by one serotype only provides temporary immunity** against other serotypes
- Furthermore, some serotypes typically produce **much worse second-infections**
  - DENV-1 and -3 generally present similar severity of symptoms whether they are the primary (first) or secondary (second) infection
  - DENV-2 and DENV-4 are typically mild as primary infections, but severe as secondary infections **>> this is where dengue is most dangerous and needs to be addressed**
- DENV-1 and DENV-2 are the most common serotypes in circulation today

What would it take to create immunity against dengue?

- A tricky question, as we have not been able to validate immune correlates of protection (the data is too diverse)
- There are exceptions, but what is generally observed in populations:
  - Infection with one dengue serotype typically produces long-lasting immunity against that serotype, and about 18 months' immunity against other serotypes
  - **Infection with two serotypes typically produces long-lasting immunity against all dengue serotypes**
- Because the 4 DENVs are distinct viruses, the desire is to build a **tetravalent vaccine** that can simultaneously produce an immune response to more than one dengue serotype *(akin to 2 natural infections)*

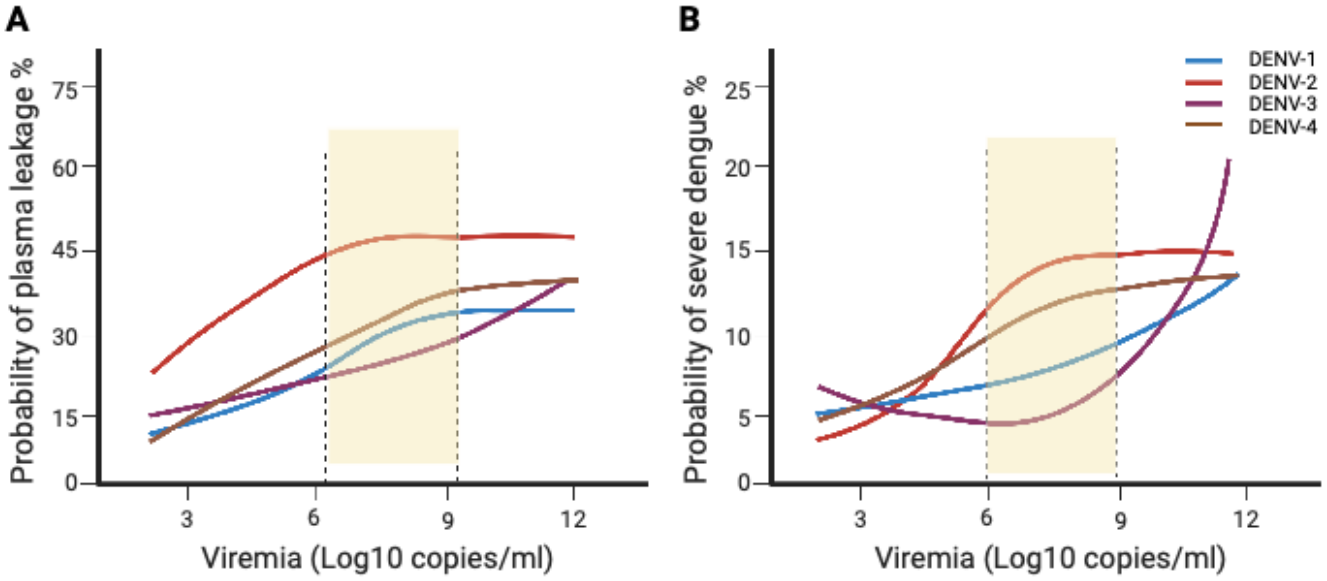
Why is the second dengue infection commonly worse than the first?

- There is much we still do not know
  - The main problem is that **because each serotype is a genetically distinct virus**, resistance to one does not equate to resistance to all
- One possibility is **Antibody-Dependent Enhancement** (ADE):
  - Some antibodies from a first infection may not be able to fully neutralise a different serotype virus
  - If not neutralised, the virus can use the antibodies to enter cells more effectively
  - A “goldilocks zone” of antibody levels *(not high enough to provide immunity, not low enough to not make a difference)* may thus facilitate more severe infection from a second serotype
- Another possibility: **original antigenic sin**
  - Some T-cells arising from a first infection only know how to respond to that infection’s serotype, so they do not work against the virus of a different serotype in a second infection

Understanding Immunity Against Dengue Serotypes

Not all DENVs are equal

Dengue serotypes present different levels of risk



- These figures show:
  A. Probability of plasma leakage in infected patients, by serotype
  B. Probability of severe dengue in patients experiencing a secondary infection, by serotype

  Shaded areas represent most common viremia levels found in symptomatic dengue patients (Vuong, et al)
- **Secondary DENV-2 presents the greatest risk of severe dengue symptoms** in most patients

Dengue serotypes require different levels of protection

- The threshold of neutralizing antibodies (nAbs) required to stave off symptomatic infection differ across the serotypes
- **DENV-2 requires the highest antibody threshold of all the serotypes**:

  Titer of nAbs associated with 50% vaccine efficacy against symptomatic infection:

  - DENV-1: 70
  - **DENV-2: 600**
  - DENV-3: 110
  - DENV-4: 20

  (Data from CYD-TDV phase III trial, measured one month after 3rd dose)
- **This is troubling**, as DENV-2 is also the serotype that causes the severest secondary infections

Antibodies vs. T-cells: what's the difference?

- Our immune system requires a **multi-layered defense system** to not just prevent infection, but also effectively deal with viruses if infection does occur *("breakthrough infections")*
- **Antibodies are better at preventing infection**: they recognise the outer layer of viruses and neutralise them before they can infect cells
  - Like border control officers – preventing entry of malignant agents
- **T-cells are better at preventing severe disease after infection has occurred**: they can detect which cells are infected and destroy them
  - Like police officers – dealing with malignant agents after they have entered
- So the most effective vaccine would stimulate <u>both</u> an antibody and T-cell response, to create robust immunity

A Brief History of Dengue Vaccination

The eight-decade quest that nobody anticipated

From WWII to the first dengue vaccine: 70 years of research

- Vaccine efforts began during WWII
- In 1978, the World Health Organisation (WHO) made the search for a dengue vaccine a globally coordinated effort
  - Experts estimated it would take 10 years
  - But effort after effort failed: the dengue virus proved very difficult to weaken, and some early vaccines gave people infections
- Efforts turned to trying to use a different but related virus as the backbone – i.e. a chimeric vaccine
- Sanofi Pasteur licensed the first dengue vaccine in 2015: Dengvaxia, using a **yellow fever** virus as a backbone

The first vaccine: **DENGVAXIA** (CYD-TDV)

- Safety and efficacy was demonstrated in 2 phase III clinical trials and one season of surveillance (one year after the 3rd dose)
- But in the second year, it was found that dengue-naïve vaccinees (typically children) experienced increased rates of hospitalization and severe dengue compared to unvaccinated peers
- Regulators modified approval to only people with a prior dengue infection, to protect against secondary infections
- **Dengvaxia remains a safe and effective vaccine against severe disease for dengue-recoverees**

The first vaccine: DENGVAXIA (CYD-TDV)

- Why did it not work well for dengue-naïve individuals? We do not know
- Possible that the vaccination **mimicked a first infection**, which allowed subsequent natural infection to act like a secondary infection – typically more severe
- Possible that because it used yellow fever as the backbone, the vaccine produced **only antibodies** that could recognize dengue, and **not T-cells** (which would only have learned to respond to yellow fever), compromising the overall immune response

Lessons from Dengvaxia experience

- Every dengue vaccine candidate since has faced even more **stringent safety and efficacy reviews**, including needing to surveil vaccinees for more than one dengue season
- An effective dengue vaccine should seek to produce **simultaneous immunity to more than one dengue serotype**, to mimic the long-lasting immunity across all serotypes that two natural infections appear to produce
- It should also be **safe and effective for both dengue-naïve and dengue-recovered individuals**, to make mass vaccination drives easier to roll out (without a requirement to first test vaccinees for prior infection)

The second vaccine: **QDENGA** (TAK-003)

- Takeda's vaccine (TAK-003 / Qdenga) is approved for use in Indonesia, the EU, Brazil, and Thailand for use in those aged 4 and older, regardless of prior infection status *(as of May 2023)*
- Uses **DENV-2** as a backbone for all four dengue serotypes
  - This creates a strong T-cell response against DENV-2
- Approval was based on safety and efficacy data collected from 19 phase I, II and III trials with more than 28,000 participants
- Surveillance was extended from the required 1 year to **4.5 years** after the 2nd dose, with no safety issues apparent for vaccinees

The second vaccine: **QDENGA** (TAK-003)

- Overall efficacy at 12-18 months:
  - 80.2% against symptomatic dengue *(12mths)*
  - 90.4% against hospitalized dengue *(18mths)*
- Efficacy by serotype at 18 months:
  - Excellent protection against **DENV-2** (97.7%)
  - Good protection against **DENV-1** (73.7%)
  - Decent protection against **DENV-3** in dengue-recovered vaccinees (61.4%)
  - No efficacy against **DENV-3** in dengue-naïve vaccinees
  - Too few cases of **DENV-4 i**n trial group to calculate value
- No increased risk of severe disease compared to unvaccinated peers

A third vaccine candidate: BUTANTAN-DV (TV-003)

- The Instituto Butantan, U.S. National Institute of Health (NIH) and Merck (MSD) recently reported the first results from a phase III trial in Brazil with over 16,000 participants
- Disease surveillance has been conducted for **2 years** so far
- Not yet licensed for use – phase III trial will continue until 2024
- MSD has also created a proprietary formulation of TV-003 known as V181 *(see later slide)*

A third vaccine candidate: **BUTANTAN-DV** (TV-003)

- Overall efficacy at 24 months:
  - 79.6% against symptomatic dengue
- Efficacy by serotype at 24 months:
  - Very good protection against **DENV-1** (89.5%)
  - Decent protection against **DENV-2** (69.6%)
    - Good in dengue-recovered vaccinees (83.6%)
    - Average in dengue-naïve vaccinees (57.9%)
  - Too few cases of **DENV-3** and **DENV-4** in circulation to calculate value
- Safety data not officially released yet, but no severe cases reported so far

On the horizon: **V181** (TV-003)

- Merck's proprietary formulation (V181) of TV-003 is undergoing clinical trials
- Phase I trial results very promising
  - Evidence of a single dose resulting in detectable viremia from all four dengue serotypes
  - This may correlate to producing an immune response across all serotypes
- Next step: phase II and III trials
  - Will be exciting to see whether this formulation is better at combating **DENV-2** than the BTT formulation
  - GDAC will track the trial and surveillance results for safety and efficacy over the next 4-5 years

In summary

- **Each vaccine is best at creating immunity to different dengue serotypes** *(see next slide)*
- **The most worrying serotype, in terms of the risk of severe dengue, is DENV-2** - it is especially important to create protection against it
  - Has highest immune requirement for protection
  - Most likely to result in severe dengue in a secondary infection
- **Dengvaxia** is safe for dengue recoverees, and effective at preventing severe disease for them, but is not suitable for the dengue-naïve
- **Qdenga** is safe for both dengue recoverees and the dengue naïve, and is effective at protecting against severe disease
- **TV-003** looks promising as a potential future vaccine candidate as well

	Efficacy by serotype & antibody/T-cell response	Effect on dengue-naïve vaccinees	Effect on dengue-recovered vaccinees
Dengvaxia (3 doses; currently available)	Predominantly produces type-specific antibodies to **DENV-4**. Does not produce any DENV T-cell response *(uses yellow fever, not dengue, as the backbone).*	*Not licensed for use*	Protects against **all** dengue and hospitalized dengue caused by **any** dengue serotype.
Qdenga (2 doses; currently available)	Predominantly produces type-specific antibodies to **DENV-2**. Produces a robust specific T-cell response against **DENV-2** *(uses DENV-2 as the backbone)*, and cross-serotype T-cell responses against **DENV-1, -3, and 4.** **Minimal side effects.**	Protects very well against symptomatic and hospitalized dengue due to **DENV-1** and **DENV-2** infections.	Protects against **all** dengue and hospitalized dengue caused by **any** dengue serotype.
TV-003 (likely 1 dose; undergoing clinical trials)	Early results indicate **possibility of producing antibodies to all serotypes**. May produce cross-serotype T-cells, probably does not produce serotype-specific T-cells. **Typically presents some side effects** (rash/fever).	Protects well against **DENV-1**, less well against **DENV-2** *(V181 formulation may improve on this).* Insufficient data for **DENV-3** and **DENV-4** (rarer serotypes).	Protects well against **DENV-1** and **DENV-2**. Insufficient data for **DENV-3** and **DENV-4** (rarer serotypes).

Options for consideration

- Option 1: QDENGA alone
  - Safe for all vaccinees
  - Provides especially robust protection against DENV-2 – important for all, and especially for anyone at risk of a secondary infection
- Option 2: QDENGA followed by DENGVAXIA as a booster
  - Would provide broad protection against all DENV serotypes
- In the future – V181 (TV-003) may be a promising single-dose candidate

The bottom line

What does all this boil down to?

Dengue protection has entered a new era

The emergence of one already-licensed *and* one more potential candidate for a safe, effective vaccine, that is suitable for both recoverees and the dengue-naïve, is historic and unprecedented.

For the first time in 75 years of research and testing, **dengue is now a vaccine-preventable disease for all**, regardless of prior infection status.

It is time to act

Even if dengue does not feel like it's your problem today, with climate change and globalisation, it may well be your problem tomorrow.

Actions taken today will have significant impact on the future distribution of dengue.

Governments cannot wait for a dengue wave to arrive before vaccinating: **to prevent hospital systems from being overwhelmed, vaccination must be done ahead of time**.

Do not let perfect be the enemy of good enough

These vaccines, even if they cannot achieve a 100% efficacy rate against infection, **can help the vast majority of vaccinees avoid severe dengue**, while not exposing them to any greater risk by becoming vaccinated.

A vaccine is not a cure, but it can prevent untold suffering and tens of thousands of deaths.