DEN-401: The Association Between Prior Exposure to Dengue Tetravalent Vaccine (Live, Attenuated) (TDV) and Dengue Hospitalization in a Pediatric and Adolescent Population: a Nested Case-Control Post-Authorization Effectiveness Study

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Disclaimer

- Takeda's tetravalent dengue vaccine candidate (TAK-003) has not been approved for use In Canada.

- TAK-003 has been approved for use by regulatory authorities in various dengue-endemic and non-endemic countries. Additional regulatory reviews are underway. However, it is important to note that there is no guarantee of TAK-003’s approval in any specific country. Indications may vary in different countries.

Conflict of interest

Dr Suely Tuboi is an employee of Takeda and holds stocks/stock options in Takeda

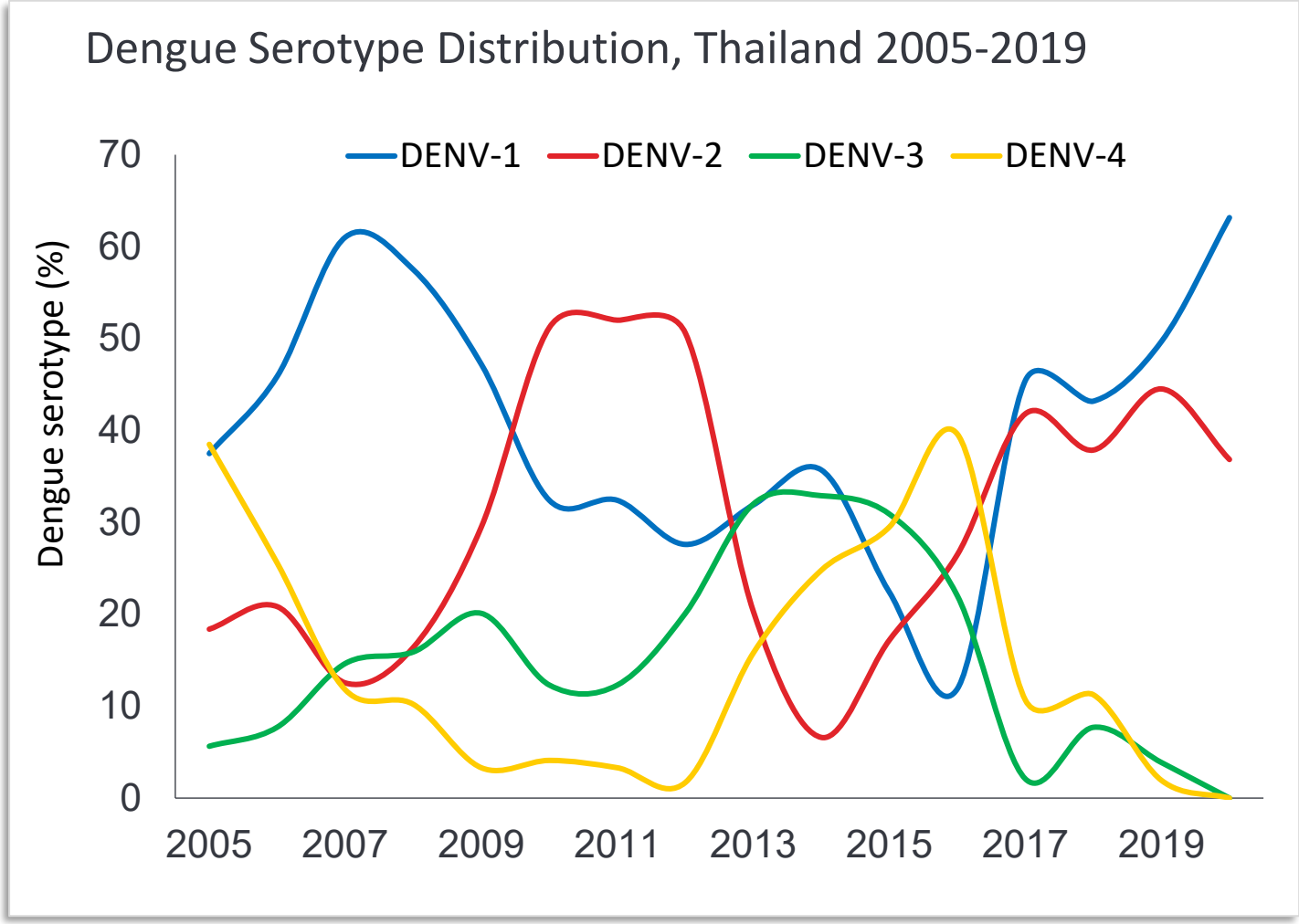
Dengue 1o1

- There are 4 dengue serotypes: DENV-1, DENV-2, DENV-3, and DENV-4
- Infection with one serotype provides lifelong immunity to that serotype, but not to the others.
- Subsequent infection with a different serotype increases risk of severe disease
- This is why people who have had dengue before (seropositive) are interested in being protected against dengue.

Gubler, *et al. Emerg Infect Dis* 1995;1:55–7

Dengue Serotypes

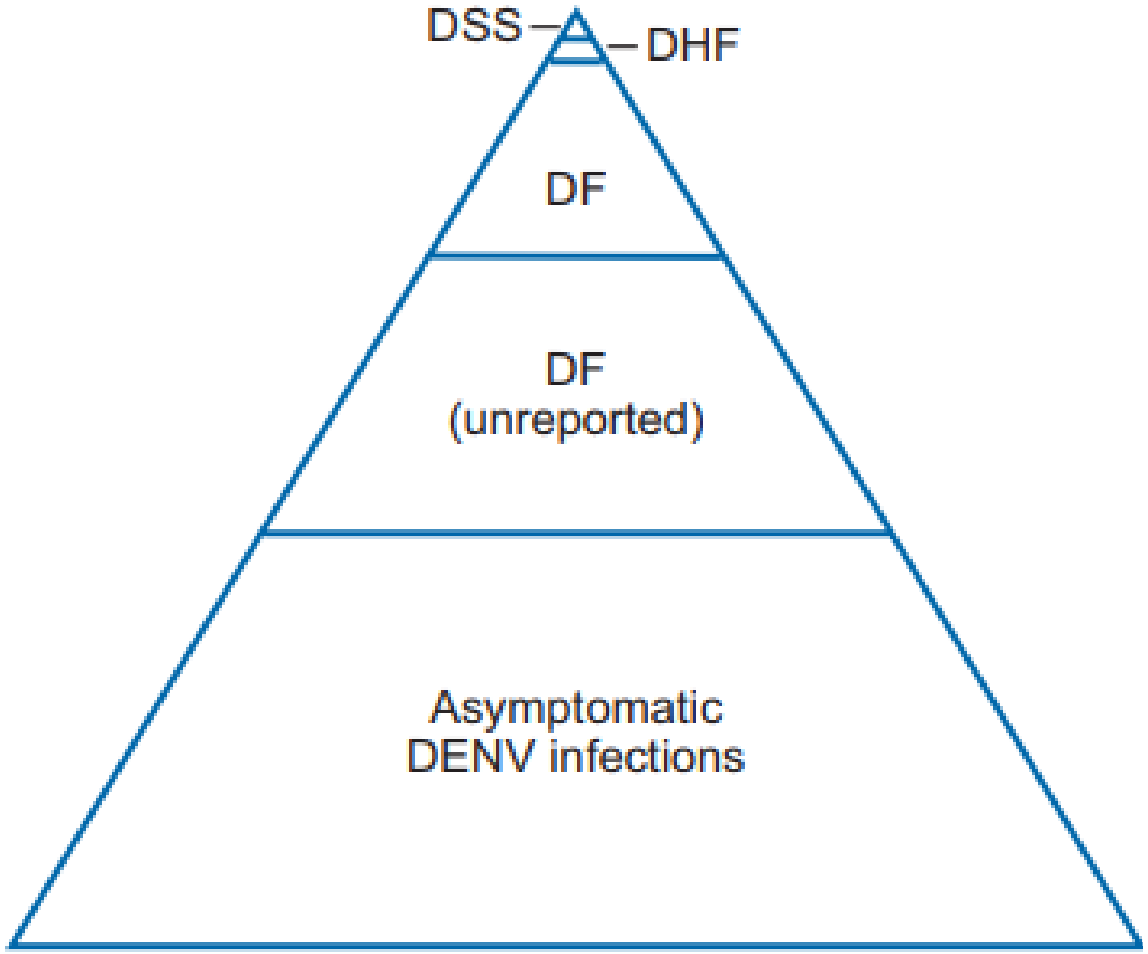
- The serotypes circulate around the world in unpredictable ways
- Predictive models cannot reliably forecast which dengue serotype will predominate in a certain area.
- In areas with a lot of dengue, more than one dengue serotype typically circulates at a time
- DENV-3 and DENV-4 are the rarest serotypes and are found more regularly in Southeast Asia.



Messina JP, Brady OJ, Scott TW, Zou C, Pigott DM, Duda KA, Bhatt S, Katzelnick L, Howes RE, Battle KE, Simmons CP, Hay SI. Global spread of dengue virus types: mapping the 70 year history. Trends Microbiol. 2014 Mar;22(3):138-46. doi: 10.1016/j.tim.2013.12.011. Epub 2014 Jan 24. PMID: 24468533; PMCID: PMC3946041.
Serotype data from National Institute of Health Thailand, Department of Medical Sciences, MoPH, Thailand

Spectrum of Disease

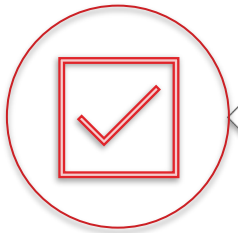
- Up to 75% of dengue infections are asymptomatic
- Many symptomatic cases go unreported:
  - Mild symptoms managed at home
  - Misdiagnosed due to similarity with other illnesses (e.g., flu, chikungunya)
- Only a small fraction of infections are seen, diagnosed, and reported in surveillance systems
- Hospitalized cases, including severe dengue, dengue hemorrhagic fever, and dengue shock syndrome represent just the 'tip of the iceberg'



DSS: Dengue Shock Syndrome; DHF: Dengue Hemorrhagic Fever; DF: Dengue Fever; DENV: Dengue Virus

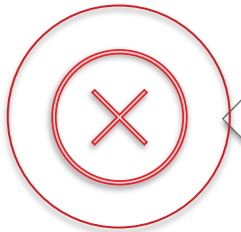
Harris et al. Annu. Rev. Microbiol. 2008.

DEN-401 was Designed to Fill the Gaps Arising From DEN-301



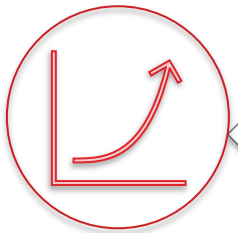
The pivotal DEN-301 efficacy trial was powered to meet and **met the primary endpoint.** All secondary endpoints were also met where there were enough dengue cases for analysis

There were a **lower number of cases hospitalized with virologically confirmed dengue due to DENV-3 and DENV-4** for analyses by serotype and serostatus.



Efficacy was not shown against DENV-3 in baseline seronegatives

The trial did not allow assessment of efficacy against DENV-4 in baseline seronegatives due to small case counts

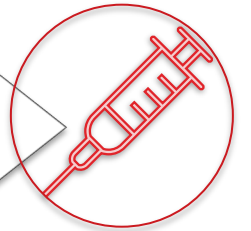


The **totality of data shows a positive benefit regardless of serostatus up to 4.5 years,** but gaps remain

DEN-401 is an EMA Post-Authorization Commitment

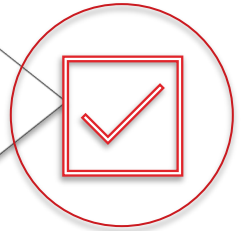
A multi-country, multi-site, hospital-based, nested case-control study; conducted in areas where we have the best likelihood of capturing DENV-3 and DENV-4, like Southeast Asia

Will assess the impact of Qdenga against hospitalized virologically confirmed dengue by serotype, independent of serostatus, over a period of 3 years



Aims to fill information gaps by providing information on hospitalization and severe dengue for each serotype and by serostatus

DEN-401 is designed to specifically provide post-marketing effectiveness data for DENV-3 and DENV-4 in seronegative subjects



DEN-401 – Study Objectives

Primary Objective

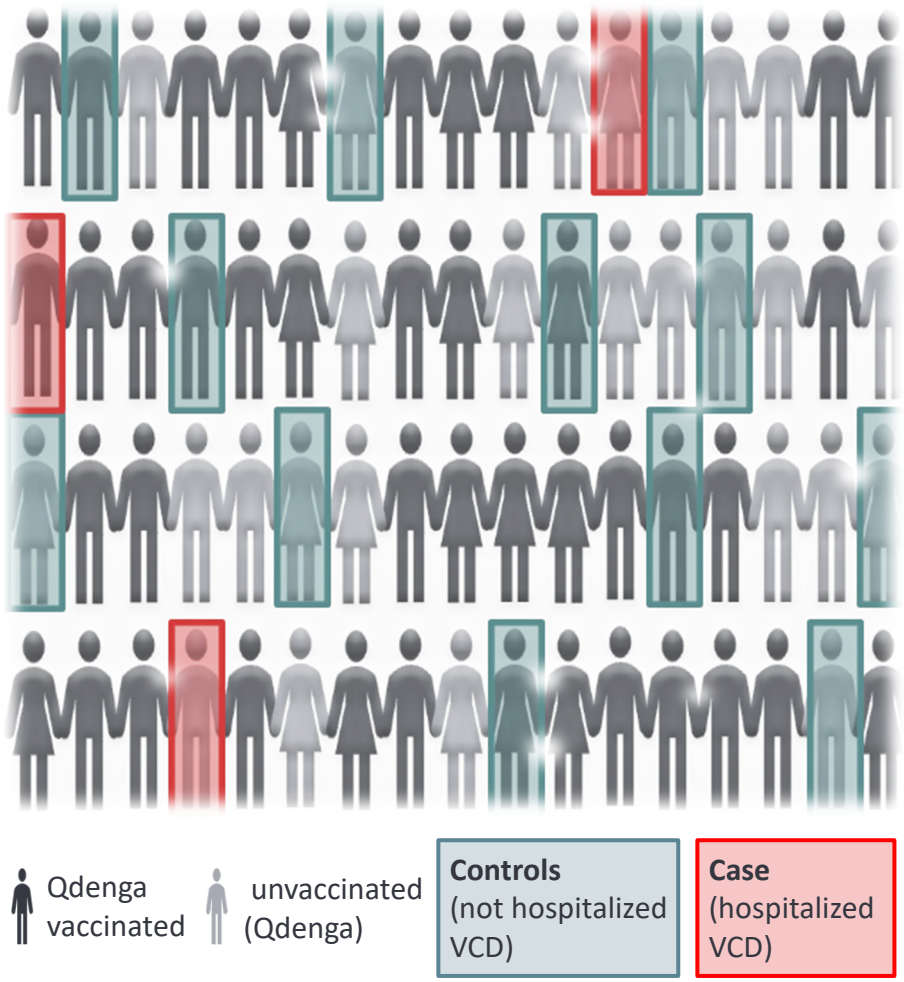
- To estimate the association between completed vaccination with Qdenga (as part of a vaccination program) and hospitalization due to VCD, including severe dengue

Secondary Objectives

- To estimate how the association between completed vaccination with Qdenga (as part of a vaccination program) and subsequent hospitalization due to VCD, including severe dengue, is modified by:
  - The infecting dengue serotype
  - The baseline dengue serostatus
  - The infecting dengue serotype and the baseline dengue serostatus

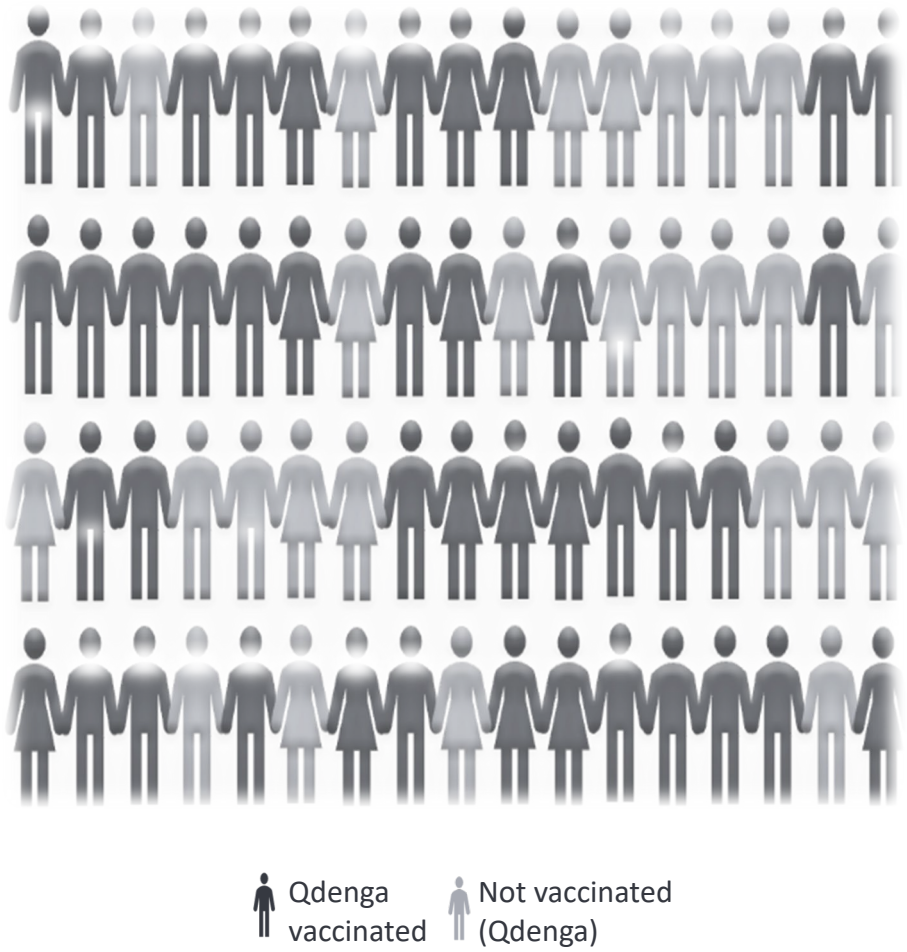
VCD: virologically confirmed dengue

DEN-401 – A Nested Case Control Study



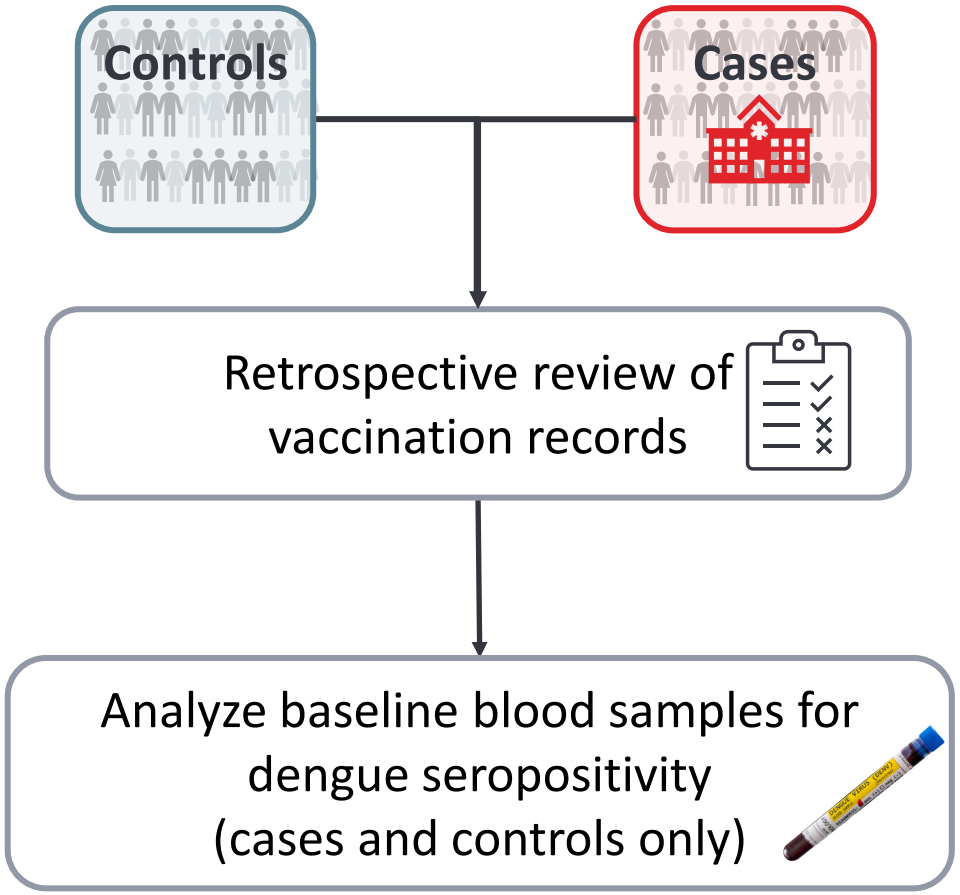
- **Cases** – study cohort participants hospitalized with virologically confirmed dengue (VCD)
- **Controls** – study cohort participants who are not hospitalized with dengue
- Cases and controls matched by age and neighborhood to minimize confounding variables

DEN-401 – The Cohort



- 70,000 individuals eligible for vaccination with Qdenga as part of a public vaccination program
- All participants are required to provide a blood sample that will be stored until required (obtained pre-vaccination, for vaccinees)
- Blood samples will be used to establish the pre vaccination serostatus of cases and controls
- Vaccinated or unvaccinated

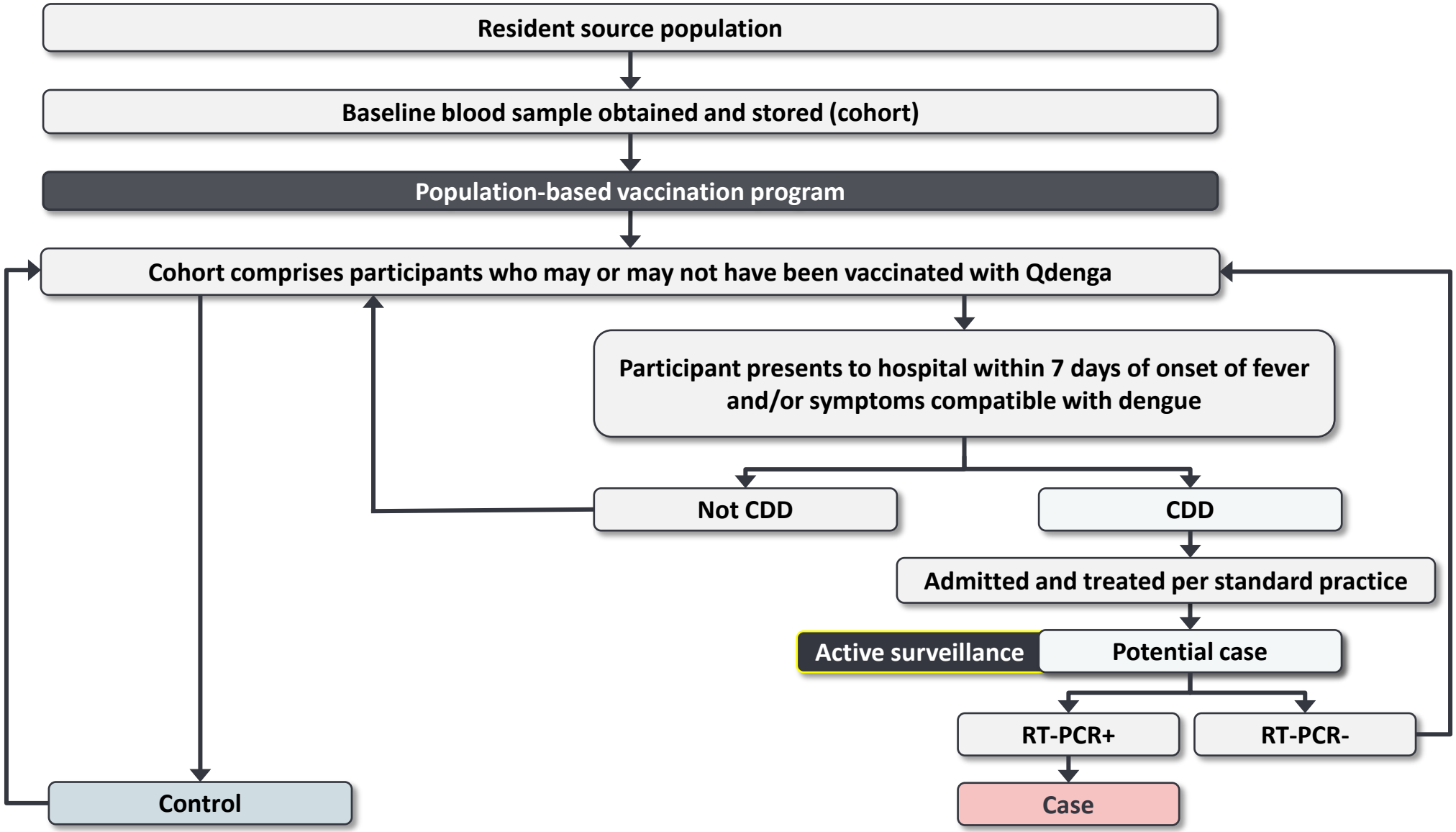
DEN-401 - Analysis of Serotype-Specific Hospitalized Dengue



- The relationship between hospitalization due to serotype-specific VCD and previous vaccination with Qdenga will be expressed as an odds ratio
- Analysis will be stratified by serotype and baseline serostatus

VCD: virologically confirmed dengue

DEN-401 - Study Schematic



CDD: Clinically Diagnosed Dengue

DEN-401 Study Assumptions – Community-Based Cohort of 70,000

50% of cohort are vaccinated (n=~35,000)[†]

20% of eligible individuals are seronegative at enrollment (n=~14,000)

1% annual baseline hospitalization rate for dengue[‡] (n=~902 unvaccinated over 3 years)

7% annual dropout due to migration

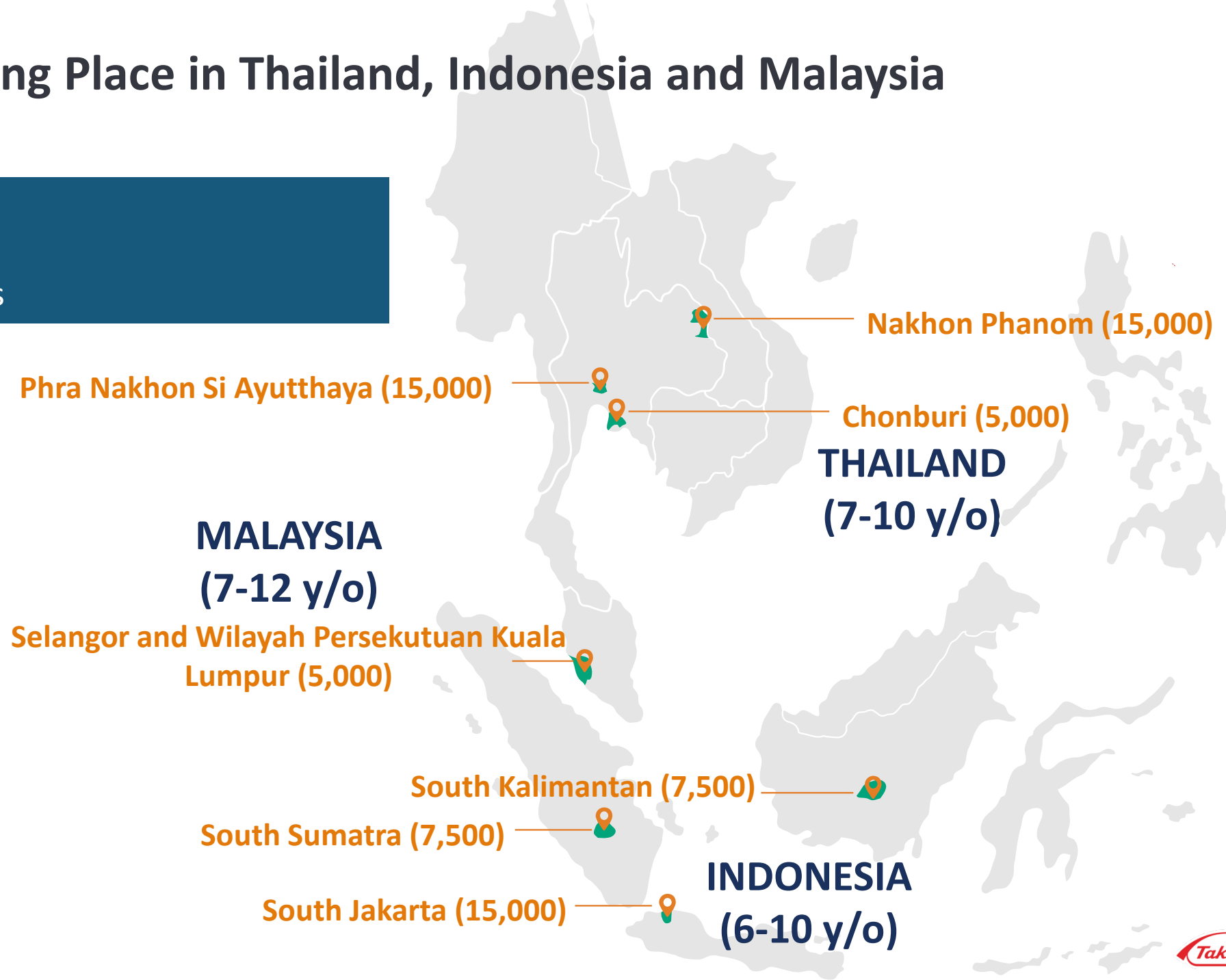
20% of cases due to DENV-3 (n=~180/902) and 14% of cases due to DENV-4[*] (n=~126/902)

Of the expected 902 DENV hospitalizations, 180 outcomes (**36/180** due to DENV-3 and **25/180** due DENV-4) are expected to be in baseline seronegative participants.

[†]Vaccination will be based on a voluntary decision to the DEN-401 cohort participants.
[‡]Calculated using the placebo data from DEN-301 and the Sanofi CYD-TDV studies.
Takeda Data on File (Dengue Tetravalent Vaccine [Live, Attenuated] - DEN-401).

DEN-401 is Taking Place in Thailand, Indonesia and Malaysia

- Multi- Site
- Multi- Country
- Study Duration = 3 years



Thank you!

Better Health, Brighter Future