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# Determining the Potential Payoff at City and District Levels from Up-Front Investments in New Technologies for Dengue Prevention in Two Endemic Countries (Thailand and Indonesia): Combining Surveillance, Screening and Interviewing

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# Disclosure

- Dr. Wilastonegoro declares no actual or potential conflicts.
- Profs. Shepard and Kongsin received grant funding from Takeda through their universities related to this study.
- However, this presentation reflects views of the authors, and not necessarily the sponsor.

# Purpose

- Recent randomized trials of two new technologies (Wolbachia and Takeda's vaccine) established that each would cut dengue by about 77% without adverse effects.
- However, deployment would require substantial up-front investment, particularly at the city and district levels.
- This presentation indicates how existing data could be used to set policy and how additional data could help refine those policies.

# Overview

- Workshop attendees should obtain a working knowledge of approaches to use existing data and refine them as needed for policy.
- Dengue and other illnesses, including COVID-19, reduce presenteeism, patients' ability to maintain usual activities, for income, household tasks, and schooling
- Prof. Donald Shepard and Dr. Nandyana Wilastonegoro will share the presentation with data from Thailand and Indonesia.

# Q1 Data poll

To guide public health on dengue, Indonesia already has information by city on reported cases, population, and area (square km)

True

False

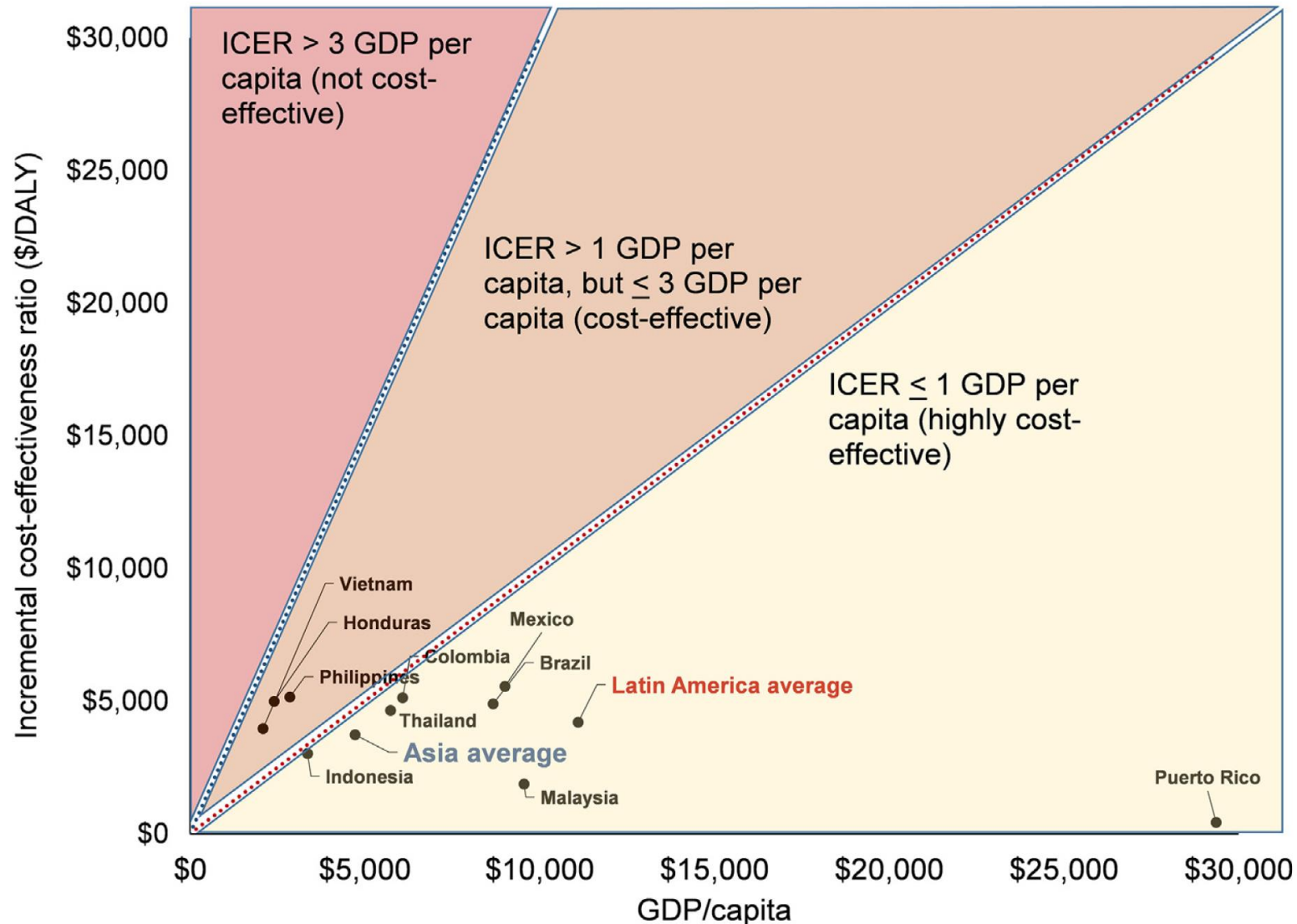
# Q1 Data poll - Answer

To guide public health on dengue, Indonesia already has information by city on reported cases, population, and area (square km)

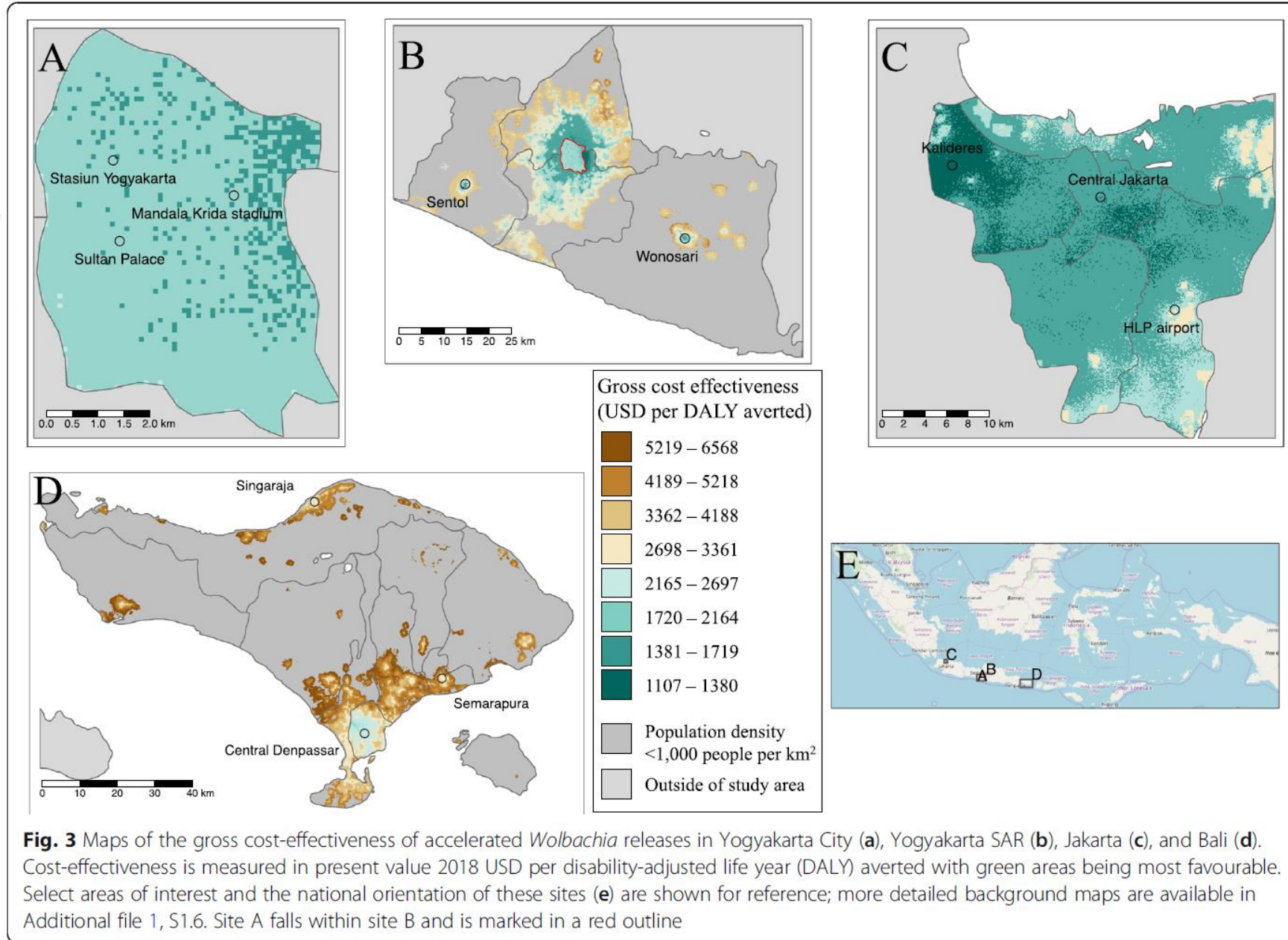
**True**

False

# Global – Incremental cost-effectiveness of dengue vaccination by country (Zeng, Vaccine 2017)



# Wolbachia by city in Indonesia (Brady, BMC Medicine, 2020)





## Q2: Cost-effectiveness poll

Based on the cost-effectiveness data, for central areas of major cities, *Wolbachia* would be more cost-effective than vaccination

True

False

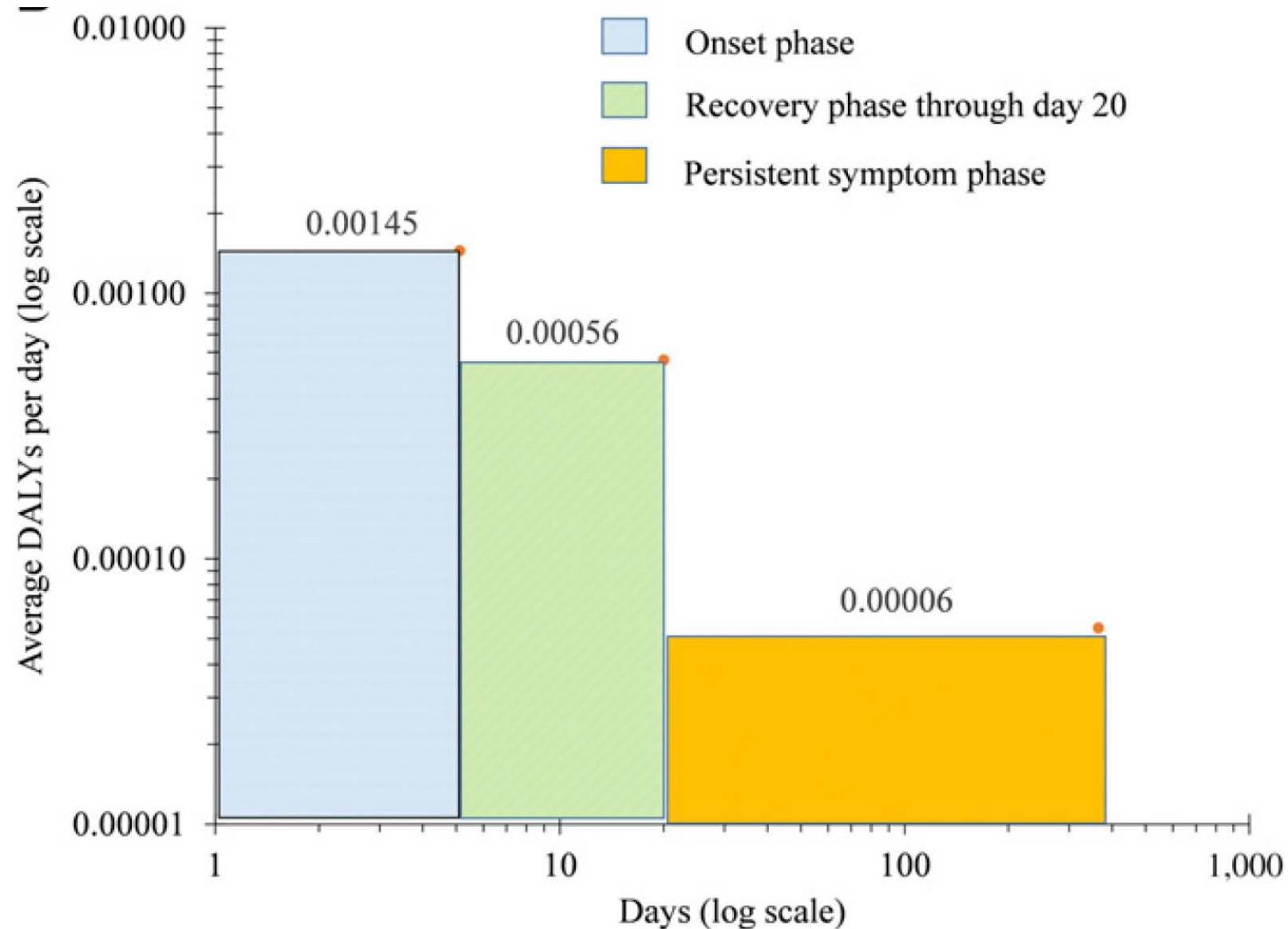
## Q2: Cost-effectiveness poll - Answer

Based on the cost-effectiveness data, for central areas of major cities, *Wolbachia* would be more cost-effective than vaccination

**True**

False

# Global: Importance of dengue persistence in non-fatal hospitalized dengue cases (Zeng 2019, Am J Trop Med Hyg)



## Q3: Duration poll

Although the acute phase of dengue is more severe per day, the persistent phase lasts much longer.

True

False

## Q3: Duration poll - Answer

Although the acute phase of dengue is more severe per day, the persistent phase lasts much longer.

**True**

False

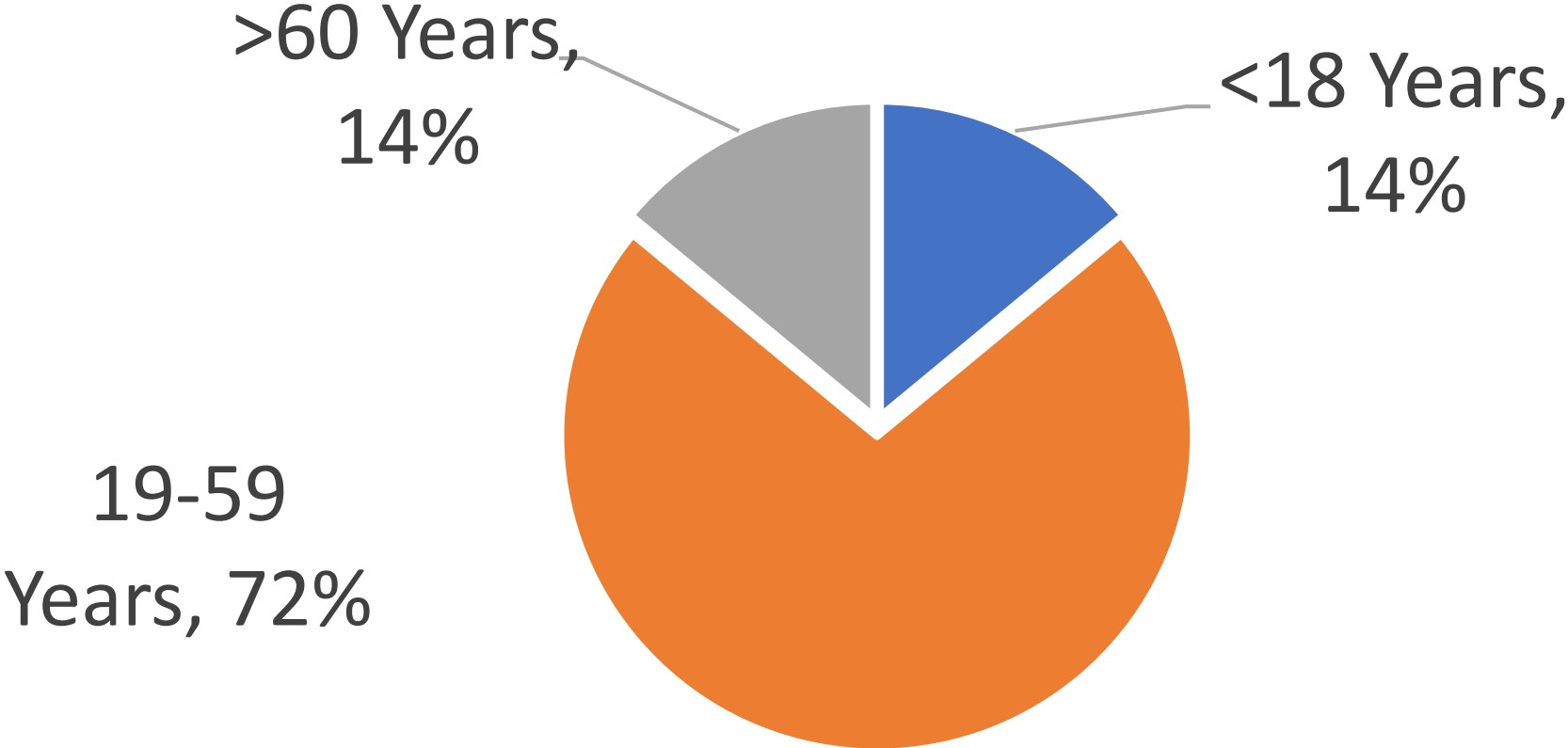
# Thailand: Setting

- Prof. Kongsin and colleagues piloted a study assessing presenteeism losses in Umphang District, Tak Province, Thailand.
- The pilot enrolled 22 laboratory-confirmed dengue patients, aged 7-78, from April-July, 2021 with interviews every 1-4 weeks for up to 6 months until symptoms ended.
- With participant incentives and well-trained staff, all enrollees completed every planned interview



# Thailand: Ages

## Varied age distribution of enrolled dengue patients



## Q4: Affected ages poll

Dengue affects only children in Thailand.

True

False



## Q4: Affected ages poll - Answer

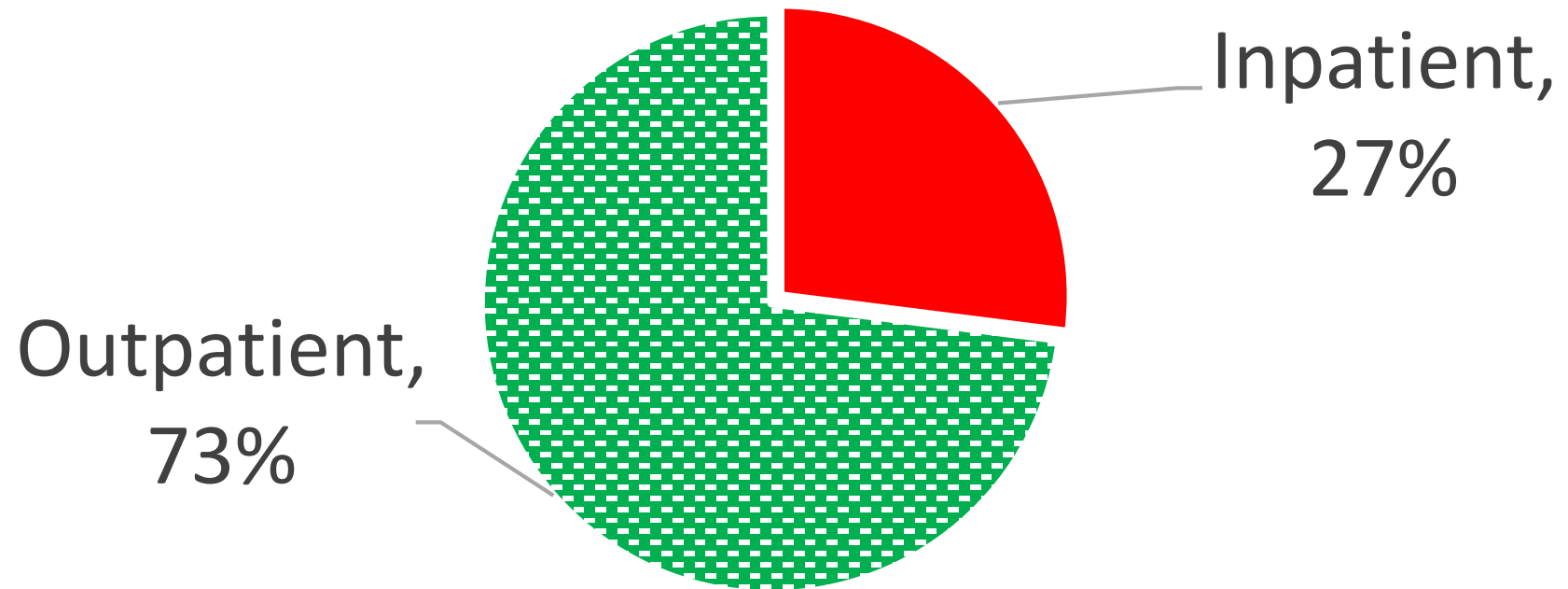
Dengue affects only children in Thailand.

True

**False**

# Thailand: Care setting

## Varied care settings of enrolled dengue patients



# Thailand 4: Dengue persistence

## Number of days from onset of fever until self-reported end of symptoms

Mean: 125

Standard deviation: 24

Shortest: 56

Longest: 140

Standard error of the mean: 5

Number of patients (N): 22

Note: Data are preliminary

# Indonesia: dengue context

- Indonesia is among countries with highest dengue burden globally (Shepard et al, 2016)
- Dengue cases were first notified in Jakarta and Surabaya in 1968 i.e., 58 hemorrhagic fever cases (Suroso and Bang, 1987)
  - There is no breakthrough intervention implemented for decades to control dengue (Dengue National Strategy 2021 – 2025, 2020)
  - Main interventions have been fumigation and public ACMS (advocacy, communication, mobilization and socialization)
- Every district/city reports monthly cases to the national dengue program. However, there is an epidemiological data gap between the reported cases and the potential actual cases
  - Annual DHF cases has been officially reported between 60 – 200 thousand, 2011 – 2020 – on average 108 thousand (National Dengue Program, 2021)
  - The national dengue program reports only DHF diagnosed at hospitals (Dengue National Strategy 2021 – 2025, 2020)
  - On the other hand, for example there is a study estimated the annual number of dengue cases about 7.5 million (O'Reilly et al, 2020)

## Q5: Completeness of reporting poll

The number of statistically estimated dengue cases is far higher than the number officially reported.

True

False

## Q5: Completeness of reporting poll - Answer

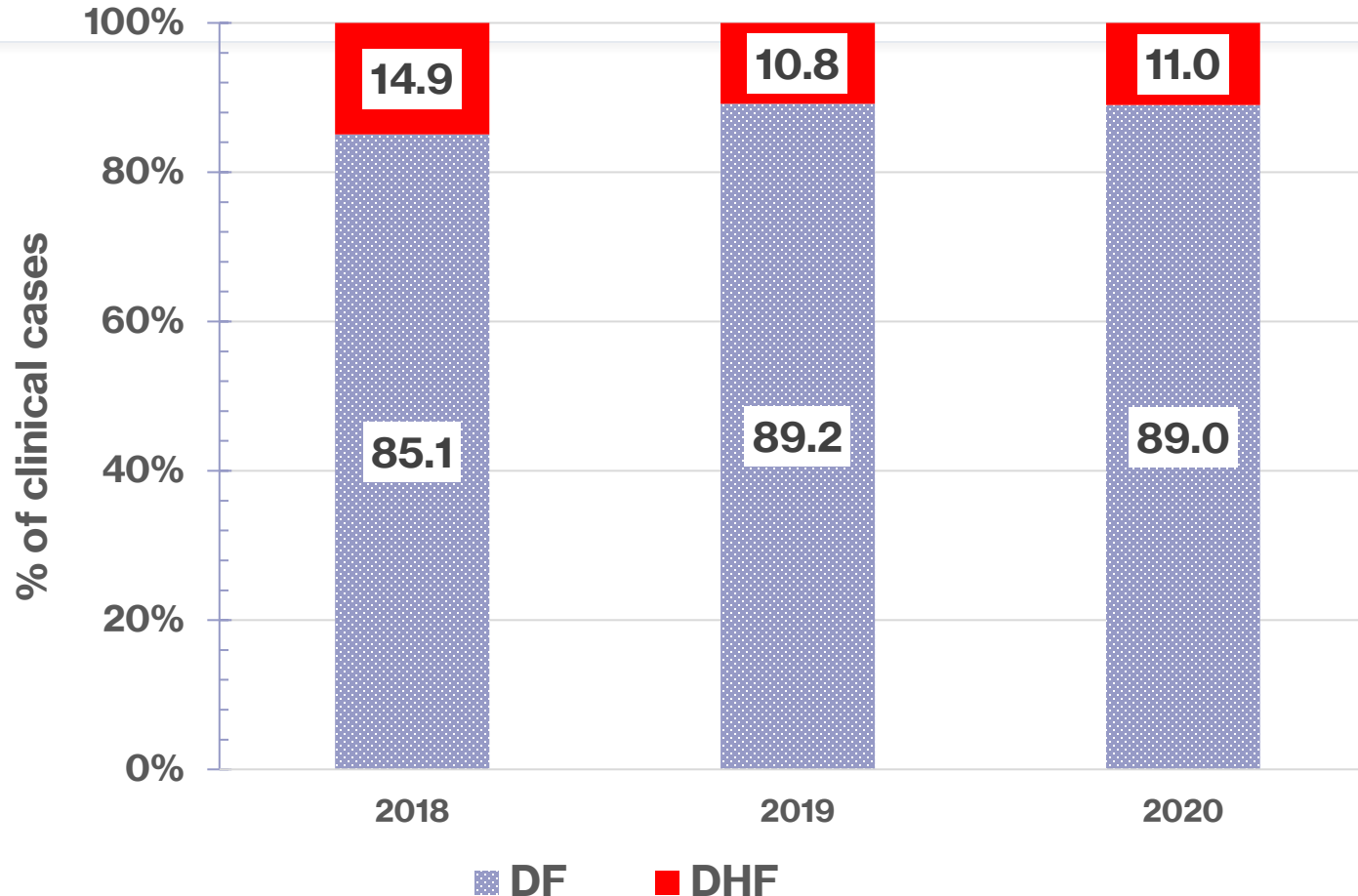
The number of statistically estimated dengue cases is far higher than the number officially reported.

**True**

False

# Indonesia: Local surveillance data officially reported cases (DF vs DHF)

DF and DHF in Semarang City



- Average DHF 12.2%
- Inverse:  $1/12.2\% = 8.2$
- Expansion factor: For every reported DHF case there are 8.2 overall cases of dengue illness

## Q6: Expansion factors poll

Based on data from Semarang, the expansion factor for dengue cases is about 2

True

False



## Q6: Expansion factors poll - Answer

Based on data from Semarang, the expansion factor for dengue cases is about 2

True

**False**

# Indonesia: control technologies

- Vaccination: Administered to susceptible persons, protecting recipients.
- *Wolbachia*: A bacteria which is inserted into the mosquito that transmits proven to reduce dengue cases by 77% in the targeted area
- Yogyakarta and surrounding districts: *Wolbachia* being deployed city-wide in 2022

# Indonesia: *Wolbachia*

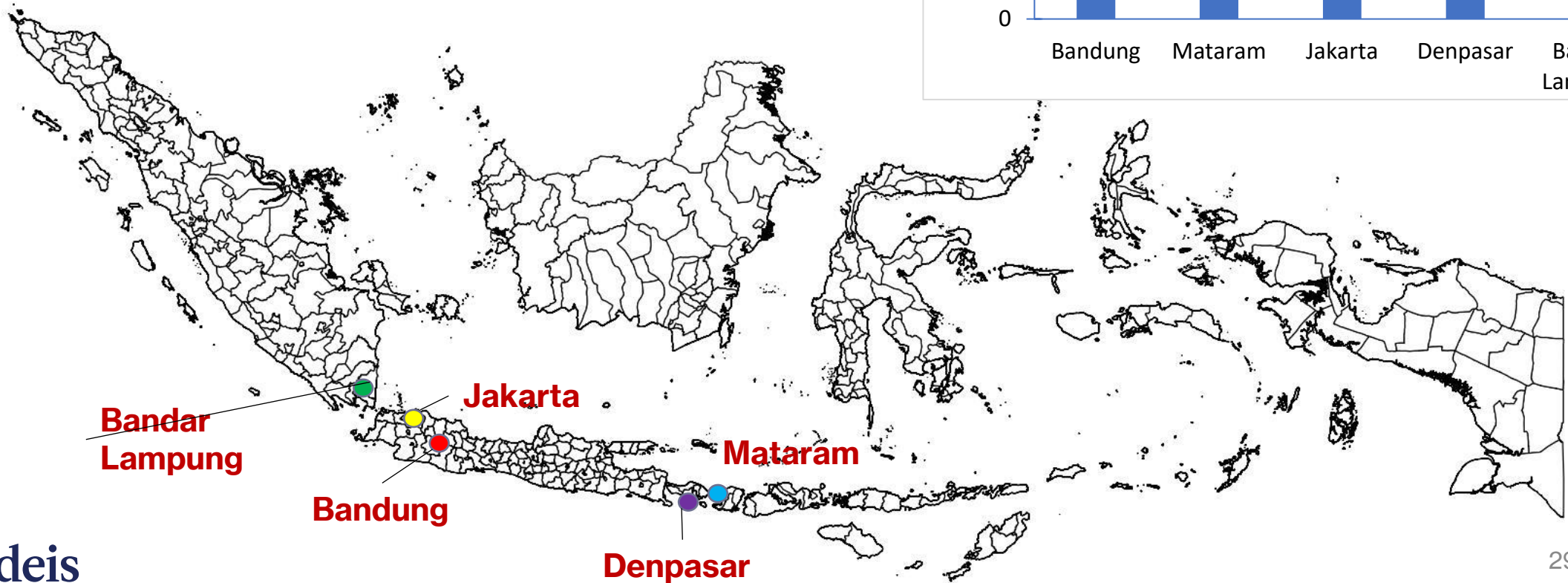
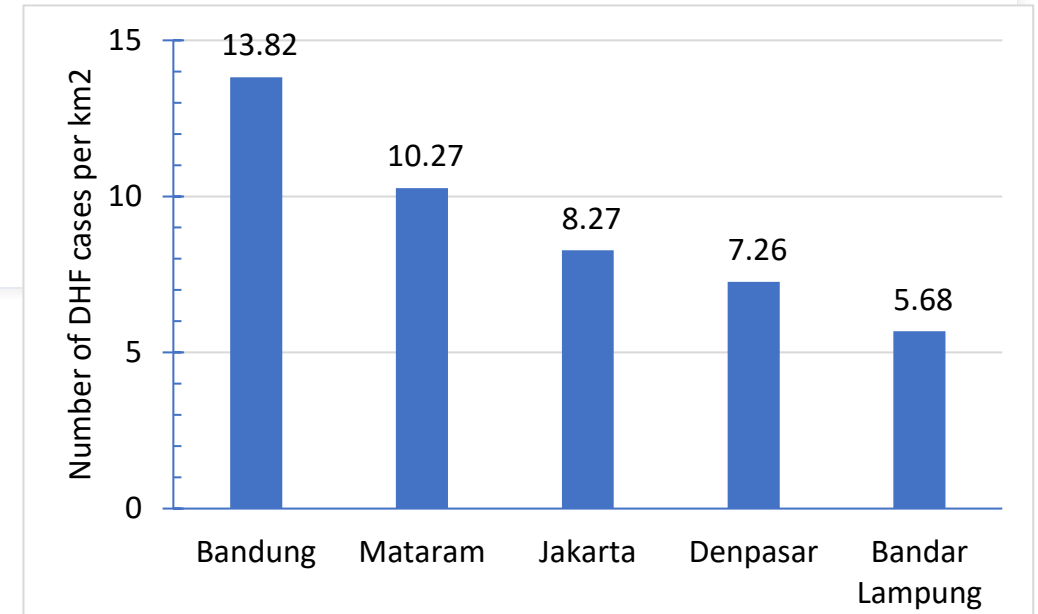
- *Wolbachia*: bacteria inserted into the mosquito that inhibits dengue transmission
- Cluster randomized trial showed 77.1% (CI: 65.3%-84.9%) reduction in dengue cases (Utarini 2021).
- Already deployed in Yogyakarta following successful completion of randomized trial
- Recommend implementation in geographical areas of exceptionally high need, high fiscal capacity and favorable cost-effectiveness.
- Benefits: expected dengue cases averted in a city
- *Wolbachia*: cost depends primarily on number of km<sup>2</sup> to be covered
- Cost-effectiveness proportional to DHF cases per km<sup>2</sup>

# Indonesia: Vaccination

- Vaccine: Sanofi vaccine licensed but little used due to need for prior testing
- Takeda vaccine licensed in August 2022
- Future policy question concerns possible inclusion in national immunization program
- Randomized trial showed 83.6% (CI: 76.8%-88.4%) reduction in virologically confirmed hospitalized dengue cases (Rivera 2022).
- Recommend implementation in geographical areas of exceptionally high need, high fiscal capacity and favorable cost-effectiveness.
- Benefits: expected dengue cases averted in a city
- Vaccine: cost depends primarily on number of people to be covered
- Cost-effectiveness is proportional to DHF cases per person

# Indonesia: Priority cities for *Wolbachia* deployment

City	Fiscal Capacity	Land Area	Population	Population density	DHF cases	Incidence rate	DHF/km2
Bandung	Very high	167.30	2,510,103	15,004	2,312	92.09	13.82
Mataram	High	61.30	429,651	7,009	629	146.48	10.27
Jakarta	Very high	661.50	10,562,088	15,967	5,472	51.80	8.27
Denpasar	High	127.80	962,879	7,534	928	96.38	7.26
Bandar Lampung	Very high	197.20	1,166,066	5,913	1,120	96.02	5.68



## Q7: Wolbachia priority cities poll

The cities with the absolute highest count of dengue cases should be prioritized for *Wolbachia*

True

False

## Q7: Wolbachia priority cities poll - Answer

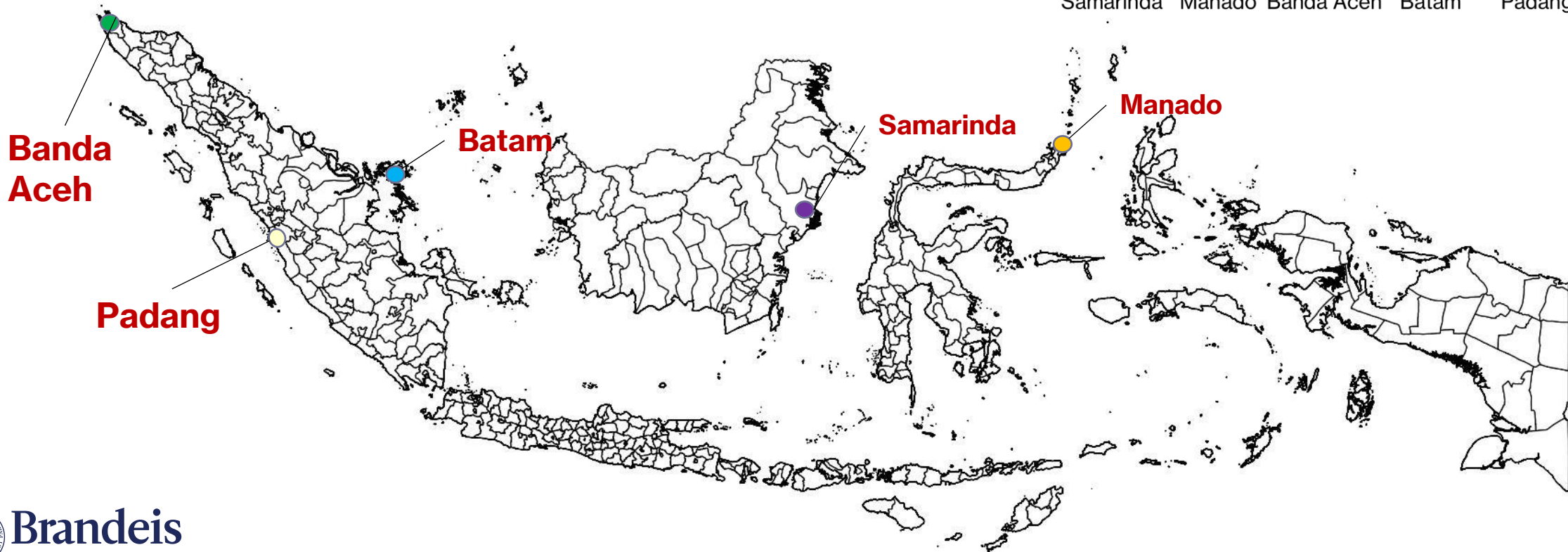
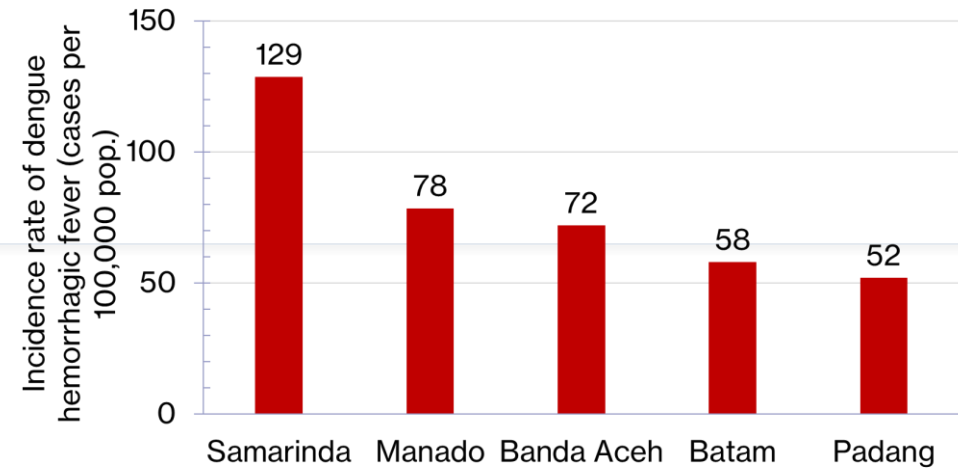
The cities with the absolute highest count of dengue cases should be prioritized for *Wolbachia*

True

**False**

# Indonesia: priority cities for vaccination

City	Fiscal Capacity	Land Area	Population	Population density	DHF cases	Incidence rate	DHF/km <sup>2</sup>
Samarinda	Very high	718.00	827,994	1,153	1,065	128.58	1.48
Manado	High	162.50	451,916	2,781	355	78.48	2.18
Banda Aceh	High	61.36	252,899	4,122	182	71.97	2.97
Batam	Very high	929.51	1,196,396	1,287	693	57.95	0.75
Padang	Very high	695.00	909,040	1,308	472	51.96	0.68





## Q8: Vaccination priority cities poll

The remaining cities with the absolute highest count of dengue cases should be prioritized for vaccination

True

False

## Q8: Vaccination priority cities poll - Answer

The remaining cities with the absolute highest count of dengue cases should be prioritized for vaccination

True

**False**

# Indonesia: identifying gaps

- National dengue program reported only DHF diagnosed at hospitals while dengue spectrum varies from asymptomatic to severe and fatal cases
- Dengue cases seek for care at other facilities are not recorded → outpatients, non-medically attended, primary health centers, private practitioners
- Dengue diagnosis mostly relies on clinical diagnosis
  - Confirmatory diagnosis with RDTs or advance lab test remains rare
  - Some reports from districts/cities were not sent in time
- Limited number of cost-of-illness studies
- Actual dengue burden remains uncertain
- Reported cases of other major diseases (e.g., tuberculosis, malaria, pneumonia, HIV) outweigh the reported dengue cases
- Dengue is not a national disease priority
- National dengue program has not changed its interventions for decades
- There is no urgency to adopt vaccine or other breakthrough interventions
- Indonesia remains among top 5 dengue endemic countries

# Indonesia: challenge

- Takeda's dengue vaccine approved by Indonesian FDA (BPOM) (August, 2022)
- In future, Ministry of Health must decide whether to recommend it as public health program
- In future, public funding may be a big challenge: old, long-established vaccines are relatively inexpensive, but new products, often with just a single manufacturer, are costly.
- Suppose that Takeda's vaccine were targeted to Indonesia's 4.4 million 4 year-old children, require 2 doses/child, and sold for \$60 per child (public sector price for Sanofi vaccine in SE Asia).
- Aggregate cost becomes 4.0 trillion IDR (Indonesian rupiah) or \$264 million US dollars (US\$0.96 per capita).

# Indonesia: Enhanced surveillance

- Dr. Wilastonegoro designed a five-step protocol for Semarang City, Indonesia (population 1.6 million):
  - (1) Using data from the surveillance system to select a small but representative sample of public and private health centers and hospitals.**
  - (2) Promptly screening their clinically diagnosed patients for laboratory confirmation.
  - (3) Inviting NS1-positive to enroll in an observational study.
  - (4) Interviewing consenting patients weekly to monthly about health care utilization, absenteeism, and presenteeism.
  - (5) Linking interviews with surveillance and screening data to weight to the city level.

## Q9: Enhanced surveillance poll

Whereas existing surveillance compares the relative incidence of one city with another, enhanced surveillance would better estimate actual incidence

True

False

## Q9: Enhanced surveillance poll - Answer

Whereas existing surveillance compares the relative incidence of one city with another, enhanced surveillance would better estimate actual incidence

**True**

False

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