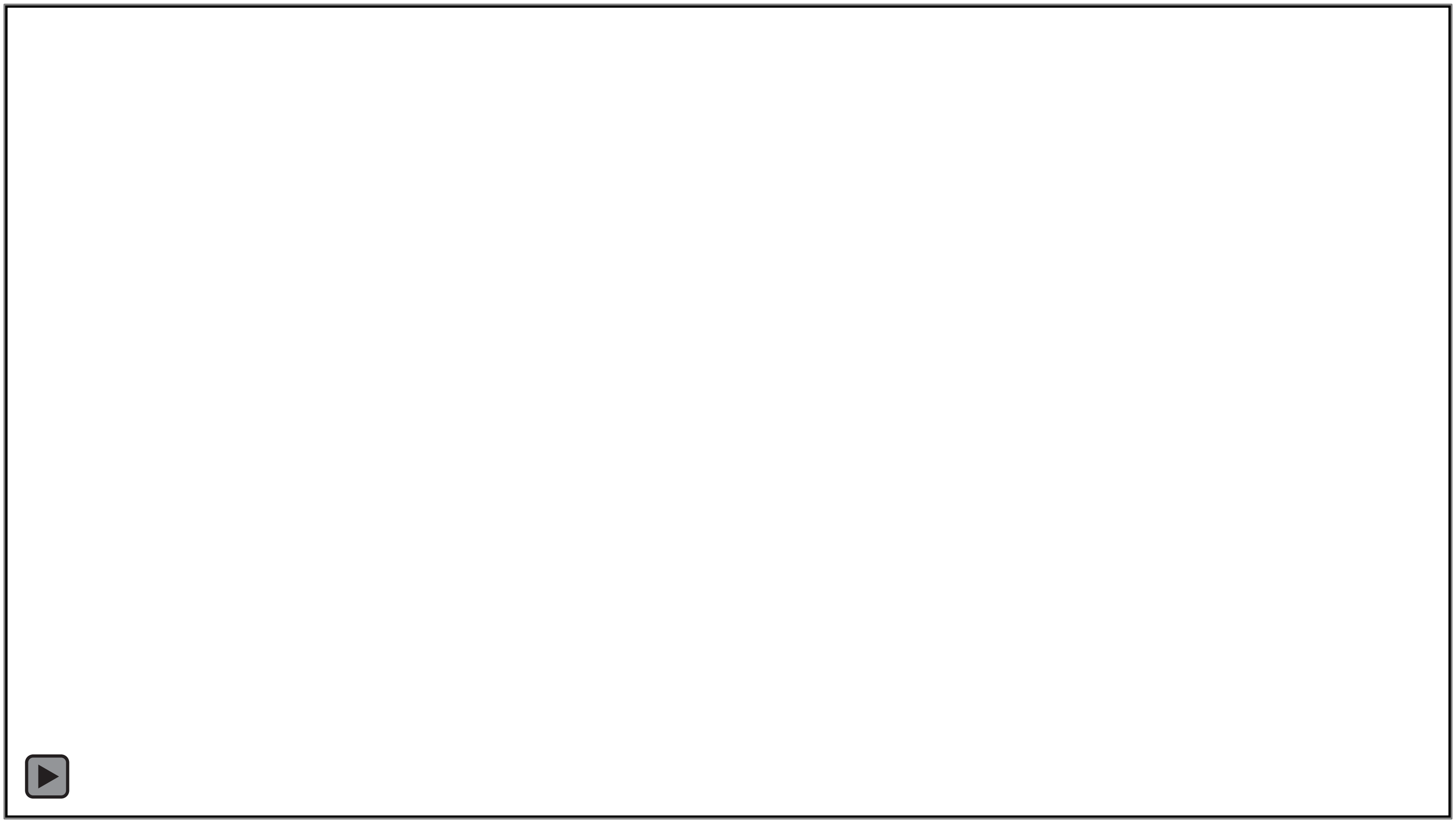
ELIMINATE DENGUE™
OUR CHALLENGE

ELIMINAR A DENGUE
DESAFIO BRASIL

ELIMINAR EL DENGUE
DESAFIO COLOMBIA

ELIMINATE DENGUE
TANTANGAN INDONESIA

HƯỚNG TỚI LOẠI TRỪ
SỐT XUẤT HUYẾT
TẠI VIỆT NAM



Global burden of dengue

$8.9B global government spend (USD) on dengue each year

45% of health costs are borne by the family.

These costs can be upwards of **3x** the family's monthly income.

40% OF THE GLOBAL POPULATION ARE AT RISK OF GETTING DENGUE.

ESTIMATED **390 MILLION** DENGUE INFECTIONS EACH YEAR.

Shephard et al 2016. Lancet Infect Dis. & http://www.ifrc.org/en/news-and-media/features/dengue/infographics-dengue---turning-up-the-volume-on-a-silent-disaster/

Zika virus outbreak

2,211 reported microcephaly cases in Brazil since February 2016, up on the previous yearly average of 163 cases nation-wide.

ZIKA HAS SPREAD RAPIDLY TO

75

COUNTRIES

OVER 60% OF THESE SINCE 2015

Photo courtesy: Antonio Lacerda, EPA

http://apps.who.int/iris/bitstream/10665/251462/1/zikasitrep17Nov16-eng.pdf

What is Wolbachia?

- Naturally occurring bacteria
- Transmitted from female insect to offspring through the eggs
- Safe for humans, animals and the environment
- **Reduces ability of mosquitoes to transmit disease (dengue, Zika, chikungunya)**

60%

OF ALL INSECT SPECIES HAVE *WOLBACHIA*

Broad range of pathogen interference

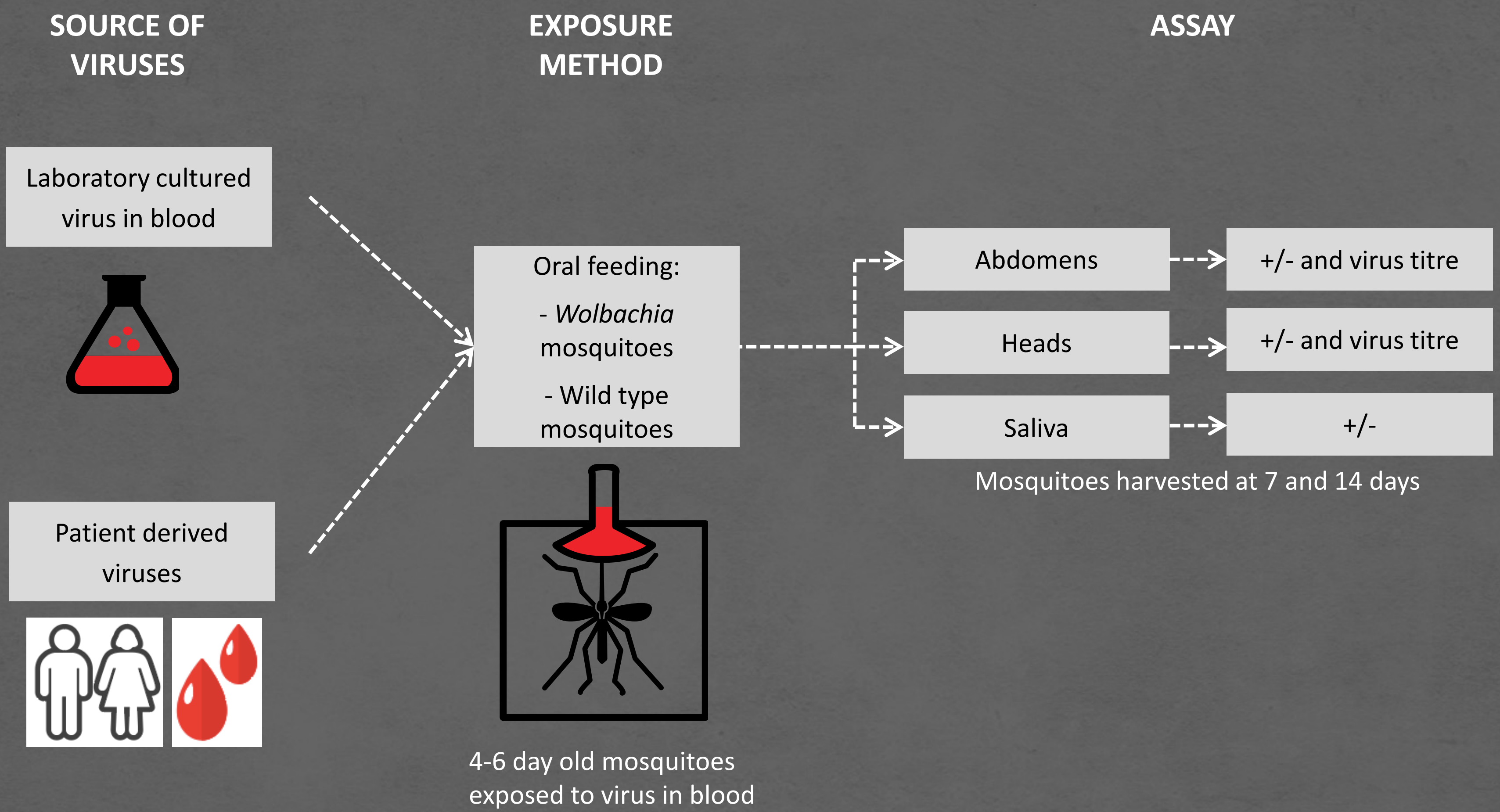
Human pathogens that *Wolbachia* has been shown to interfere with in mosquito vectors:

- ✓ Dengue viruses – all serotypes
- ✓ Yellow Fever
- ✓ West Nile
- ✓ Chikungunya
- ✓ Zika
- ✓ Filarial Nematodes – *Brugia malayi*
- ✓ Malaria parasites – *Plasmodium gallanaceum*, *P. falciparum*, *P. berghei*

Human pathogens where *Wolbachia* interference is not yet demonstrated but predicted:

- Other Flaviviruses – eg Japanese encephalitis
- Other Alphaviruses – eg Semliki Forest virus, Venezuelan Equine encephalitis
- Other species of Plasmodium and Filarial nematodes

Testing of *Wolbachia Aedes aegypti*



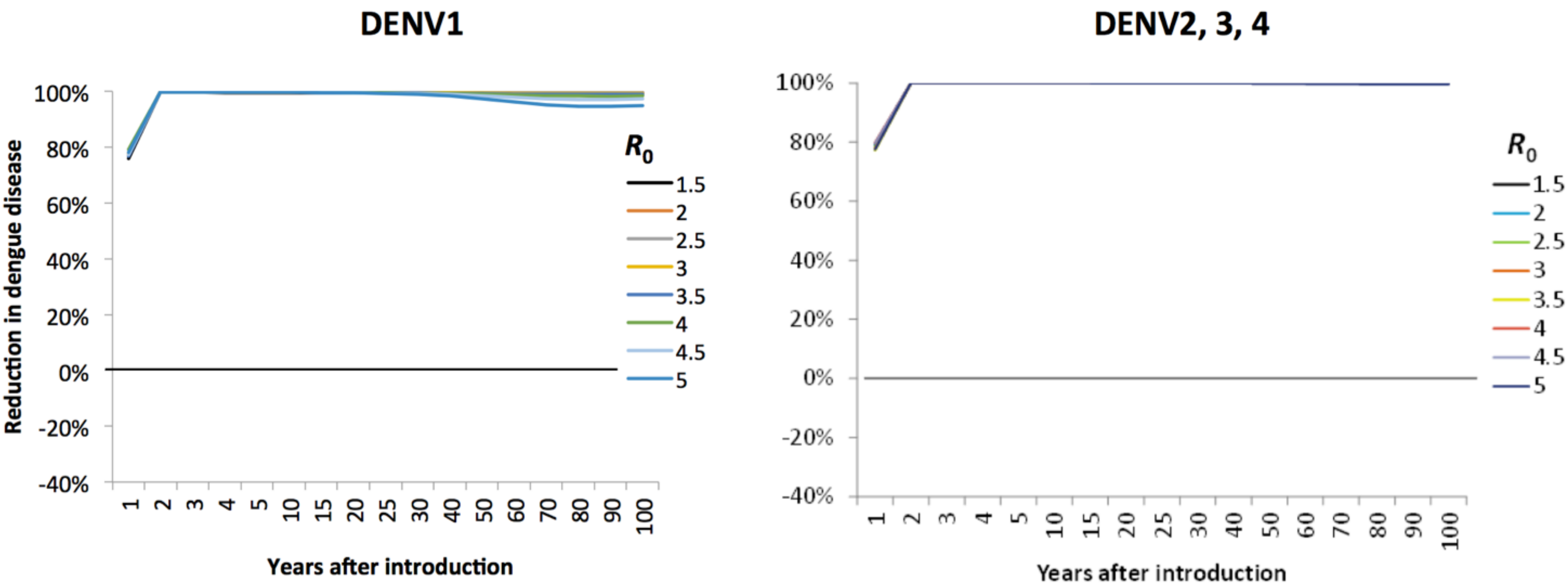
DENV-1 viremic blood feeds (n=29)

			% Saliva +ve DENV			
			Day 10		Day 14	
Patient	Serotype	Log10 Viremia	WT	wMel	WT	wMel
30DX/69	DENV-1	5.42	0.00	0.00		
30DX/188		5.99	0.00	0.00	0.33	0.00
30DX/68		6.04	0.00	0.00	0.50	0.00
30DX/187		6.95	0.67	0.09	0.88	0.33
30DX/114		7.31	0.13			
29DX/51		7.45	0.77	0.00	0.86	0.00
30DX/191		7.61	0.42	0.00	0.58	0.00
30DX/181		7.64	0.30	0.10	0.75	0.17
30DX/121		7.67	0.20	0.00	0.80	0.00
13DX1/1191		7.73	0.38	0.00	0.75	0.80
13DX16/244		7.78	0.33	0.40	1.00	0.40
30DX/70		7.86	0.30	0.00	0.86	0.00
13DX16/174		7.91	0.25	0.14	0.75	0.20
30DX/113		7.91	1.00	0.00	0.40	0.20
30DX/128		7.91	0.70	0.33	1.00	0.71
13DX1/1183		8.19	0.75	0.00	0.89	0.42
30DX/196		8.25	0.57	0.20	0.67	0.00
30DX/173		8.29	0.50	0.30	0.67	0.00
30DX/175		8.35	0.22	0.00	0.00	
13DX3/863		8.45	0.57	0.20	0.40	0.83
30DX/81		8.57	0.10	0.00	0.10	0.10
30DX/184		8.92	0.75	0.38	0.75	0.33
30DX/75		9.07	0.50	0.00	1.00	0.10
13DX16/172		9.12	0.13	0.20	0.70	1.00
30DX/189		9.28	0.58	0.13	0.80	0.40
30DX/194		9.73	0.67	0.29	0.75	0.22
30DX/193		9.91	0.83	0.00	1.00	0.25
30DX/82		9.93	0.60	0.10	0.60	0.10
30DX/195		10.57	0.91	0.18	1.00	0.17

DENV-2, -3, -4 viremic blood feeds (n=32)

Patient	Serotype	Log10 Viremia	% Saliva +ve DENV Day 10 WT	% Saliva +ve DENV Day 10 wMel	% Saliva +ve DENV Day 14 WT	% Saliva +ve DENV Day 14 wMel
09DX/749	DENV-2	6.01	0.00	0.00	0.00	0.00
09DX/747		6.13	0.17	0.00	0.14	0.00
30DX/182		6.26	0.00	0.00	0.40	
09DX/750		6.97	0.00	0.00	0.00	0.00
30DX/83		7.13	0.20	0.00	0.13	0.00
30DX/92		7.41	0.00	0.00	0.00	0.00
13DX3/861		8.59	0.20	0.00	0.67	0.50
29DX/31		8.95	0.25	0.00		
13DX6/372	DENV-3	6.10	0.00	0.00	0.10	0.00
29DX/58		6.73	0.36	0.19	0.69	0.11
30DX/127		8.47	0.00	0.00	0.00	0.00
09DX/746		8.82	0.33	0.00	0.33	0.17
30DX/125	DENV-4	5.37	0.00	0.00	0.00	
13DX3/938		5.42	0.00		0.00	0.00
30DX/122		5.43	0.22	0.00	0.50	0.00
30DX/76		6.61	0.00	0.00	0.00	0.00
09DX/745		6.91	0.00	0.00	0.00	0.00
30DX/71		6.93	0.00	0.00	0.00	0.00
30DX/72		7.01	0.00	0.00		
30DX/202		7.22	0.00	0.00	0.17	0.00
30DX/174		7.63	0.10	0.00	0.60	
29DX/59		7.73	0.21	0.00	0.65	0.00
29DX/30		8.06	0.00			
30DX/192		8.28	0.25	0.00	0.57	0.00
30DX/198		8.41	0.50	0.00	0.60	0.00
30DX/197		8.51	0.38	0.00	0.50	0.00
13DX4/611		8.58	0.17	0.00	0.89	0.33
30DX/85		8.68	0.00	0.00	0.50	0.00
30DX/201		8.68	0.70	0.00	0.86	0.00
29DX/69		8.82	0.00	0.00	0.44	0.10
30DX/190		8.86	0.64	0.00	0.33	0.00

*w*Mel deployment and dengue disease



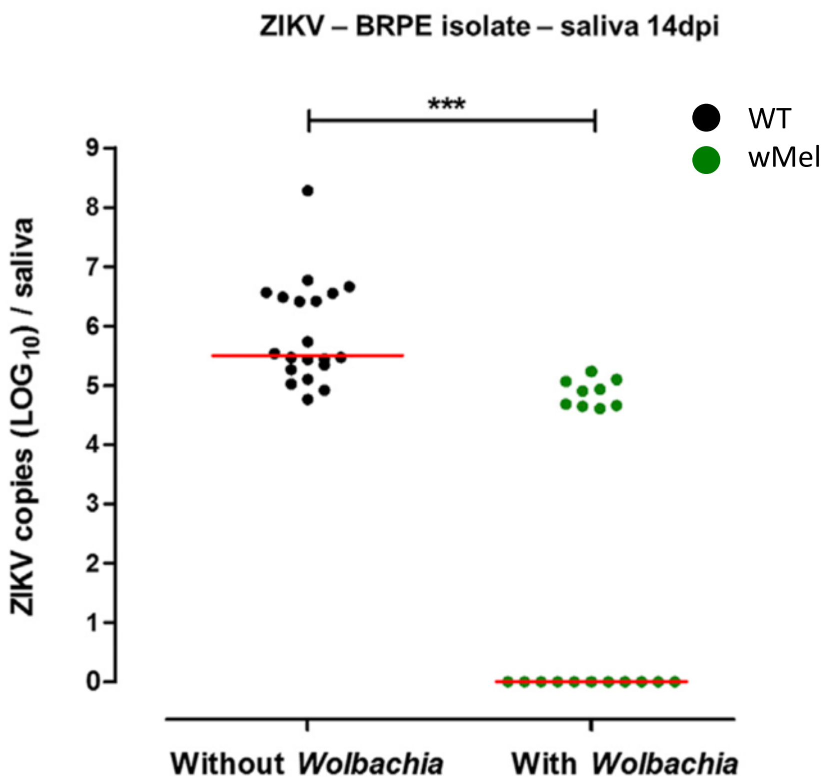
90% transmission of *w*Mel from female to progeny;
15% fitness cost

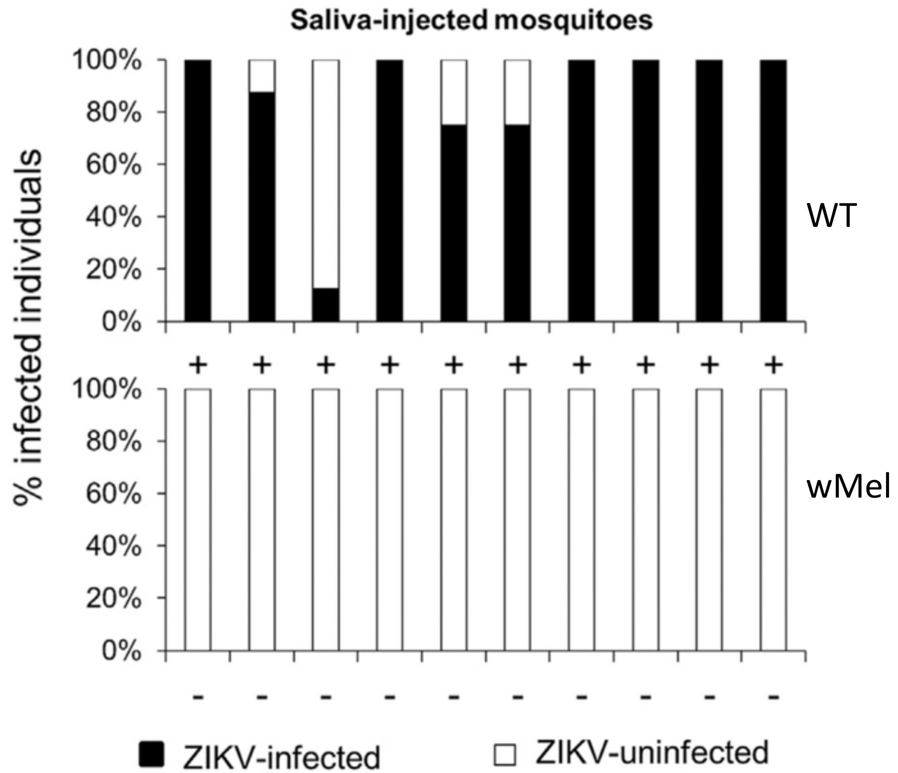
Imperial College London

Neil Ferguson, Imperial College London, 2015

MRC Centre for Outbreak Analysis and Modelling

Zika virus titre in *w*Mel *Aedes aegypti* (Brazil)

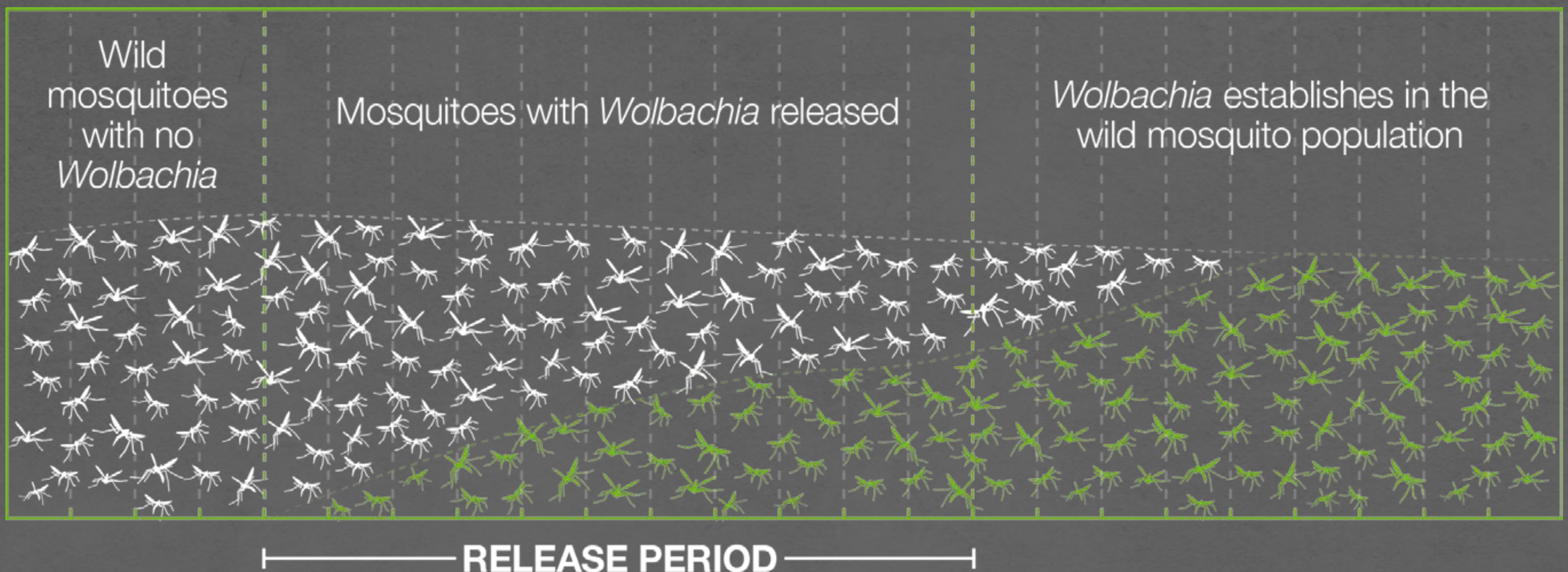




Mosquitoes (Brazil background) exposed to Zika virus 5.0 x 10^6 PFU/ml (**BRPE**) and 8.7 x 10^3 PFU/ml (**SPH**)
n = 20 mosquitoes were assayed at each time point
* *P* Value <0.0001 (Mann-Whitney U Test)

Dutra HLC et al 2016. Cell Host & Microbe 19, 1-4

Release of Wolbachia mosquitoes

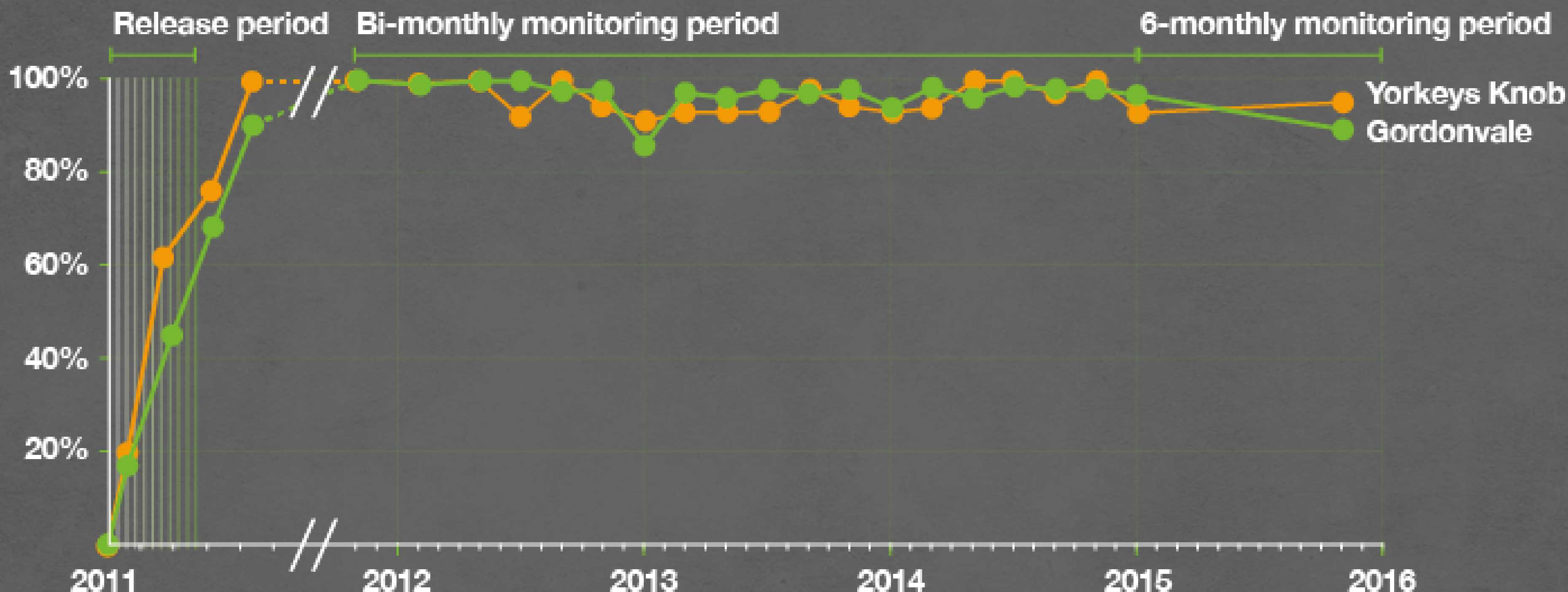


Townsville Mozzie box in action

Eliminate Dengue Project Sites

Current field sites

Self-sustaining intervention



2011 – 2017: Cairns, Australia

- 28 suburbs over seven years
- High levels of *Wolbachia* in all areas
- No significant local dengue transmission

41km^2

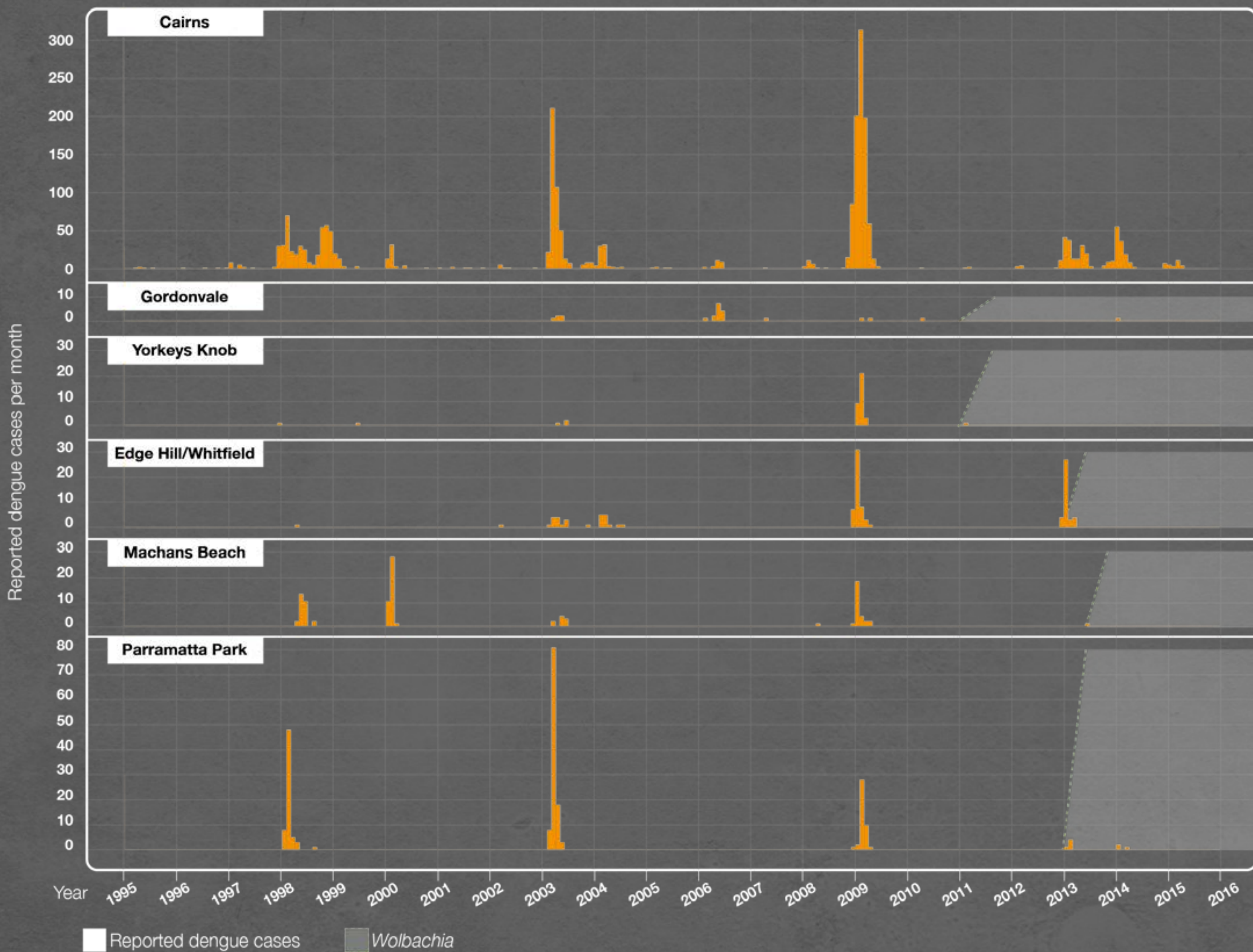
93,456 people

35,000 households

Disease surveillance, before vs after

Cairns, Australia

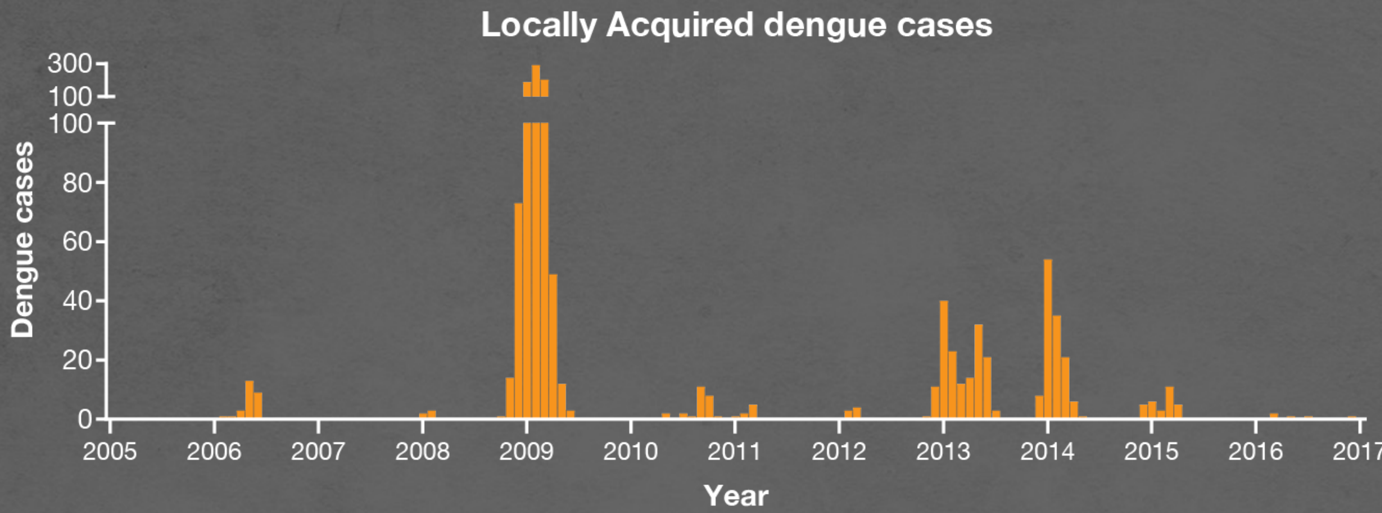
(*Wolbachia* coverage = population 93,456)

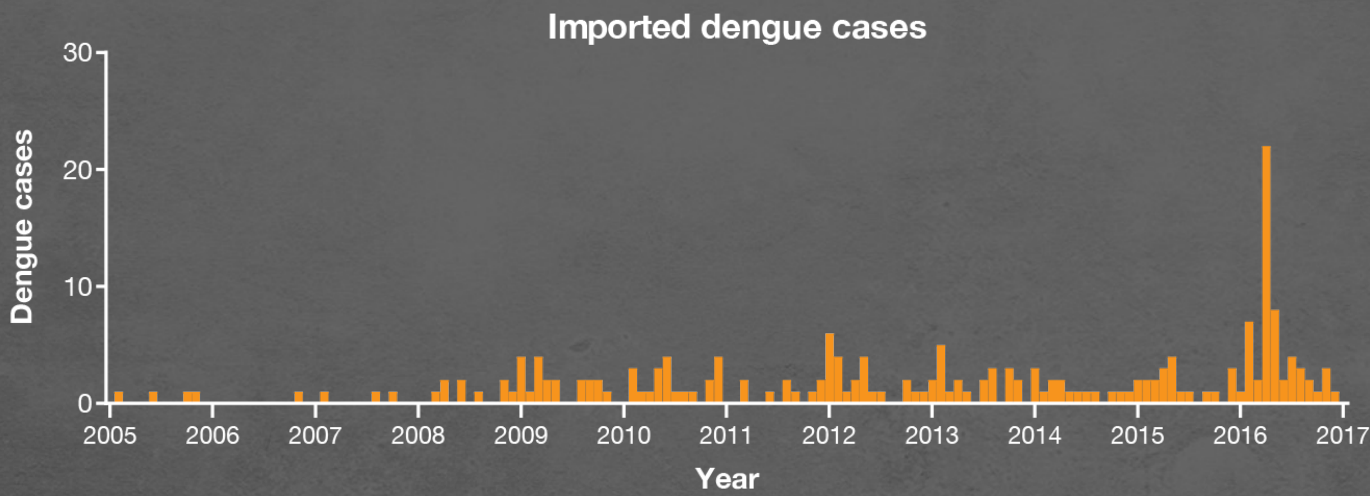


Disease surveillance, before vs after

Cairns, Australia

(*Wolbachia* coverage = population 93,456)

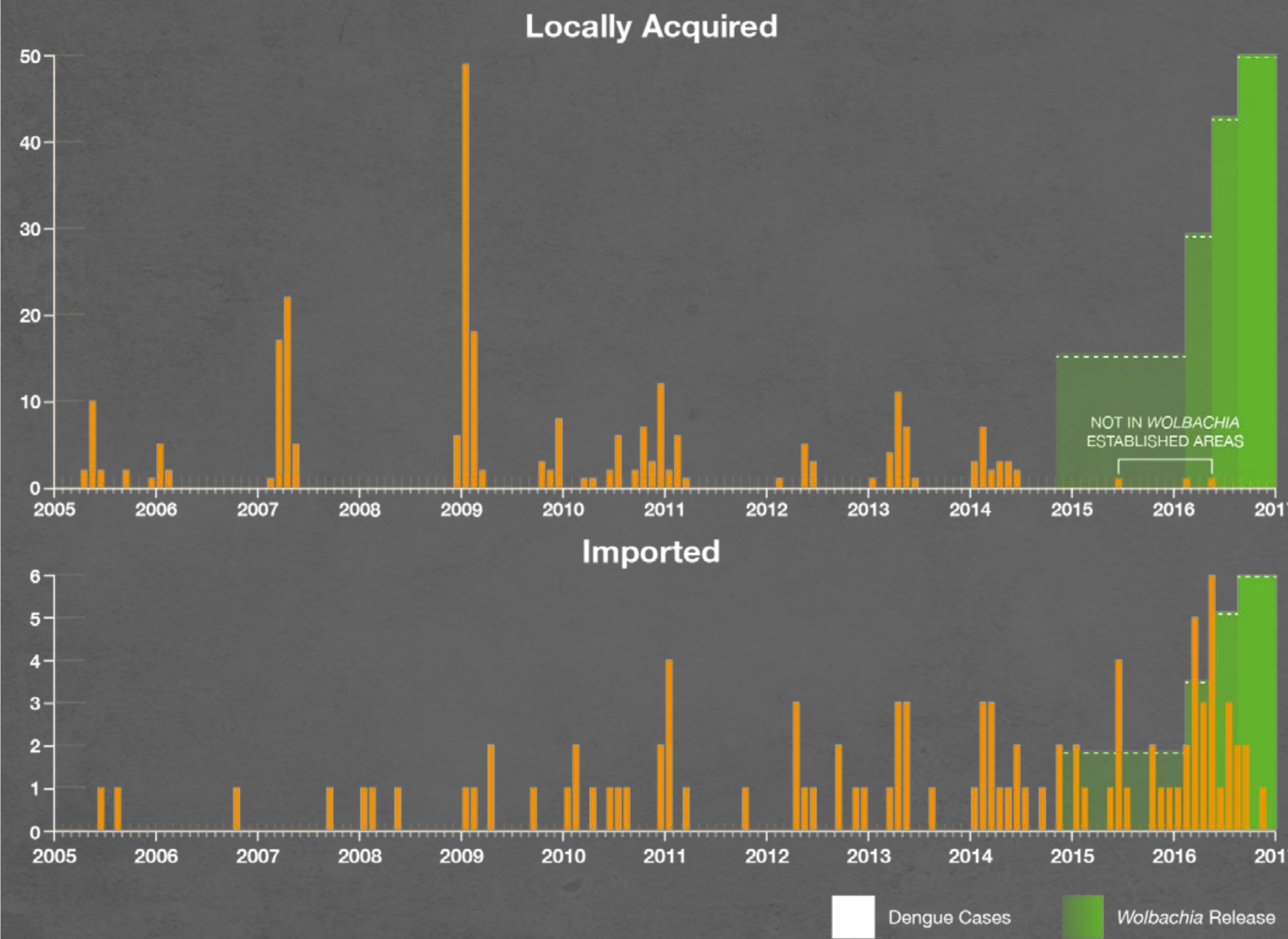


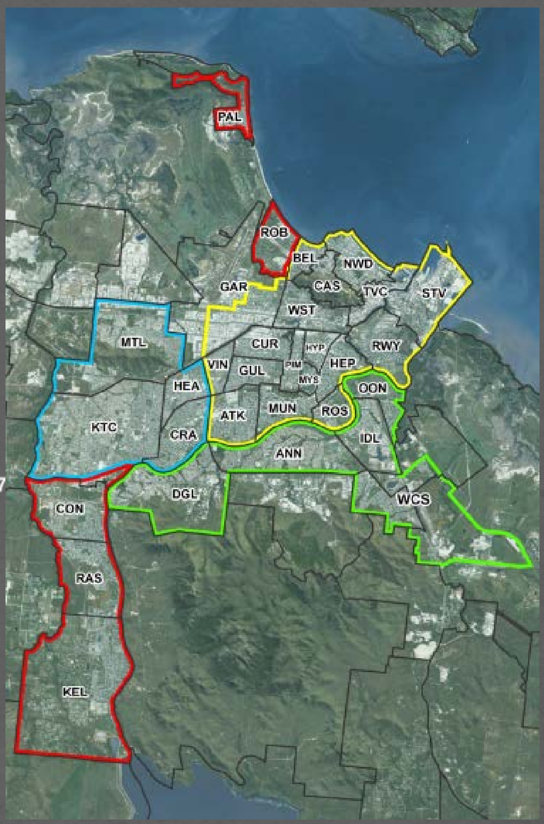


Disease surveillance, before vs after

Townsville, Australia

(*Wolbachia* coverage = population 139,757)





18SUBURBS
43KM^2
12MONTHS

US$16
PER PERSON

50,000 people

15,000 households

3,000 release containers

1.3M mosquitoes

180 BG traps (adult capture)

30% DEPLOYMENT

21% MONITORING

24% COMMUNITY ENGAGEMENT

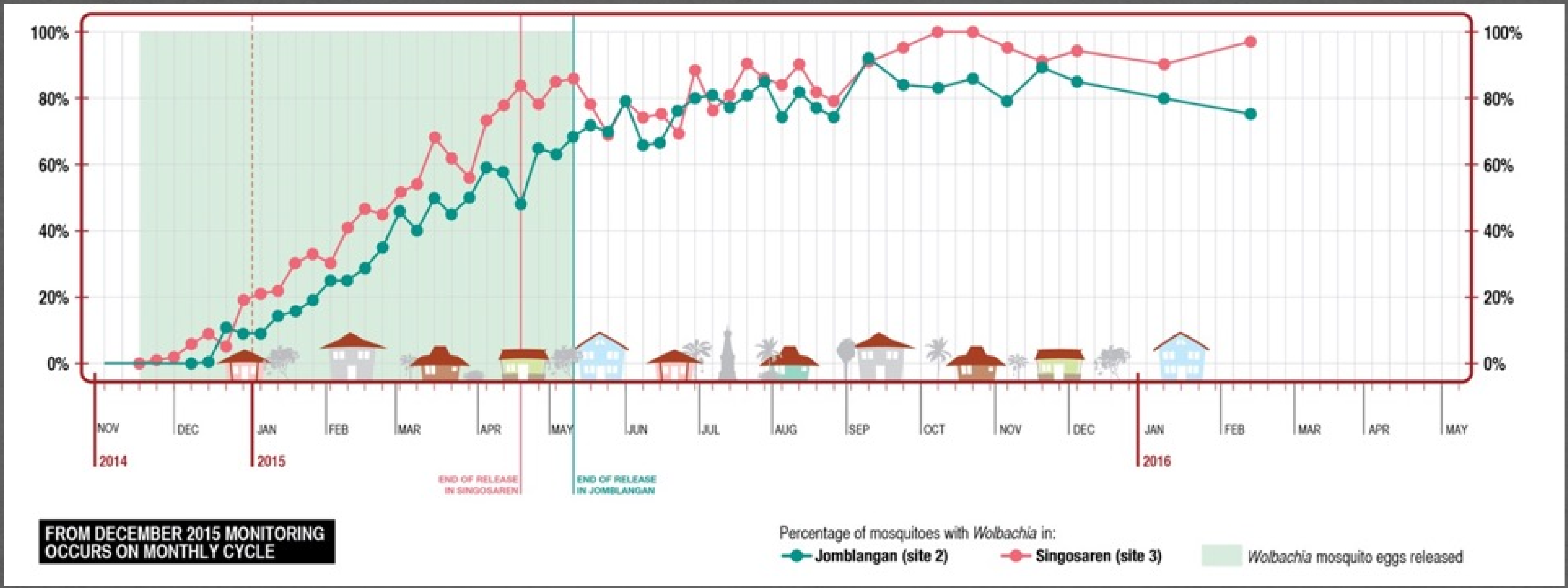
25% OTHER

Indonesia

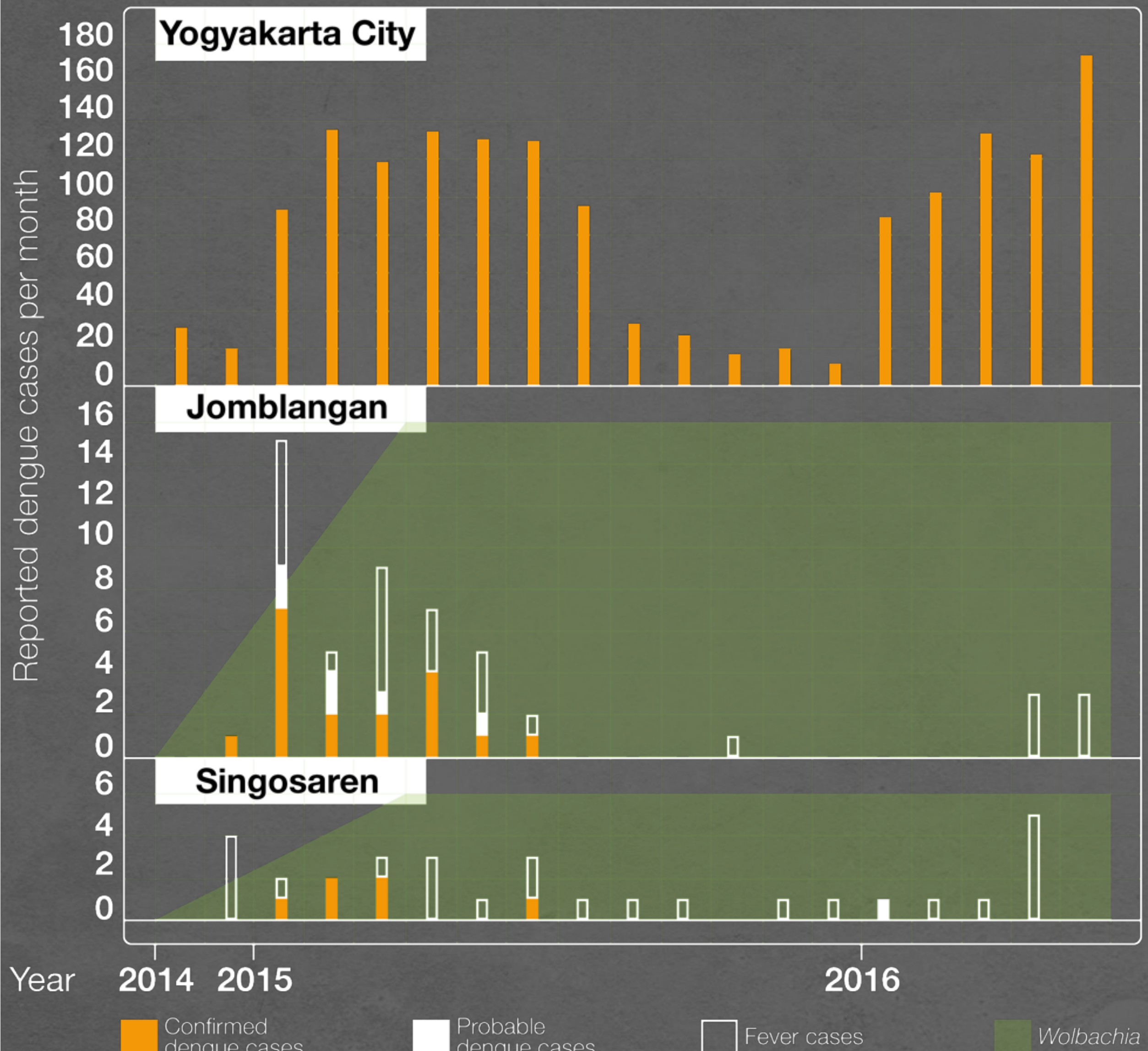
- **2014**:
  Small scale releases in Nogotirto, Kronggahan, Jomblangan and Singosaren

- **2016 – 2019**:
  Large scale release and impact study in Yogyakarta city

Jomblangan & Singosaren, Yogyakarta

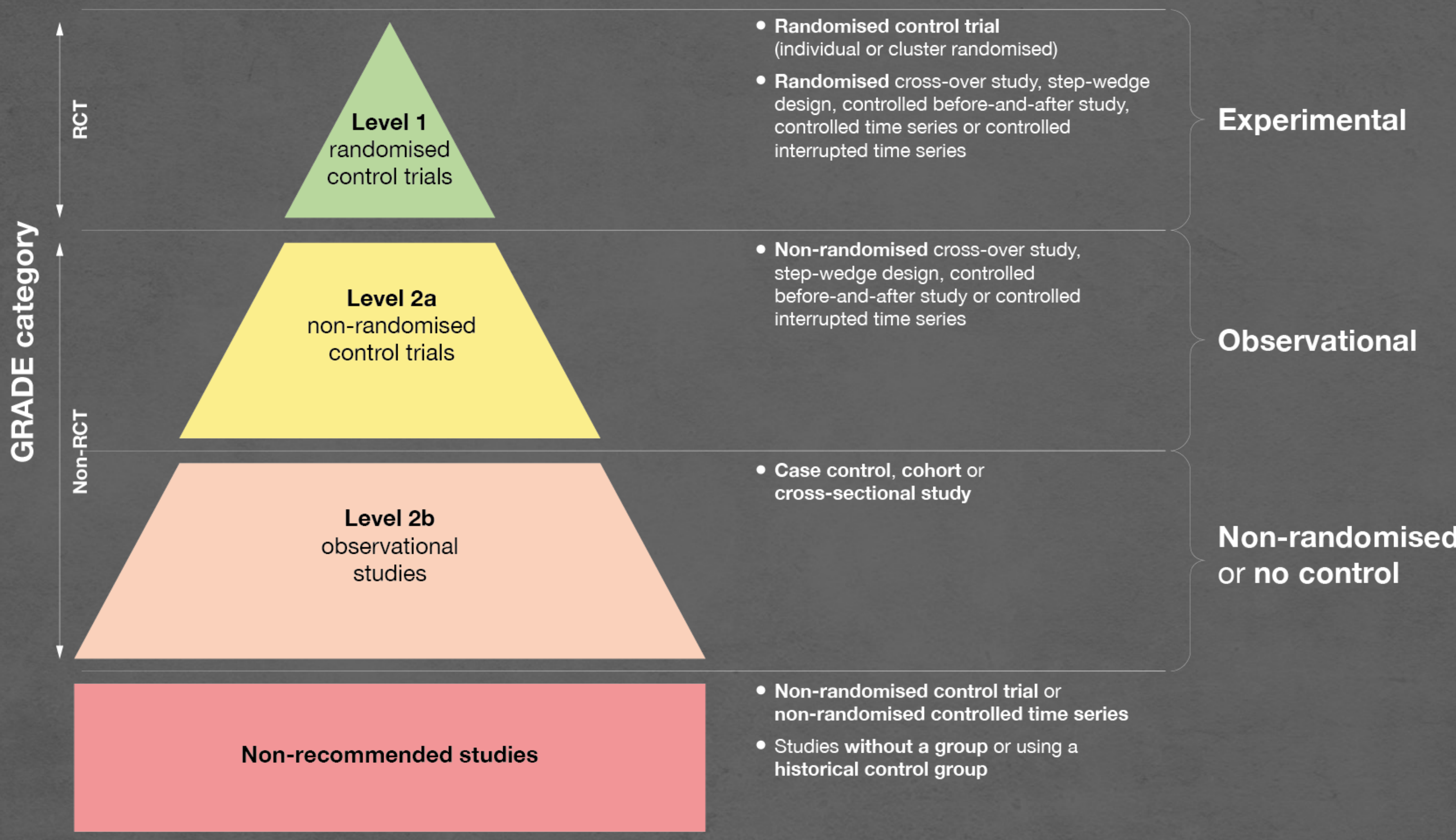


Dengue cases in Yogyakarta City, Indonesia Jomblangan and Singosaren
(Nov 2014 – May 2016)

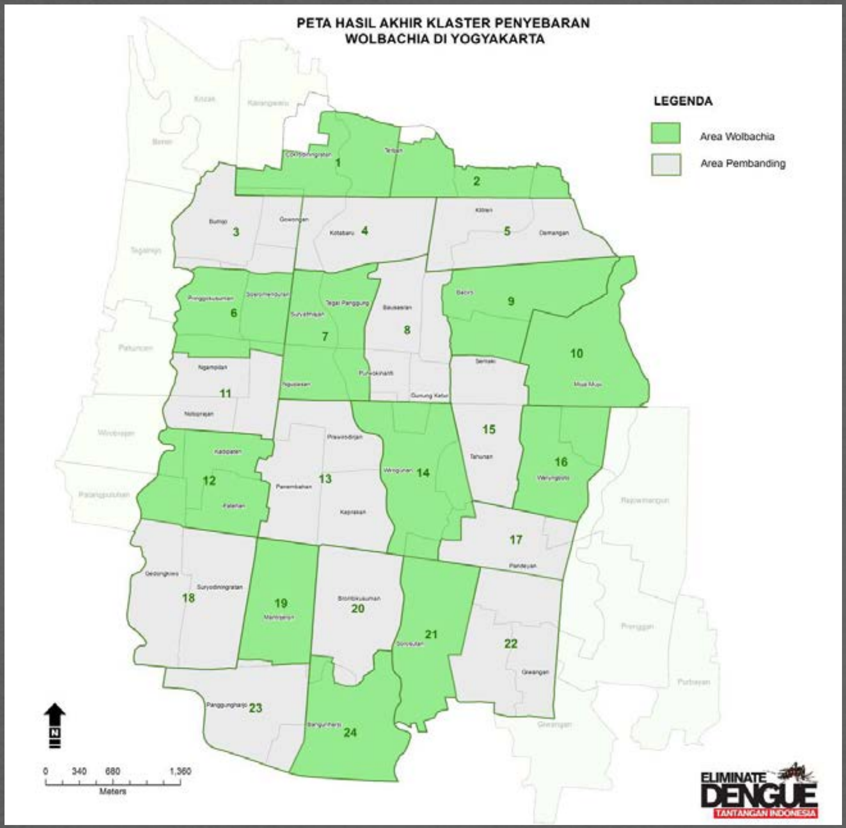


Confirmed and probable cases, identified through active febrile illness surveillance

Hierarchy of study designs for assessing the efficacy of vector control interventions



Clustered randomised trial of the effect of *Wolbachia* releases on dengue



Study area:

- ~26km^2 (Yogyakarta City & Bantul District)
- Population 325,000
- 37 Kelurahans (administrative areas) within study site
- Divided into 24 clusters, using natural borders where possible

Study arms (each 12 clusters):

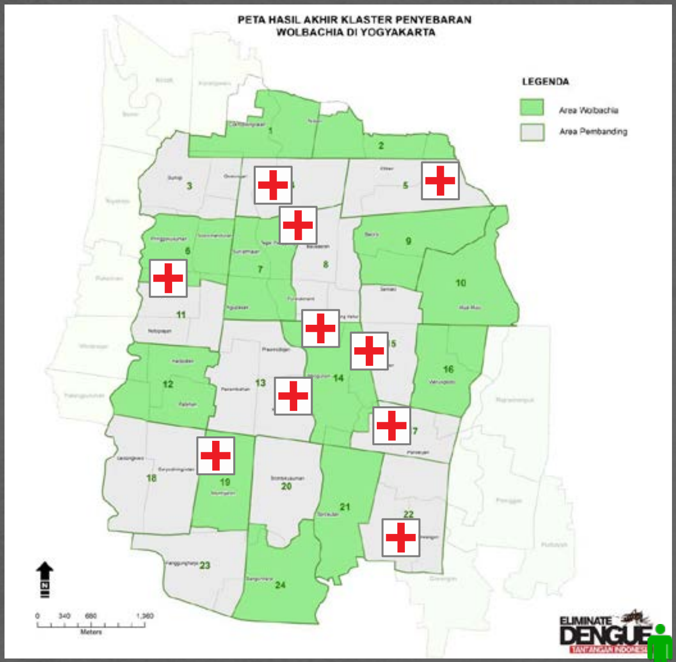
- Un-treated: standard practice vector control
- Treated: Deployment of *Wolbachia* mosquitoes in addition to standard practice

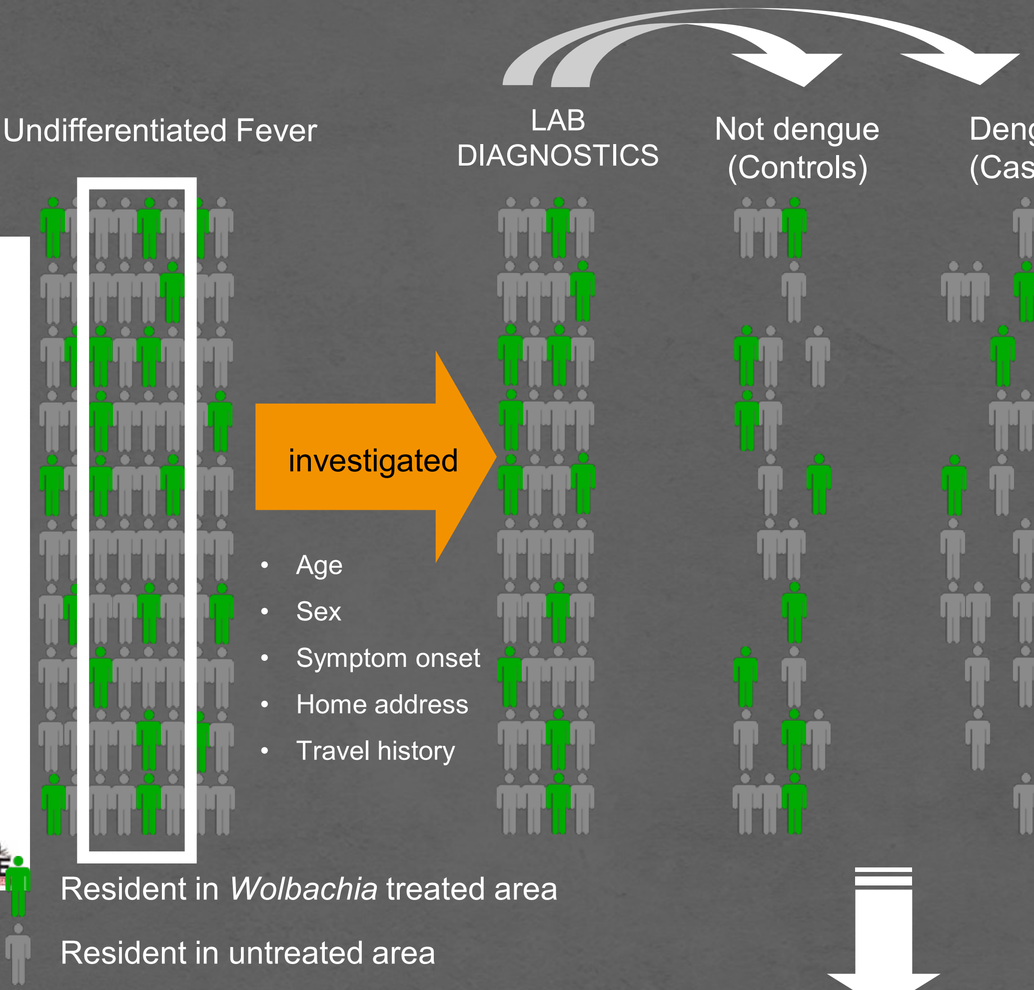
Allocation:

- Constrained randomisation, balancing on demographic characteristics and other covariates associated with dengue risk

Randomised Control Trial
Yogyakarta, Indonesia

Randomised Control Trial





Efficacy = [1 – OR] x 100%

– Adjust for age and time

WHO Vector Control Advisory Group (VCAG)

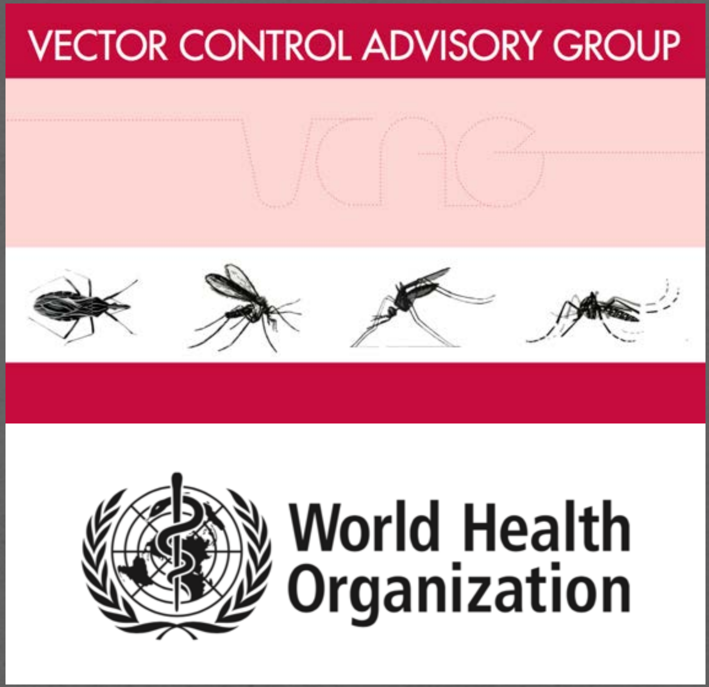
18 March 2016: WHO-VCAG reviewed new vector control tools for use in response to the Zika virus outbreak.

Statements:

- *Wolbachia* reduce the mosquito's ability to transmit arboviruses to humans
- *Wolbachia* infection reduces viral replication of dengue, chikungunya and Zika viruses

Recommendations:

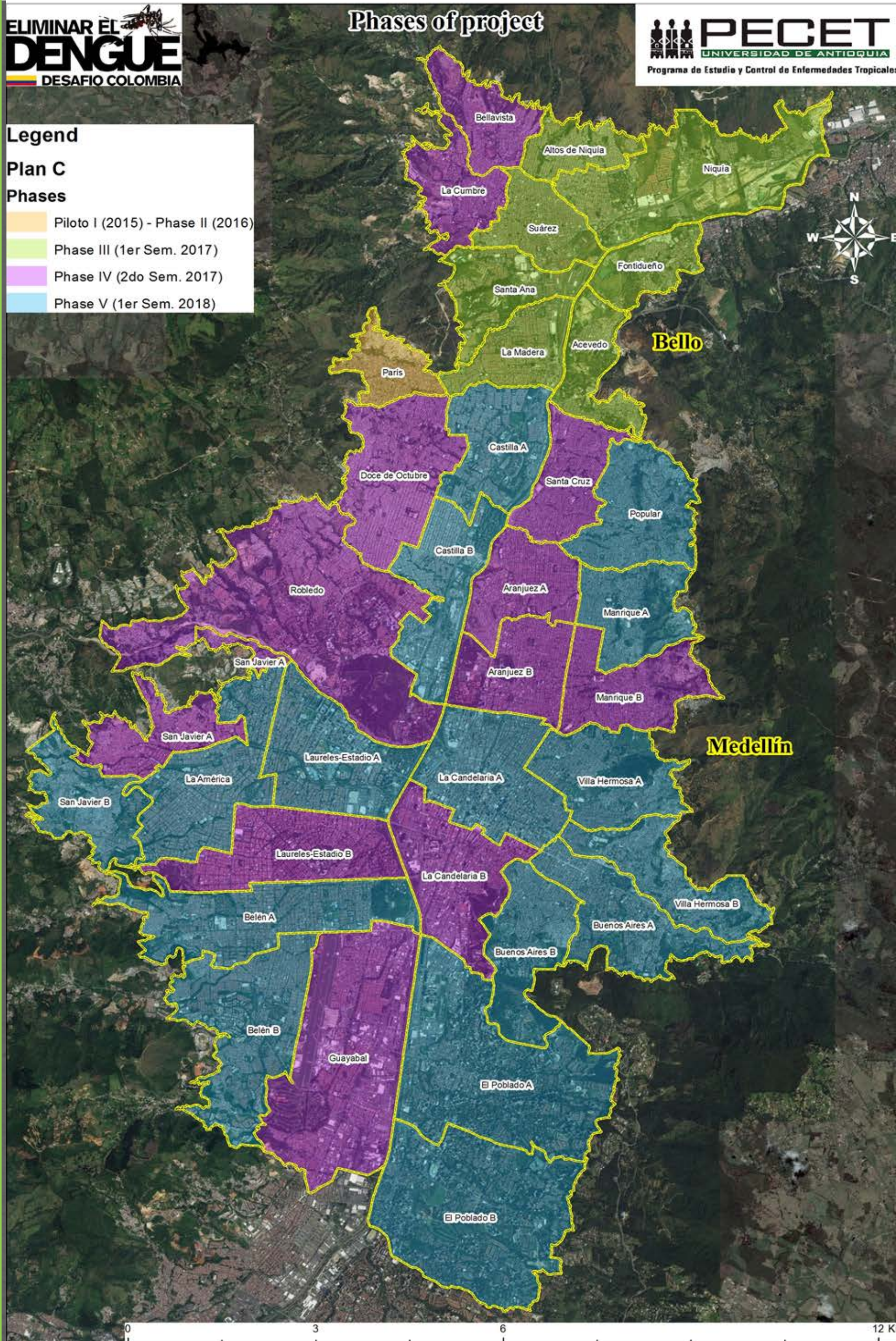
- Pilot deployments under operational conditions & rigorous independent monitoring and evaluation
- Continue with plans for randomised control trials (RCTs) with epidemiological outcome



Current field sites

Colombia: scale up

2016-2018 – **2.5 M people**



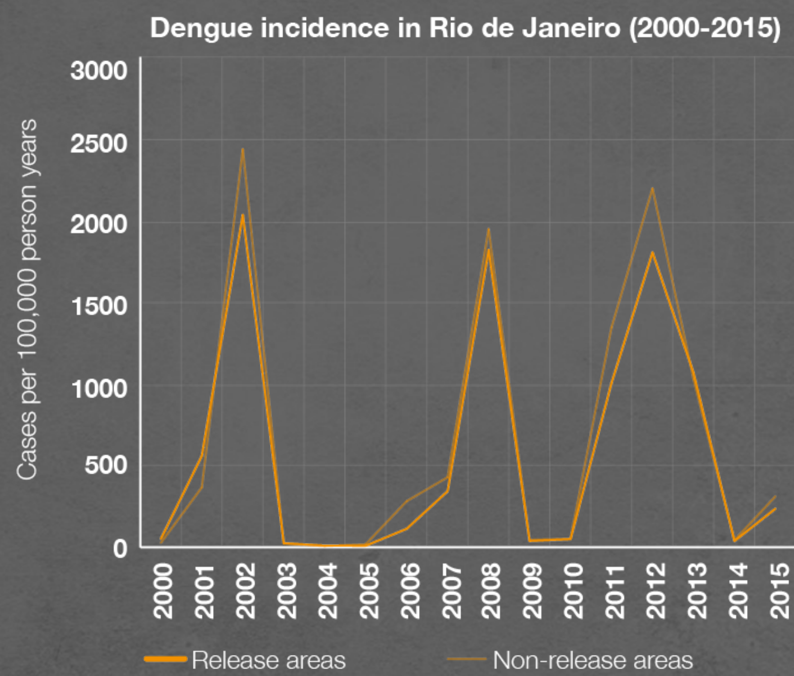
Current field sites

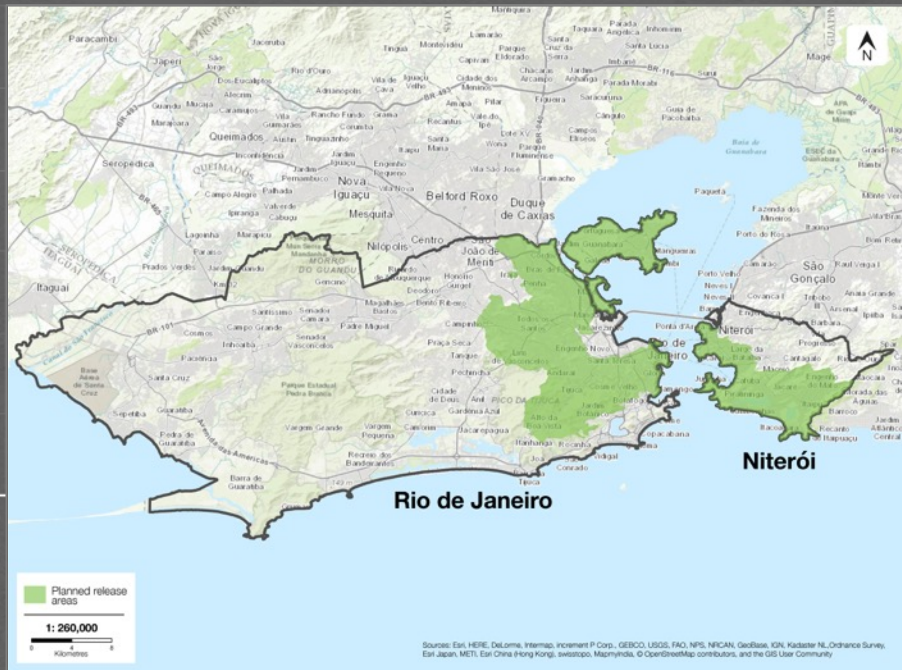
Brazil: scale up

2016-2018 – **2.5 M people**

Disease surveillance, release vs non-release areas
Rio de Janeiro, Brazil

- Compare IRR between planned release & non-release areas, before & after deployment
- Planned release & non-release areas in Rio have comparable historical dengue time series
    - ➢ Incidence rate ratio pre-intervention ≈ 1



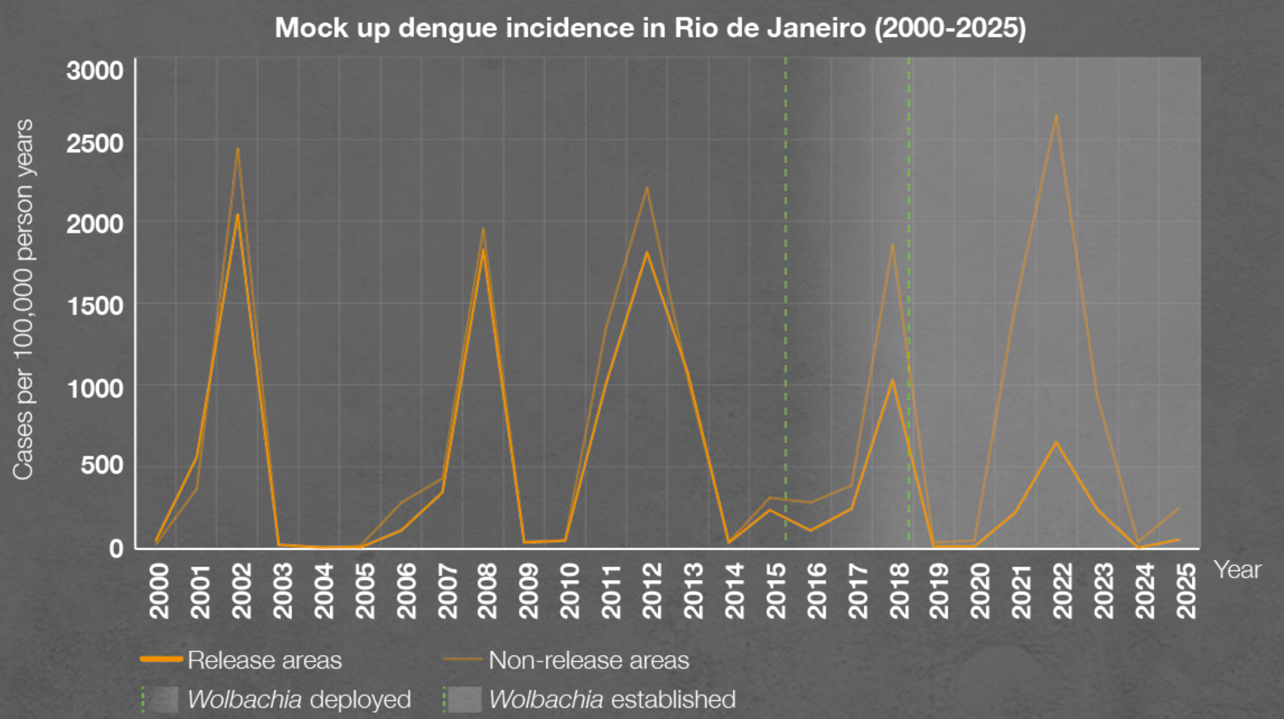


Disease surveillance, release vs non-release areas
Rio de Janeiro, Brazil

- Calculate IRRs stratified by deployment status (municipality level):

  Pre-intervention > During deployment > Post-deployment (annually)

- Test null hypothesis of no change in IRR with deployments
  (Mantel Haenszel Chi-Square test of homogeneity)



Global Evidence Picture

LABORATORY DATA
Mosquitoes reduced vector competence

PILOT DEPLOYMENTS
Medellin, Colombia - 2017-2019
Rio de Janeiro, Brazil - 2017-2019

MATHEMATICAL MODELLING
Transmission collapses

RANDOMISED TRIALS
Yogyakarta, Indonesia - 2016-2018
Nha Trang, Vietnam - 2017-2019

OBSERVATIONAL DATA
No local virus transmission in any sites where *Wolbachia* has been deployed over the last 6 years

Future goals

- Continue to accumulate evidence of impact
- Reduce cost of deployment to less than $1 per person
- Partner with and initiate projects in the top 20 dengue burden countries
- Establish capacity, expertise and infrastructure in those countries
- Develop and assist with National rollout strategies as required in countries according to their wishes

An international research collaboration

Scientific collaborators:

- Đặng Đức Anh, Vietnam National Institute of Hygiene and Epidemiology
- Adi Utarini, Universitas Gadjah Mada
- Cam Simmons, Oxford University Clinical Research Unit & Monash University
- Luciano Moreira, FIOCRUZ/Centro de Pesquisas René Rachou
- Ivan Velez & Jorge E.Osorio, PECET Universidad de Antioquia, Colombia
- Michael Turelli, University of California, Davis

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- Foundation for the National Institutes of Health
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- The Wellcome Trust
- DFID
- The Australian and Queensland Governments
- The Brazilian Government
- USAID
- The Gillespie Family Foundation

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