Using *Wolbachia*: World Mosquito Program (Eliminate Dengue Project)

Jorge Osorio, PhD

World Mosquito Program™

World Mosquito Program

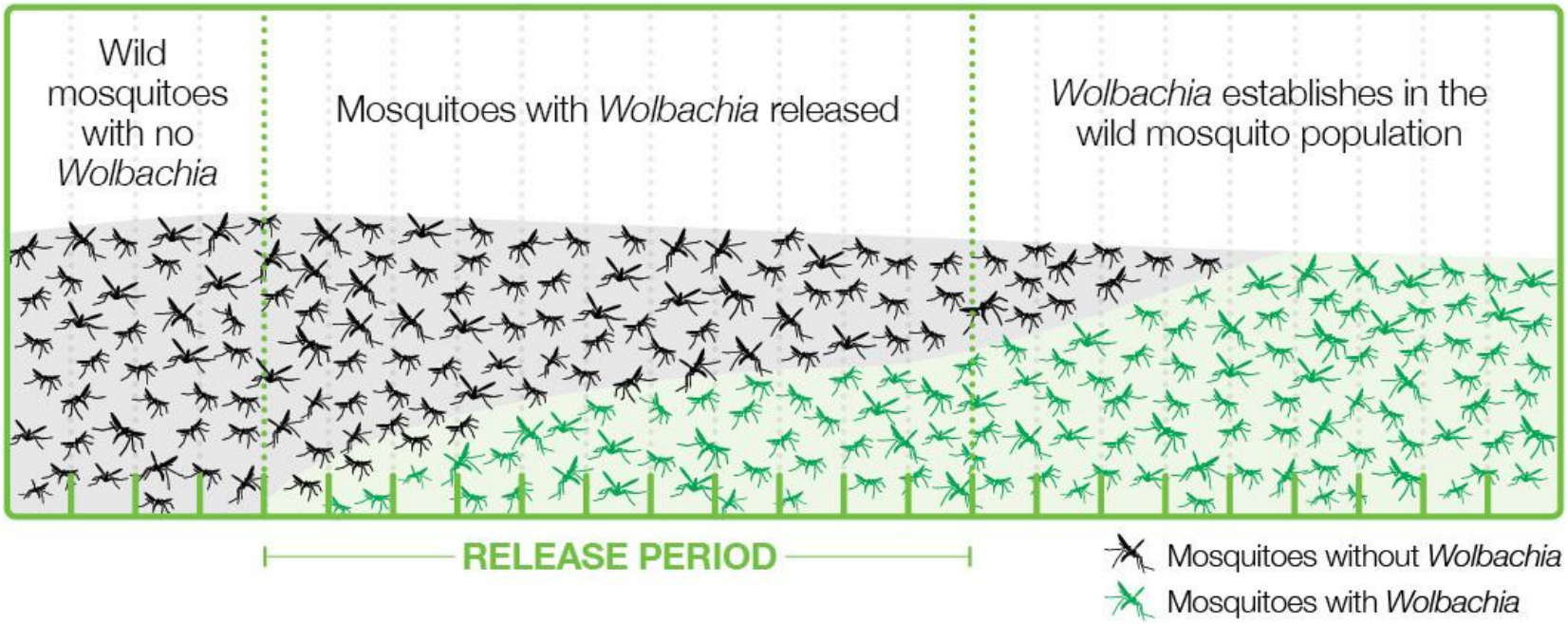
- We are an international, not-for-profit group working to develop and implement *Wolbachia* as an effective method of reducing *Aedes*-borne diseases
- We are currently working with 5 countries to deploy *Wolbachia* at different scales – from small pilot projects to citywide deployments over millions of people.
- In 2017 we will increase to 11 countries and by 2021 we hope to be assisting 20 countries with the highest arbovirus burdens

Current & planned field sites

How we differ from methods of population suppression

World Mosquito Program	Suppression methods (SIT, IIL, GMO)
Wolbachia	Irradiation, *Wolbachia*, GMO
Release mate and female mosquitoes	Release males only
Aims to reduce pathogen transmission	Aims to reduce mosquito population
Short-term releases, of 2-5 mosquitoes per person per week	Ongoing releases, of up to 100s of mosquitoes per person per week
Have shown we can deploy over large areas	Scale yet to be demonstrated
Inexpensive and sustainable	Ongoing and expensive
Evidence of impact on disease	No evidence of impact on disease

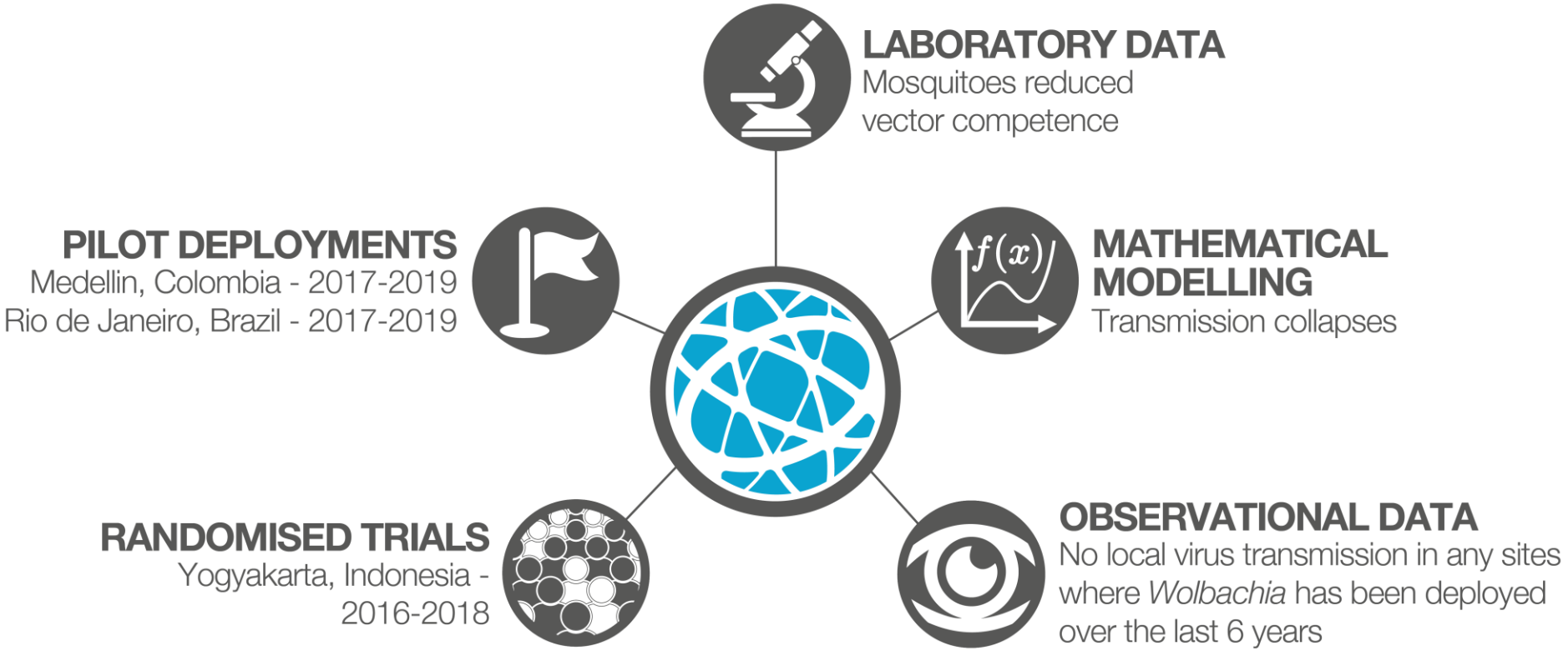
Release of *Wolbachia* mosquitoes



What we do to help project sites

- Help with selection of field site (~250,000 people) & design of initial pilot deployment
- Provide technology at no cost
- Provide training and on line learning platform for ongoing support and capacity building
- Provide tools to help with mosquito rearing, data management, field deployment - free of charge
- Help with scale up if desired

Global Evidence Picture



Broad range of pathogen interference with stable phenotype

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

- ✓ Dengue viruses – all serotypes
- ✓ Yellow fever
- ✓ West Nile
- ✓ Chikungunya
- ✓ Zika

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

PLoS Negl Trop Dis. 2017 May 19;11(5):e0005496.
Aliota MT *et al*, Sci Rep. 2016 Jul 1;6:28792.
Aliota MT *et al*, PLoS Negl Trop Dis. 2016 Apr 28;10(4):
Frentiu FD et al, PLoS Negl Trop Dis. 2014 Feb 20;8(2):e2688.
Joubert DA, et al PLoS Pathog. 2016 Feb 18;12(2):e1005434.
Ye YH et al, Am J Trop Med Hyg. 2016 Apr;94(4):812-9
Amuzu HE et al, Parasit **Vectors**. 2015 Apr 24;8:246
Ferguson NM *et al* , Sci Transl Med. 2015 Mar 18;7(279):279ra37
Walker T *et al*, Nature. 2011 Aug 24;476(7361):450-3.
Moreira LA *et al,* Cell. 2009 Dec 24;139(7):1268-78.

Human safety – field trials

Open field trials >160 sites. **No reported adverse events** associated with field trials (> 1 million total population)

Australia

Cairns (2011-17): 28 field sites & 93,556 population

Townsville (2014-16): 32 field sites & 139,757 population

Charters Towers, Douglas, Innisfail (2016-17): 14 field sites & 21,248 population

Vietnam

Central Vietnam (2013-15):
1 field site & 6,000 population

Serological surveys (145 volunteers) pre & post release – test for antibodies to *Wolbachia*

Indonesia

- Yogyakarta (2014-15): 23 field sites & 247,958 population
- Serological surveys (100 volunteers) pre & post release – test for antibodies to *Wolbachia*

Brazil

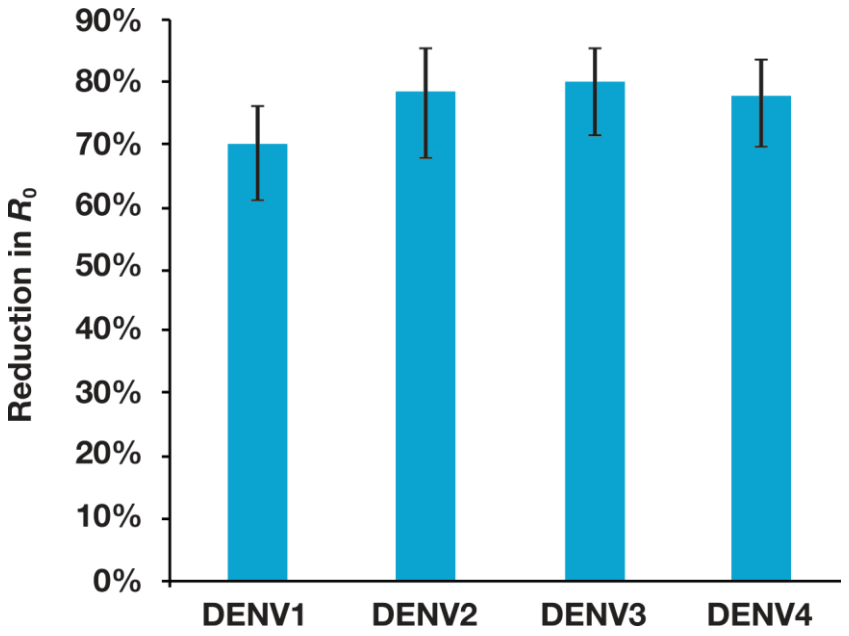
- Niteroi and Rio de Janeiro (2015-17): 5 field sites & 26,172 population

Colombia

- Bello (2015-17): 10 field sites & 500,000 population

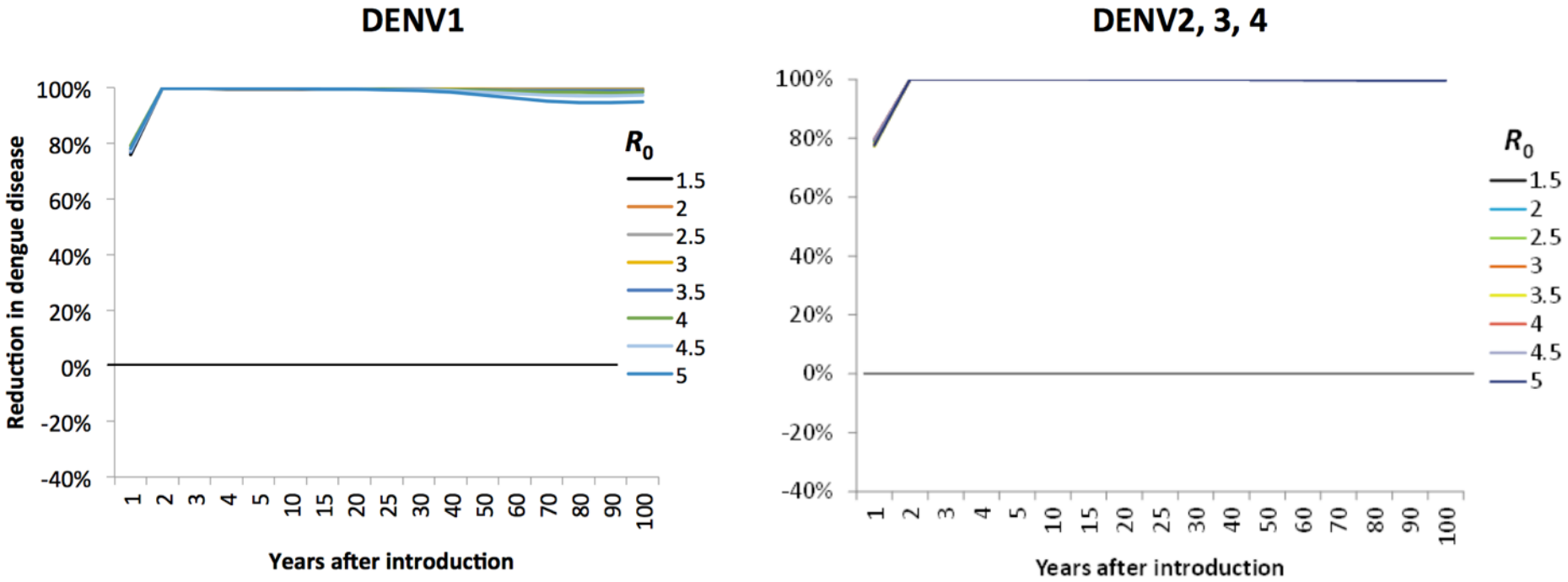
Modelling of *w*Mel impact is forecast to reduce the R0 for DENV transmission by ≥70%

- Data from feeds on 62 dengue patients
- % reduction in transmissibility (R0)
- ~70% reduction for DENV1,
  77-80% for DENV2-4
- Consistent DENV blocking phenotype in field collected *w*Mel mosquitoes



Ferguson et al, Sci Trans Med, 2015

≥70% reduction in R0 should eliminate local transmission in most settings



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

Imperial College London

MRC Centre for Outbreak Analysis and Modelling

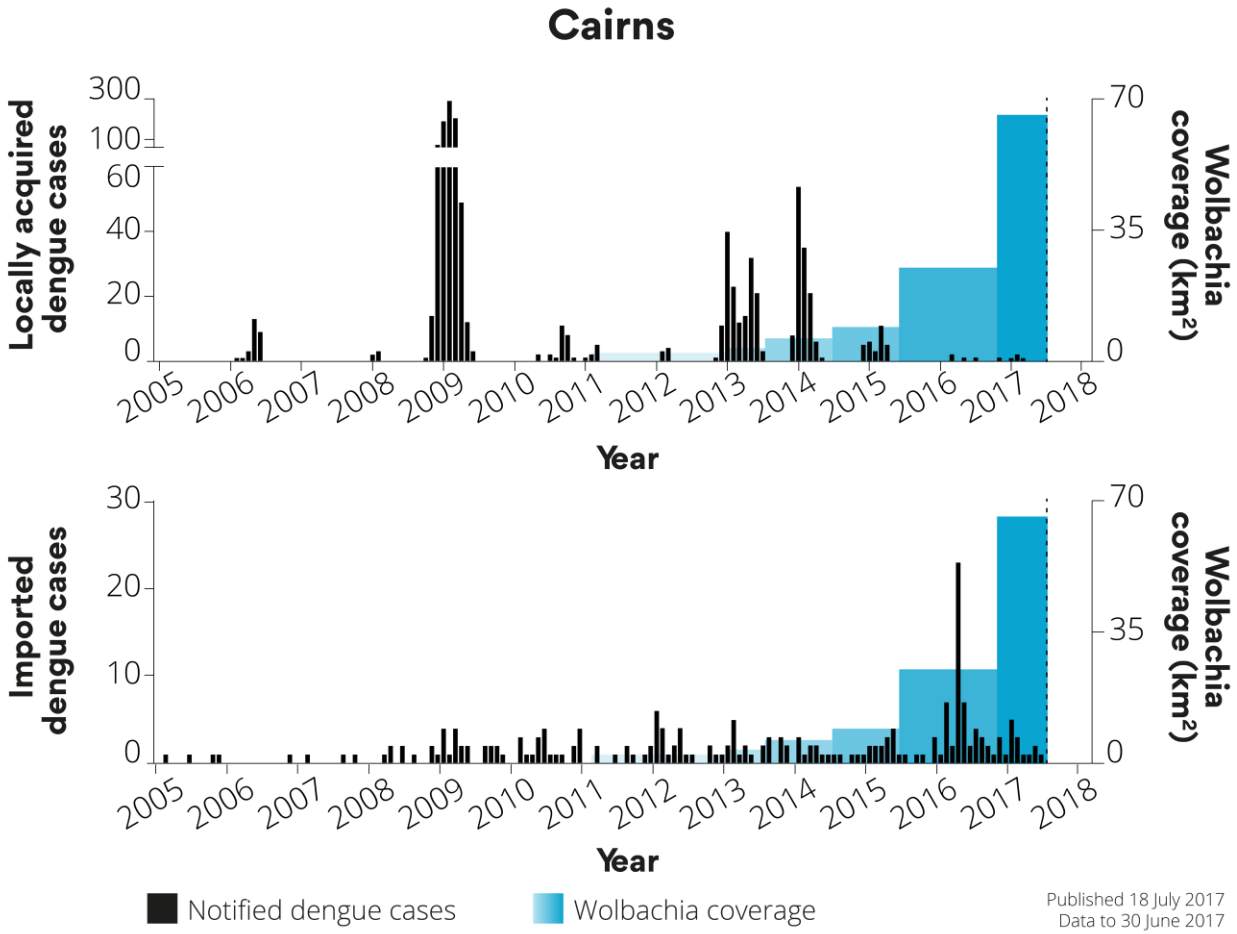
Ferguson et al. 2015

Field-based methods to measure the impact of *Wolbachia* on dengue incidence

	Disease surveillance data, before vs after	Disease surveillance data, release vs non-release areas	Spatial-temporal clustering analysis	Large-scale deployment with case-control study	Randomised controlled trial
Australia (Cairns & Townsville)	Underway		Underway		
Indonesia (Yogyakarta City)	Underway	Underway	Underway		Underway
Central Vietnam (Khanh Hoa Province)	Underway	Underway			
Southern Vietnam	Planned	Planned	Planned		Planned
Colombia (Medellin & Bello)	Underway	Underway	Planned	Underway	
Brazil (Rio & Niteroi)	Underway	Underway	Planned		
Pacific (Fiji, Vanuatu, Kiribati, New Cal)	Underway				

Underway **Planned**

Observational data from all field sites continues to be supportive



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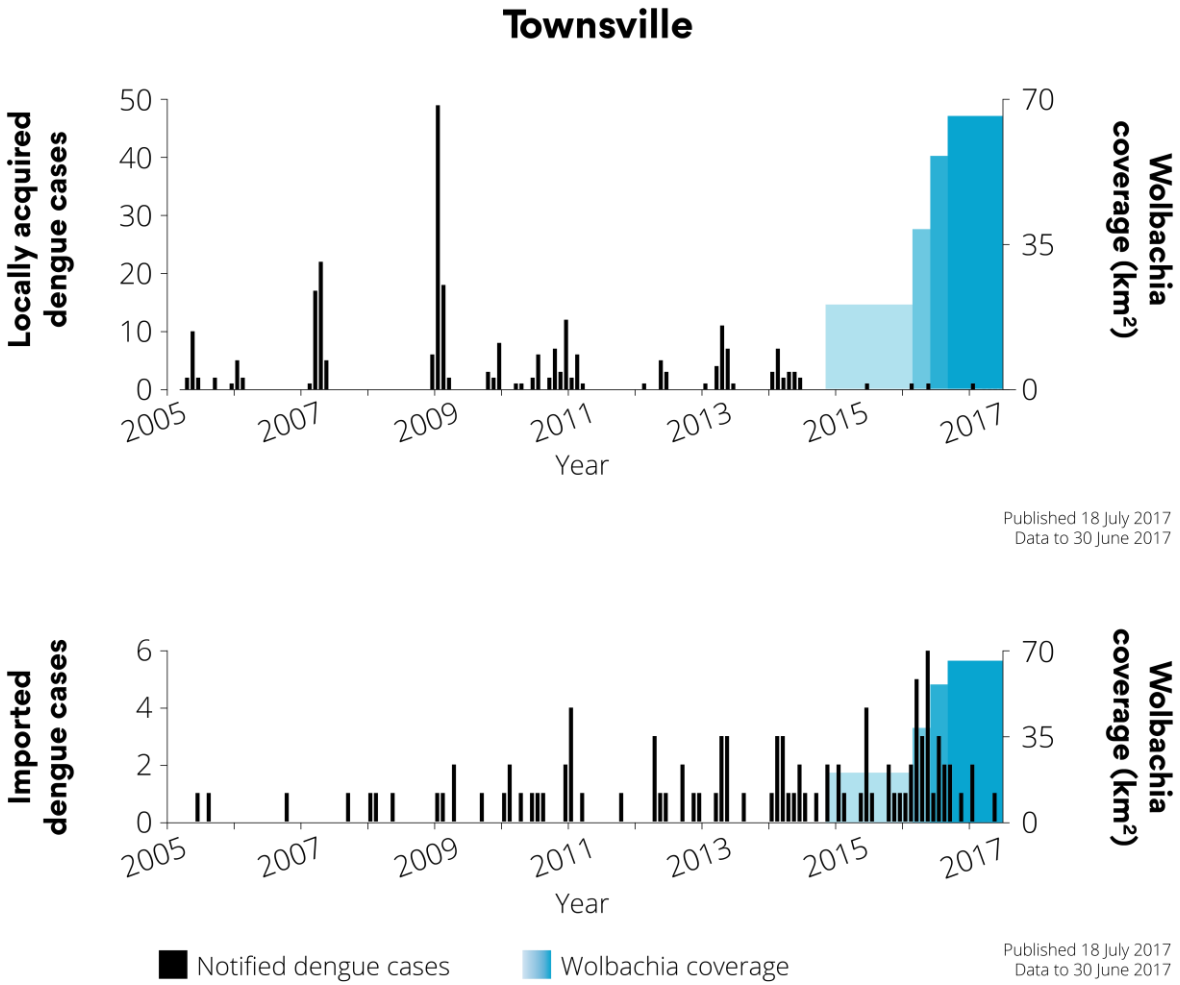
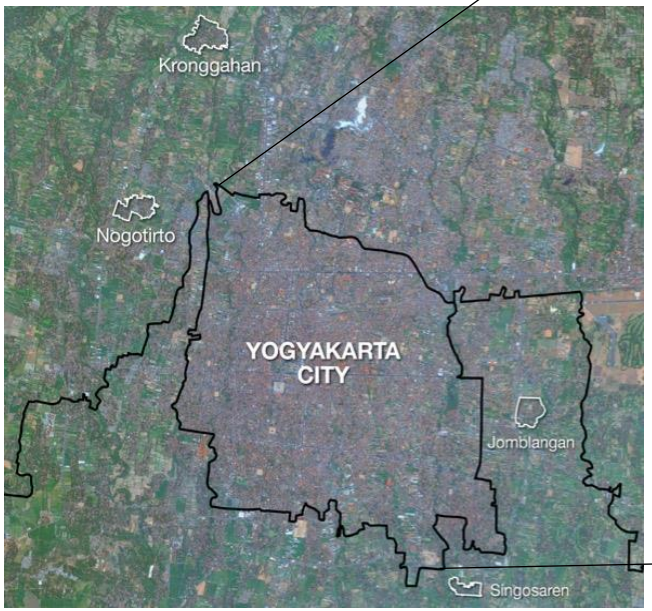


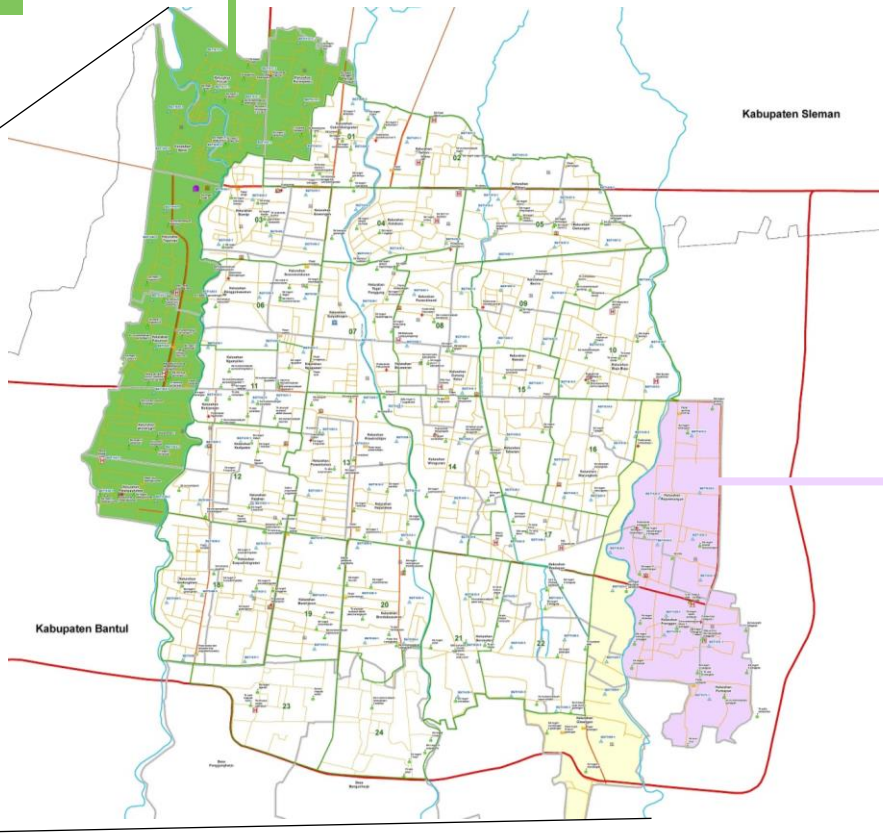
Observational data – *Wolbachia* treated vs control area

Quasi experiment
Wolbachia release area
(green, ~50,000 people)

Control area
(purple, ~25,000 people)

Yogyakarta, Indonesia





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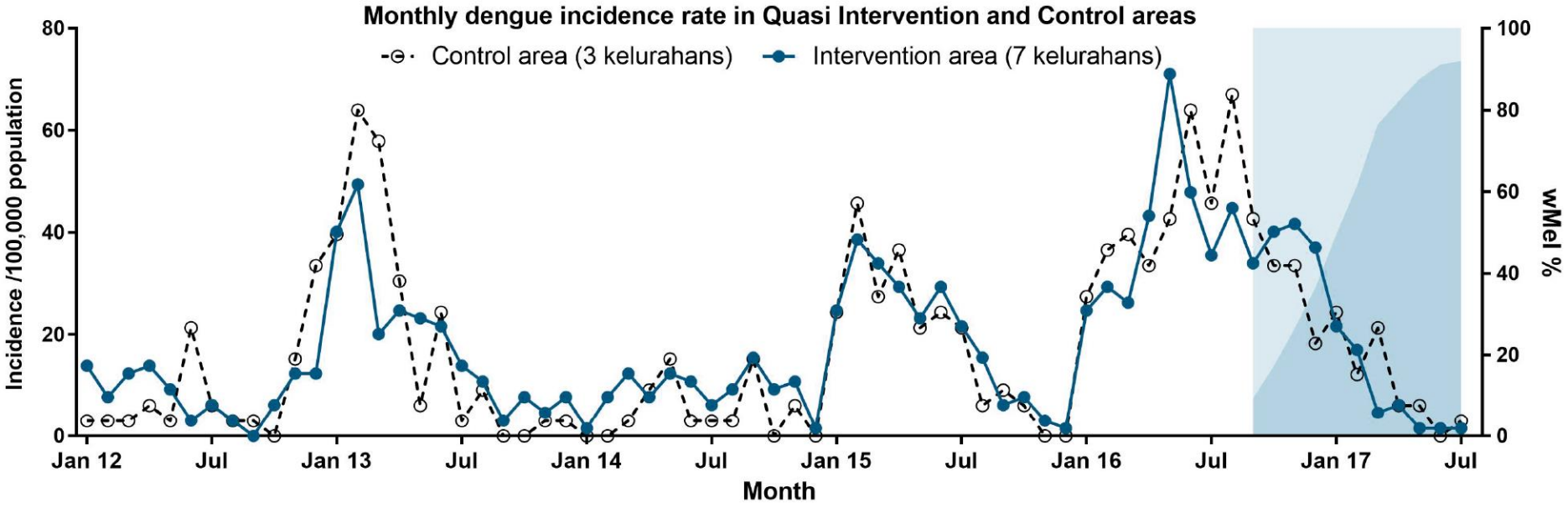
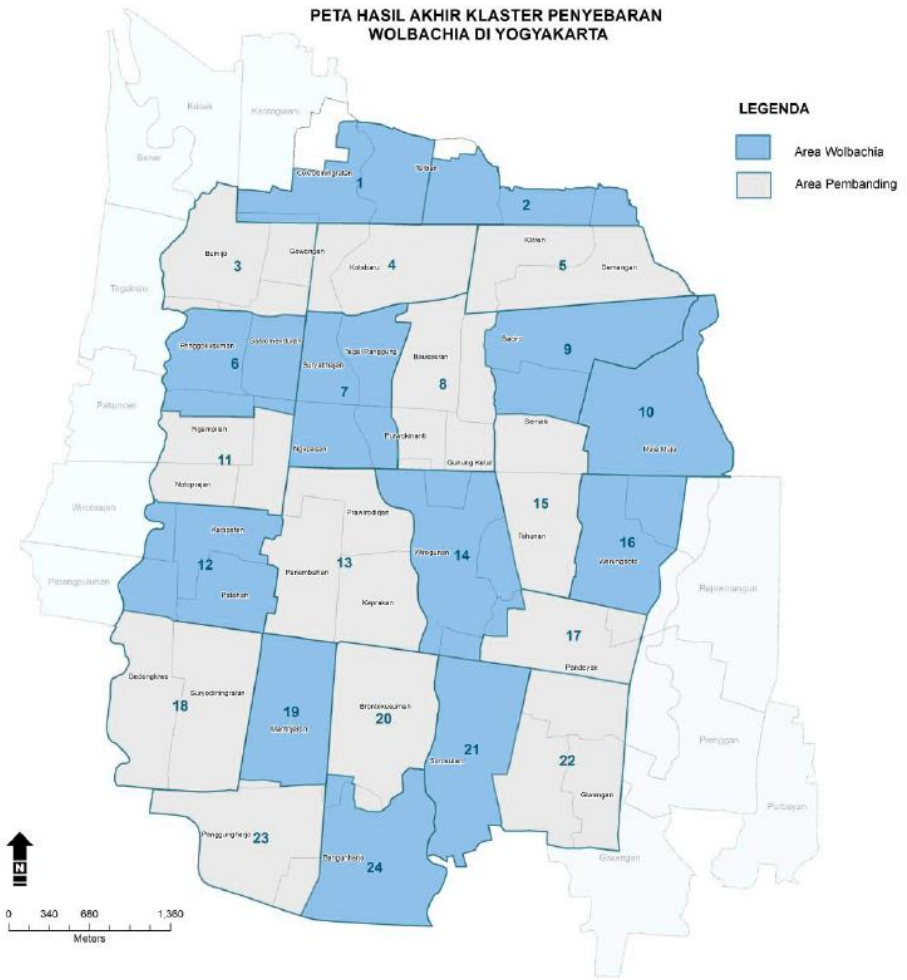


Published: 28 August 2017
Data to: 31 July 2017

Cluster randomised trial of *Wolbachia* in Yogykarta, Indonesia



Commenced January 2017
ClinicalTrials.gov: NCT03055585

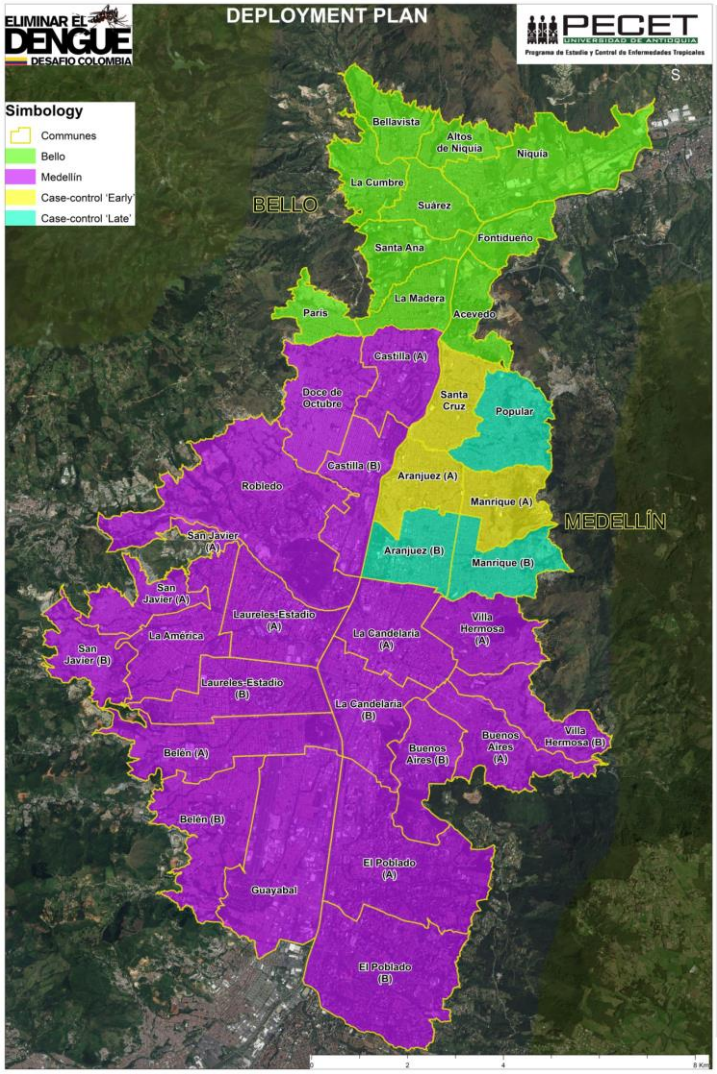
Test Negative Design prospective clinical study:

- Enrol febrile patients in a network of primary care clinics, and collect blood
- Laboratory diagnostics to classify dengue cases (test-positive) and non-dengue controls (test-negative)

Estimate effect of Wolbachia on dengue incidence:

- Compare odds of residence in a treated vs untreated cluster in cases vs controls (Odds Ratio)
- Odds Ratio approximates Incidence Rate Ratio: <<1
- Intention-to-treat analysis: binary classification of Wolbachia exposure based on cluster of residence
- Per-protocol analysis: adjust for time spent outside cluster of residence, and measured local *Wolbachia* frequency

City wide deployment underway in Bello/Medellín with nested case-control study



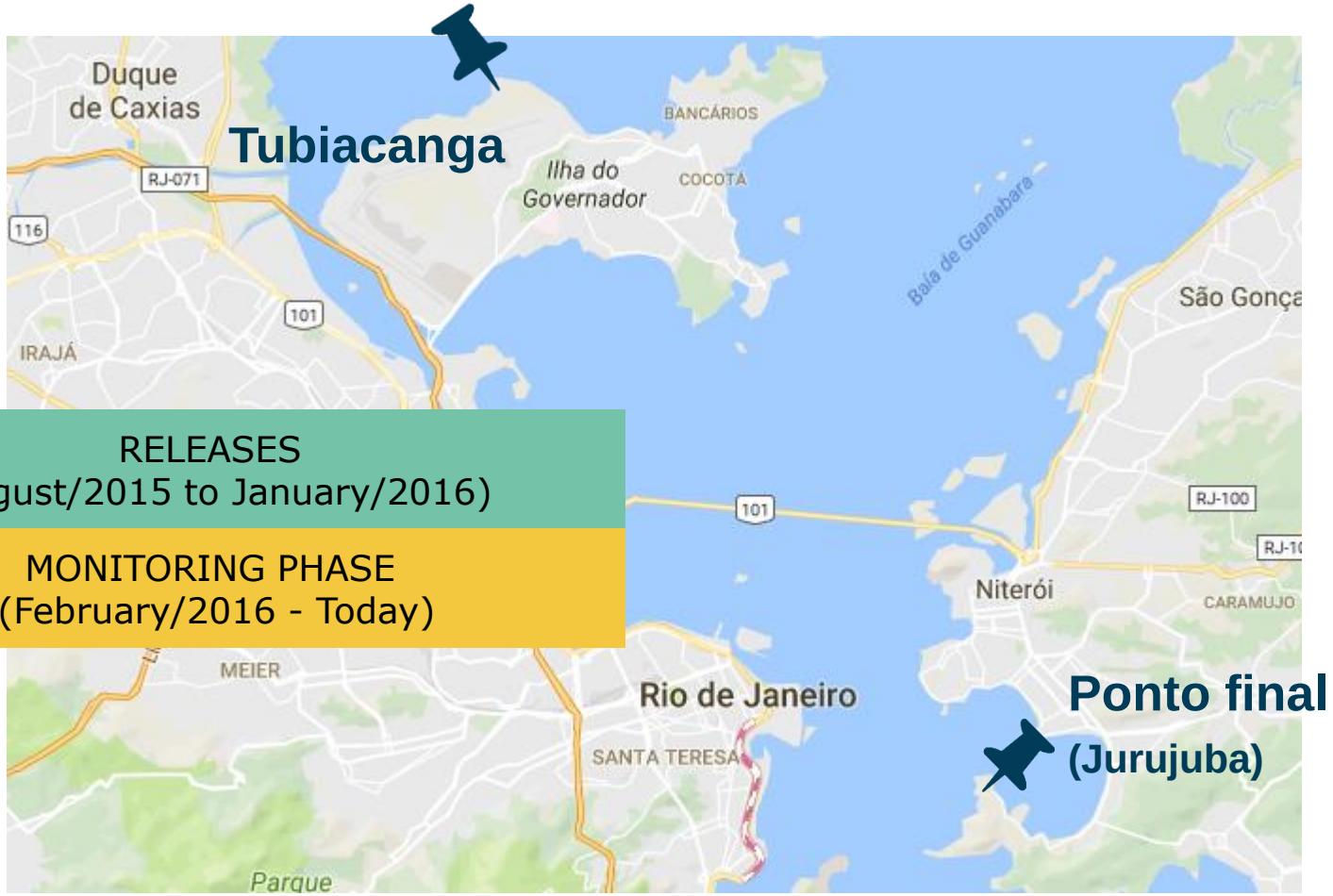
Title	The impact of city-wide deployment of *Wolbachia*-infected mosquitoes on arboviral disease incidence in Medellin, Colombia
Short title	*Wolbachia* disease impact in Medellin
Health condition(s) studied	Dengue, Zika and chikungunya virus infection
Intervention	Intervention arm: Deployment of *Wolbachia*-infected Aedes aegypti mosquitoes, in addition to standard practice dengue control activities.
	Comparison arm: Standard practice dengue control activities.
Primary endpoint	Symptomatic, virologically-confirmed dengue virus (DENV) infection of any severity.
Secondary endpoints	Symptomatic, virologically-confirmed Zika virus (ZIKV) infection of any severity.
	Symptomatic, virologically-confirmed chikungunya virus (CHIKV) infection of any severity.
Study design	Study type: case-control study
	Allocation: cluster non-randomised
	Assignment: parallel 1:1
	Masking: non-blinded
	Primary purpose: prevention
Study duration	Approximately 12 months
Target sample size	100 dengue cases and ≥400 non-dengue controls
Analysis	The intention-to-treat analysis will consider *Wolbachia* exposure as binary depending on the allocation of the cluster of residence.
	The per-protocol analysis will consider *Wolbachia* exposure as a continuous weighted index based on *Wolbachia* prevalence in trapped mosquitoes in the zone of residence and time spent in other zones visited during the ten days prior to illness onset.

Eliminar a Dengue

Desafio Brasil

World Mosquito Program™

First **Pilot Studies** in Brazil

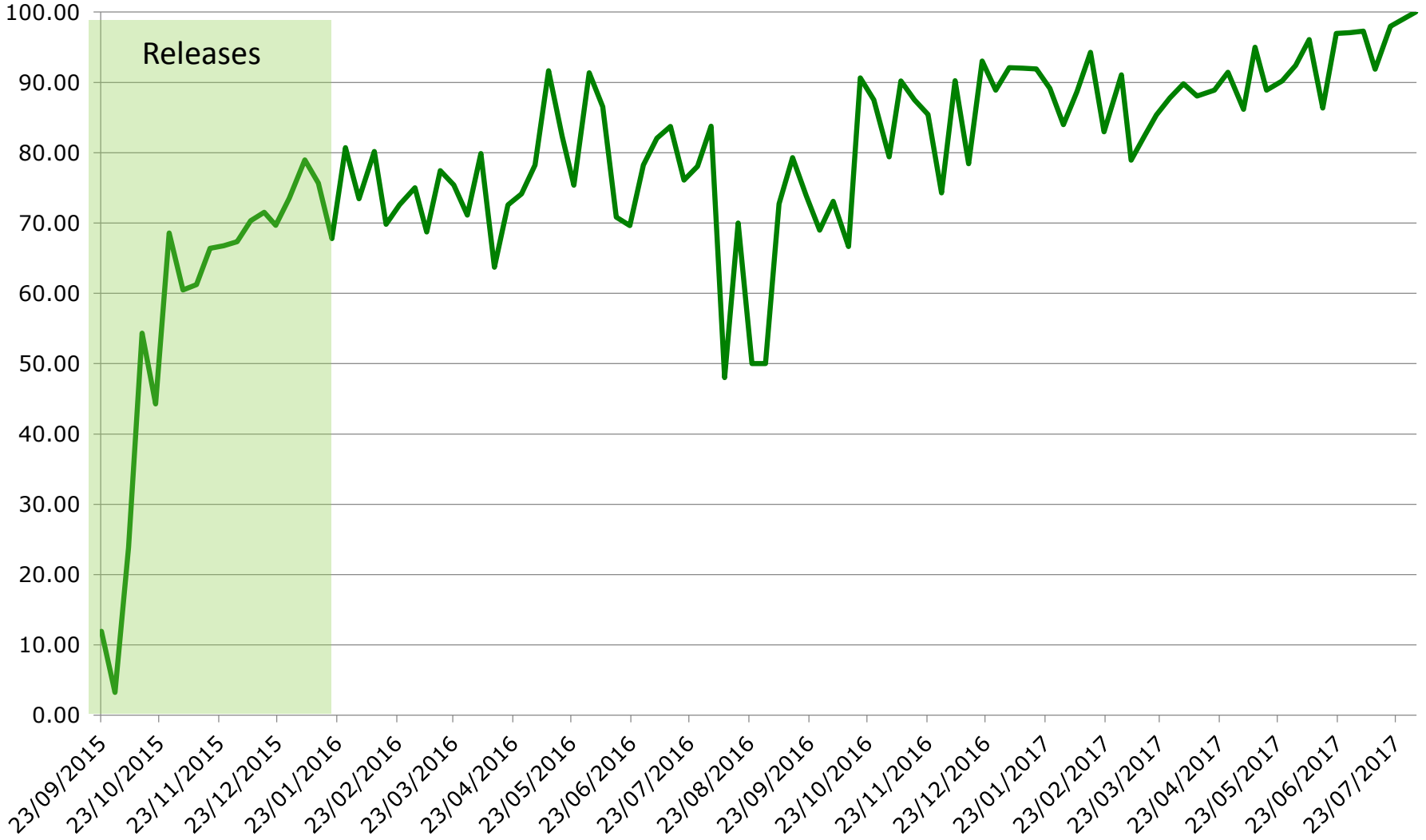


RELEASES
(August/2015 to January/2016)

MONITORING PHASE
(February/2016 - Today)

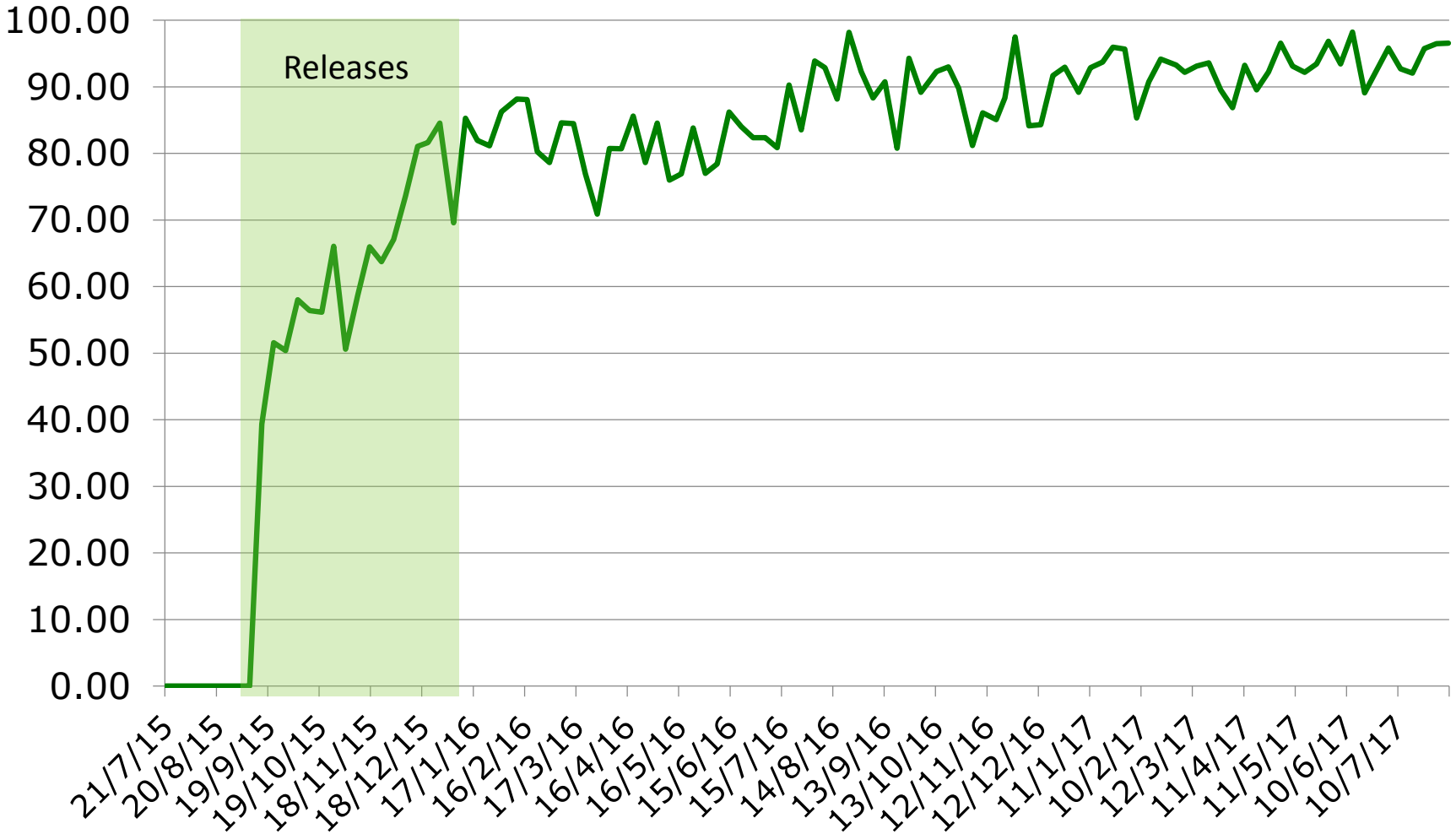
Pilot-site : Tubiacanga

Sustainability

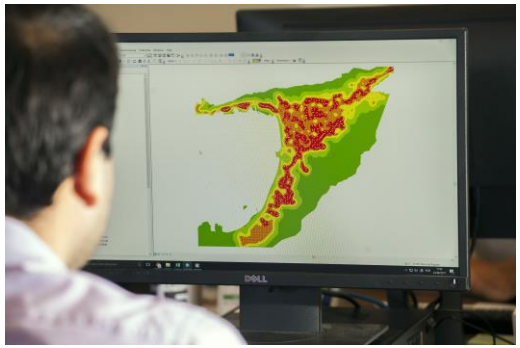


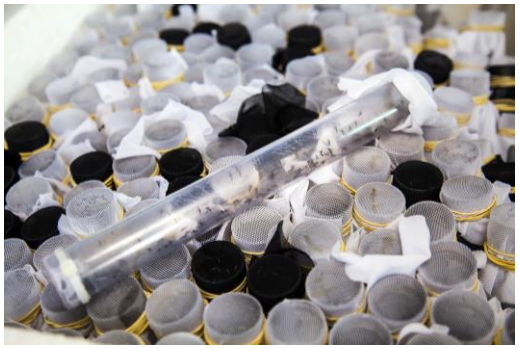
Pilot-site : Ponto Final (Jurujuba)

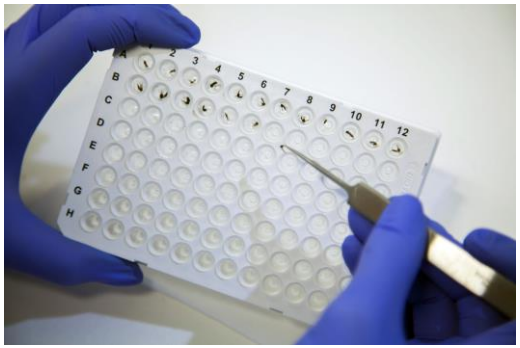
Sustainability



Many steps are done **before** and **after** mosquito releases







We do **trainings** within municipality health units


We organize **talks and functions** in schools

We partner with **social groups** within each territory

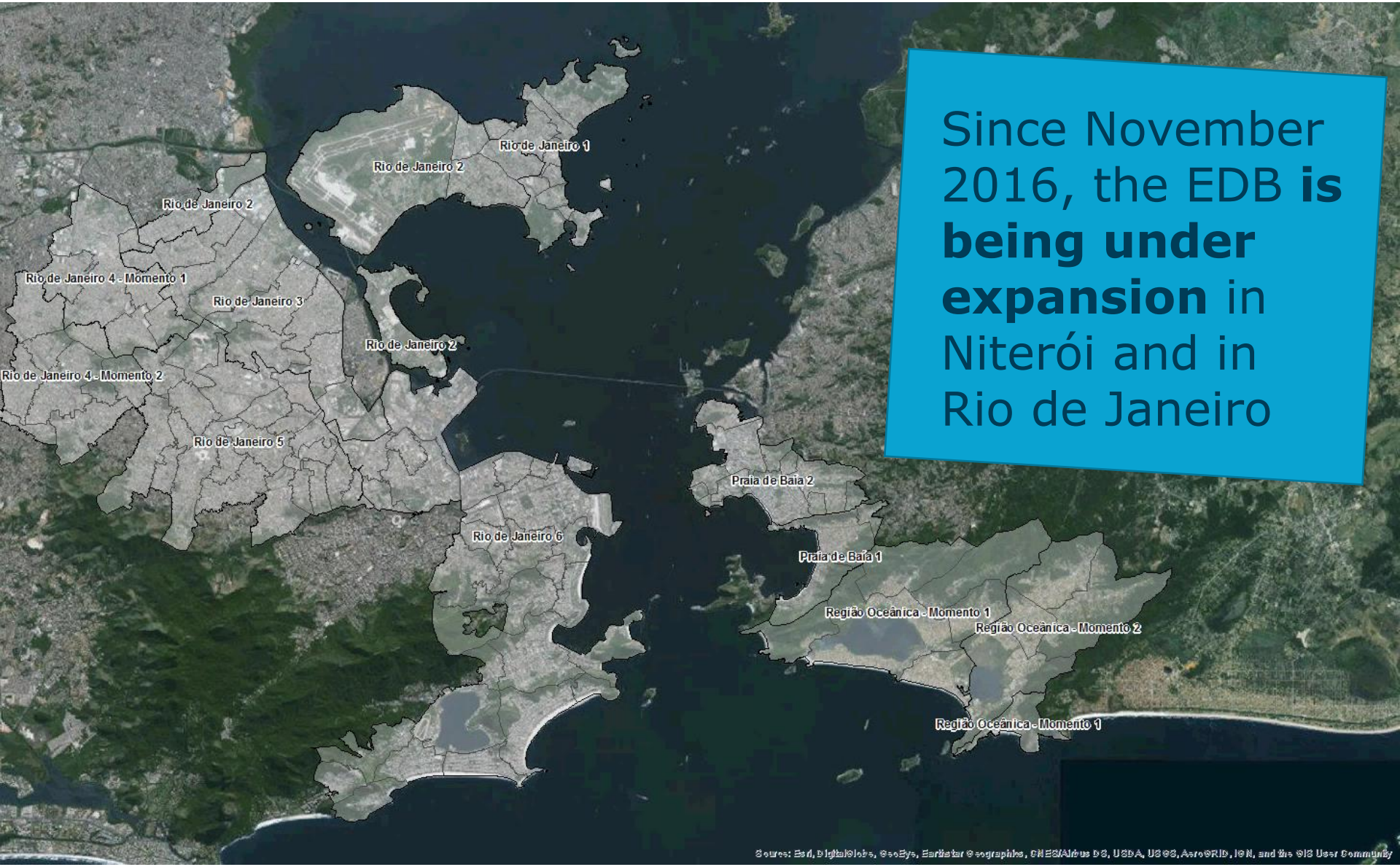
And **cultural events** in areas where we work


We release mosquitoes with *Wolbachia* during **a few weeks** so they can reproduce with the local mosquito population

In **some areas releases are done on foot,** with the help of municipality agents

To monitor mosquitoes with *Wolbachia*, **we install traps** in residences or merchants


And **every week** we visit them to collect mosquitoes


Rio de Janeiro 1
Rio de Janeiro 2
Rio de Janeiro 2
Rio de Janeiro 4 - Momento 1
Rio de Janeiro 3
Rio de Janeiro 2
Rio de Janeiro 4 - Momento 2
Rio de Janeiro 5
Rio de Janeiro 6
Praia de Baia 2
Praia de Baia 1
Região Oceânica - Momento 1
Região Oceânica - Momento 2
Região Oceânica - Momento 1
Since November 2016, the EDB **is being under expansion** in Niterói and in Rio de Janeiro
Source: Esri, DigitalGlobe, GeoEye, Earthstar Geographics, CNES/Airbus DS, USDA, USGS, AeroGRID, IGN, and the GIS User Community

LARGE SCALE IMPLEMENTATION- RESULTS

World Mosquito Program™

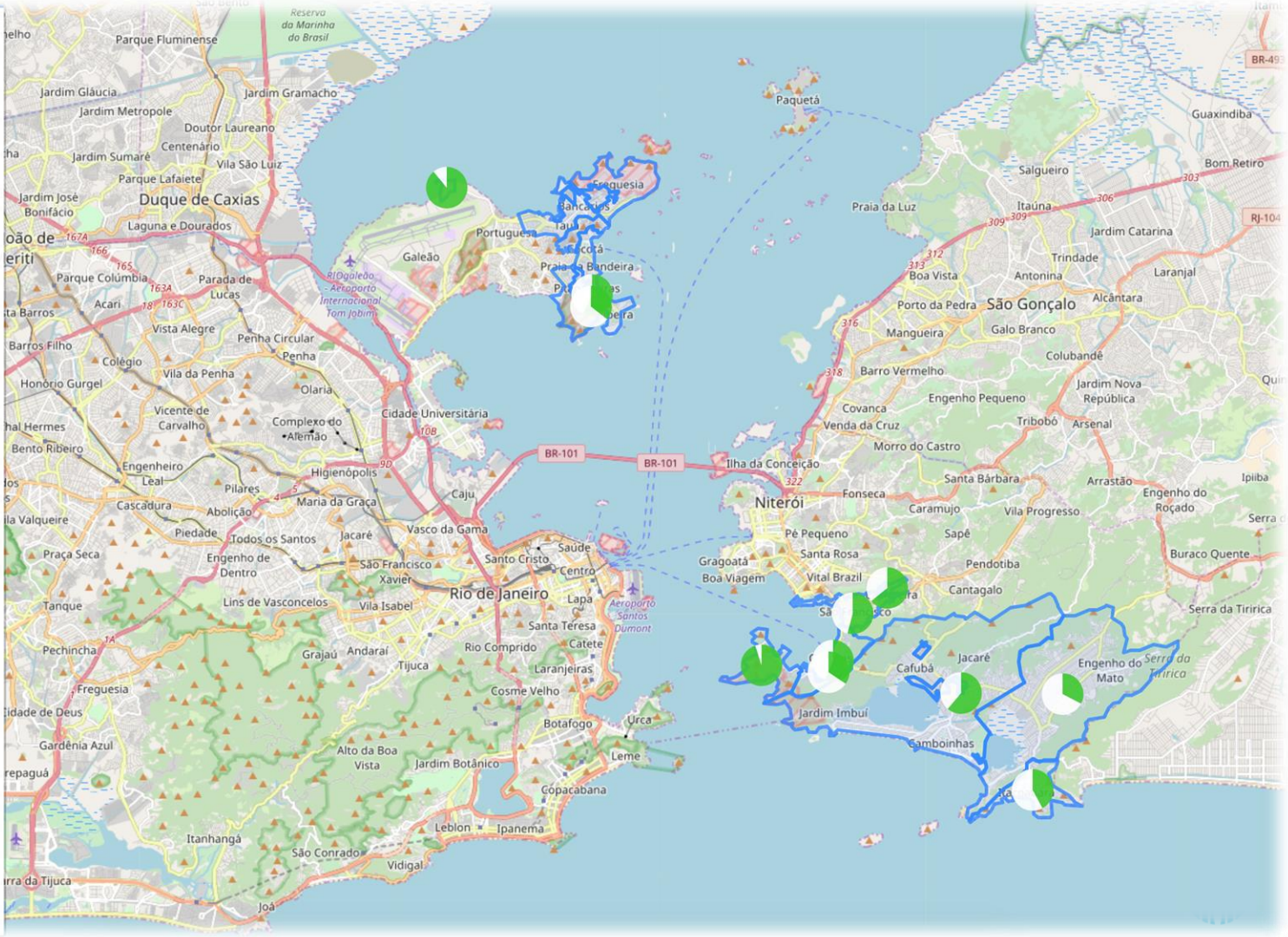
Current Status

30th – 5th November, 2017

Reporting period

201744

Reporting area	wMel %	MCPTPD
Jurujuba Release Sites		
Jurujuba	95.65	0.25
PB1.B2_Reporting		
PB1.B2	64.29	0.25
PB1.V1_Reporting		
Charitas	56.82	0.62
PB1.V2-Reporting		
PB1.V2	54.17	1.02
Preventorio		
Preventorio	34.62	2.61
RJ1.B_Reporting		
RJ1.B	35.90	0.46
RJ1.V_Reporting		
RJ1.V	57.27	1.39
ROC.B1_Reporting		
ROCB1	61.54	0.29
ROC.V1_Reporting		
ROCV1	42.21	0.46
ROC.V2_Reporting		
ROCV2	32.85	0.39
Tubiacanga		
Tubiacanga	89.47	2.34



EPIDEMIOLOGICAL ANALYSIS

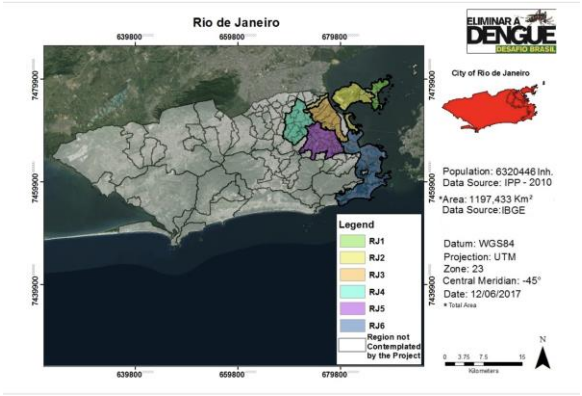
World Mosquito Program™

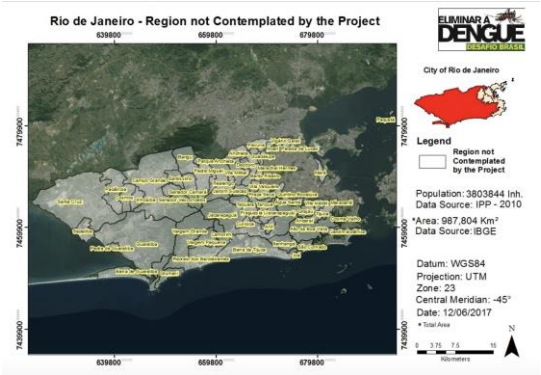
Epidemiological Analysis

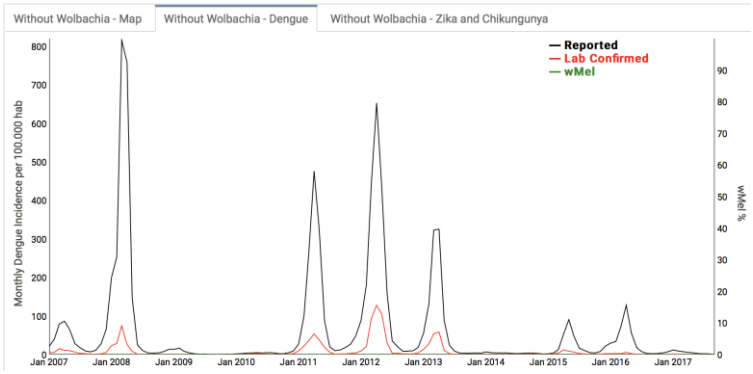
- Following cases (historical data): before and after
- Following the absence of case clustering
- Active monitoring: primary care
- Vector competence of field mosquitoes

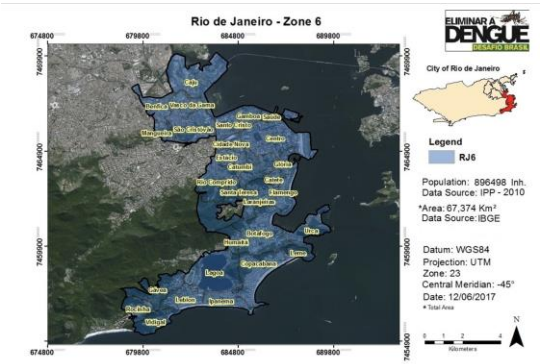
Epidemiological Analysis

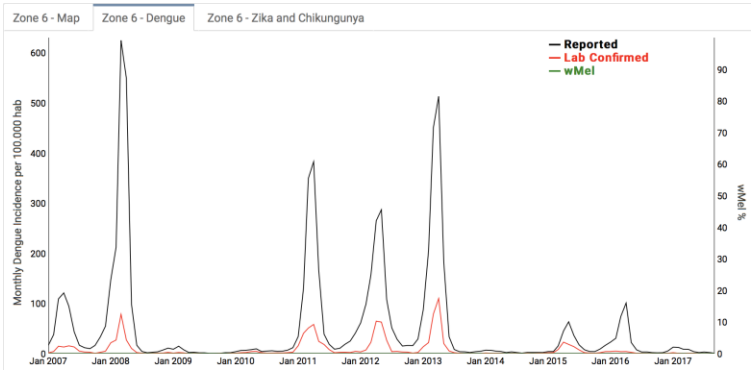
Rio de Janeiro





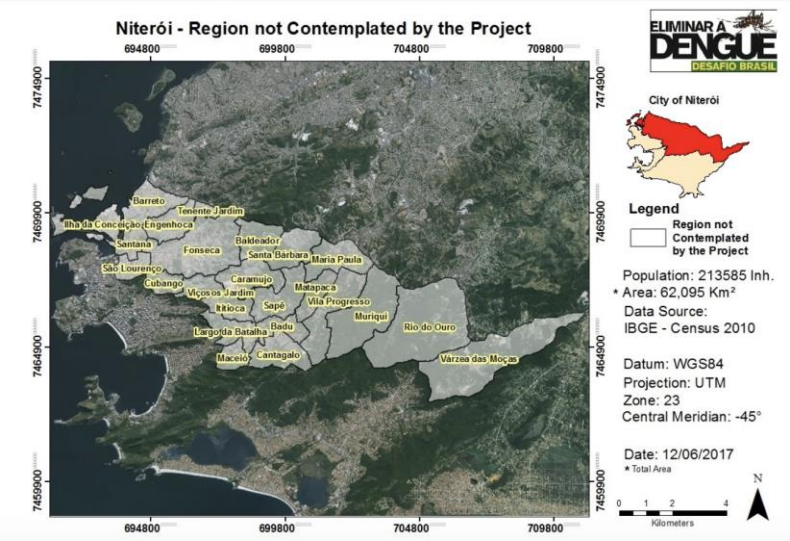


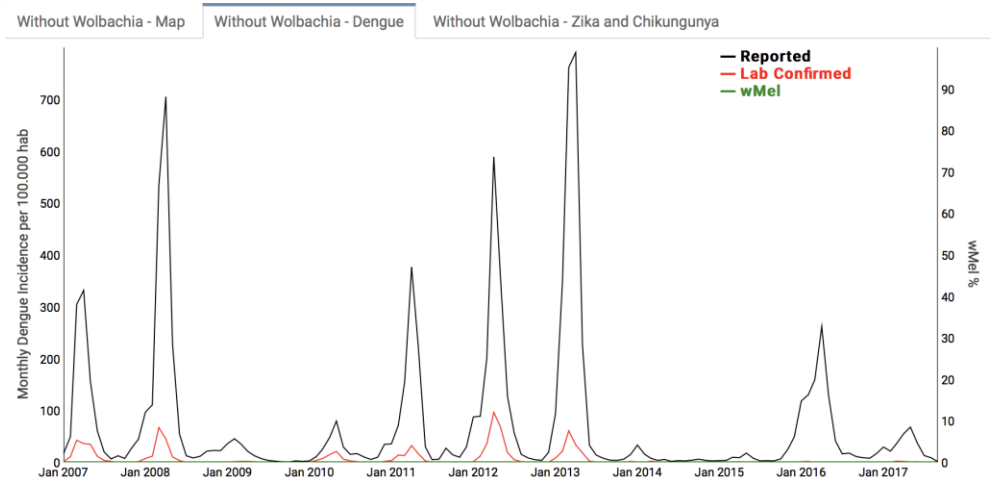


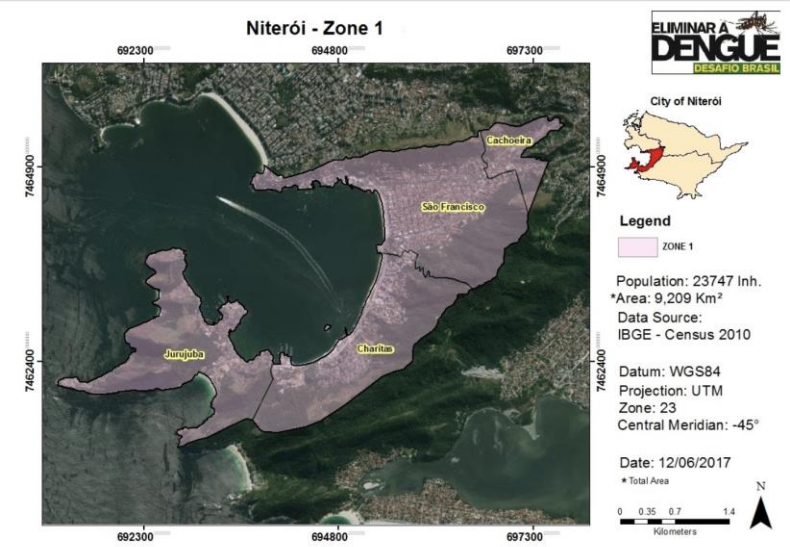


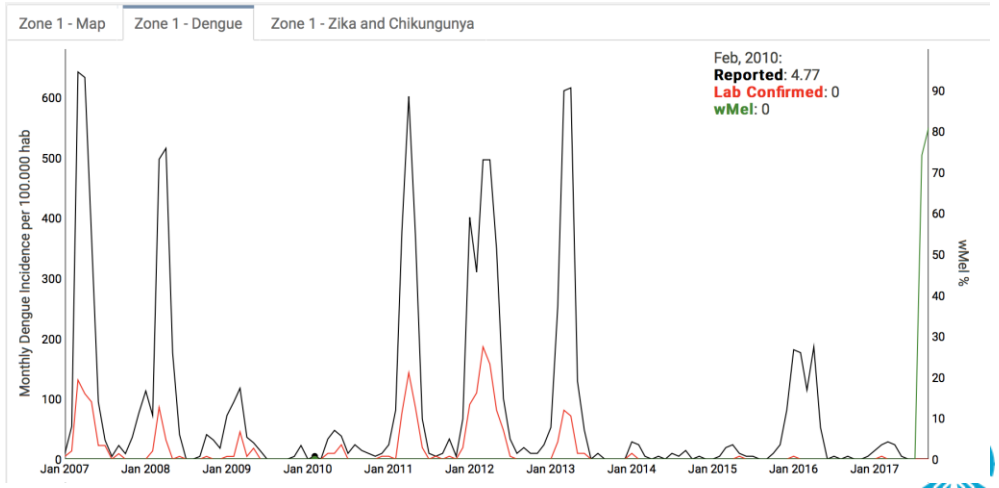
Epidemiological Analysis

Niterói

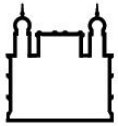








Funders and Partners



Brazilian Ministry of Health

FIOCRUZ
Oswaldo Cruz Foundation

BILL & MELINDA GATES foundation

SUS MINISTÉRIO DA SAÚDE

BRASIL GOVERNO FEDERAL

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

Partners

Health Secretariat – Rio de Janeiro
Health Secretariat – Niterói

Thank you/ Gracias/ Obrigado

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