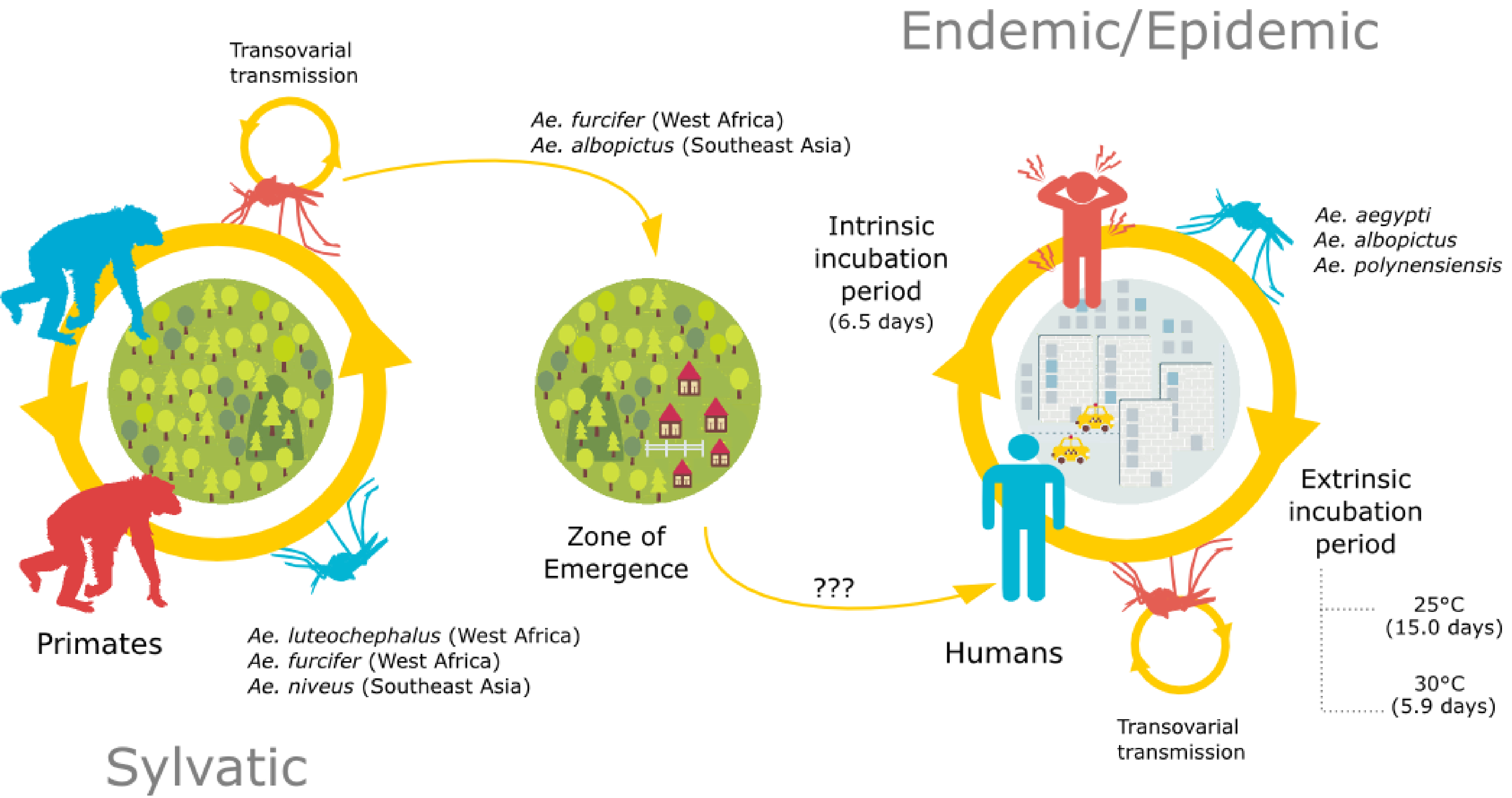
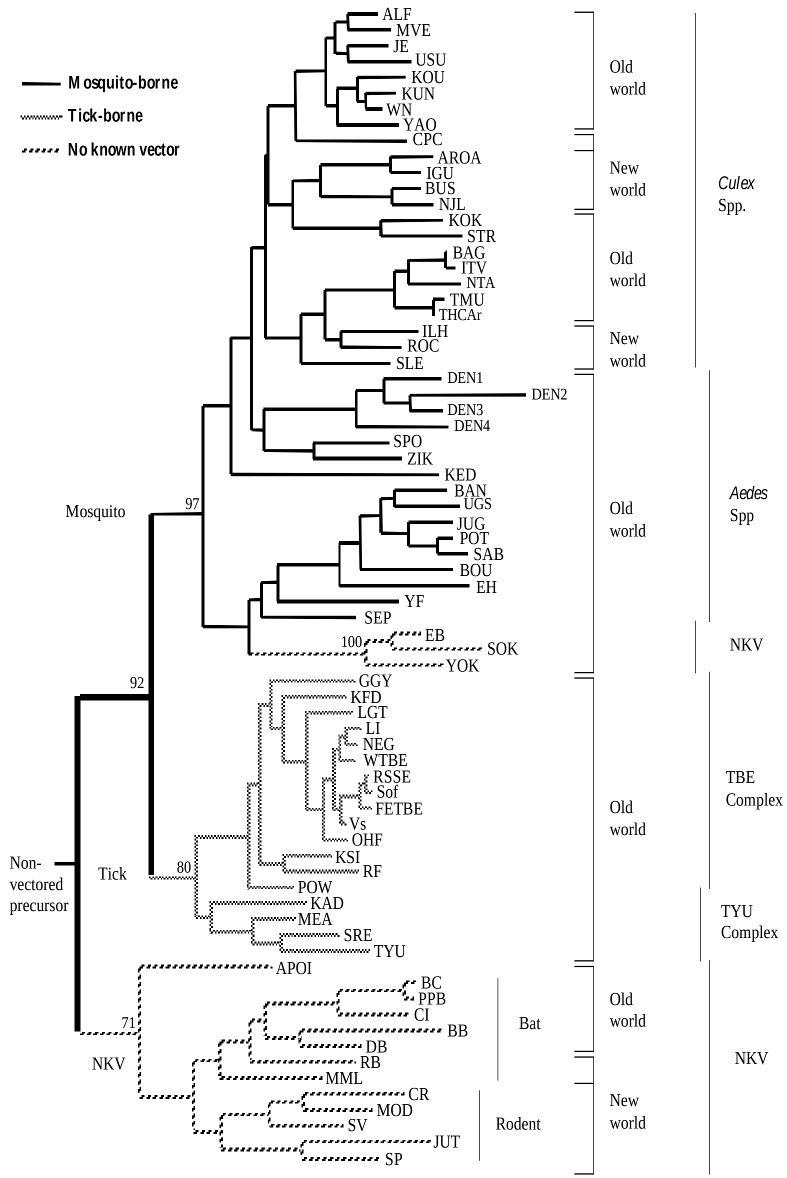
The 2013 outbreak of DENV in Guarujá

Grandes Endemias - 2015

Life Cycle of DENV



Flavivirus vector associations



Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 545–546, January 1996

Sean Nee & Phylodynamics

Commentary

Evolving virus plagues

John J. Holland

Department of Biology, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0116

Recently, the AIDS pandemic and other new or emerging viruses have focused attention on emerging infectious diseases (1, 2). The factors involved in emergence are diverse and include global transportation, urban crowding and poverty, changing behavioral patterns, rapid virus evolution, human population growth, etc. Until now, no studies have clearly linked human population expansion with in- of Europe and Asia are mainly zoonoses. Tick-borne encephalitis (TBE) viruses exist almost exclusively in "forest cycles" involving ticks and various vertebrate hosts. Humans play little if any role in these cycles, and human disease is accidental and dead-end (albeit sometimes severe). In work described in this issue of the *Proceedings* (pages 548–553), Zanotto *et al.* (6) have compared the molecular

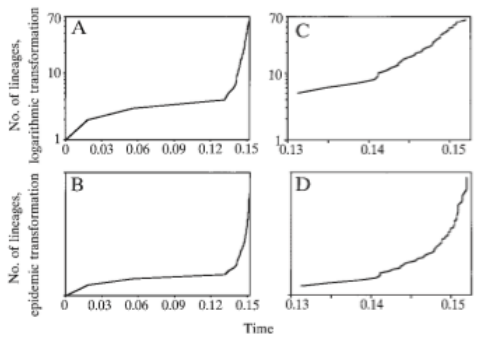


FIG. 2. (*A*) Lineages through time of 66 dengue viruses. The time at which each lineage division occurs on a constant-rate (KITSCH) phylogenetic tree is plotted with the time axis scaled as the number of nucleotide substitutions from the root of the tree to the tips. (*B*) Epidemic transformation of the same data. This transformation of the *y* axis determines whether the rate of population growth has been constant through time (straight line), increasing (upward curvature, as here), or decreasing (downward curvature). (*C*) Lineages through time of the most recent 62 nodes of dengue viruses. (*D*) Epidemic transformation of the same data.

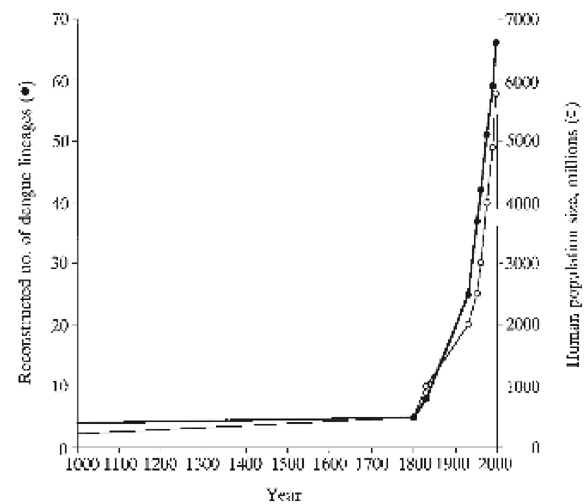
Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 548–553, January 1996
Evolution

Population dynamics of flaviviruses revealed by molecular phylogenies

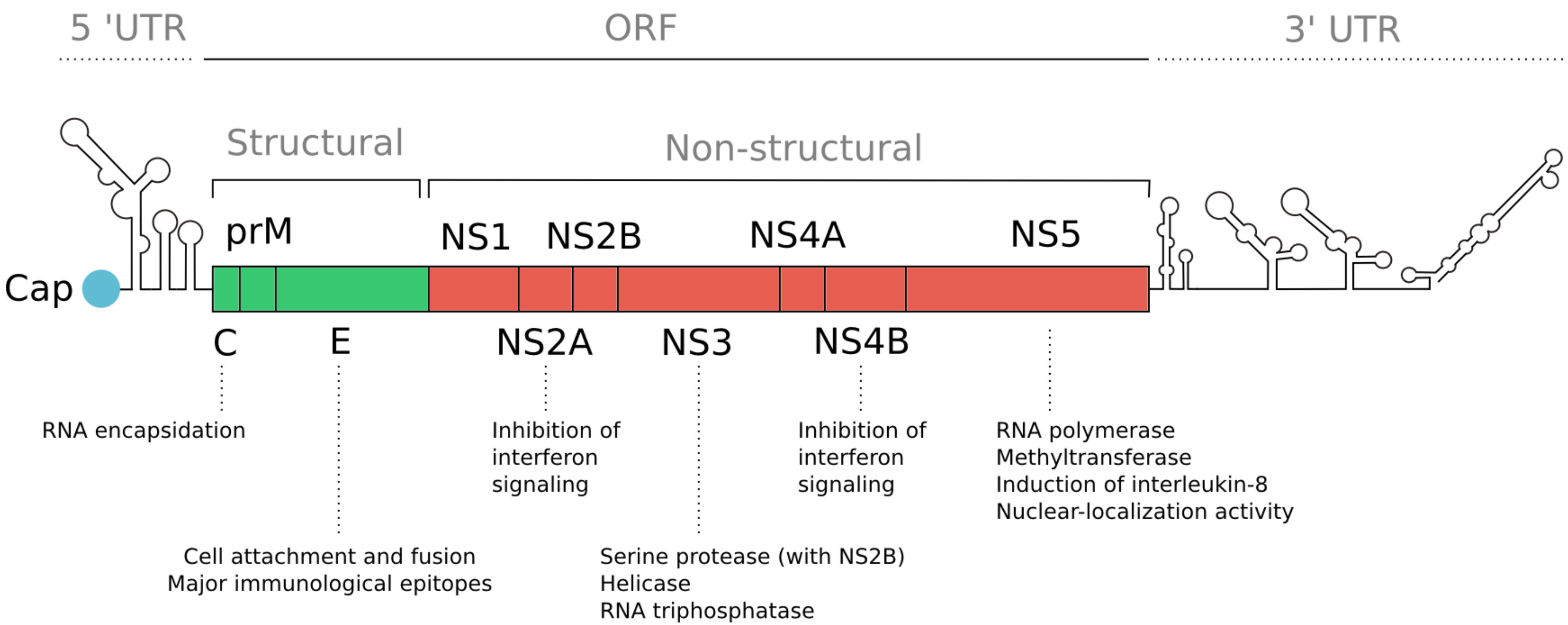
PAOLO M. DE A. ZANOTTO*, ERNEST A. GOULD*, GEORGE F. GAO*, PAUL H. HARVEY†, AND EDWARD C. HOLMES†‡

*National Environment Research Council Institute of Virology and Environmental Microbiology, Mansfield Road, Oxford, OX1 3SR, United Kingdom; and †Wellcome Centre for the Epidemiology of Infectious Disease, Department of Zoology, University of Oxford, South Parks Road, Oxford, OX1 3PS, United Kingdom

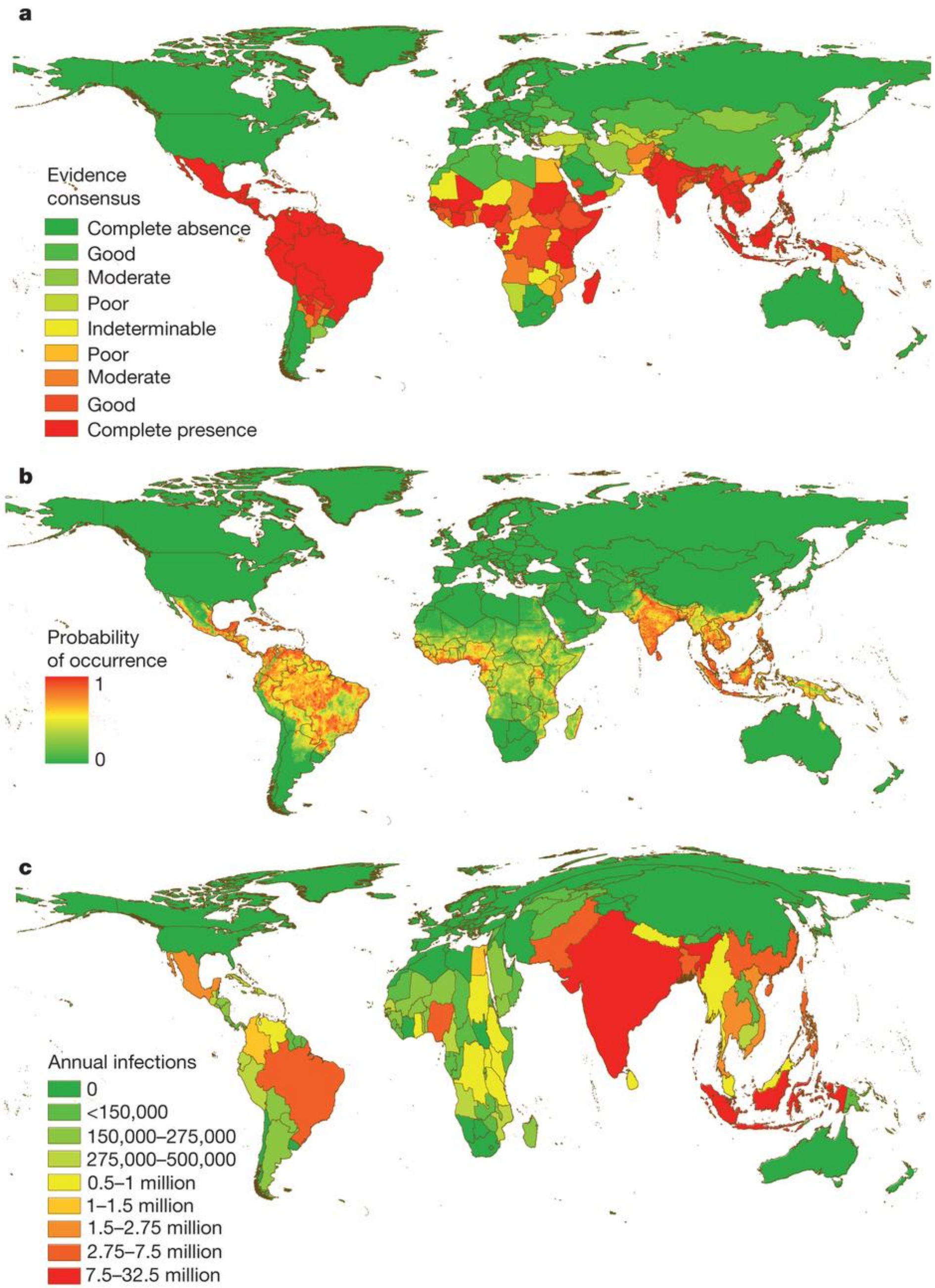
Communicated by Robert M. May, University of Oxford, Oxford, United Kingdom, October 20, 1995 (received for review August 1, 1995)

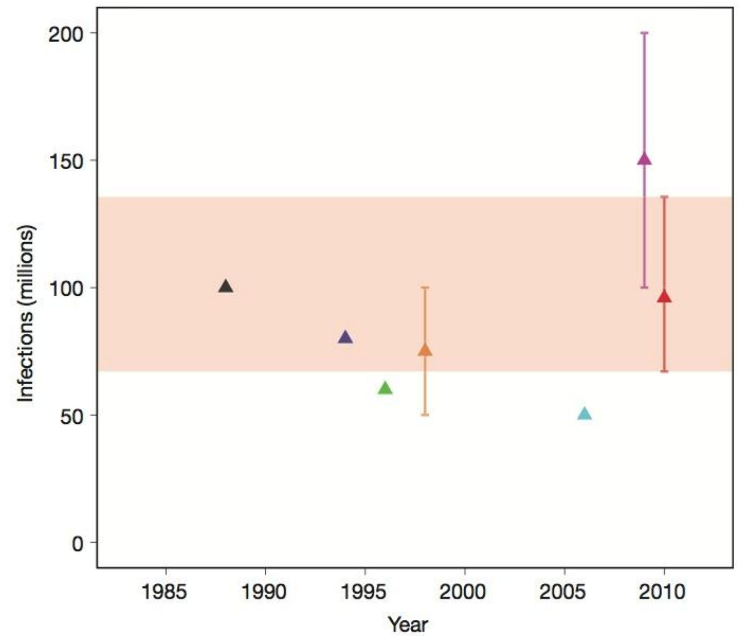


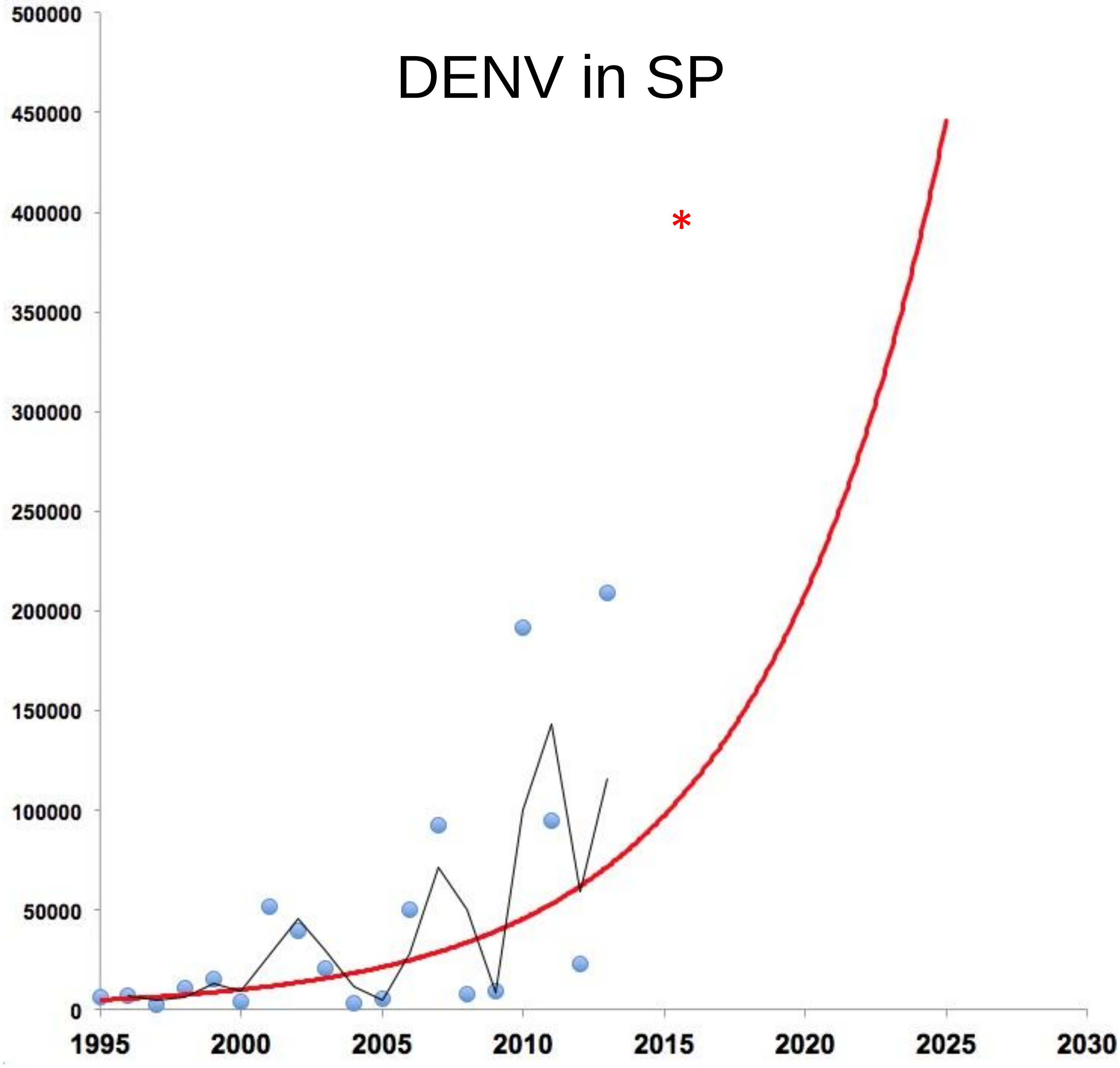
DENV Genome


5 'UTR
ORF
3' UTR
Structural
Non-structural
Cap
prM
NS1
NS2B
NS4A
NS5
C
E
NS2A
NS3
NS4B
RNA encapsidation
Inhibition of interferon signaling
Inhibition of interferon signaling
RNA polymerase
Methyltransferase
Induction of interleukin-8
Nuclear-localization activity
Cell attachment and fusion
Major immunological epitopes
Serine protease (with NS2B)
Helicase
RNA triphosphatase

DENV Burden


a
Evidence consensus
Complete absence
Good
Moderate
Poor
Indeterminable
Poor
Moderate
Good
Complete presence
b
Probability of occurrence
1
0
c
Annual infections
0
<150,000
150,000–275,000
275,000–500,000
0.5–1 million
1–1.5 million
1.5–2.75 million
2.75–7.5 million
7.5–32.5 million


Infections (millions)
200
150
100
50
0
1985
1990
1995
2000
2005
2010
Year


DENV in SP
*
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
1995
2000
2005
2010
2015
2020
2025
2030

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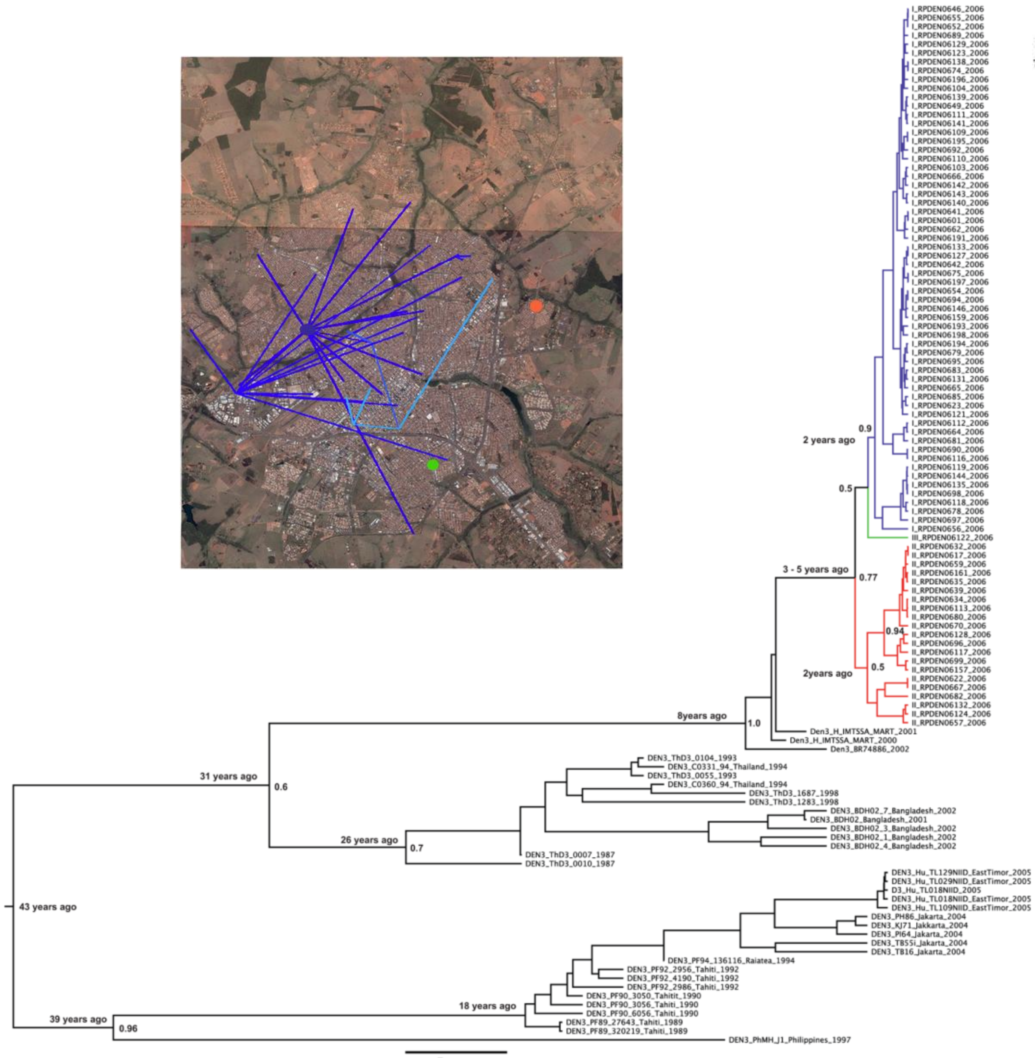
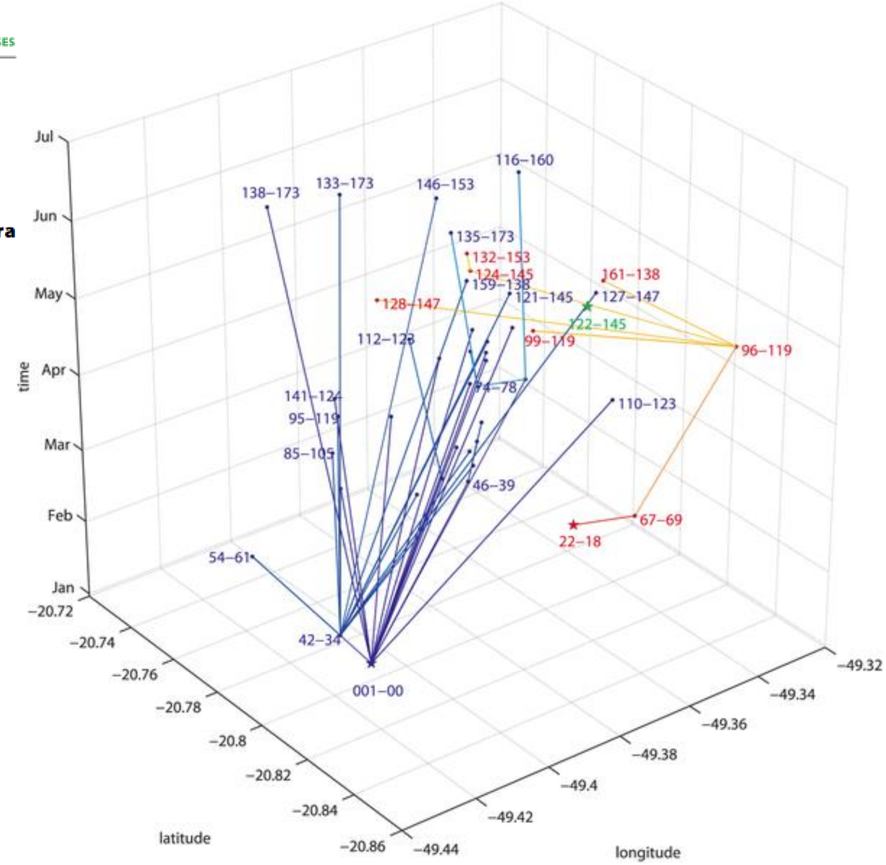
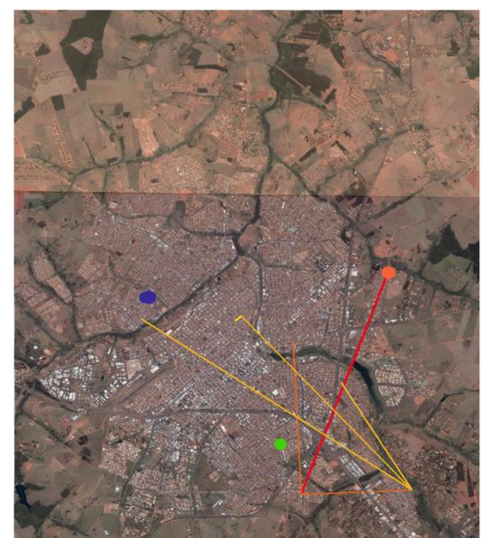
PLoS NEGLECTED TROPICAL DISEASES

Spatio-Temporal Tracking and Phylodynamics of an Urban Dengue 3 Outbreak in São Paulo, Brazil

Adriano Mondini[1], Roberta Vieira de Moraes Bronzoni[1], Silvia Helena Pereira Nunes[1], Francisco Chiaravalloti Neto[1,2], Eduardo Massad[3], Wladimir J. Alonso[4], Eduardo S. M. Lázzaro[5], Amena Alcântara Ferraz[5], Paolo Marinho de Andrade Zanotto[6], Maurício Lacerda Nogueira[1]*







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PLOS | NEGLECTED TROPICAL DISEASES

Viewpoints

Detection of Four Dengue Serotypes Suggests Rise in Hyperendemicity in Urban Centers of Brazil

Christian Julián Villabona-Arenas[1], Jessica Luana de Oliveira[1], Carla de Sousa Capra[2], Karime Balarini[3], Mauricio Loureiro[4], Celso Ricardo Theoto P. Fonseca[3], Saulo Duarte Passos[4], Paolo Marinho de Andrade Zanotto[1]*

1 Laboratório de Evolução Molecular e Bioinformática, Departamento de Microbiologia, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, São Paulo, Brazil, 2 Laboratório de Saúde Pública, Secretaria da Saúde, Prefeitura Municipal de Guarujá, Guarujá, São Paulo, Brazil, 3 Itapema Laboratório de Análises Clínicas, Guarujá, São Paulo, Brazil, 4 Laboratório de Infectologia Pediátrica, Faculdade de Medicina de Jundiaí, Jundiaí, São Paulo, Brazil

DENV-3 samples were from genotype V

- Genotype III has been the most prevalent in Brazil. However, genotypes I and V were associated with dengue outbreaks in Brazil.

- Cryptic circulation of DENV-3 in the region?

- A new introduction from Asia?

- Q: "What is the *A. aegypti* lineage in Santos?" R: "Singapore"!

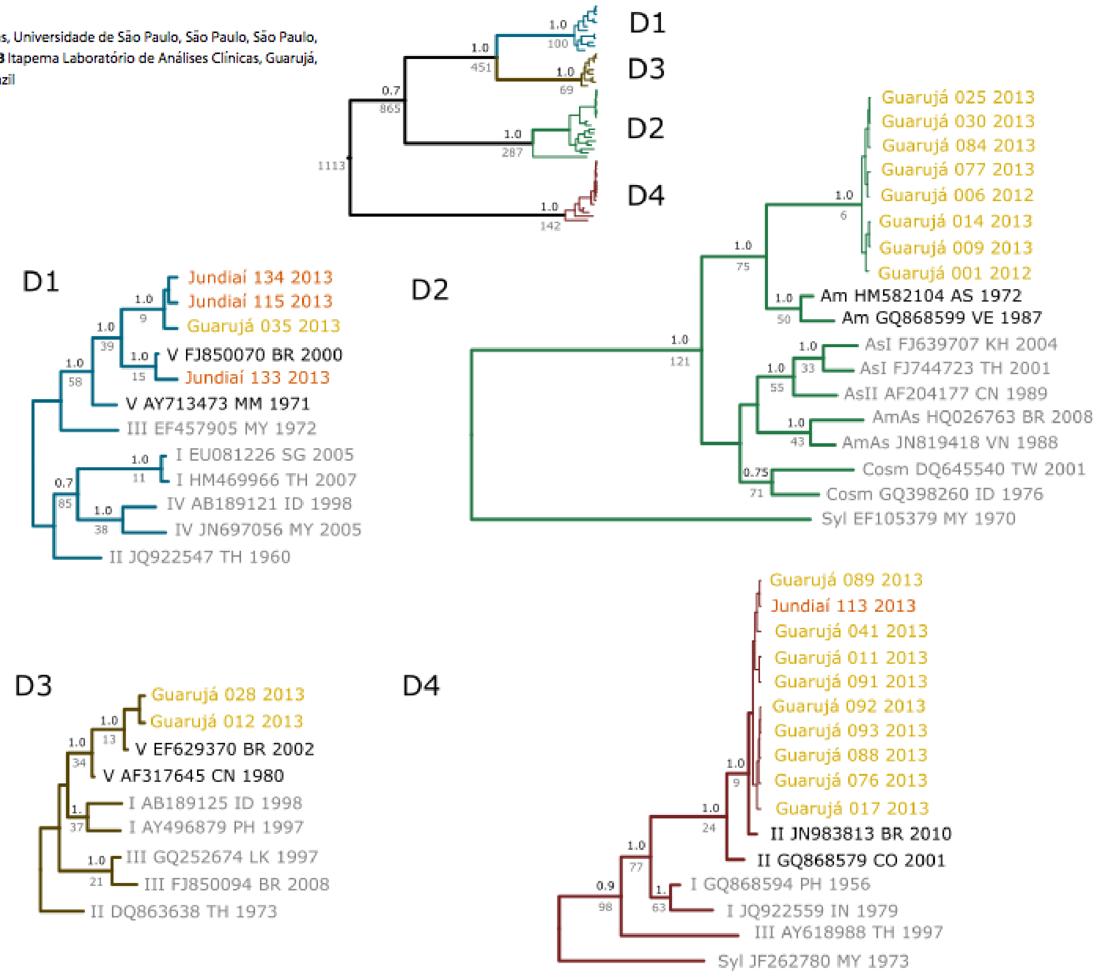
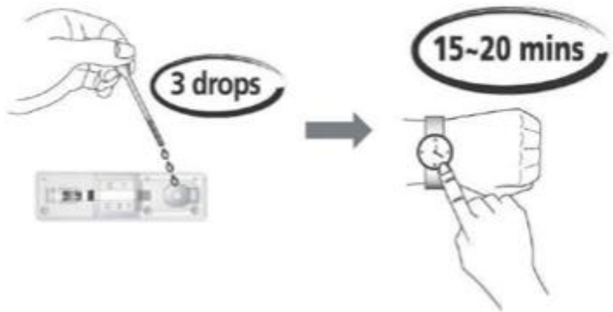


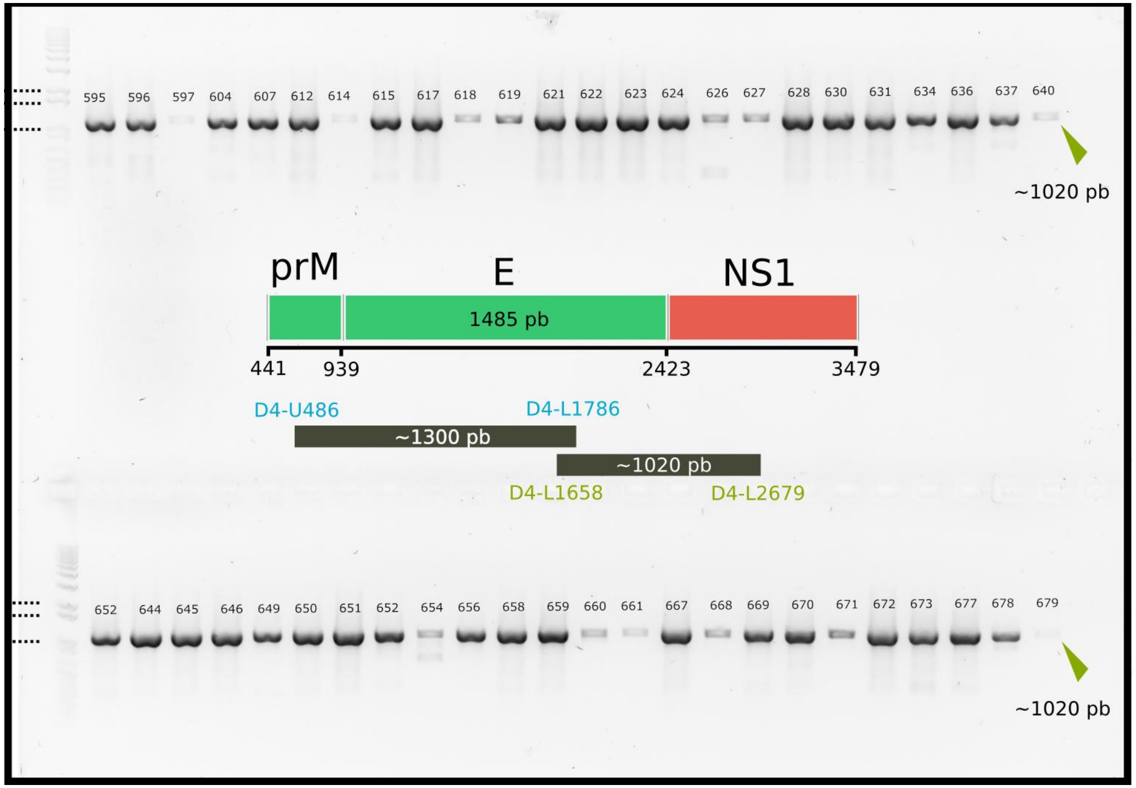
Figure 1. Maximum credibility tree (and its four serotype subtrees) showing the evolutionary relationships among the capsid/premembrane junction sequences of 55 strains. Posterior probability support values are shown over the nodes and TMRCAs values below the nodes. Reference sequences abbreviated by serotype (D1–4), genotype (*Am*: American, *AmAs*: American/Asian, *As*: Asian, *Cosm*: Cosmopolitan, *Syl*: Sylvatic, *I*, *II*, *III*, *IV*, or *V*), GenBank accession, ISO code for country, and isolation year.
doi:10.1371/journal.pntd.0002620.g001

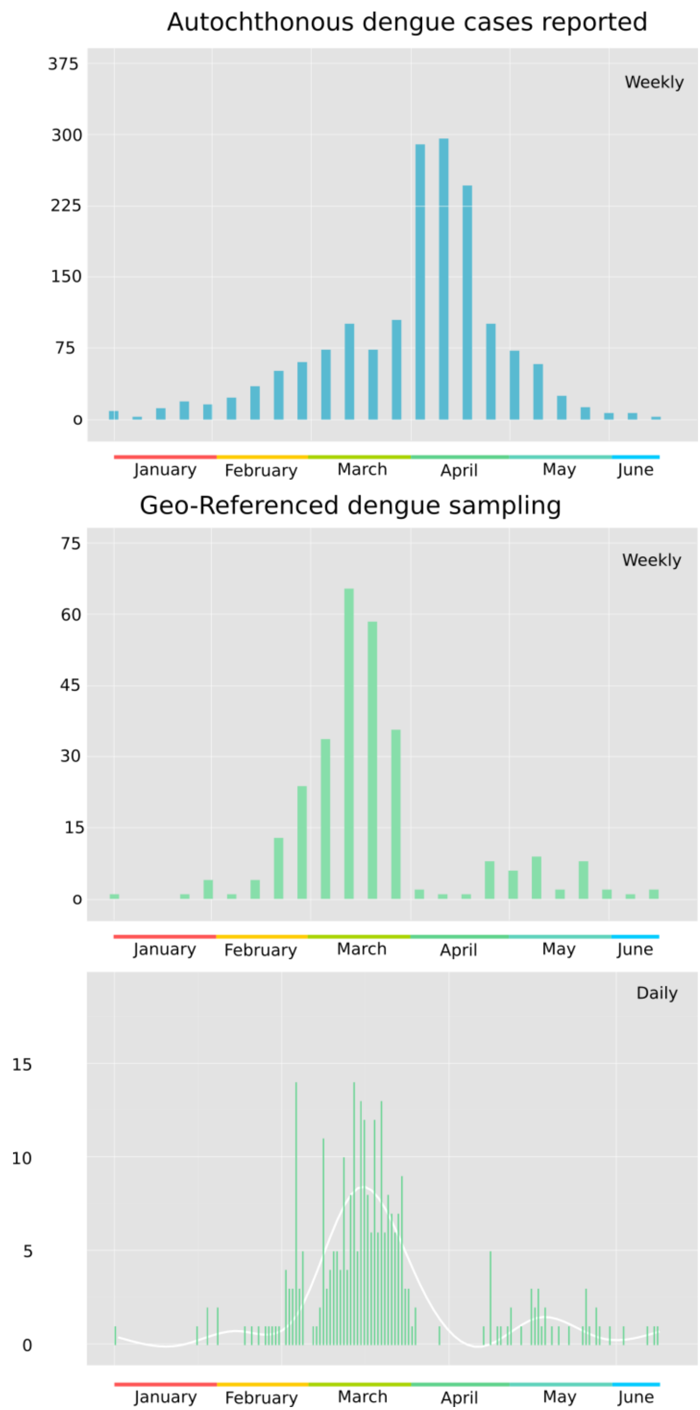
DENV-4 Outbreak in Guarujá

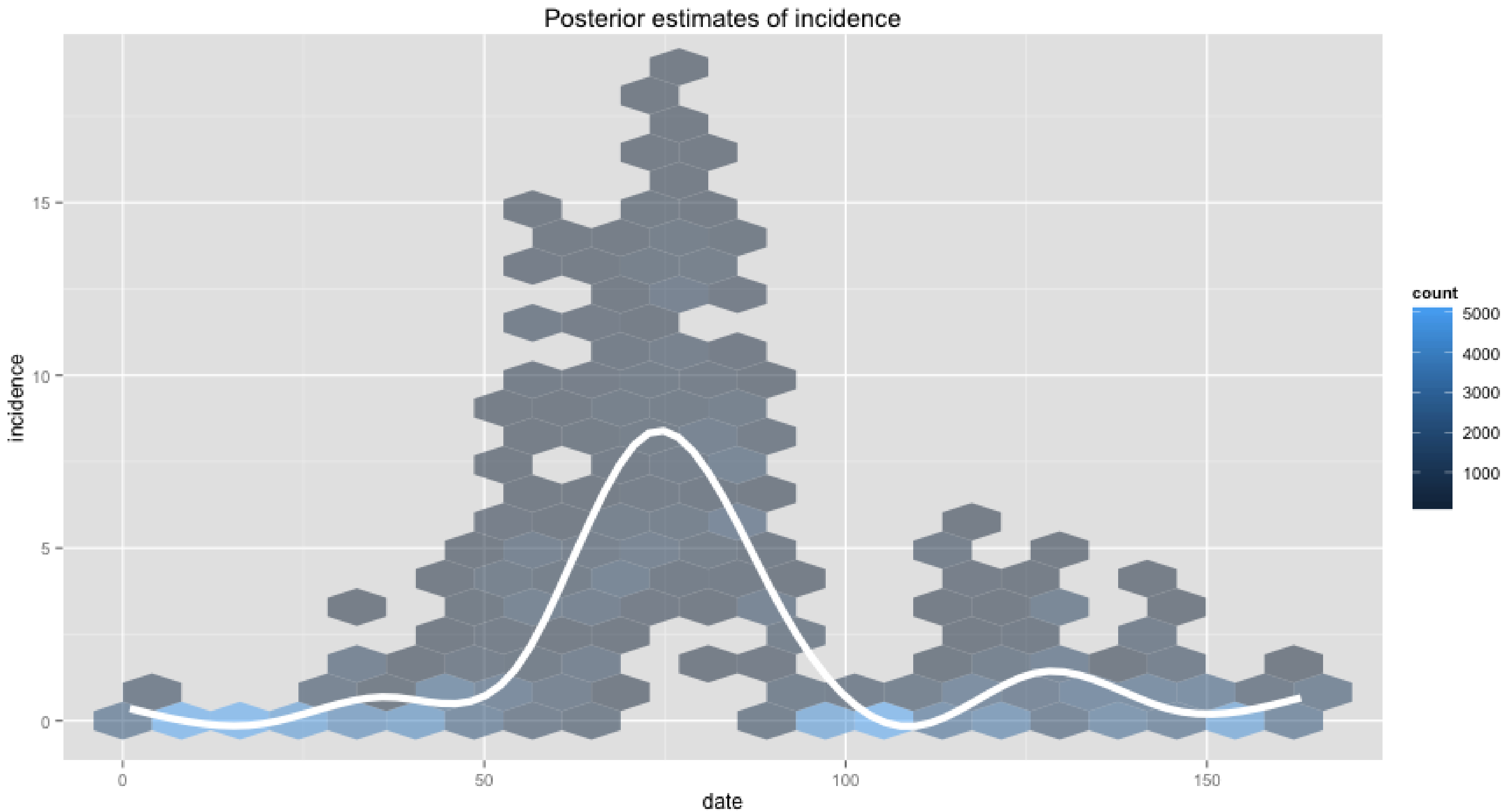
- 1216 serum samples from January to June 2013.
- 879 samples were tested in our laboratory for dengue: 525 (60% of processed samples) were positive for dengue.
- 505 (96% of positive samples) were positive for DENV-4 and 20 belong to any of the other three serotypes (10 DENV-1, 8 DENV-2 and 2 DENV-3).
- 354 DENV-4 (70% of positive) were sequenced1485 bp-long envelope gene from viral genomic RNA amplified directly.
- 285 patients (81%) geo-locate based on the addresses provided, from the cohort of 354 patients.

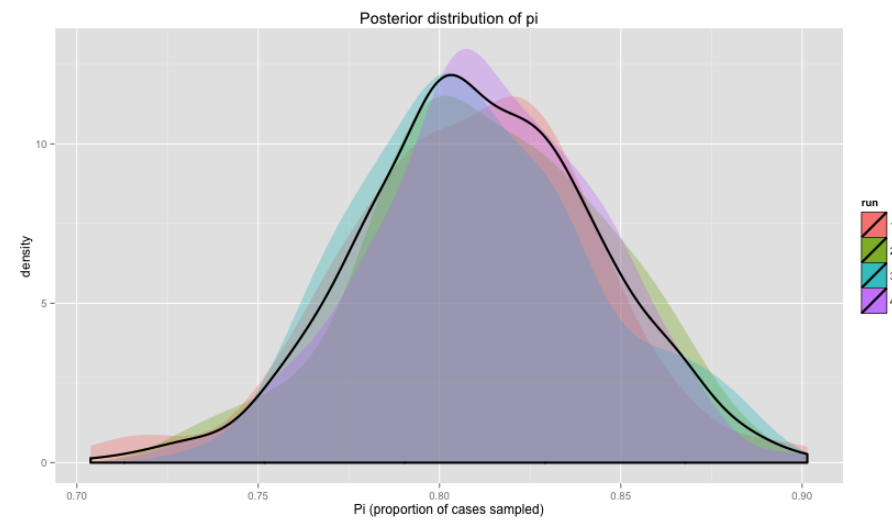
Immunochromatography for IgM, IgG & NS1





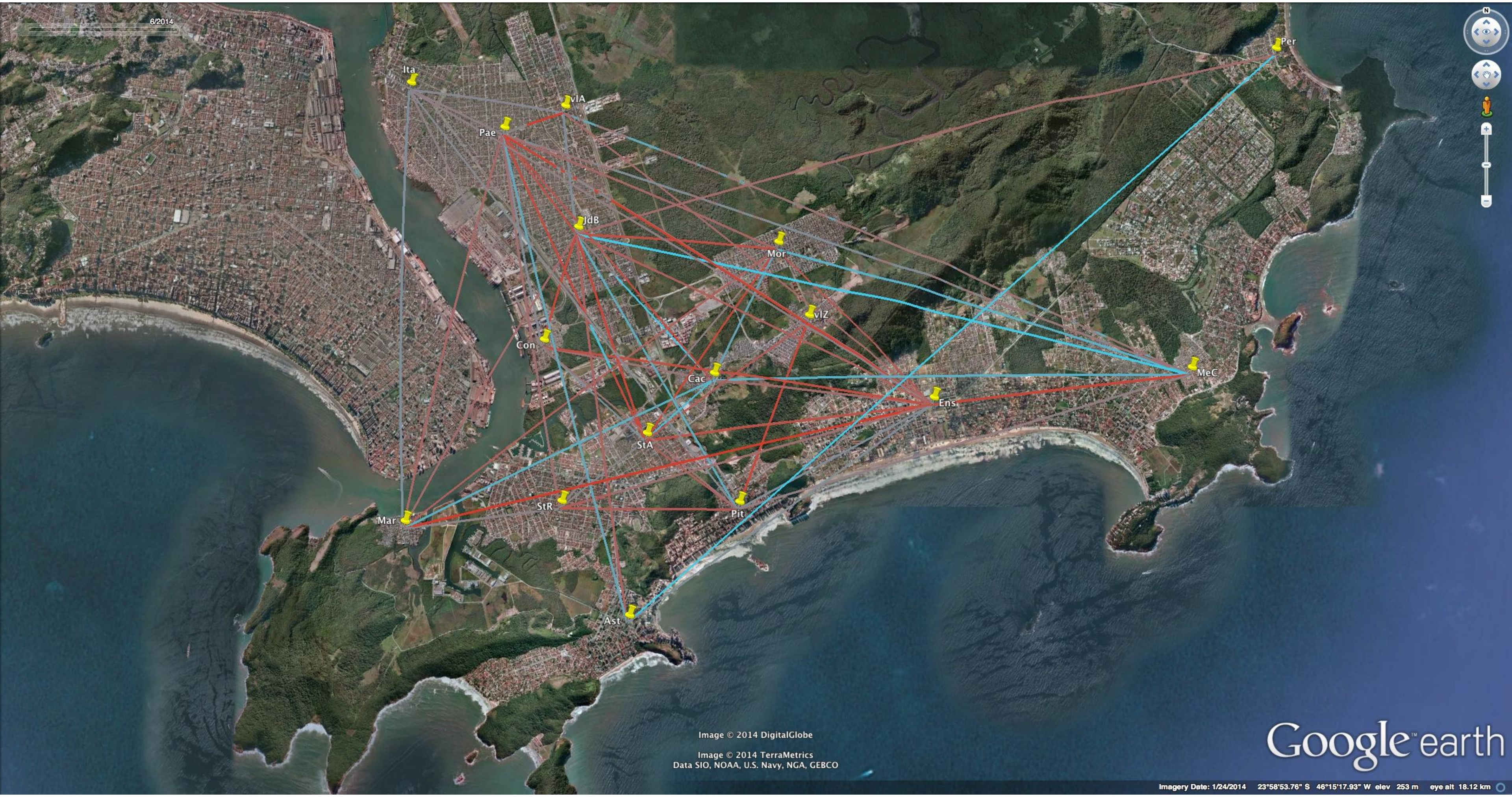

Autochthonous dengue cases reported
375
300
225
150
75
0
Weekly
January
February
March
April
May
June
Geo-Referenced dengue sampling
75
60
45
30
15
0
Weekly
January
February
March
April
May
June
15
10
5
0
Daily
January
February
March
April
May
June

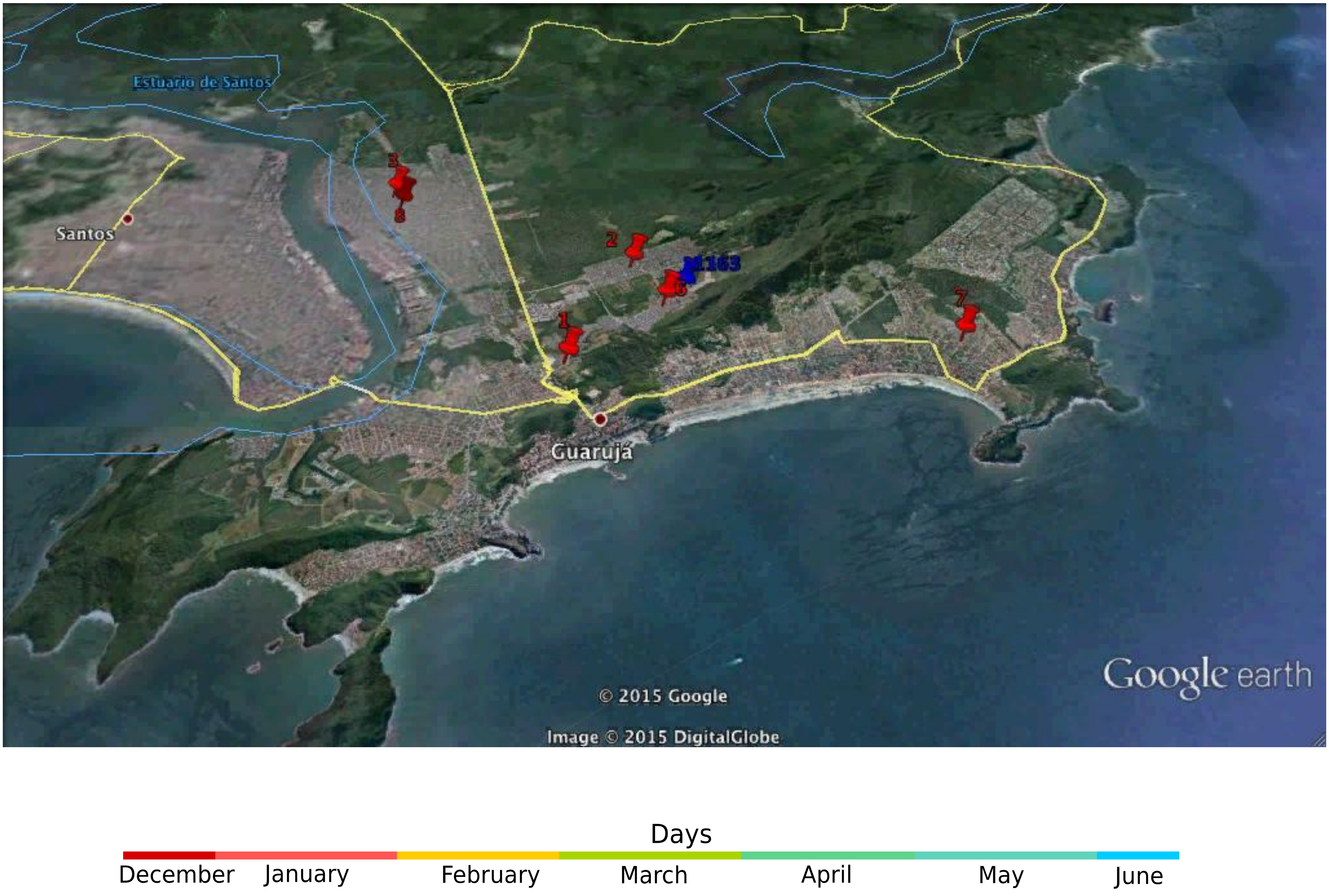

Posterior estimates of incidence
incidence
date
count
5000
4000
3000
2000
1000
0
50
100
150
5
10
15

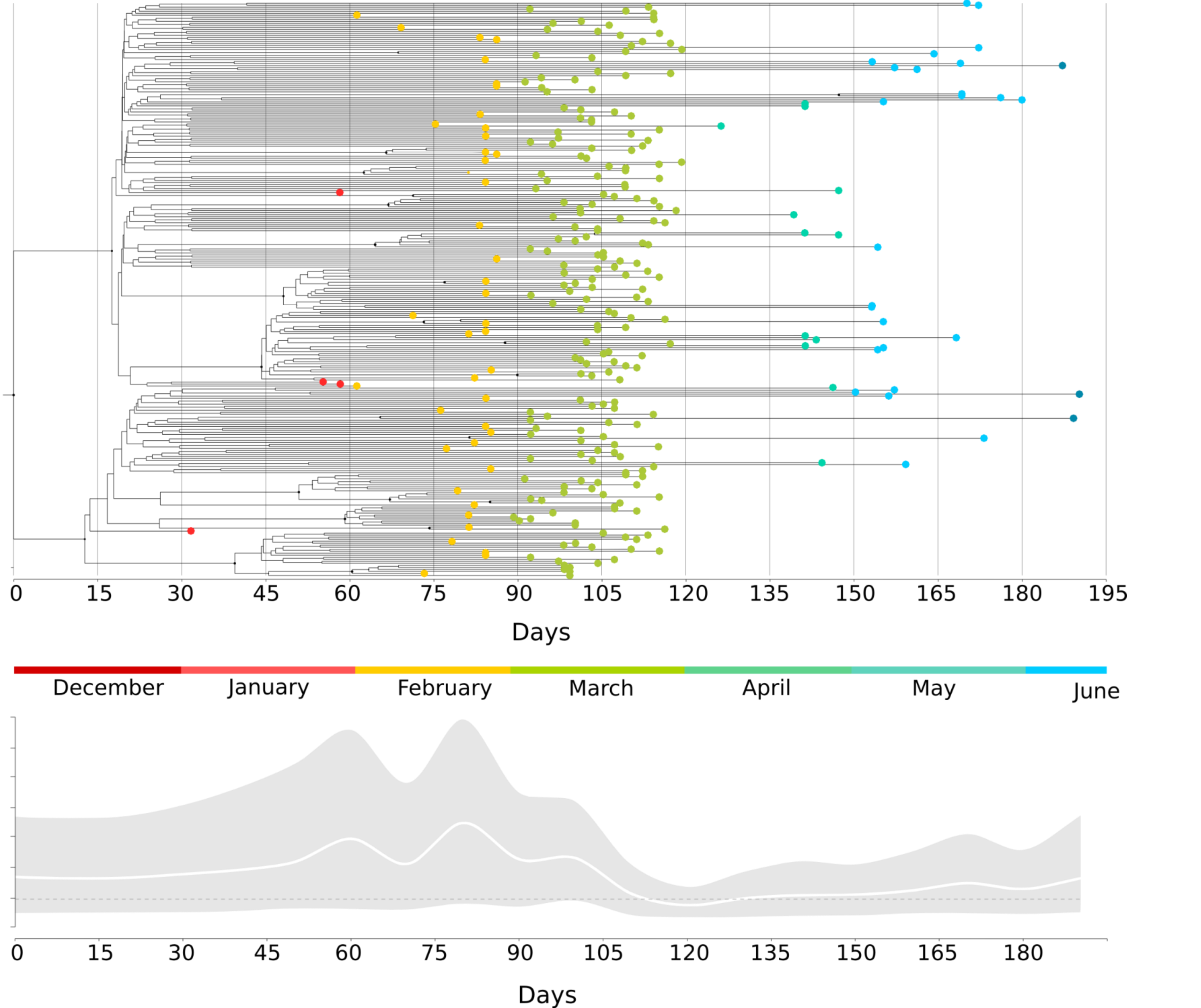

Posterior distribution of pi
density
Pi (proportion of cases sampled)
run
1
2
3
4
0.70
0.75
0.80
0.85
0.90
0
5
10

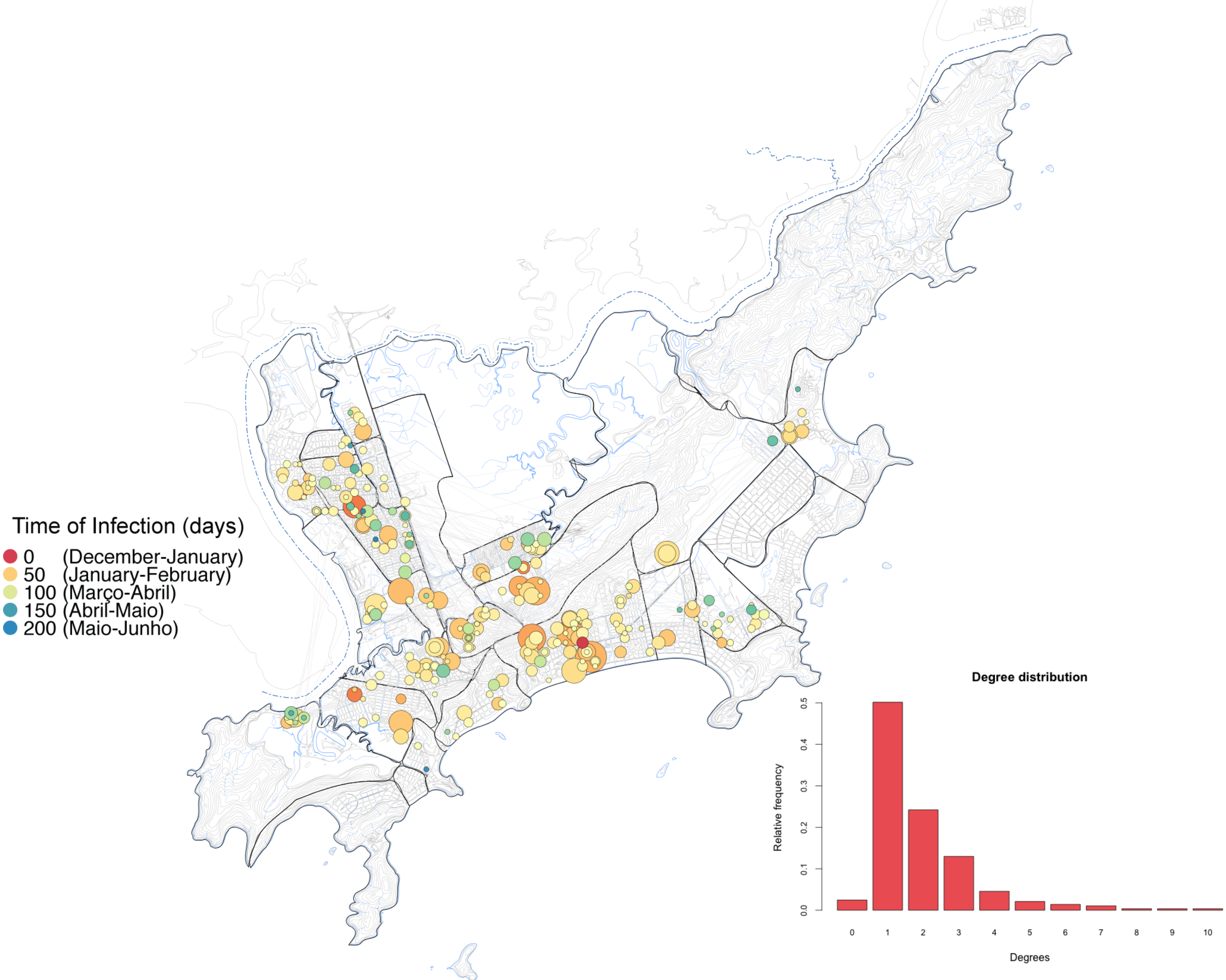
Widely dispersed “outset” of the DENV 4 Outbreak

Widely-dispersed “end” of the DENV 4 outbreak

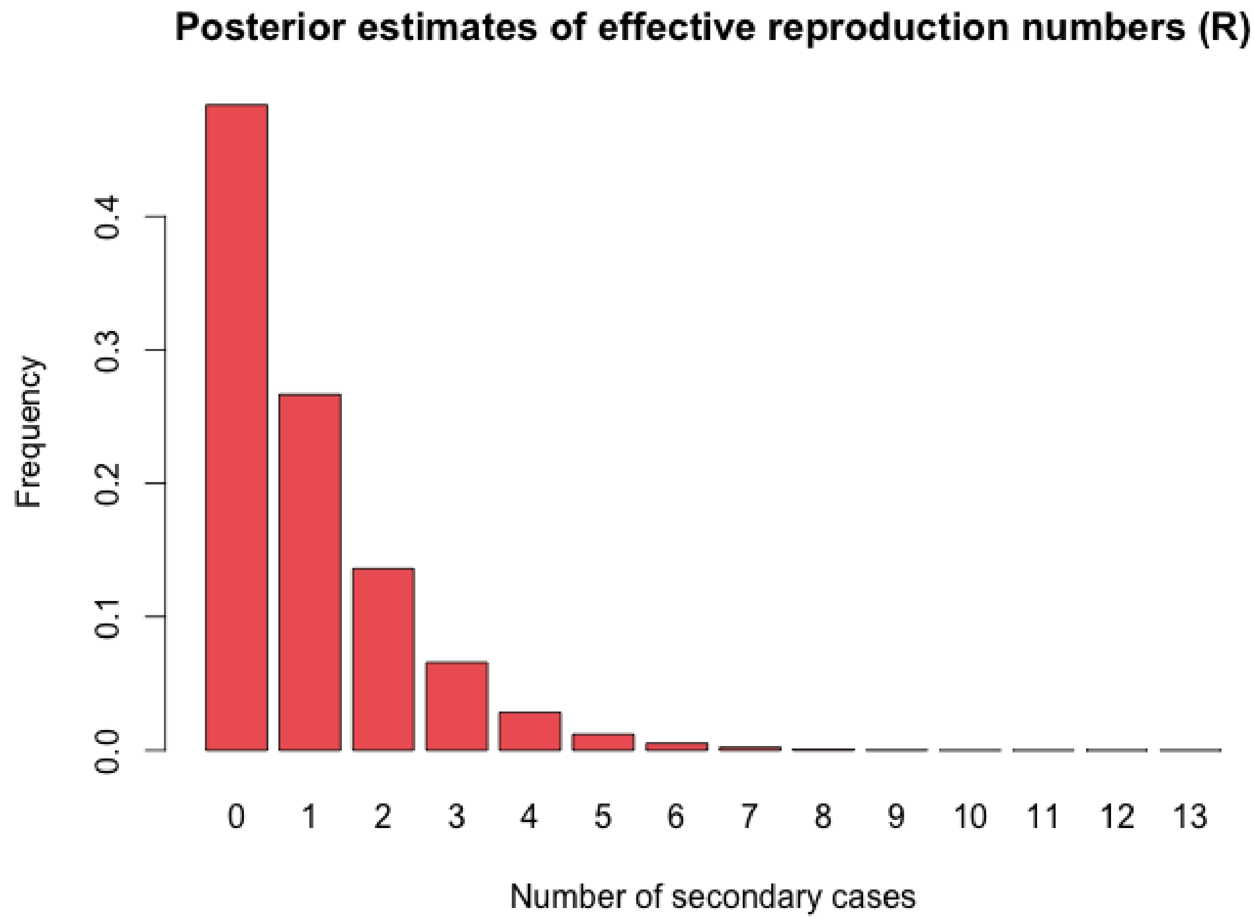



Estuario de Santos
Santos
Guarujá
3
8
2
M163
6
1
7
© 2015 Google
Image © 2015 DigitalGlobe
Google earth
Days
December
January
February
March
April
May
June

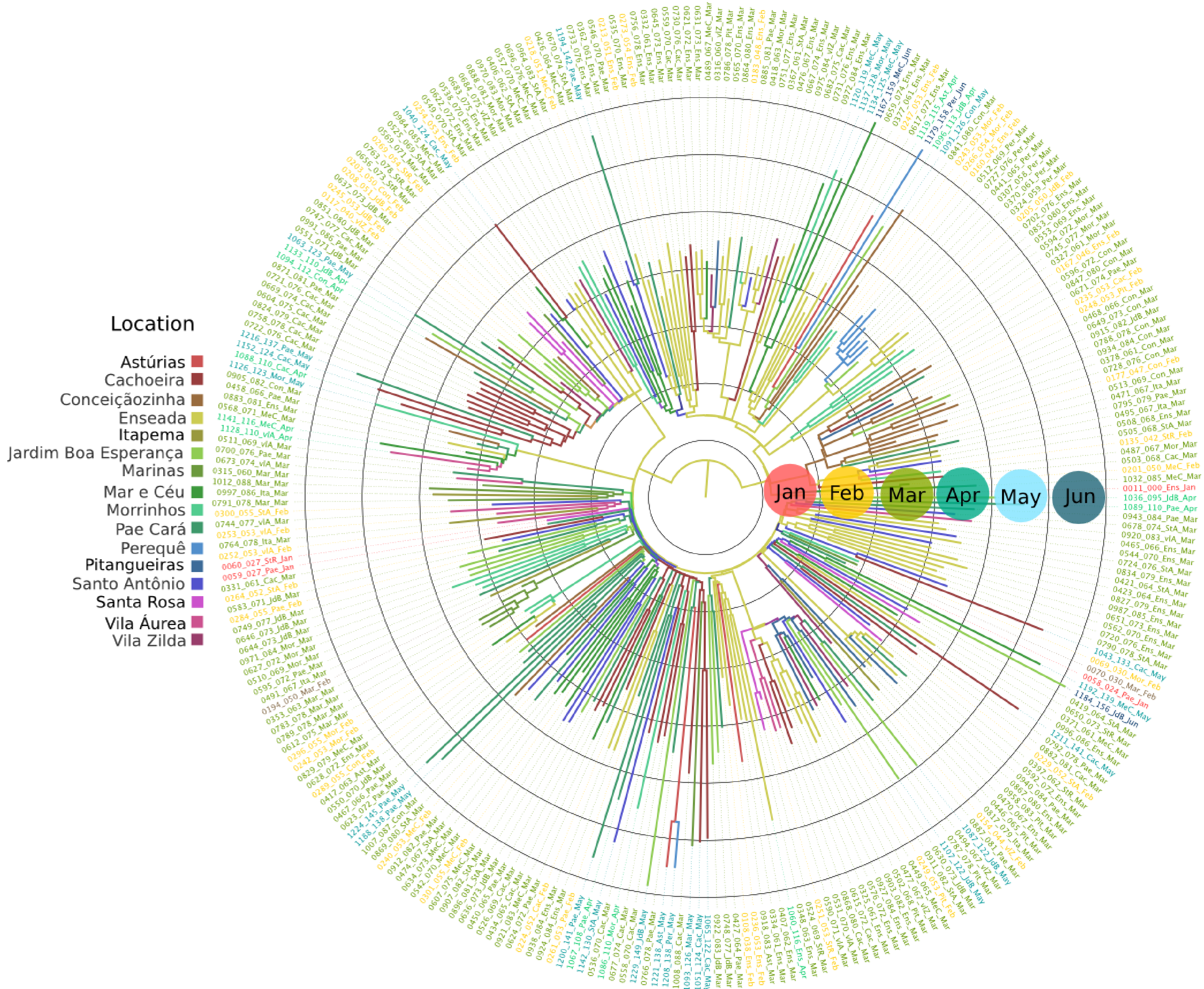

0
15
30
45
60
75
90
105
120
135
150
165
180
195
Days
December
January
February
March
April
May
June
7.0
5.0
3.0
1.0
R0
0
15
30
45
60
75
90
105
120
135
150
165
180
Days



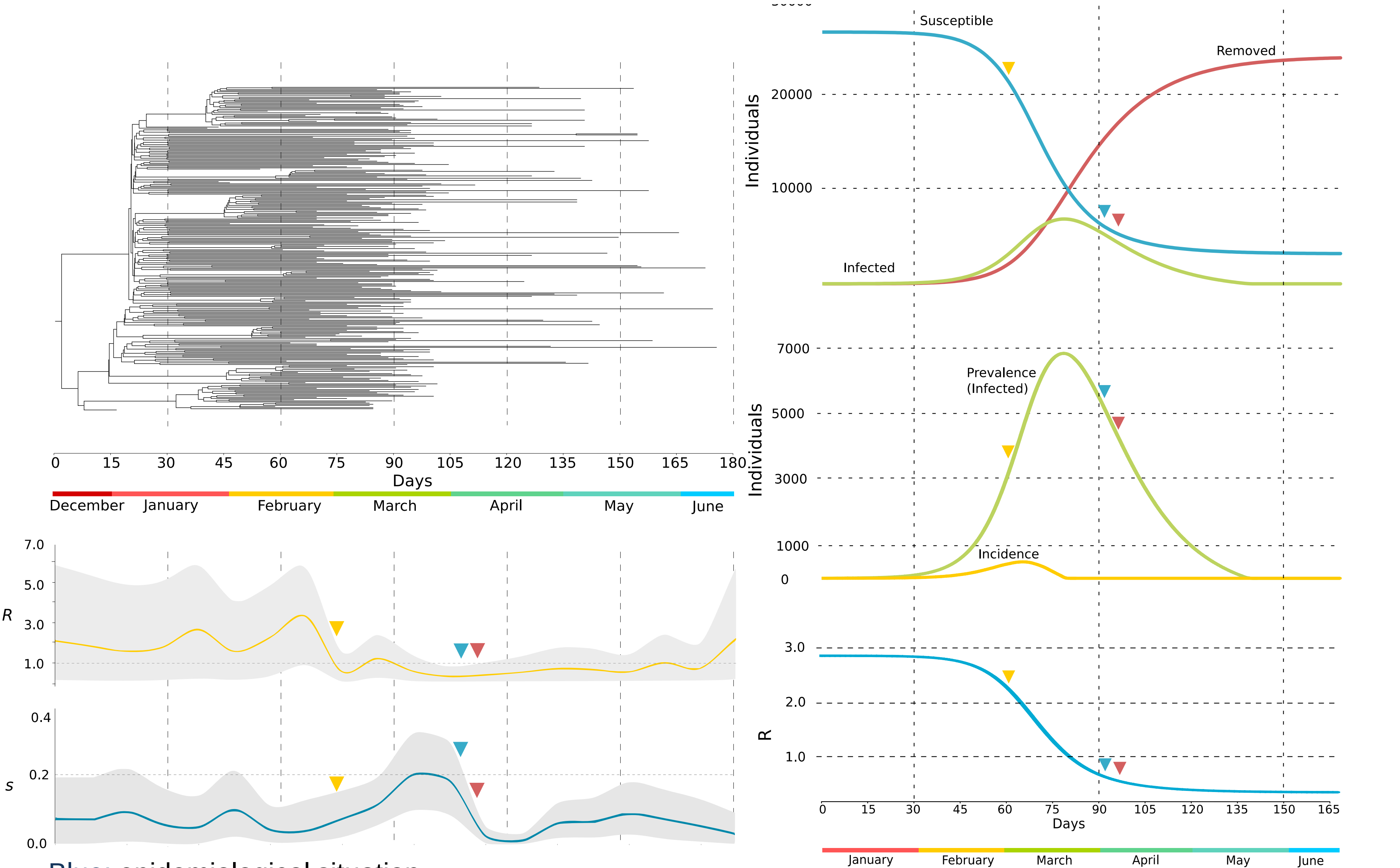
Time of Infection (days)
0 (December-January)
50 (January-February)
100 (Março-Abril)
150 (Abril-Maio)
200 (Maio-Junho)
Degree distribution
Relative frequency
0.0
0.1
0.2
0.3
0.4
0.5
0 1 2 3 4 5 6 7 8 9 10
Degrees



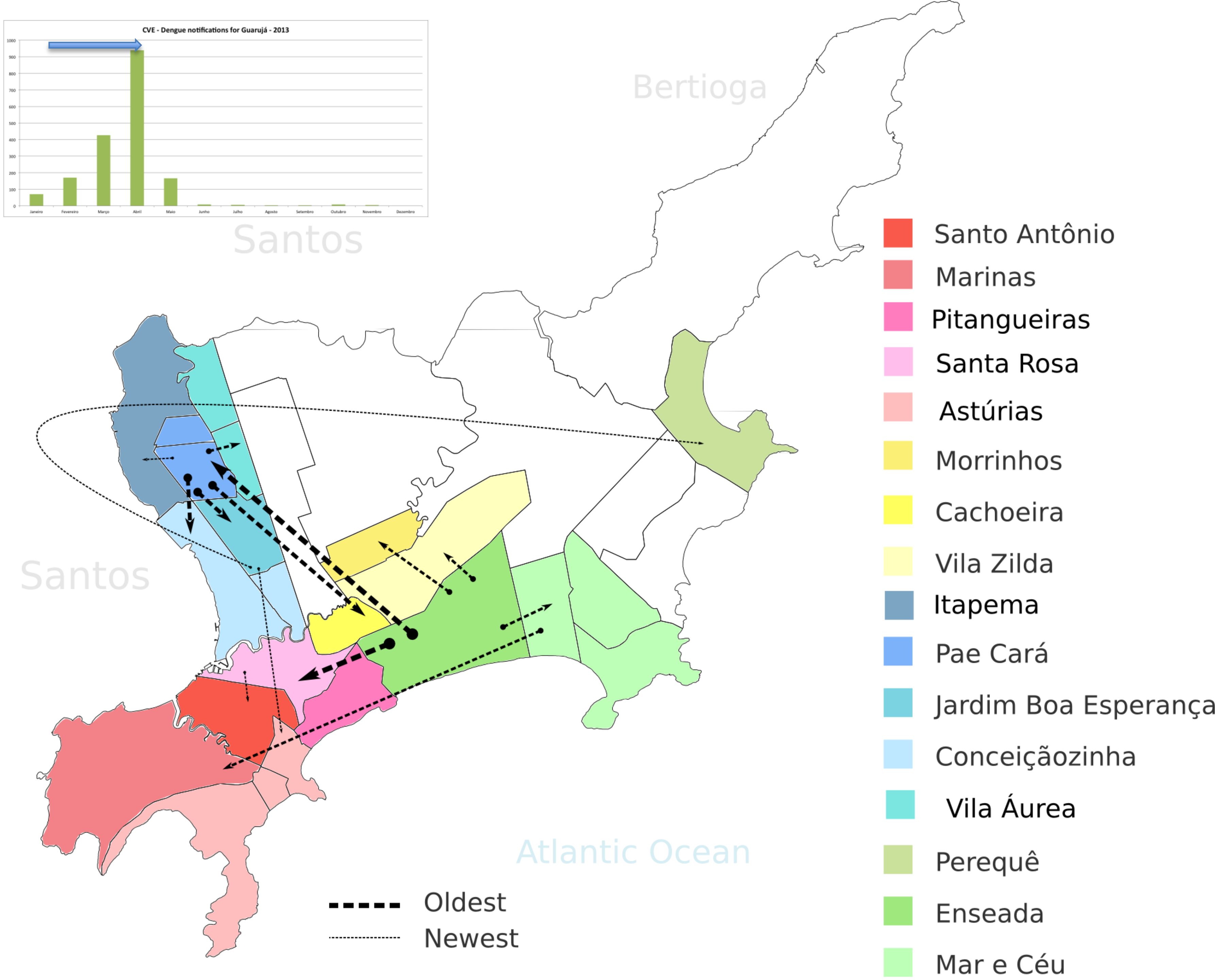
The basic reproduction number, R, is the number of secondary infections that results from a single infected human. Basic reproduction numbers estimated for dengue range between 1.33 and 11.6 (Halstead, 2008). Favier *et al.* and Massad *et al.* analyzed epidemic data from several cities in Brazil and developed values ranging from 3.8 to 5.1 and from 2.7 to 11.6, respectively.

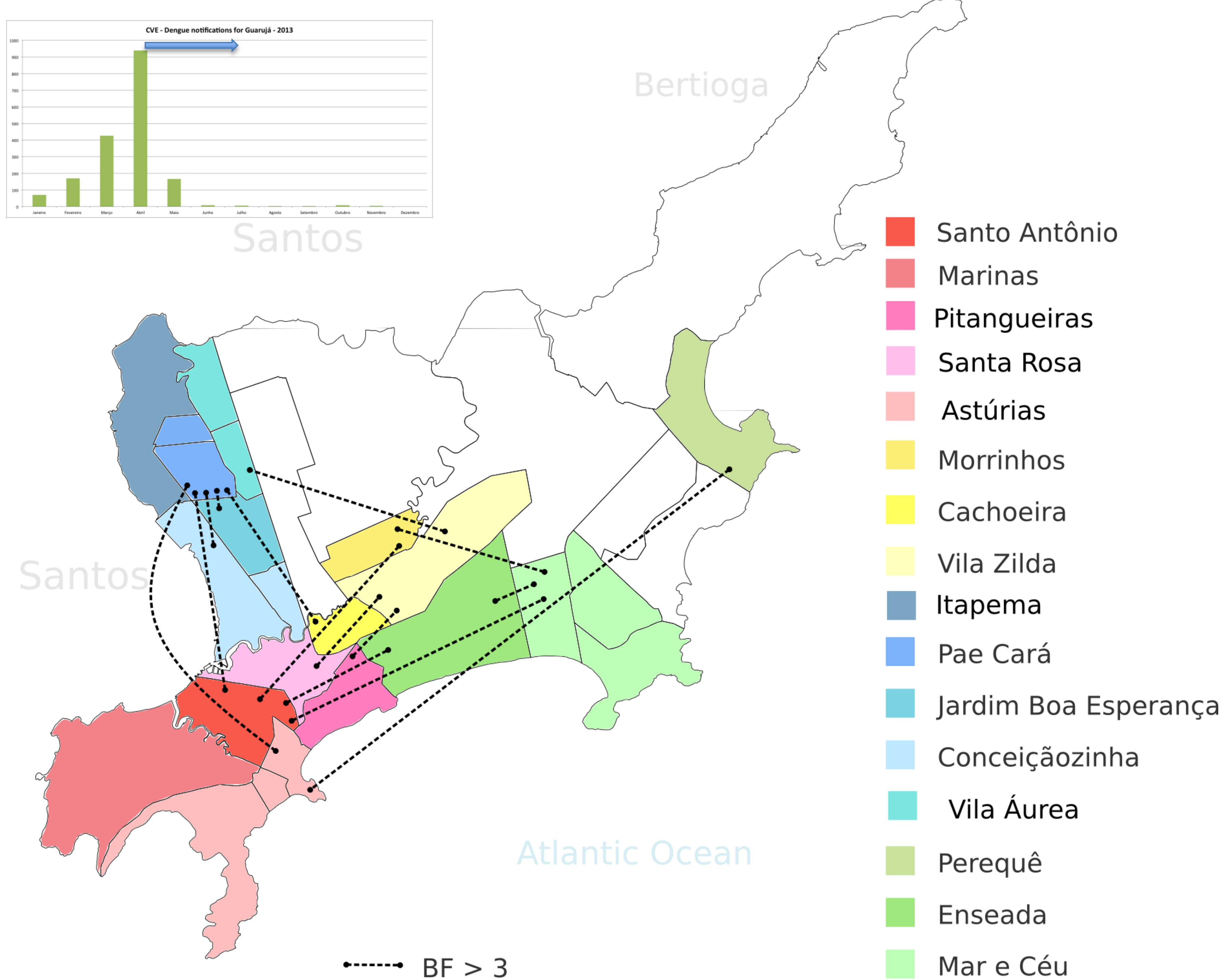

Location
Astúrias
Cachoeira
Conceiçãozinha
Enseada
Itapema
Jardim Boa Esperança
Marinas
Mar e Céu
Morrinhos
Pae Cará
Perequê
Pitangueiras
Santo Antônio
Santa Rosa
Vila Áurea
Vila Zilda
Jan
Feb
Mar
Apr
May
Jun

BDSKY, R & SP & SIR model

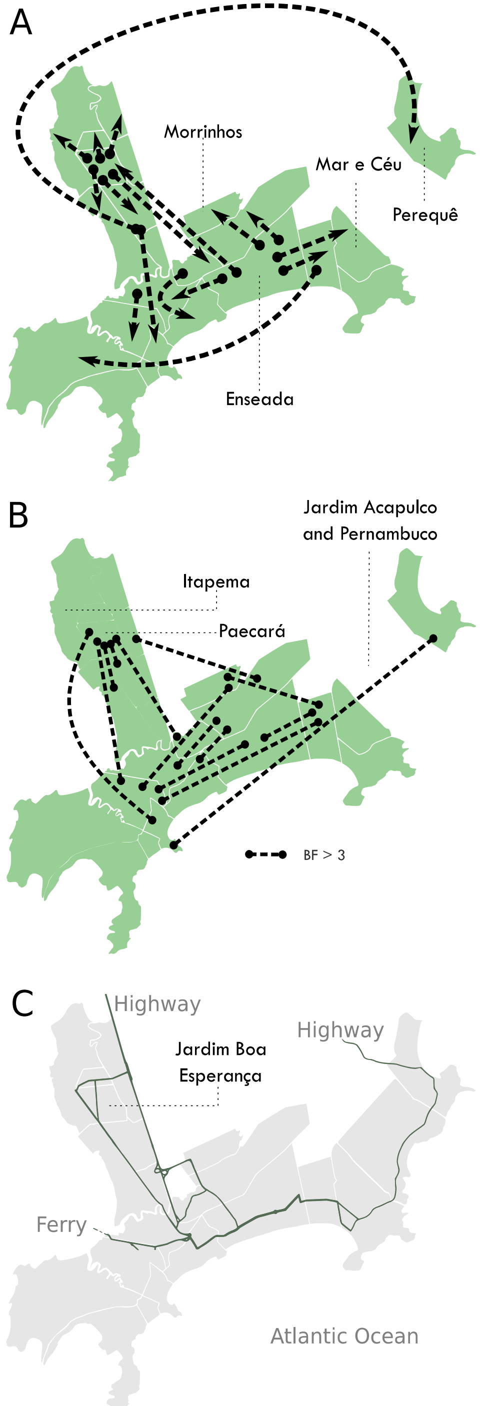


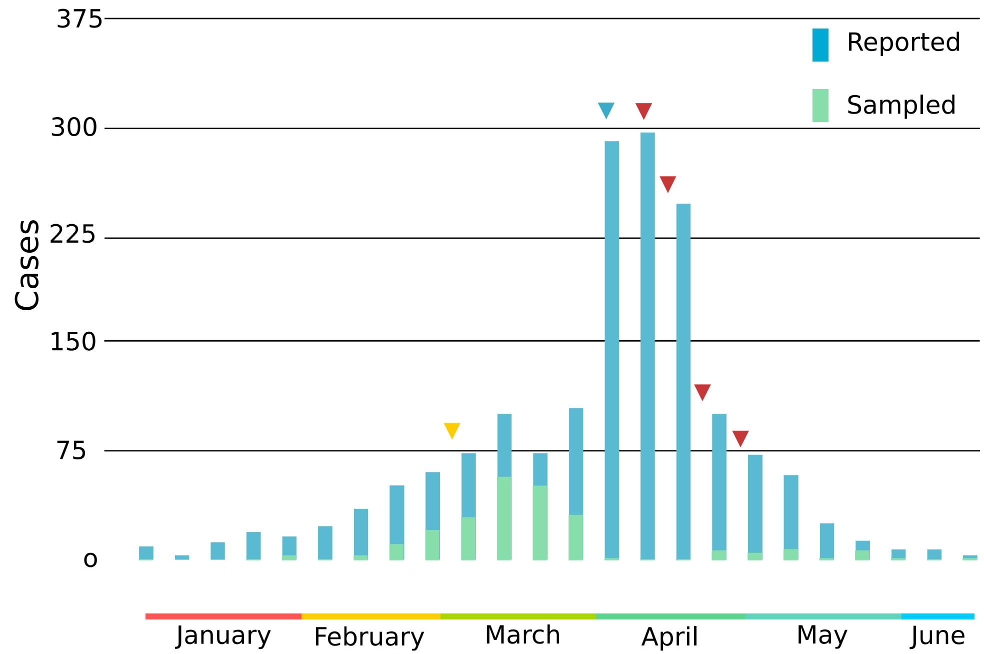
Blue: epidemiological situation.
Yellow: source reduction initiatives in shantytowns started.
Red: insecticide


CVE - Dengue notifications for Guarujá - 2013
1000
900
800
700
600
500
400
300
200
100
0
Janeiro
Fevereiro
Março
Abril
Maio
Junho
Julho
Agosto
Setembro
Outubro
Novembro
Dezembro
Bertioga
Santos
Santos
Atlantic Ocean
Santo Antônio
Marinas
Pitangueiras
Santa Rosa
Astúrias
Morrinhos
Cachoeira
Vila Zilda
Itapema
Pae Cará
Jardim Boa Esperança
Conceiçãozinha
Vila Áurea
Perequê
Enseada
Mar e Céu
Oldest
Newest



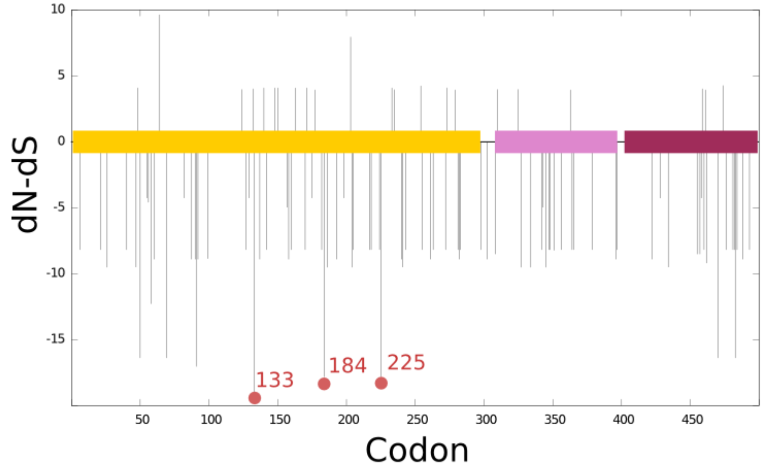
CVE - Dengue notifications for Guarujá - 2013
1000
900
800
700
600
500
400
300
200
100
0
Janeiro
Fevereiro
Março
Abril
Maio
Junho
Julho
Agosto
Setembro
Outubro
Novembro
Dezembro
Bertioga
Santos
Santos
Atlantic Ocean
Santo Antônio
Marinas
Pitangueiras
Santa Rosa
Astúrias
Morrinhos
Cachoeira
Vila Zilda
Itapema
Pae Cará
Jardim Boa Esperança
Conceiçãozinha
Vila Áurea
Perequê
Enseada
Mar e Céu
BF > 3



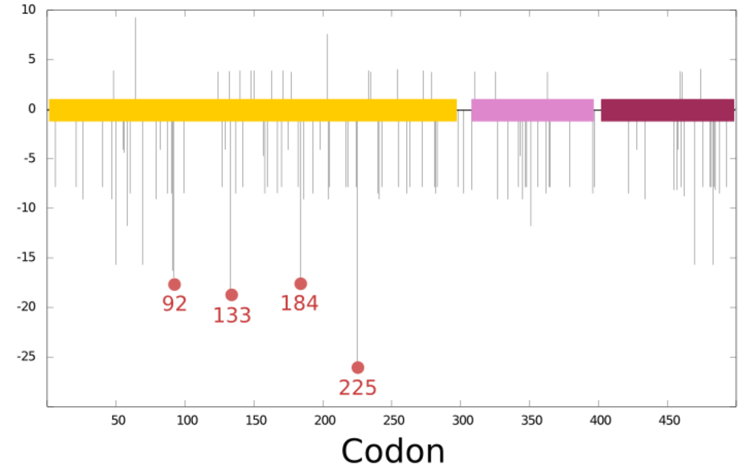


Blue: epidemiological situation.
Yellow: source reduction initiatives in shantytowns started.
Red: insecticide

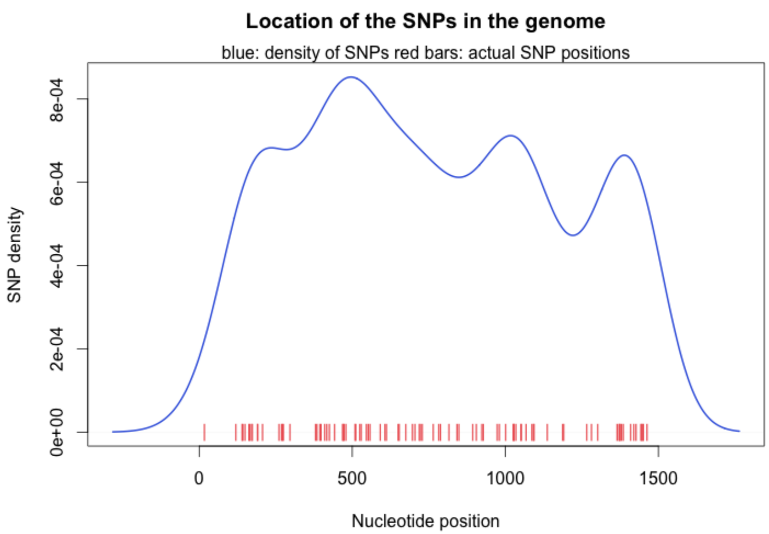
SLAC

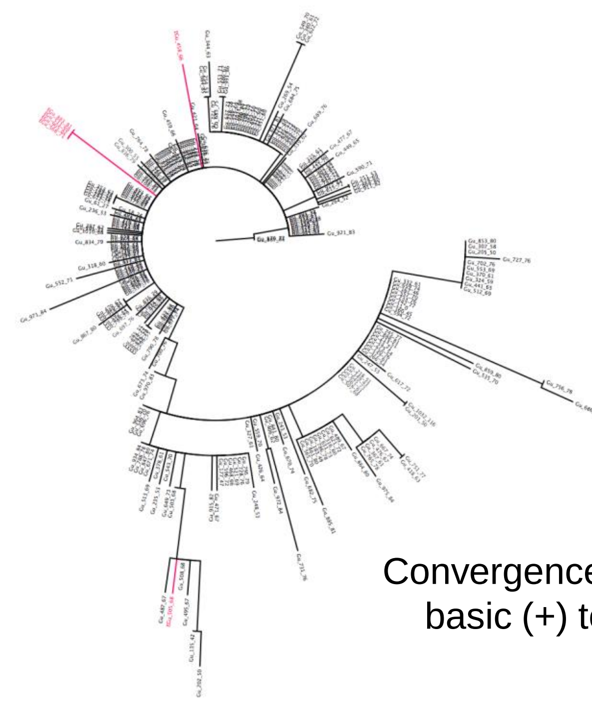


FEL

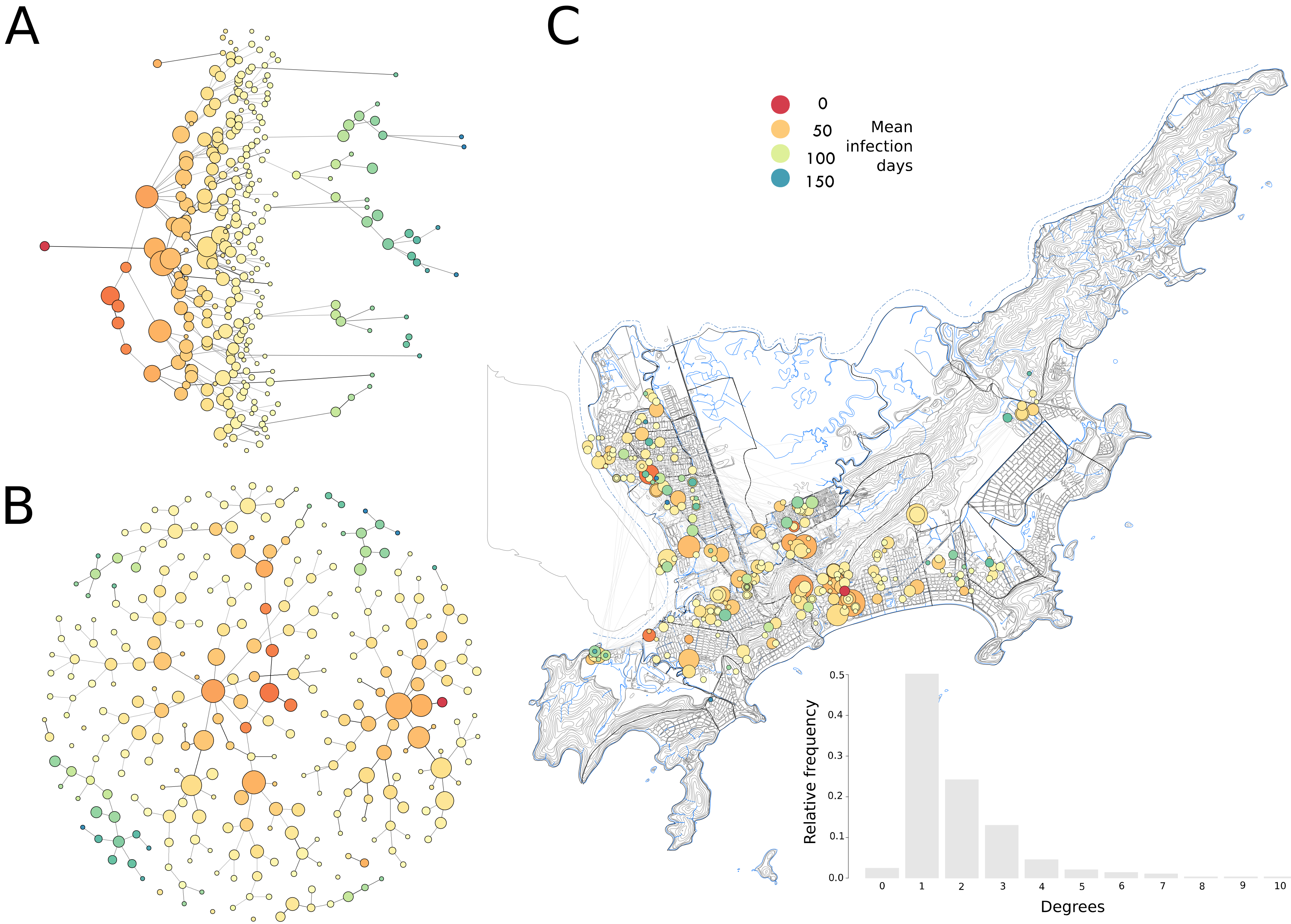


E gene domains

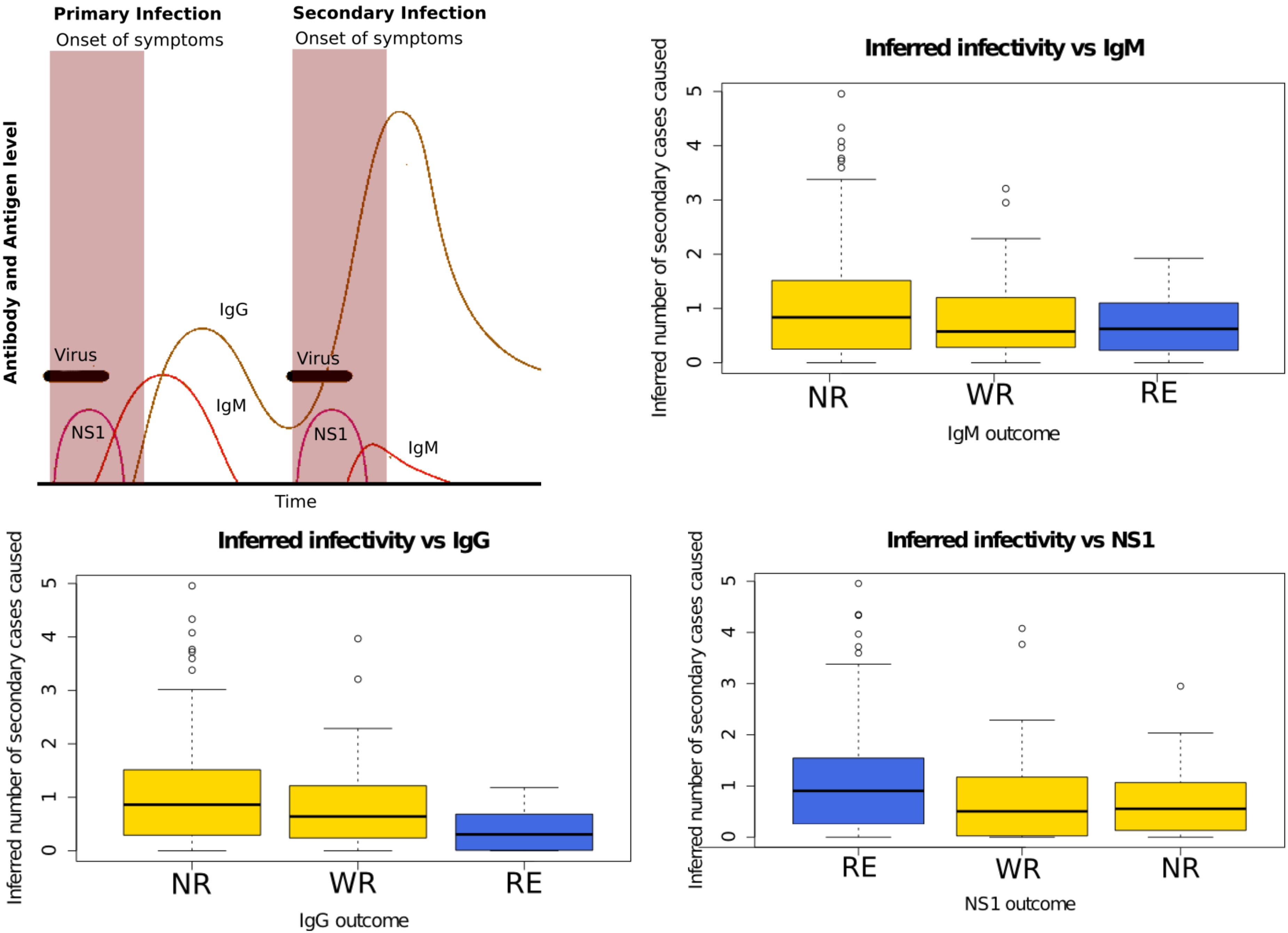


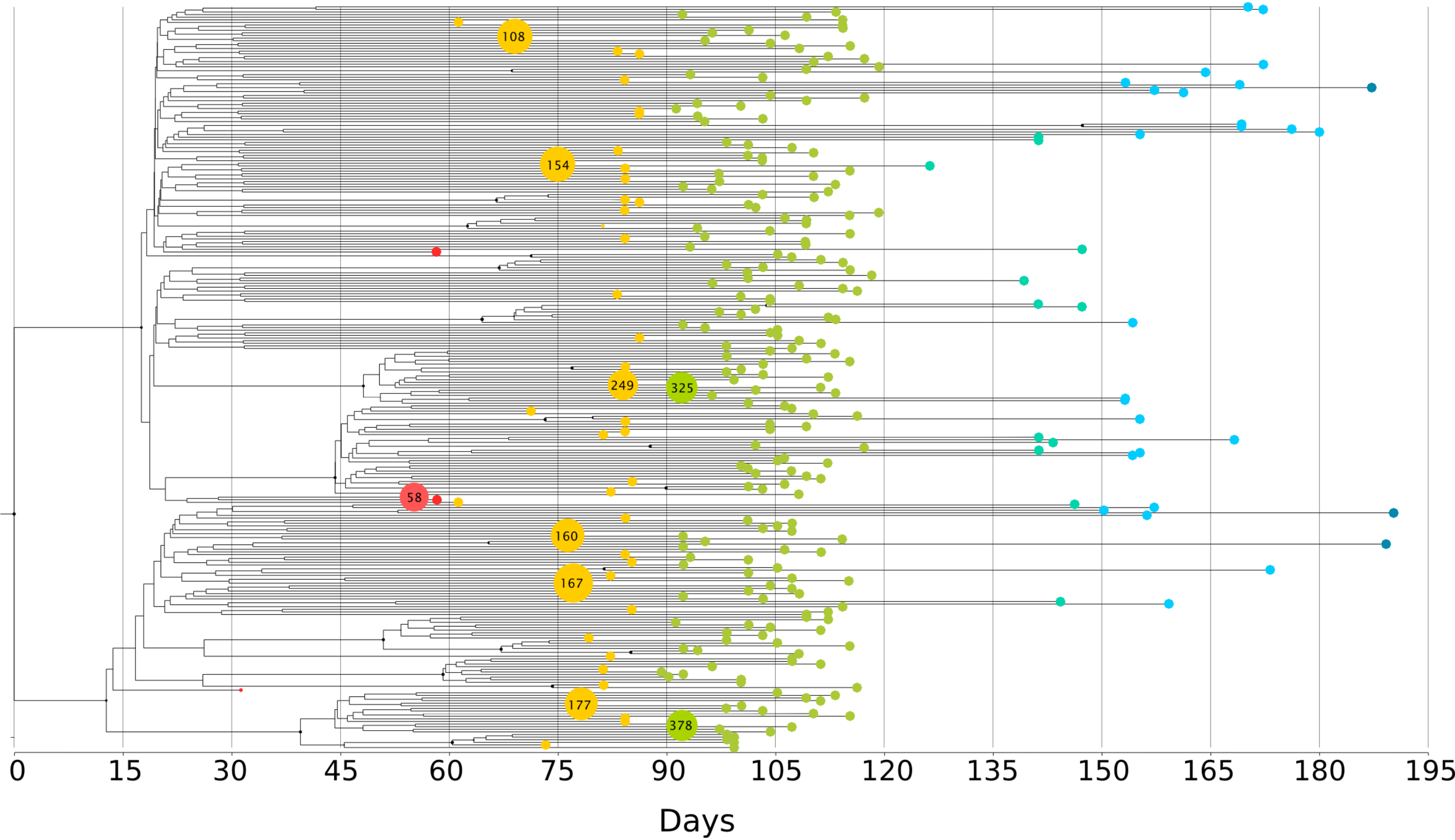


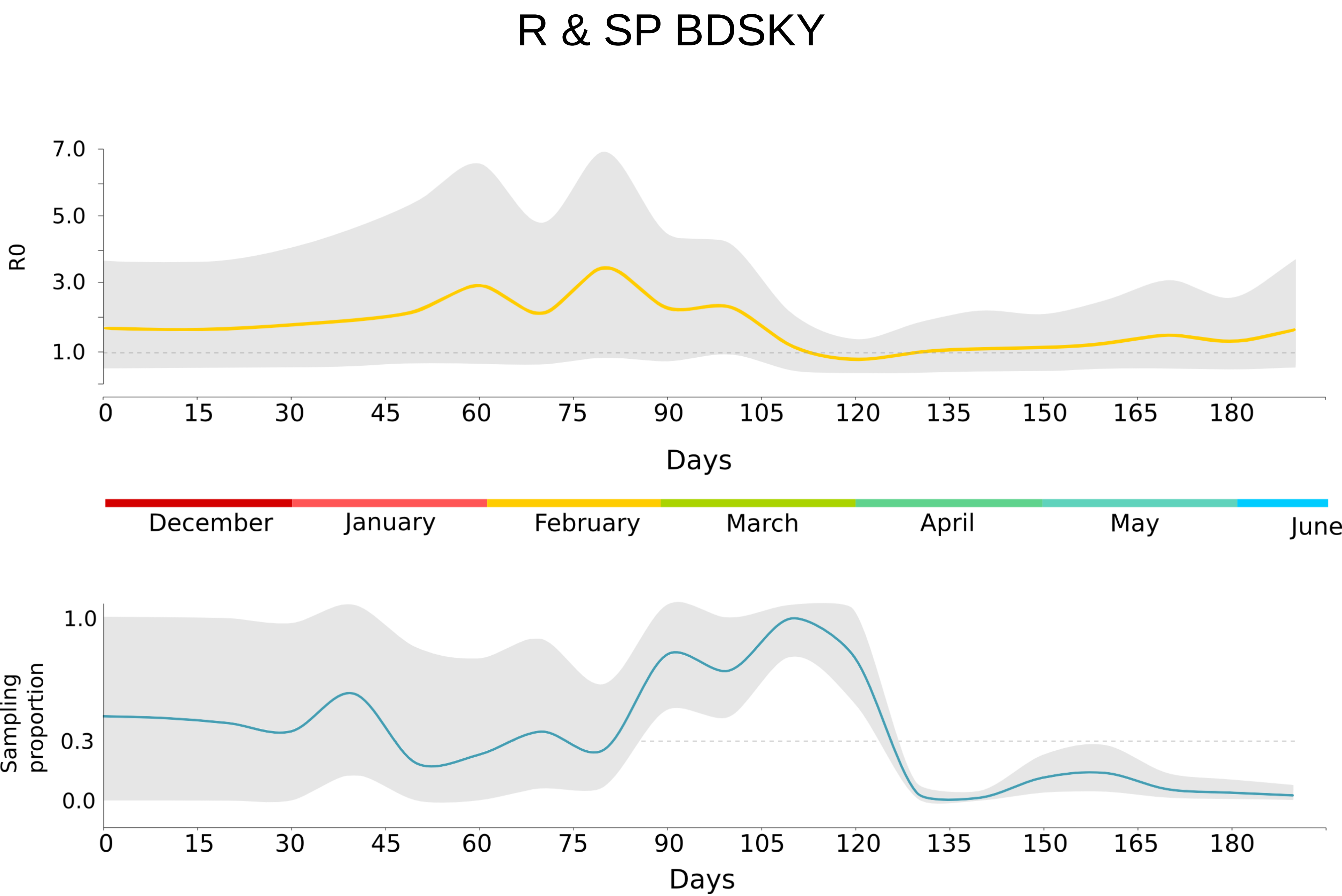
Convergence on K203E
basic (+) to acid (-)



A
B
C
0
50
100
150
Mean infection days
Relative frequency
0.0
0.1
0.2
0.3
0.4
0.5
0
1
2
3
4
5
6
7
8
9
10
Degrees

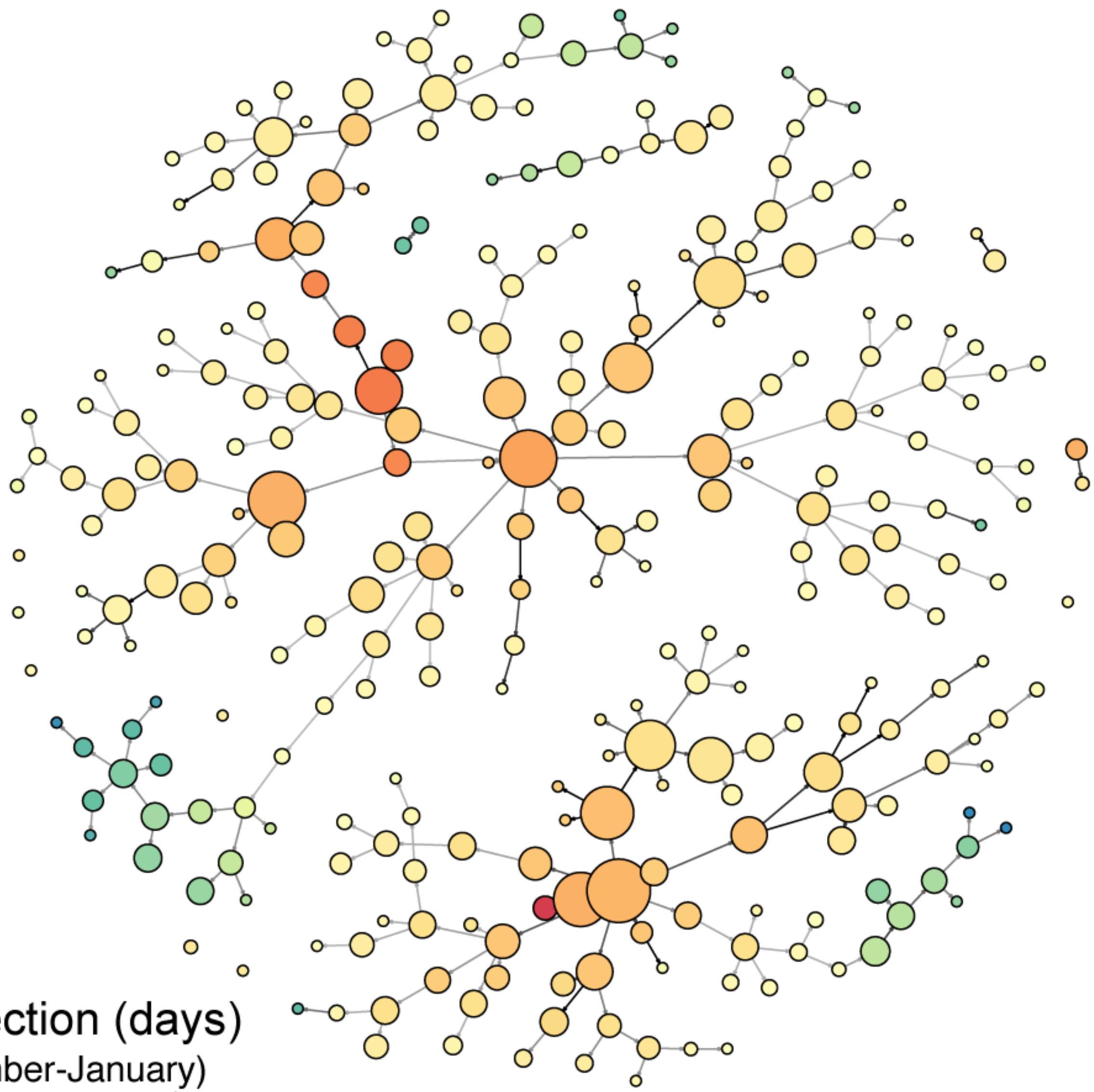

Primary Infection
Onset of symptoms
Secondary Infection
Onset of symptoms
Antibody and Antigen level
Virus
NS1
IgG
IgM
Virus
NS1
IgM
Time
Inferred infectivity vs IgM
Inferred number of secondary cases caused
0
1
2
3
4
5
NR
WR
RE
IgM outcome
Inferred infectivity vs IgG
Inferred number of secondary cases caused
0
1
2
3
4
5
NR
WR
RE
IgG outcome
Inferred infectivity vs NS1
Inferred number of secondary cases caused
0
1
2
3
4
5
RE
WR
NR
NS1 outcome


108
154
249
325
58
160
167
177
378
0
15
30
45
60
75
90
105
120
135
150
165
180
195
Days



R & SP BDSKY
R0
7.0
5.0
3.0
1.0
0
15
30
45
60
75
90
105
120
135
150
165
180
Days
December
January
February
March
April
May
June
Sampling proportion
1.0
0.3
0.0
0
15
30
45
60
75
90
105
120
135
150
165
180
Days

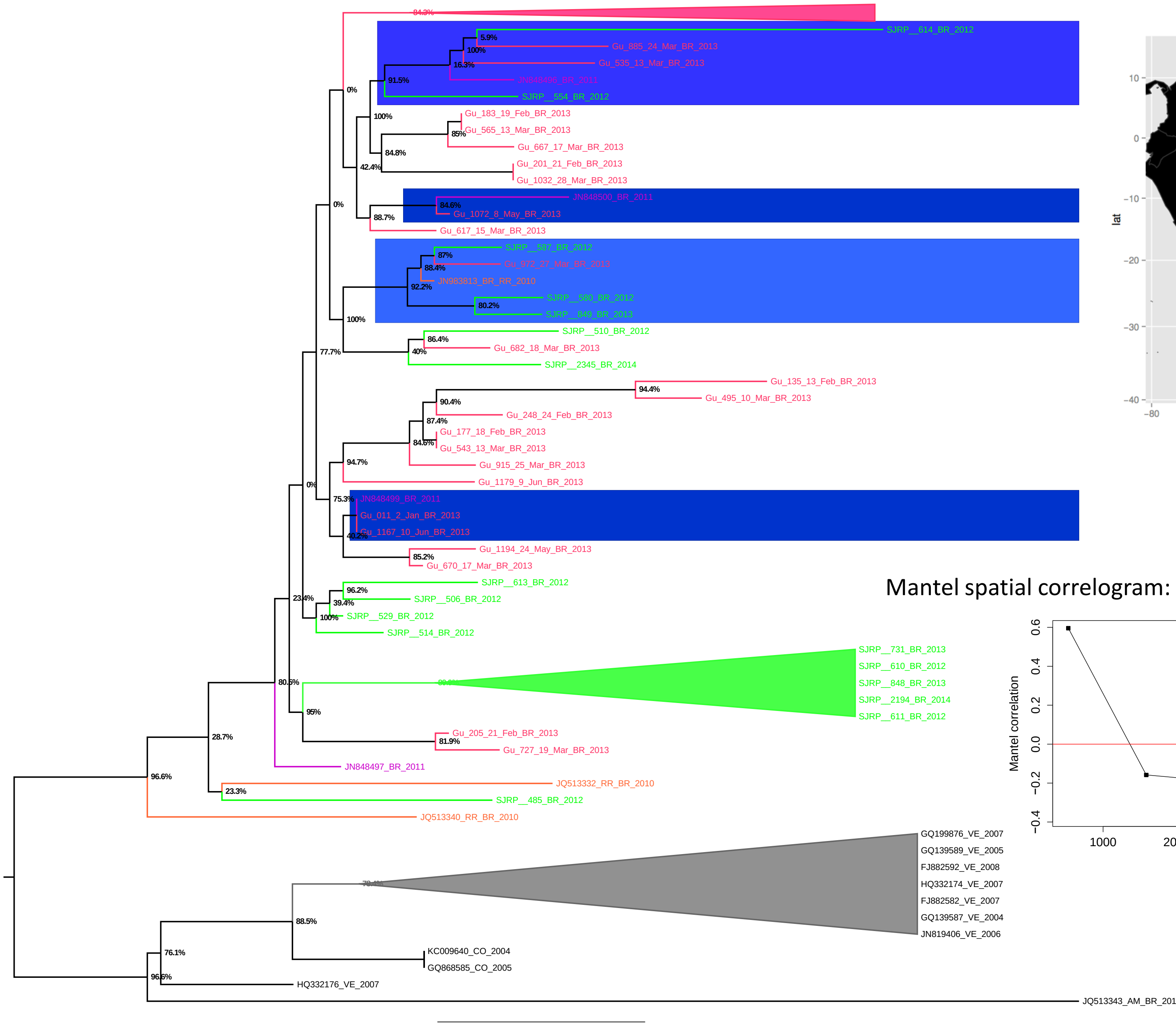
DENV4 - Transmission Network

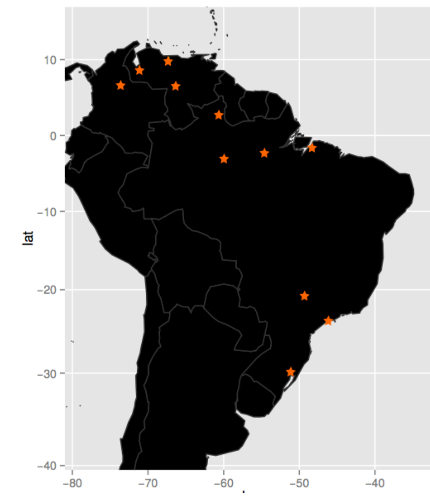


Time of Infection (days)

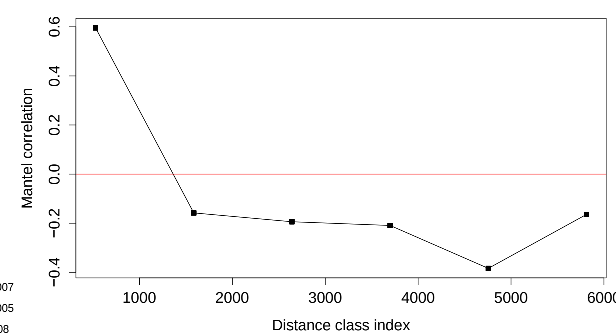
- 0 (December-January)
- 50 (January-February)
- 100 (Março-Abril)
- 150 (Abril-Maio)
- 200 (Maio-Junho)

Detecting wide & fast spatial DENV dispersal

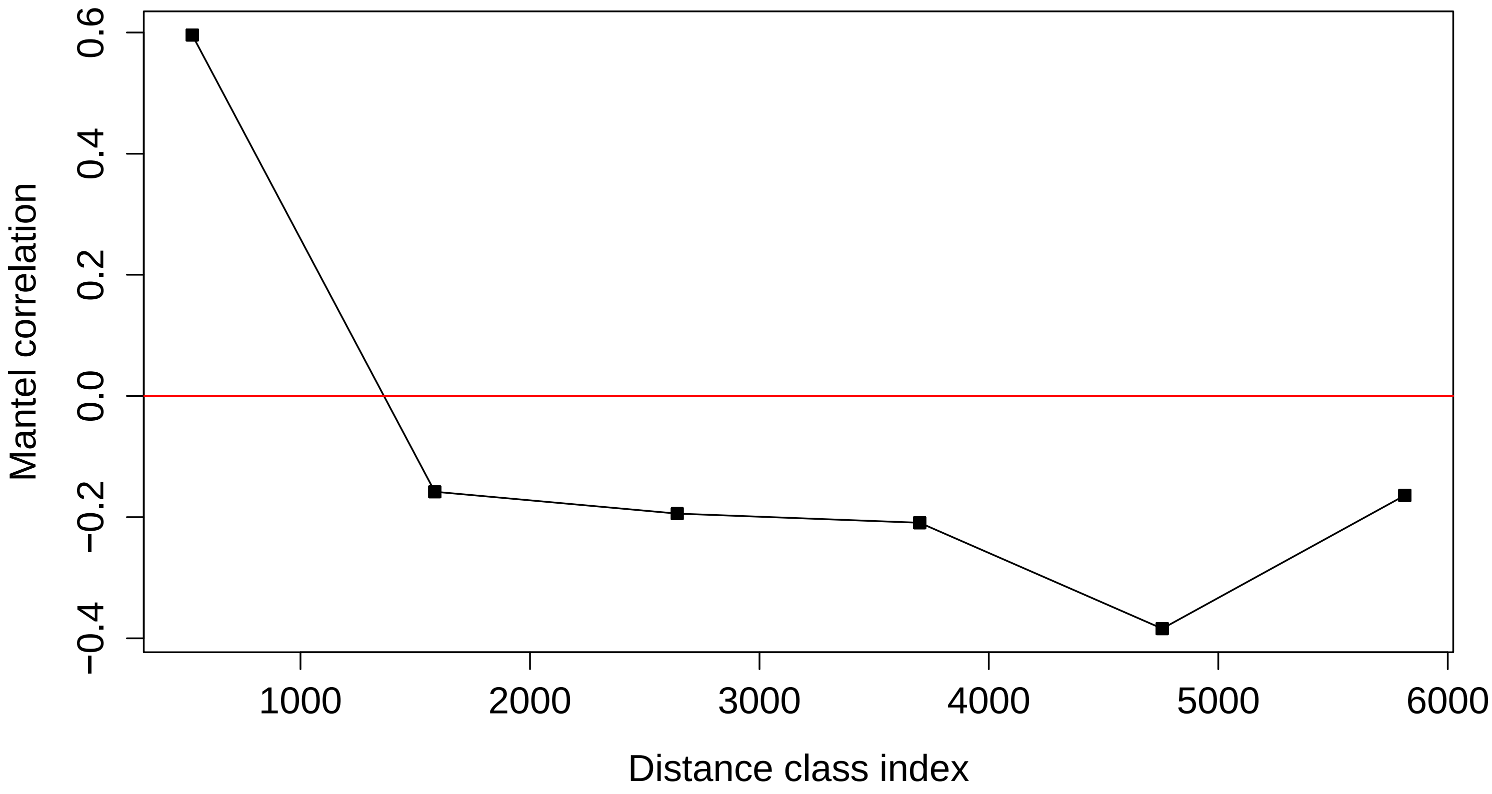




Mantel spatial correlogram: *patristic* vs *geographic* distances



Mantel spatial correlogram: *patristic* vs *geographic* distances



Based on Carrel *et al.*, 2010

Conclusions

- Phylodynamics of DENV works! *i.e.*, E gene good maker, stable rates of change, stable nucleotide composition, no significant recombination systematic error.
- We need to incorporate viral genealogy & patient data to better understand the evolution of an outbreak.
- Real time follow-up of dengue outbreaks can be useful for control: Guarujá stands as a proof of concept.
- "Where there is no overlap there is gap" – Mark Miller, MD.

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