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Recent Yellow Fever Epidemics in Brazil: Evolving Challenges

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INI/FIOCRUZ

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Outline

1. Yellow fever in Brazil

- a) Historical remarks
- b) Control efforts in the early 20th century
- c) Recent epidemiology and strategies
 - a) Decision to restrict vaccination areas

2. Recent (?current) outbreak

- a) Expansion of geographical area
- b) Challenges for clinical management
- c) Therapeutic strategies

3. Vaccine shortage and fractional-dose vaccination

- 1. Current knowledge
- 2. Outstanding issues



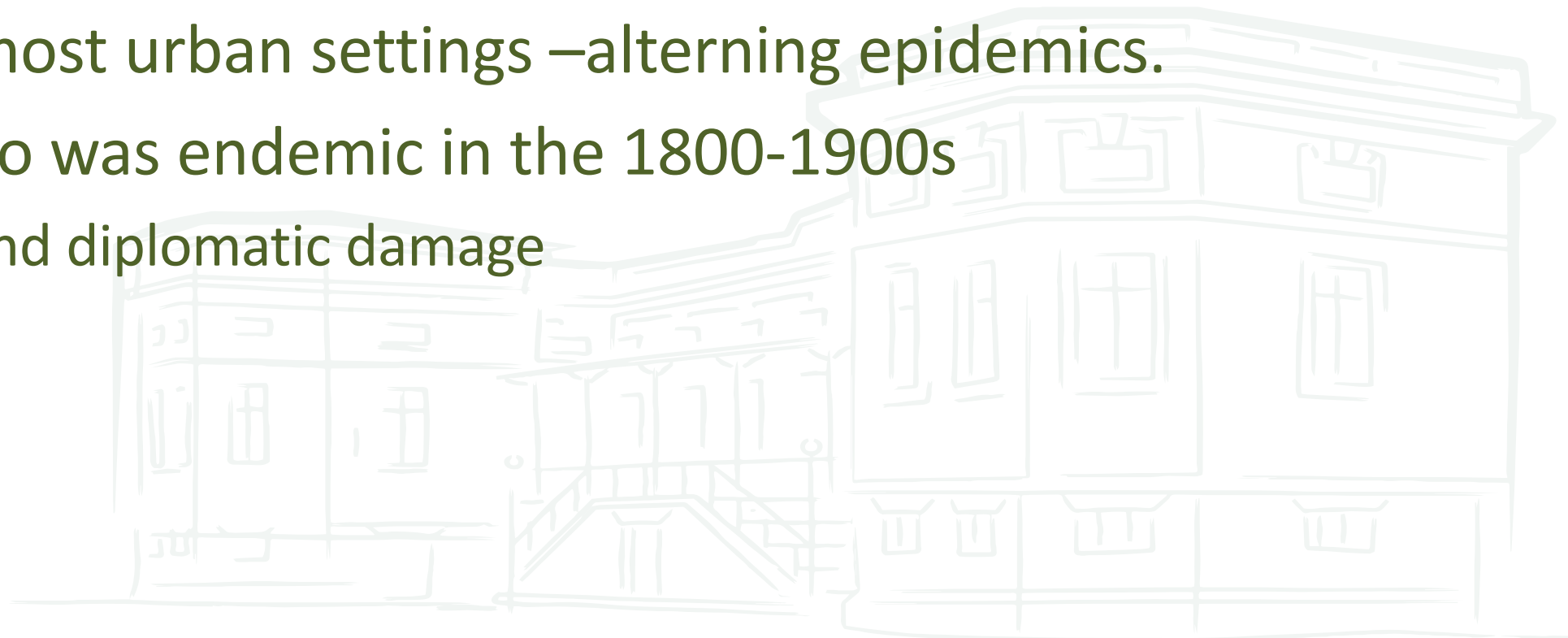
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Yellow Fever in Brazil

- First outbreak in Recife, 1685 followed by Salvador
 - 150 “silence”
- Endemic in most urban settings –alternating epidemics.
- Rio de Janeiro was endemic in the 1800-1900s
 - Economic and diplomatic damage





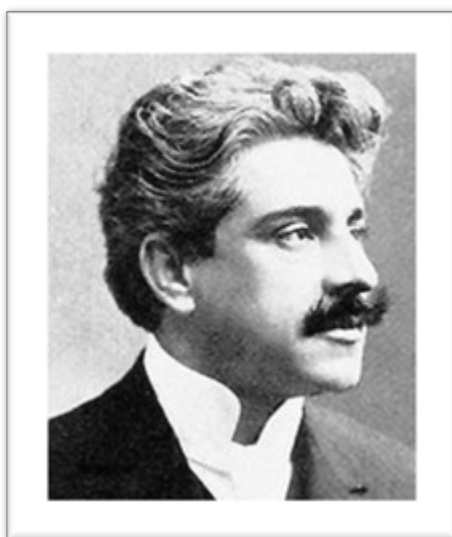
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Initial Control Efforts





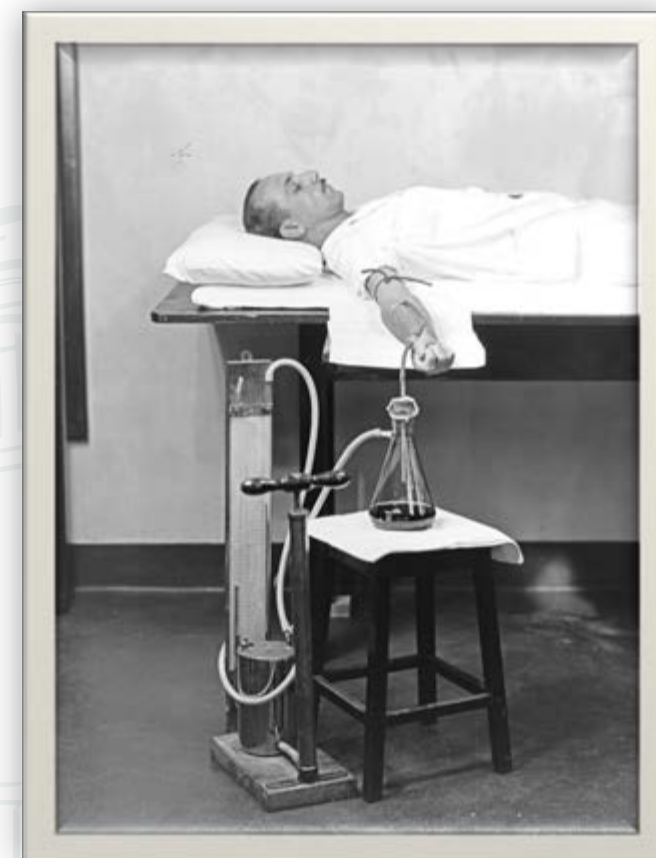
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Initial Control Efforts





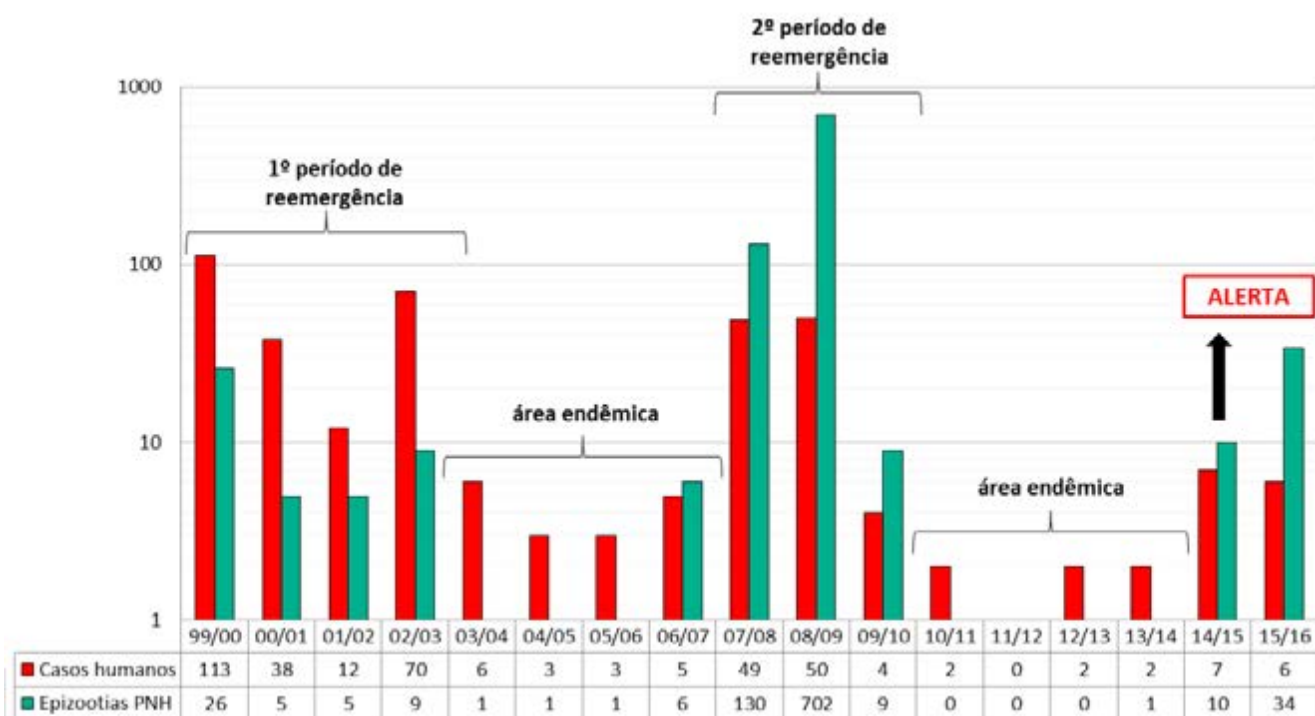
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Recent (pre-2016) epidemiology and control





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Recommended areas for vaccination

ARTICLES

Articles

Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases

Pedro F C Vasconcelos, Expedito J Luna, Ricardo Galler, Luiz J Silva, Terezinha L Coimbra, Vera L R S Barros, Thomas P Monath, Sueli G Rodrigues, Cristina Laval, Zouralde G Costa, Maria F G Vilela, Cecília L S Santos, Cristina M O Papaioordanou, Venancio A F Alves, Liliãna D Andrade, Helena K Sato, Elisabeth S T Rosa, Gustavo B Froguas, Ethel Lacava, Leda M R Almeida, Ana C R Cruz, Iray M Rocco, Raimunda T M Santos, Otávio F P Oliva, and the Brazilian Yellow Fever Vaccine Evaluation Group*

Summary

Background The yellow fever vaccine is regarded as one of the safest attenuated virus vaccines, with few side-effects or adverse events. We report the occurrence of two fatal cases of haemorrhagic fever associated with yellow fever 17DD substrain vaccine in Brazil.

Methods We obtained epidemiological, serological, virological, pathological, immunocytochemical, and molecular biological data on the two cases to determine the cause of the illnesses.

Findings The first case, in a 5-year-old white girl, was characterised by sudden onset of fever accompanied by

in case 1 and positive in case 2; similar tests for dengue, hantaviruses, arenaviruses, *Leptospira*, and hepatitis viruses A–D were negative. Tissue injuries from both patients were typical of wild-type yellow fever.

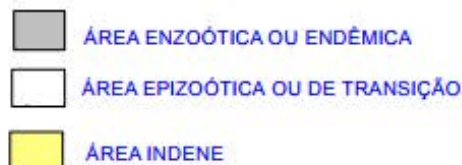
Interpretation These serious and hitherto unknown complications of yellow fever vaccination are extremely rare, but the safety of yellow fever 17DD vaccine needs to be reviewed. Host factors, probably idiosyncratic reactions, might have had a substantial contributed to the unexpected outcome.

Lancet 2001; **358**: 91–97
See Commentary page 84

1998



Fonte: MS/FNS





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Rev Saúde Pública 2010;44(3)

Comments

Pedro Luiz Taail

Critical aspects of yellow fever control in Brazil

1. Recommendations for vaccination only after cases and deaths have been recorded in such areas should be avoided; 2. The risk of urban transmission of the disease needs to be reduced, given the immense dispersion of *Ae. aegypti* and *Ae. albopictus* and the recent episode that occurred in Paraguay; 3. The worldwide scarcity of vaccine that could be used for urgent vaccination of populations in large urban centers if a disease outbreak occurred, either transmitted by *Ae. aegypti*, or resulting from a wild cycle on the periphery of these centers; 4. The difficulty in achieving timely vaccination (ten

days before traveling) among tourists and migrants to areas with virus circulation; 5. Occurrences of serious adverse events associated with the vaccine have mainly been registered at the time of implementing vaccination in situations when thousands of people make demands on vaccination units within a short space of time and contraindications are often not respected; 6. The risk of adverse events is often greater among people receiving the vaccine for the first time than among revaccinated individuals, and this is the situation of the vast majority of people living in areas that are not considered endemic. Initially, the vaccine should be included in the child immunization calendar throughout the country and should be applied to people living in and visitors to areas that are characterized as receptive to transmission of the wild cycle of the disease, even if these areas have been silent for many years.



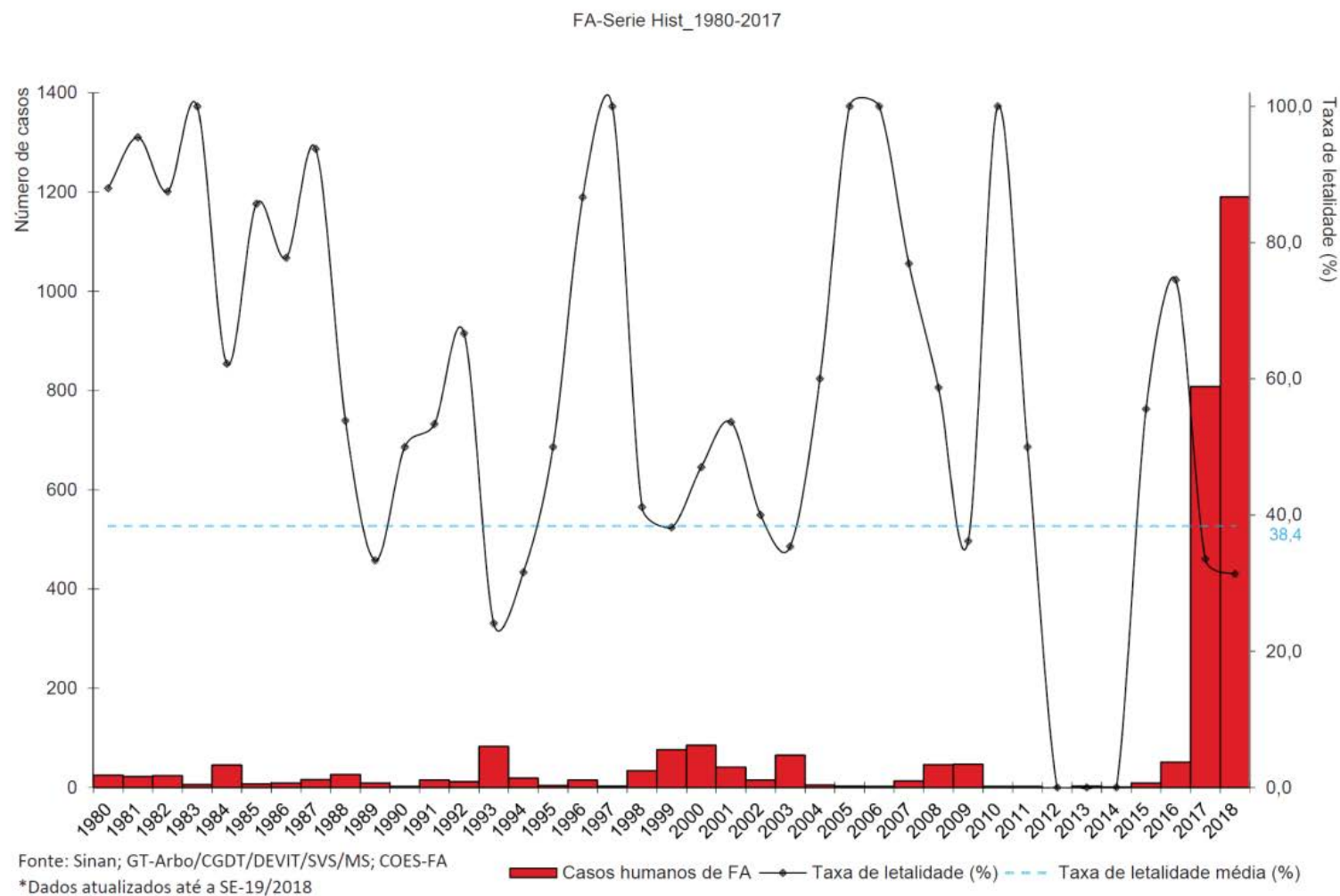
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Current scenario





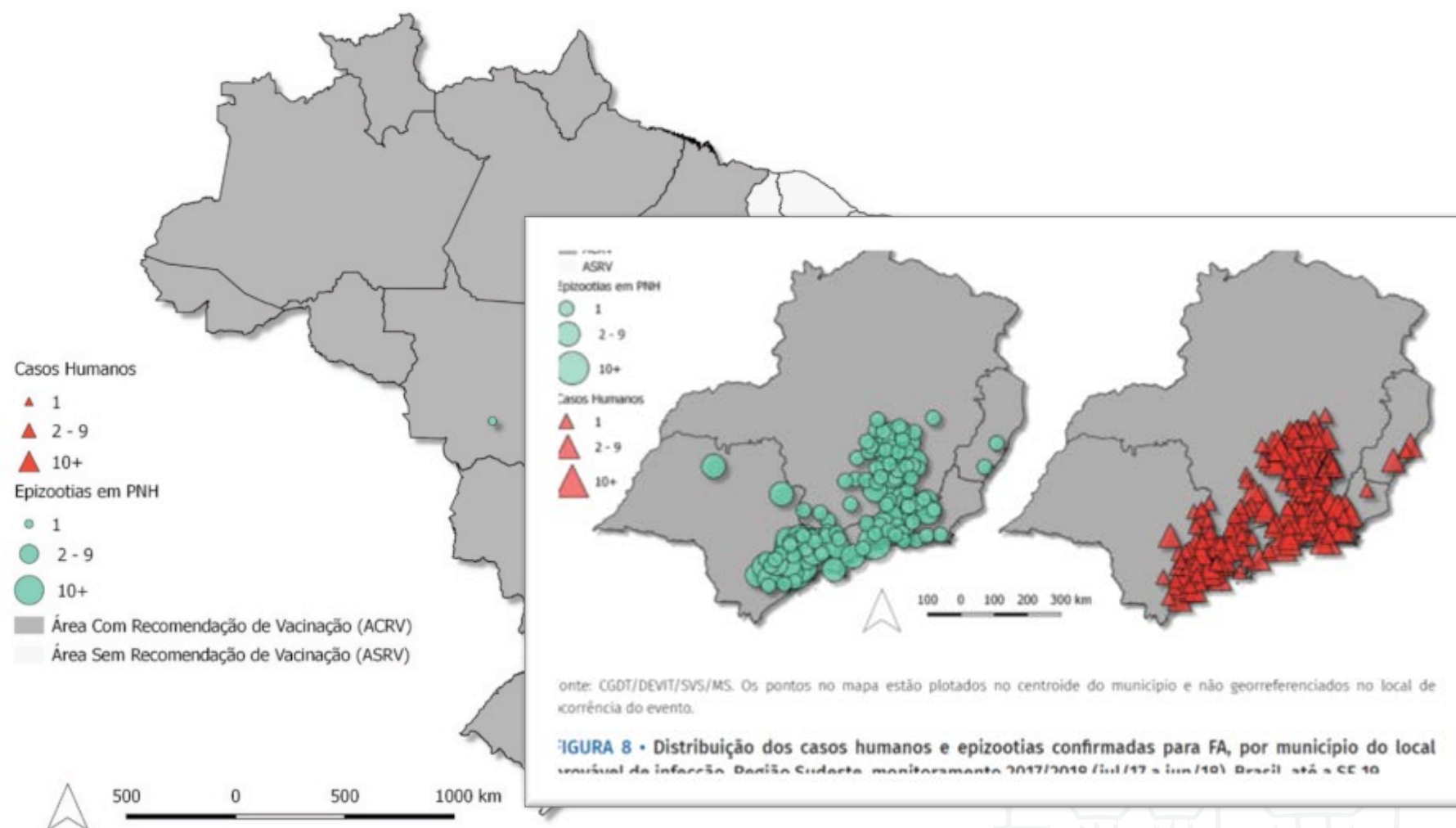
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Recommended areas for vaccination



Fonte: CGDT/DEVIT/SVS/MS. Os pontos no mapa estão plotados no centroide do município e não georreferenciados no local de ocorrência do evento.



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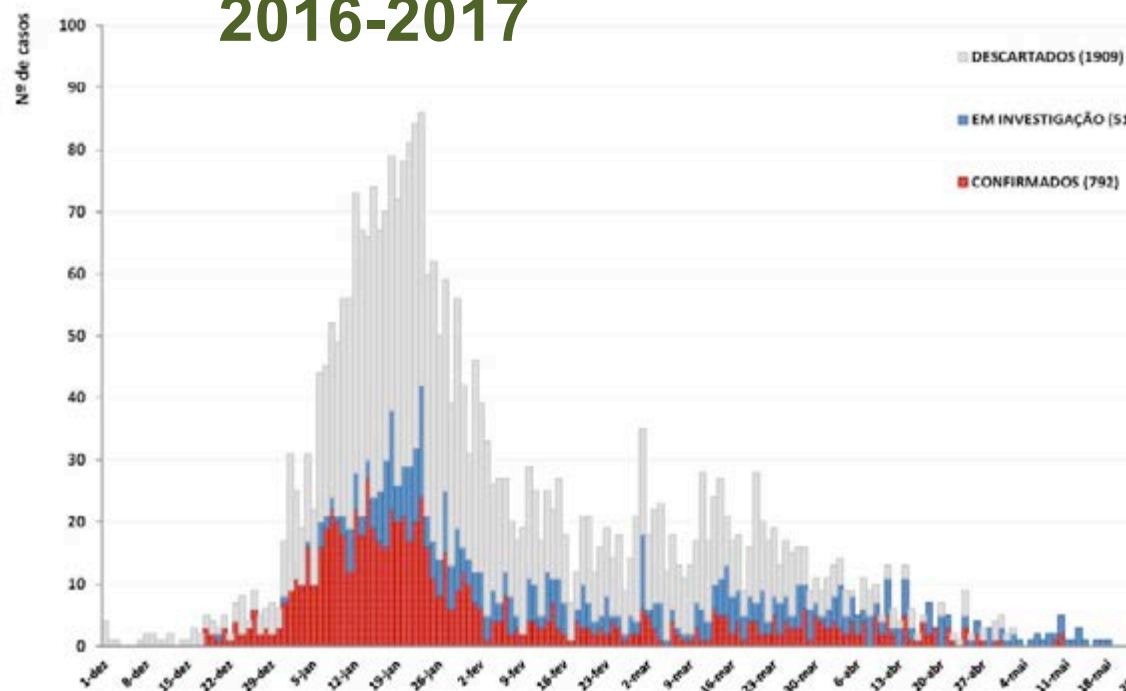
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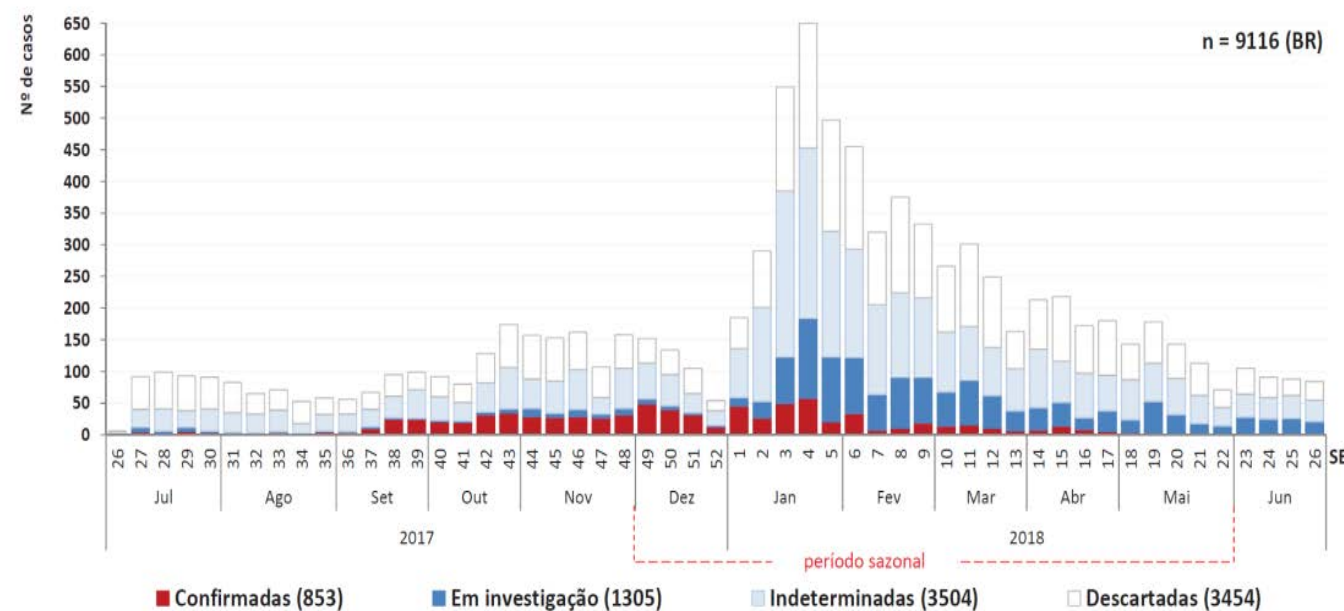
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Current scenario

2016-2017



2017-2018



Fonte: CGDT/DEVIT/SVS/MS. Dados preliminares e sujeitos à revisão. A data de ocorrência não estava registrada em 38 das notificações.



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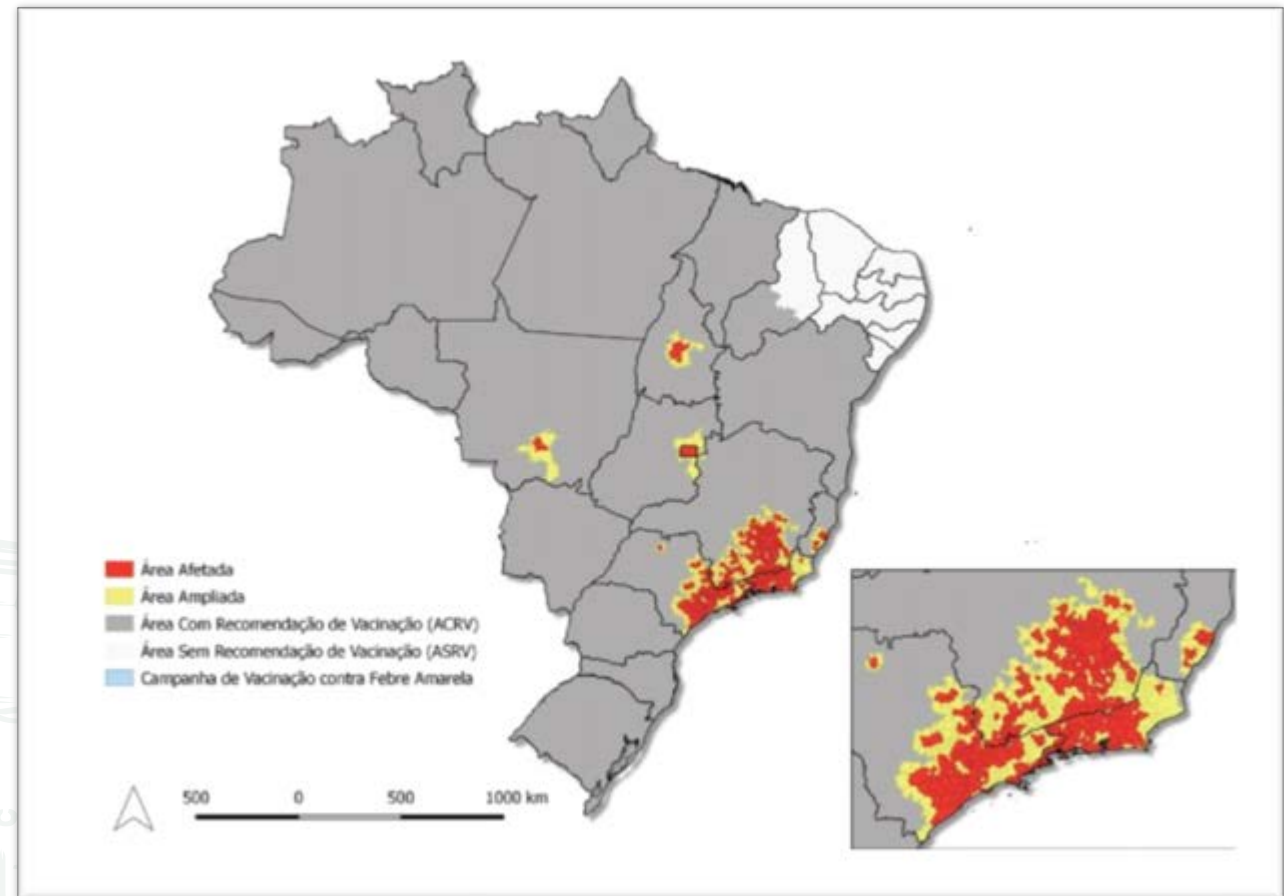
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Recent Outbreak

- 2016: 779 confirmed cases
 - 262 deaths (33.6% lethality)
- 2016: 7,518 suspected cases
 - 1376 confirmed
 - Lethality: 35.1%





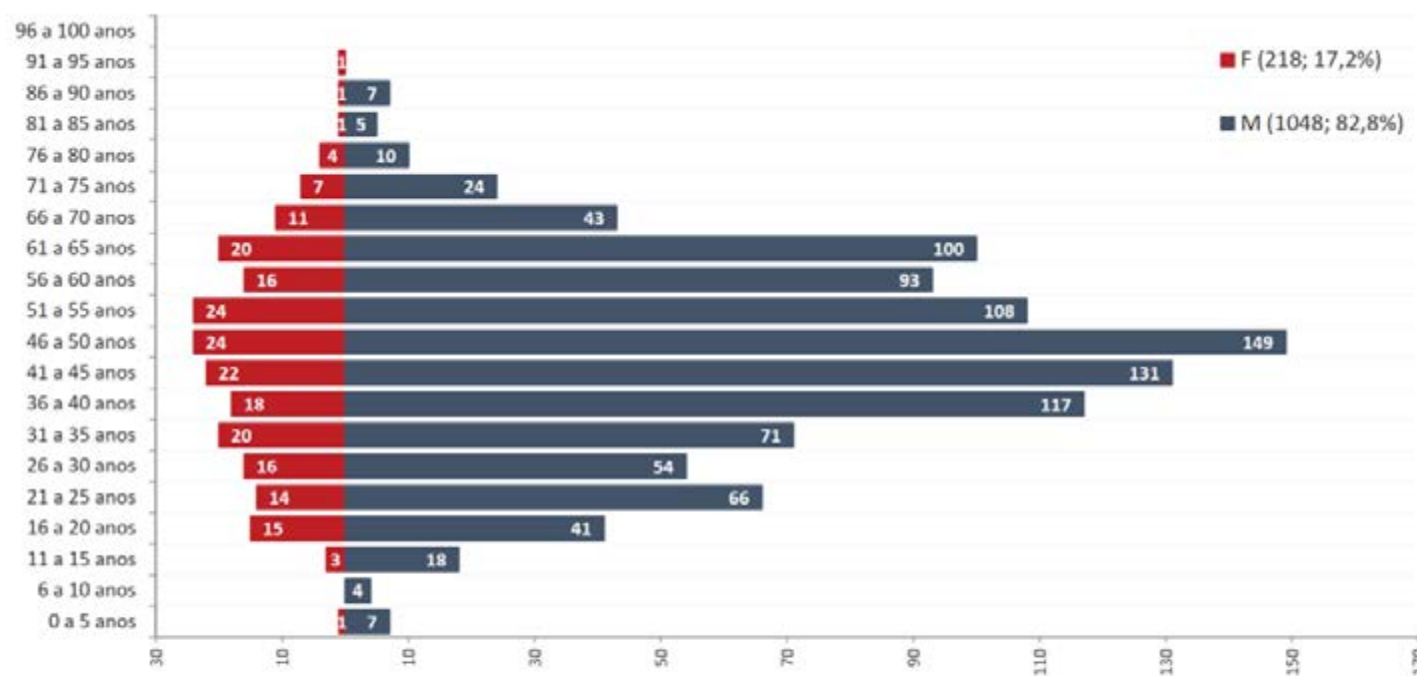
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Age and gender distribution



Fonte: CGDT/DEVIT/SVS/MS. *Dados preliminares e sujeitos à revisão.

FIGURA 5 • Distribuição por sexo e faixa etária dos casos confirmados de febre amarela notificados à SVS/MS, período de monitoramento 2017/2018 (jul/17 a jun/18), Brasil, até a SE 19*.





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Challenges in management

- Severity of cases in ICUs
- Tentative strategies
 - Liver transplant
 - Sofosbuvir
 - Plasmapheresis





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HEPATOLOGY

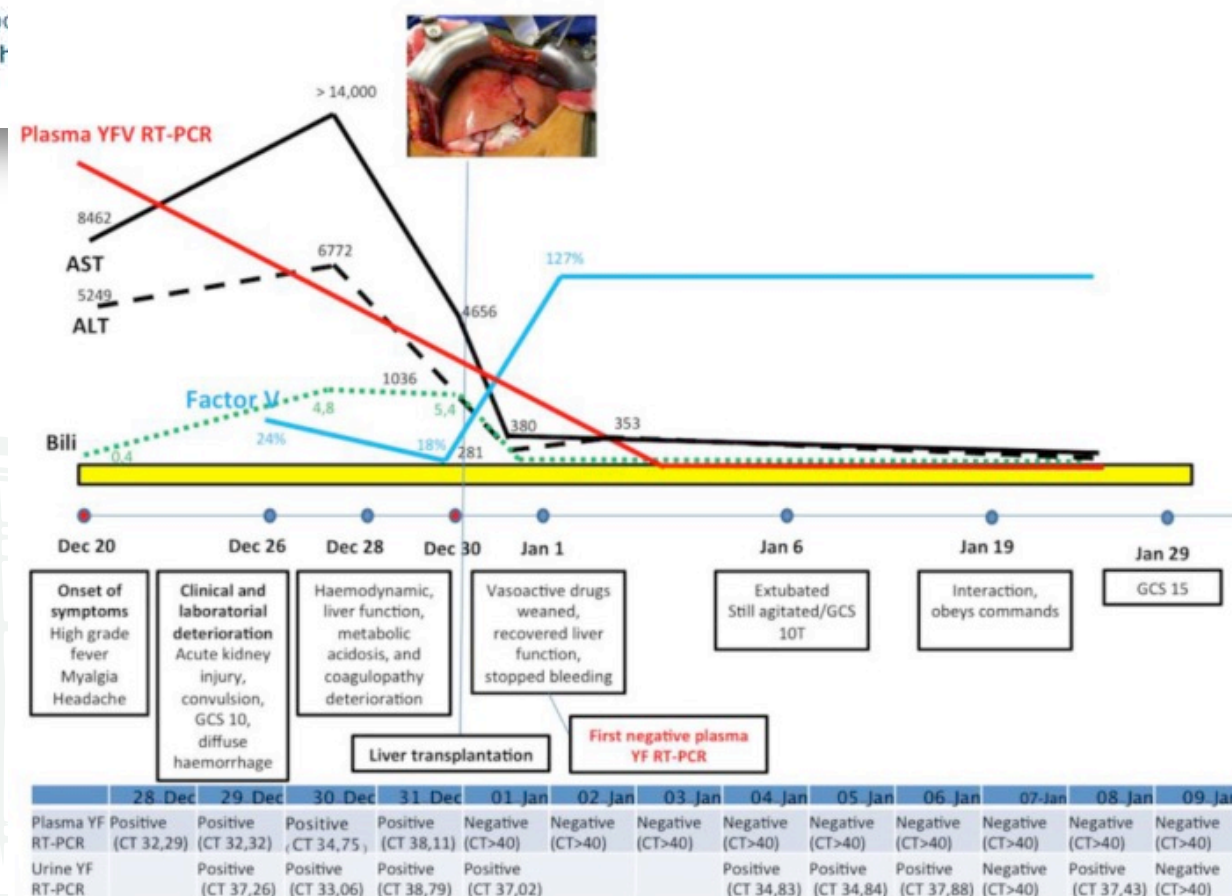


Clinical Observations in Hepatology | [Full Access](#)

Liver transplantation for fulminant hepatitis due to yellow fever

Alice Tung Wan Song, Edson Abdala, Rodrigo Bronze de Martino, Luis Marcelo Sá Malb, Ryan Yukimatsu Tanigawa, Guilherme Marques Andrade, Liliana Ducatti, ... See all authors

First published: 15 September 2018 | <https://doi.org/10.1002/hep.30273>





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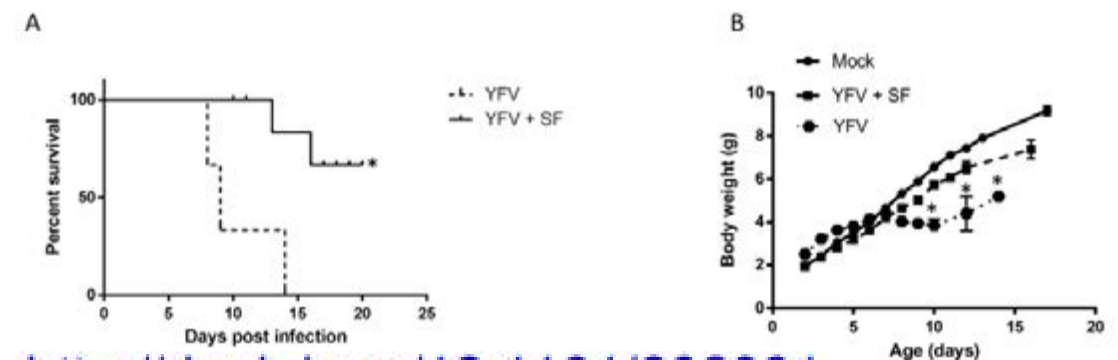


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Challenges for management

1. Lack of point-of-care diagnostics
 1. Possible differential diagnosis
2. Low evidence of adjunctive and/or specific therapeutics
 1. Liver transplant: HCFMUSP: 7 performed (3 alive)
 2. Sofosbuvir – *in vitro* response
 1. Unclear role in patients
3. Plasmapheresis

Figure 4



<http://dx.doi.org/10.1101/266361>



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Vaccine shortage and strategies

1. Biomanguinhos – biggest manufacturer
 1. 9 million doses per month
 2. Estimated need: 26.9 million unvaccinated individuals





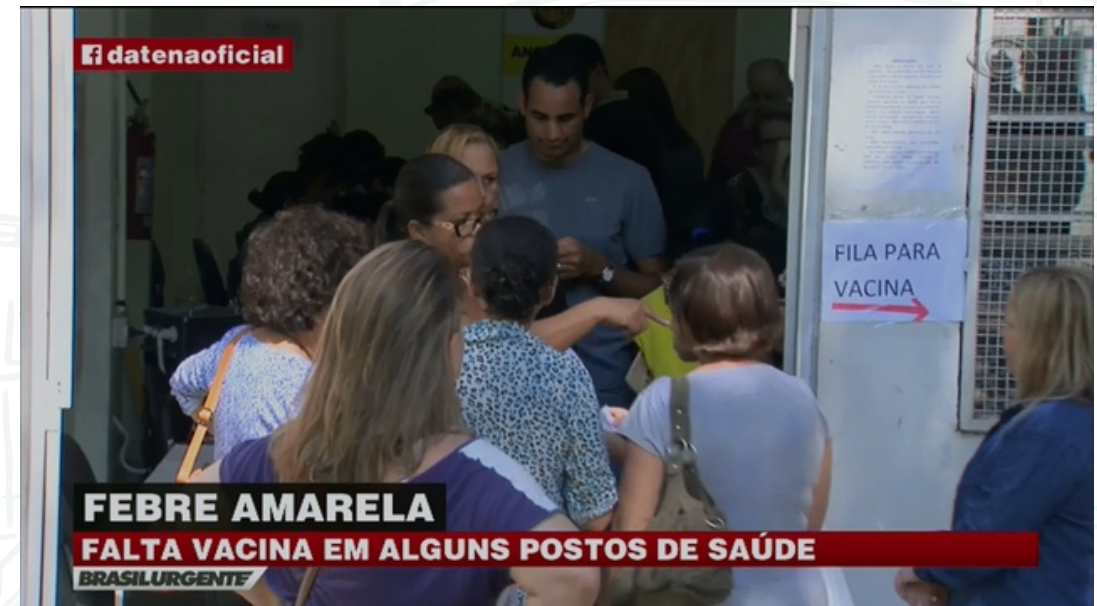
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Reverse vaccine Revolution?





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Fractional dose

1. Rapid expanding area for YF transmission
2. Poor vaccine coverage
3. Decision to promote mass campaign with fractional (1/5) dose
4. Current estimated coverage: 55.5%
 1. Registration is a problem:

Vaccine doses

Total pop.



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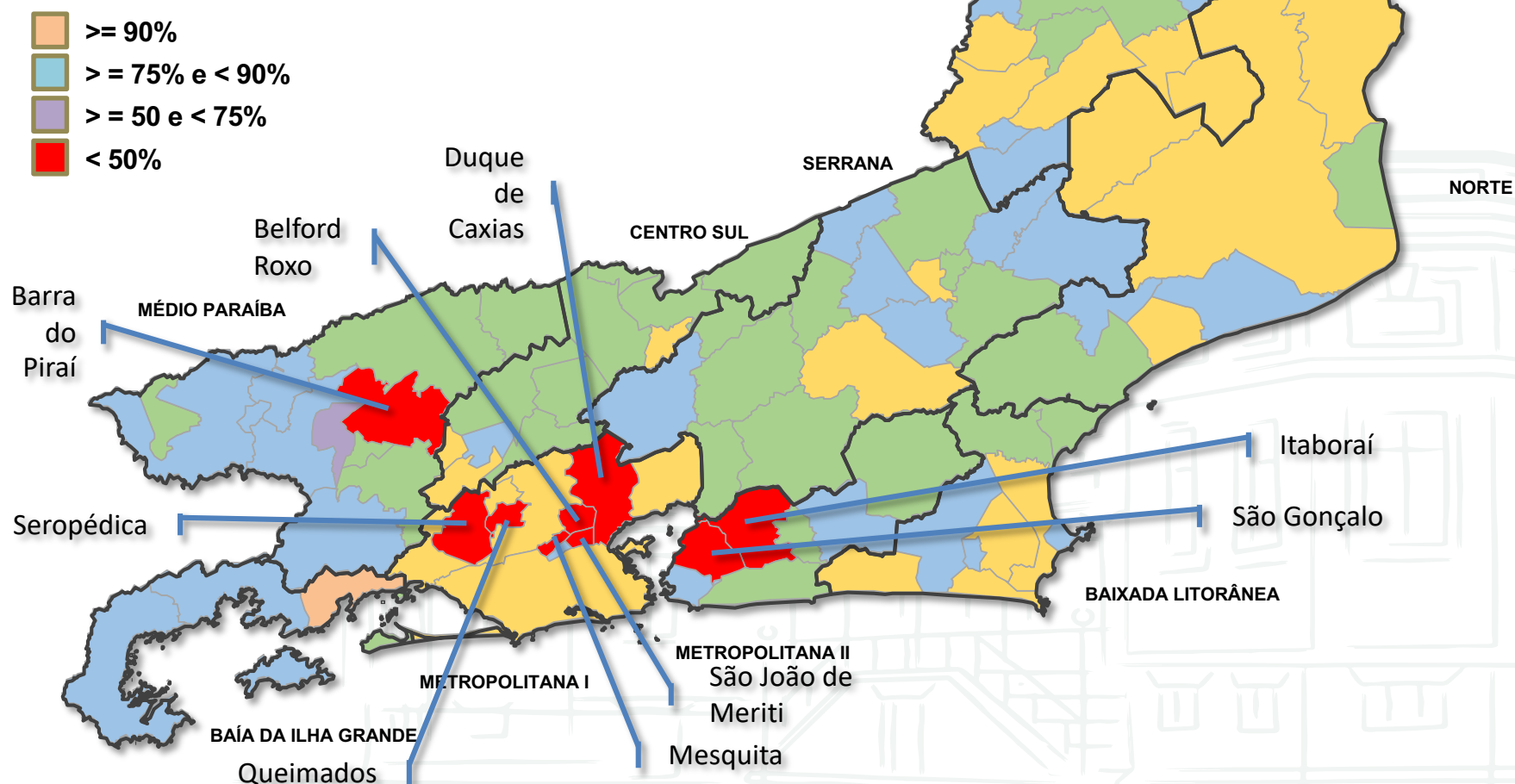


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FEBRE AMARELA: COBERTURA VACINAL

Municípios

2008 à 2018





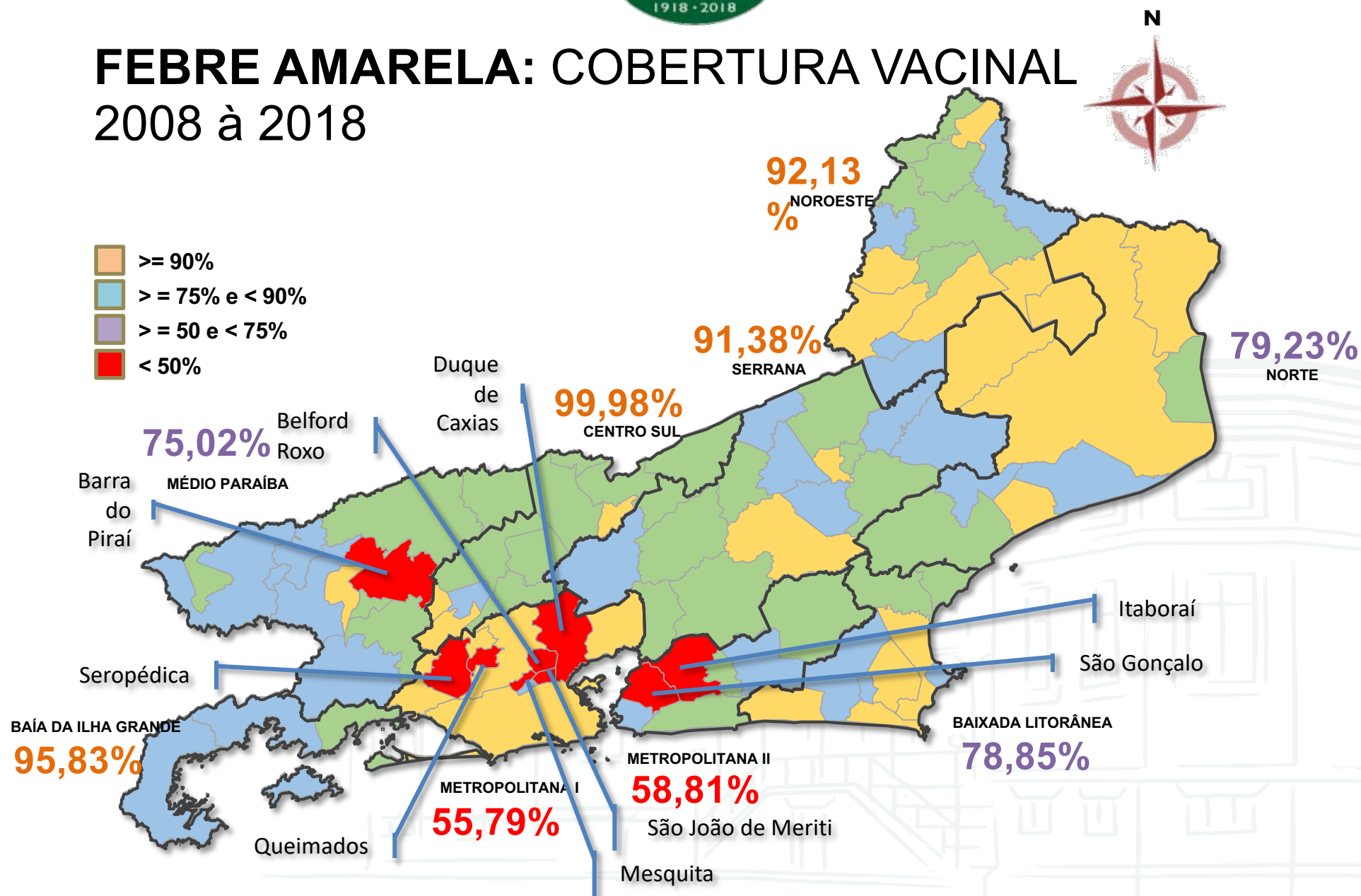
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FEBRE AMARELA: COBERTURA VACINAL 2008 à 2018





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Human Vaccines & Immunotherapeutics 9:4, 879–888; April 2013; © 2013 Landes Bioscience

RESEARCH PAPER

Vaccine 36 (2018) 4112–4117

17DD yellow fever vaccine

A double blind, randomized clinical trial of immunogenicity and safety on a dose-response study

Reinaldo M. Martins,^{1,*} Maria de Lourdes S. Maia,¹ Roberto Henrique G. Farias,¹ Luiz Antonio B. Camacho,² Marcos S. Freire,¹ Ricardo Galler,¹ Anna Maya Yoshida Yamamura,¹ Luiz Fernando C. Almeida,¹ Sheila Maria B. Lima,² Rita Maria R. Nogueira,³ Gloria Regina S. Sá,¹ Darcy A. Hokama,¹ Ricardo de Carvalho,¹ Ricardo Aguiar V. Freire,⁴ Edson Pereira Filho,⁴ Maria da Luz Fernandes Leal¹ and Akira Homma¹

Campi-Azevedo et al. *BMC Infectious Diseases* 2014, **14**:391
<http://www.biomedcentral.com/1471-2334/14/391>

RESEARCH ARTICLE

Open Access

Subdoses of 17DD yellow fever vaccine elicit equivalent virological/immunological kinetics timeline



Contents lists available at [ScienceDirect](#)

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Duration of post-vaccination immunity to yellow fever in volunteers eight years after a dose-response study

Reinaldo de Menezes Martins^{a,*}, Maria de Lourdes S. Maia^a, Sheila Maria Barbosa de Lima^a, Tatiana Guimarães de Noronha^a, Janaina Reis Xavier^a, Luiz Antonio Bastos Camacho^b, Elizabeth Maciel de Albuquerque^a, Roberto Henrique Guedes Farias^c, Thalita da Matta de Castro^a, Akira Homma^a, Collaborative Group for Studies on Duration of Immunity from Yellow Fever Vaccine

^a Bio-Manguinhos/Fiocruz, Brazil

^b National School of Public Health, Fiocruz, Brazil

^c Brazilian Army Health Service, Brazil





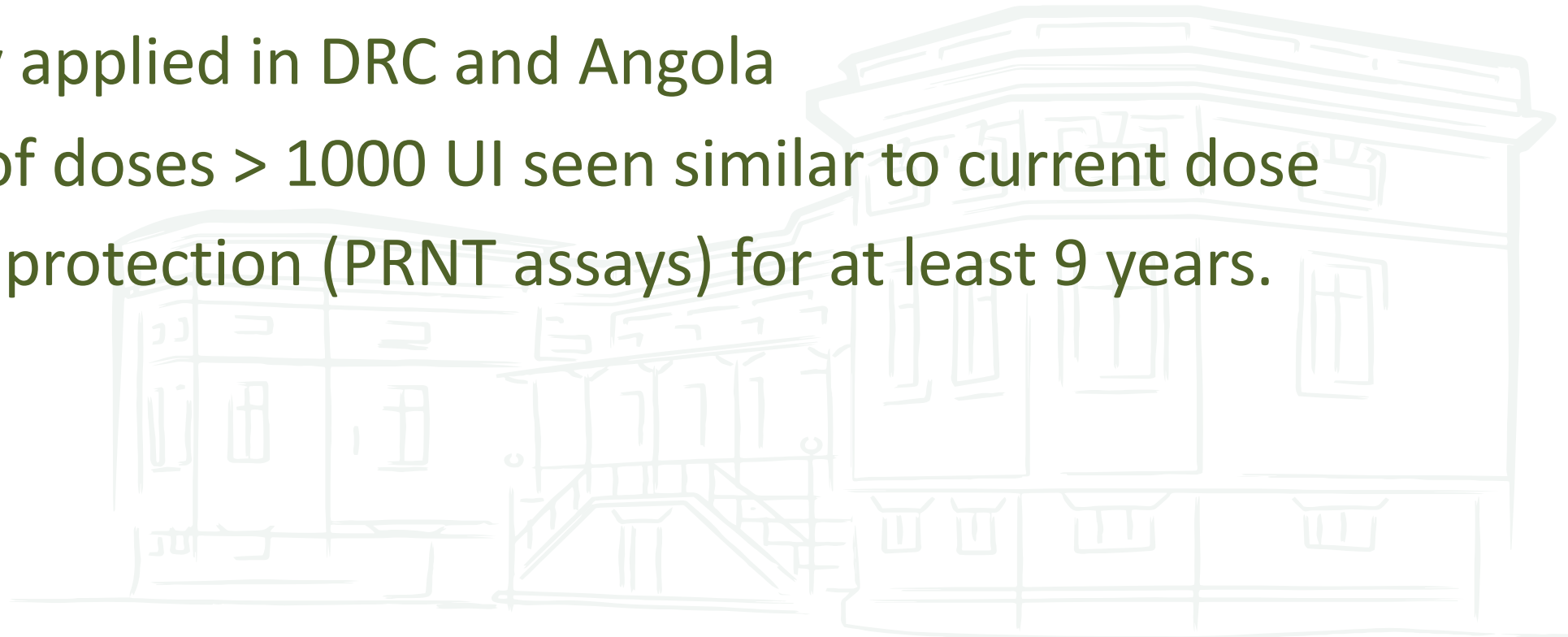
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Fractional dose

1. Option due to shortage of vaccine
2. Recommended by WHO in outbreak situations
3. Successfully applied in DRC and Angola
4. Protection of doses > 1000 UI seen similar to current dose
5. Duration of protection (PRNT assays) for at least 9 years.





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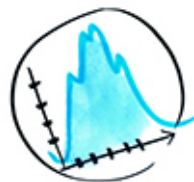


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ELIMINATING YELLOW FEVER

EPIDEMICS

UPDATED
STRATEGY
FOR THE
elimination
of Yellow Fever
Epidemics (EYE)



PARTNERS
MEETING:
SEPT. 12 2016

TODAY



TIME IS NOW

- increased urbanization
- recent outbreaks in Angola under **CONTROL**
- increased global mobility challenges for containment

BACKGROUND



ANGOLA + DRC
S.P.R.E.A.D
Decision to use effective, fractional dose

11 cases in CHINA!

134M PEOPLE PROTECTED

BEFORE 2006
2016: NO OUTBREAKS of Yellow Fever

POSITION PAPERS, STRATEGIC FRAMEWORK, FINAL IC

LONG TERM STRATEGY STARTS **today**

RISK FORECASTING

YF HAS SIMILAR CONTEXT
NOT IF, WHEN YF will spread to ASIA
global distribution of DENGUE VIRUSES since 1970s

WHY HASN'T IT SPREAD?
■ geographic/logistic barriers
■ cross protective flavivirus immunity
■ low vector competence of mosquito in Asia(?)
■ evolutionary exclusion

INCLUDE YF VACCINE in EPI of **every** risk country

Yellow Fever HAS 2.5 BILLION at RISK

risks for SOUTH AMERICA:
YF doesn't have URBAN cycle yet
WHERE CAN I GO IN 48 HRS BY PLANE?
= REACH > 1B. PEOPLE

Speeds up EVERYTHING

VECTOR CONTROLS

WHAT'S WORKING?
spraying, but needs to be sustained

CONTROLLING MOSQUITOES will take MULTIPLE APPROACHES



other controls needed in strategy...



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Challenges

- Can we predict and anticipate epidemics?
 - Role and how to perform epizootic surveillance
- How to best manage clinical cases
- Do we need new products and vaccination strategies?

YES!



A photograph of a rural landscape. In the foreground, a red cloth is draped over a dark post, partially obscuring the view. The ground is covered in reddish-brown soil and some sparse vegetation. In the middle ground, there is a small, simple wooden structure, possibly a shed or a small house, with a few people standing near it. The background is filled with lush green trees and a clear blue sky. The overall scene suggests a rural or agricultural setting.

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