



CURRENT VACCINES: PROGRESS & CHALLENGES

The resurgence of Yellow Fever and role of the vaccine

XI Intl Symposium for Latin American Experts
Fondation Mérieux and Latin American Society
for Pediatric Infectious Diseases (SLIPE)
17-21 October 2018

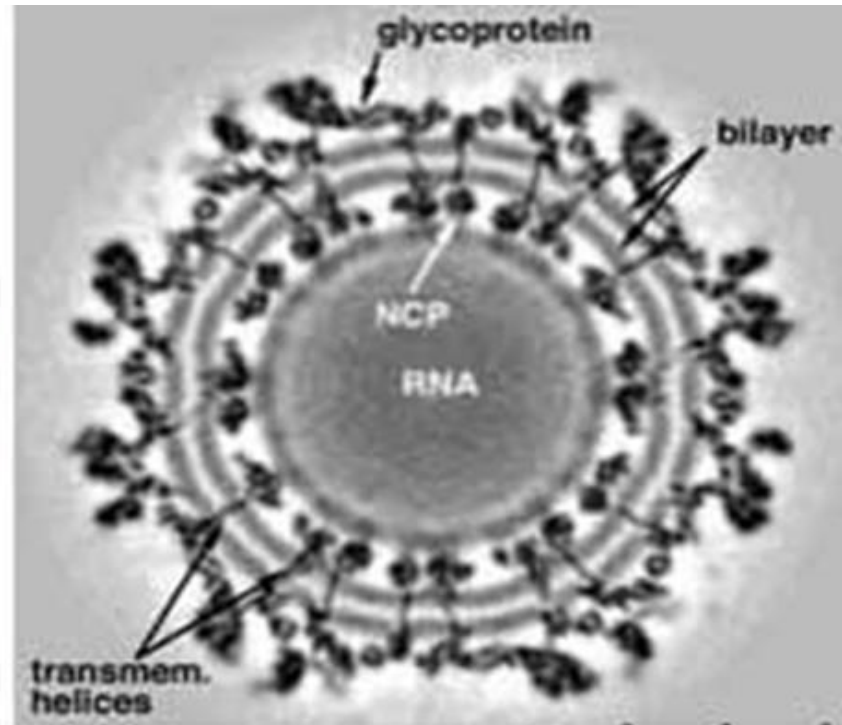
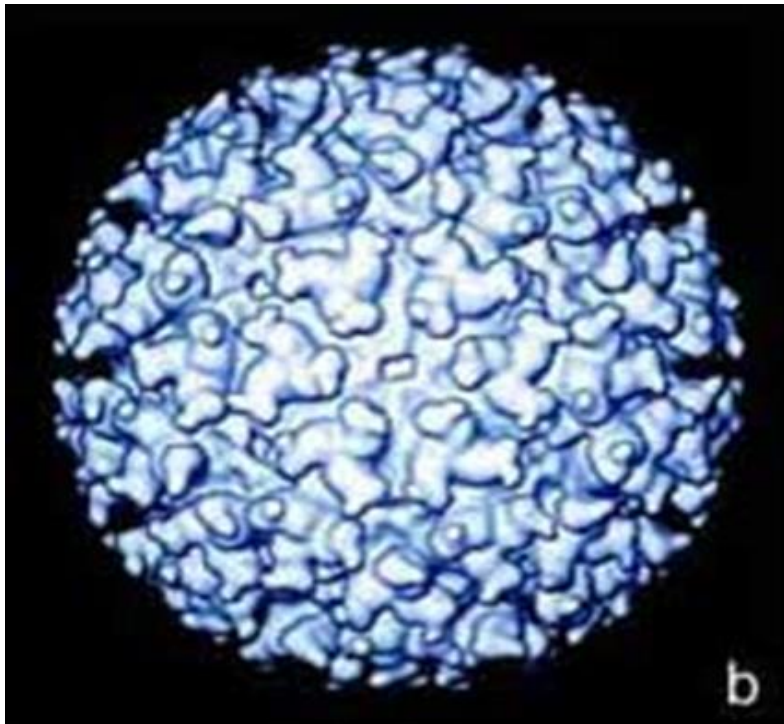
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Yellow Fever

Aetiologic agent:



Family: Flaviridae; Genus: flavirus – small enveloped with RNA genomes of 9000 – 13 000 bases



Yellow Fever: endemic regions



Yellow Fever: 200,000 annual cases and 30,000 deaths - 2010

Fig. 6. The yellow fever endemic zone. The maps depict the areas in (A) Africa and (B) the Americas that are at risk for yellow fever virus transmission in 2009. (From Brunette GW, Kozarsky PE, Magill AJ, et al. CDC Health Information for International Travel 2010. Elsevier; 2009.)

Source: Gardner CL, Ryman KD. Clin Lab Med. 2010 Mar;30(1):237-60.



- Yellow Fever global
2013 – 84.000/170.000 cases
29.000 deaths
- Endemic in 47 countries
 - 34 countries in Africa
 - 13 countries in Central and South America

➤ 2006 – WHO - The Initiative against Yellow Fever



➤ 2016 – EYE - Eliminating Yellow Fever Epidemics WHO, UNICEF, GAVI

- Protect at-risk population
- Prevent Intl spread
- Contain outbreaks rapidly

➤ Eliminating YF (2016-2026)

➤ Targeting 40 countries; 50 partners; 40 billion YF doses over 10 years

YF in Latin America



In the 21th Century, Yellow Fever virus has circulated in Paraguay, Argentina, Bolivia, Colombia, Venezuela, Peru....



BRAZIL - Epidemiological evolution



1903 - Oswaldo Cruz assigned by Rodrigues Alves as Director of Health Services

1942 - Brazil has eradicated *Aedes aegypti* in two states

1937, início da vacinação no Brasil

- . Mosquito-kill brigade, sulphur and pyrethrum;
- . Isolation of sick people in São Sebastião Hospital;
- . YFPS adopt the Fire Corps procedures;

YF in Brazil



In 1900, the Federal Serotherapeutic Institute was created, today Oswaldo Cruz Foundation - to control and eliminate pestis, small pox and **Yellow Fever** from Rio de Janeiro. Oswaldo Cruz took over **Carlos Finlay's** Discovery (1881) on Yellow Fever transmission and eradicated *Aedes aegypti* from Rio de Janeiro – **Walter Reed/William Gorgas** did the same during Panama Canal (1901) construction



Transmission cycles: primates reservoir and vectors



3,1% das notificações
Cebus sp.
(macaco-prego)

Alouatta sp.
(guariba; bugio; gritador)
84% das notificações



Callithrix sp.
(soim)
9,9% das notificações

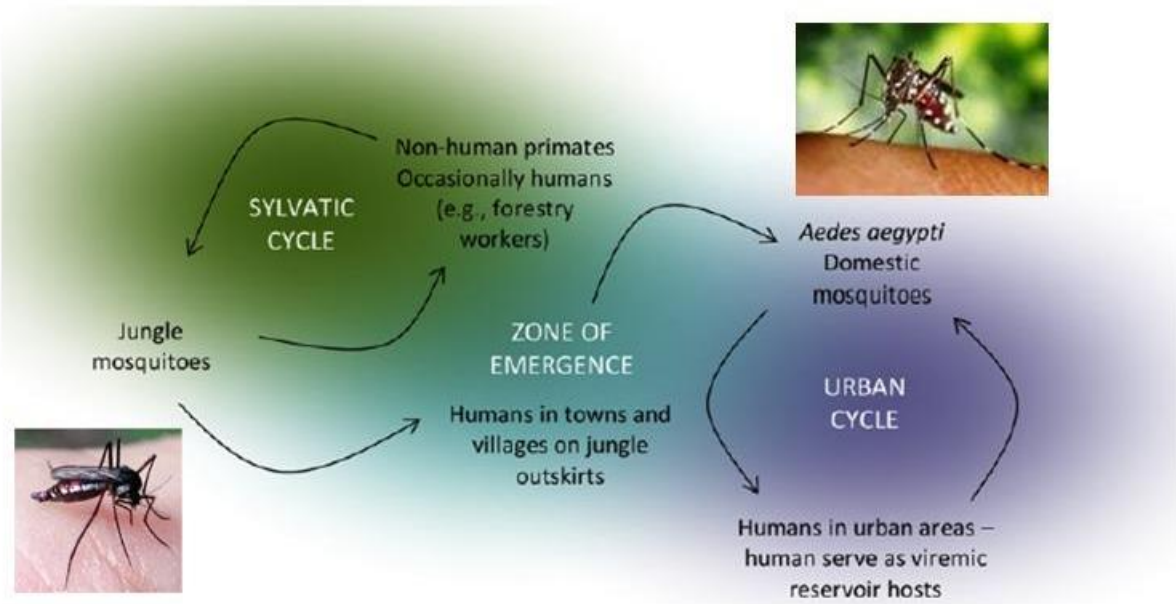


Fig. 5. Yellow fever transmission cycles. The yellow fever virus is transmitted between human and nonhuman primate hosts by mosquitoes in 3 cycles: the sylvatic (jungle) cycle in which mosquitoes of the forest canopy transmit virus to monkeys and secondarily to humans entering the jungle; the intermediate cycle (or zone of emergence) in which virus enters rural towns and villages bordering jungle areas; and the urban cycle in which humans serve as the viremic host and virus is transmitted from human to human by the domesticated *Aedes aegypti* mosquito.

Sources: SVS/MS

Gardner CL, Ryman KD. Clin Lab Med. 2010 Mar;30(1):237-60.

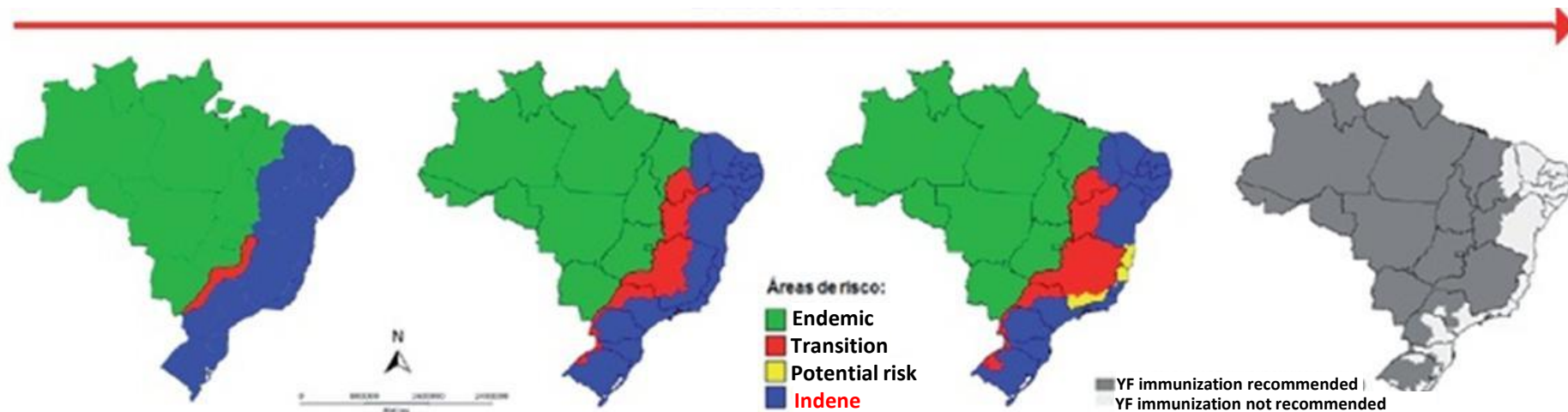
Vasconcelos PF. Rev Soc Bras Med Trop. 2003 Mar-Apr;36(2):275-93



Brazil, risk areas - 1997 to 2008

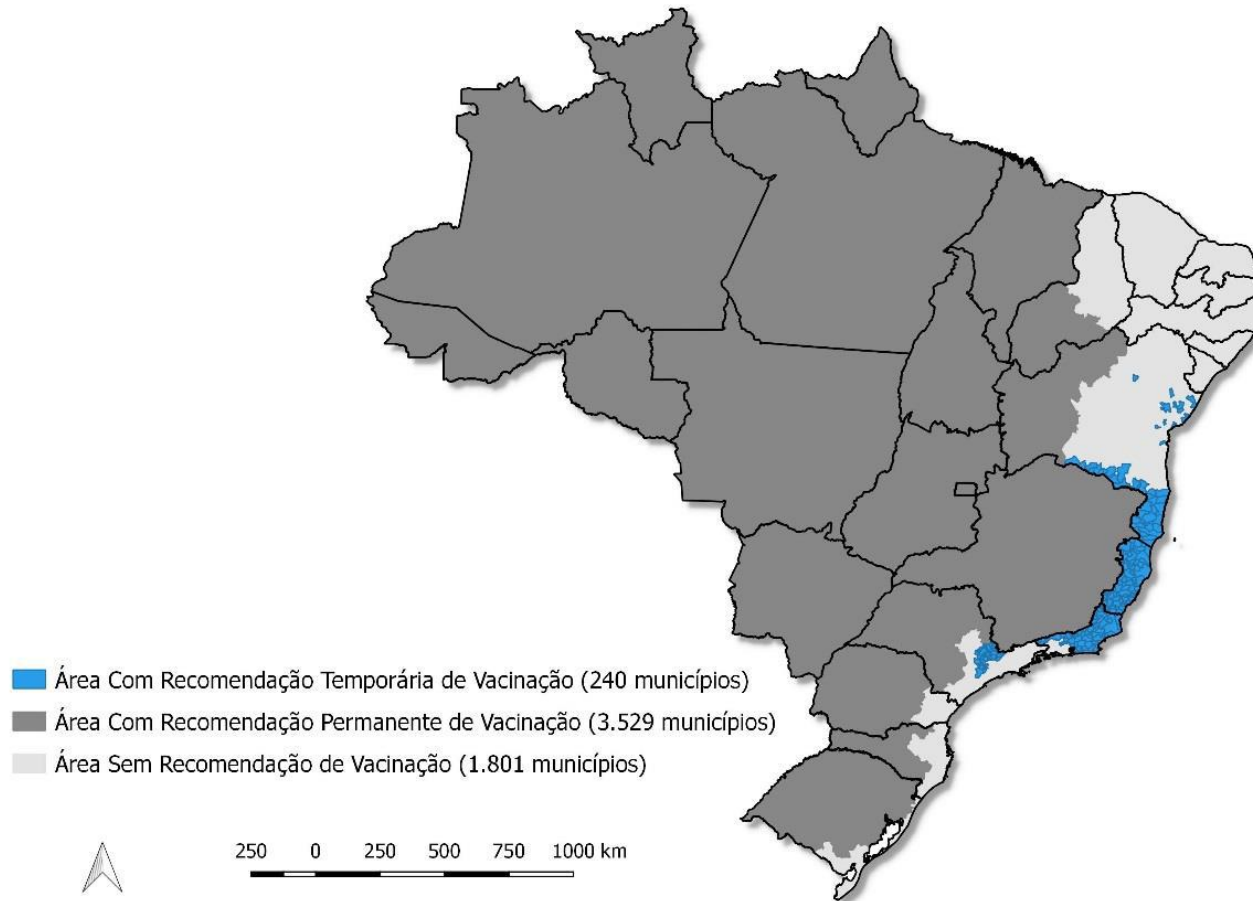
1997

2008

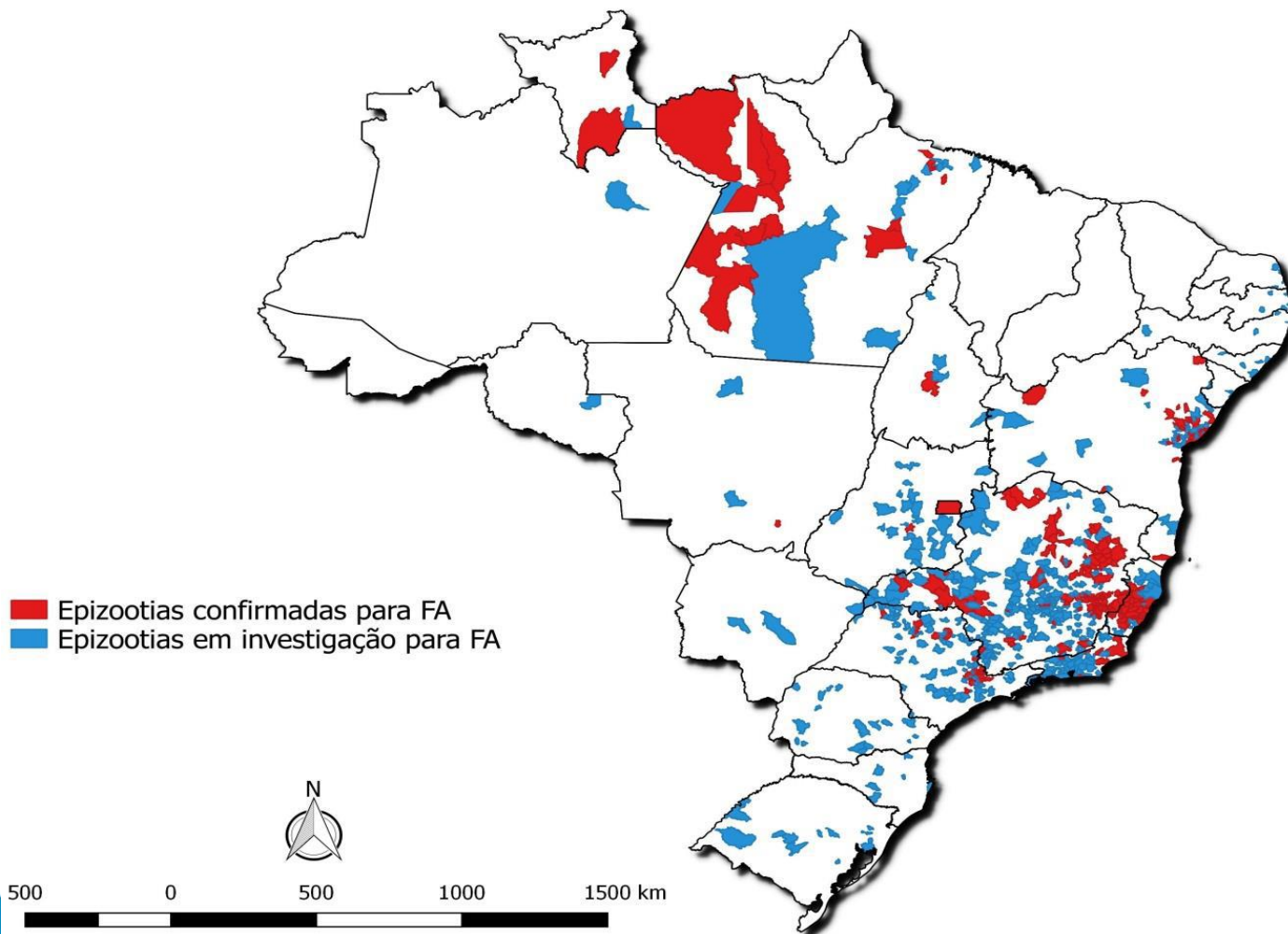


Áreas de Risco Febre Amarela e com recomendação para vacinação, 1997 a 2008
Fonte: SVS/MS.

Brazilian regions according to the recommendation of vaccination of Yellow Fever, Brazil, 2017



Geographic distribution of NHP epizooties suspects YF cases notified to SVS/MS from 01 December 2016, up to 31 may 2017, per municípalites and classified as Confirmed and under investigation for YF



Yellow Fever Human cases and case fatalities. Brazil 1930-2017

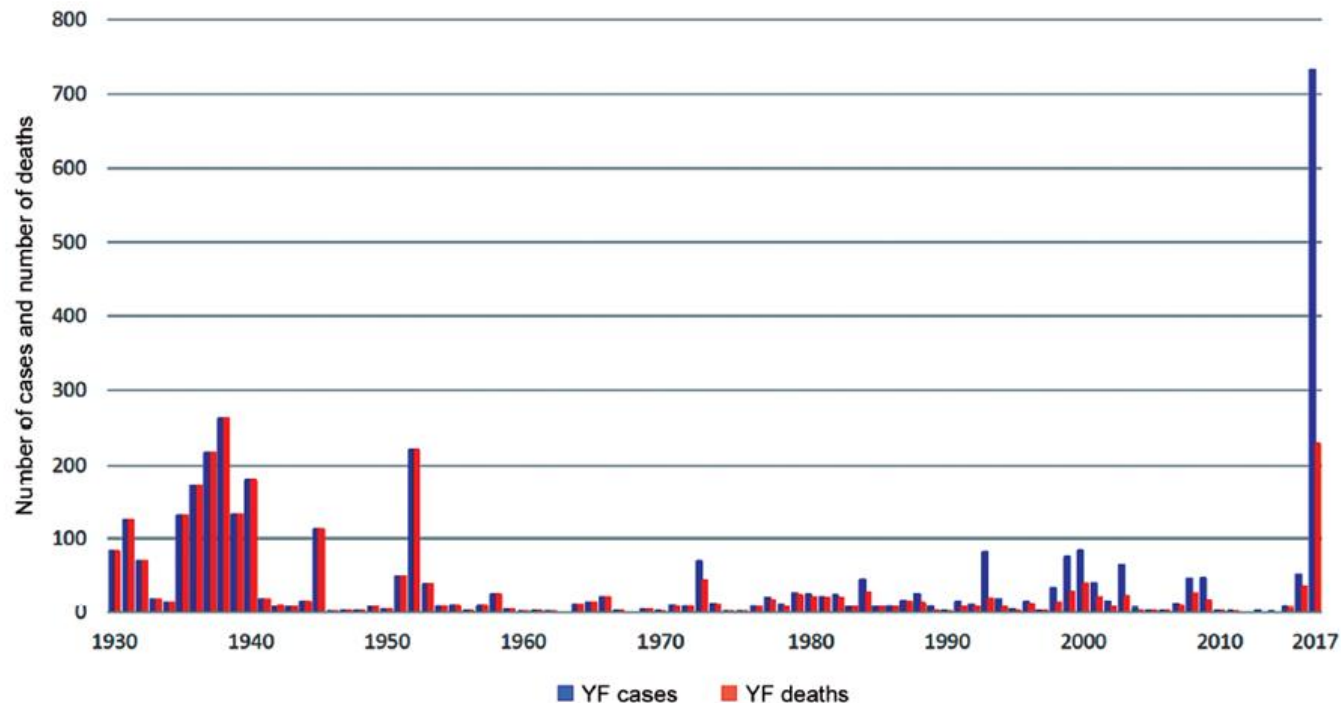


Fig. 1: yellow fever: human cases and case fatalities in Brazil 1930-2017. Source: Brazilian Ministry of Health, YF Epidemiological reports 1930-2018.

- Started Dec 2016 and still on going, the largest epizootic Yellow Fever registered over the last 90 years....

Update on Yellow Fever cases in Brazil

- From Dec 2016 to 30 June 2017 – 3.564 cases notified; 2.270 dismissed; 213 under investigation; 304 no conclusion
 - **772 confirmed; 261 deaths;**
 - From 01 July 2017 to 30 June 2018 - 7.518 cases notified – 5.364 dismissed; 778 under investigation
 - **1.376 cases confirmed; 483 deaths**
- Case Fatality rate – 34-35%
- ✓ Intensive vaccination enforced in the regions with NHP epizooties
 - ✓ New areas recommended for YF vaccination
 - ✓ All the country will be vaccinated by 2019
- Since May 2018, decay of YF cases

Source: Boletim epidemiológico MS

YF cases in Brazil



- All YF cases were classified as sylvatic; the vectors involved were *Haemagogus* or *Sabethes*.
- No cases involved *Aedes aegypti* vector, although many human and NHP cases occurred in peri-urban areas and parks inside of cities
- This situation poses a potentiality of re-urbanization and the control of *A. aegypti* is essential

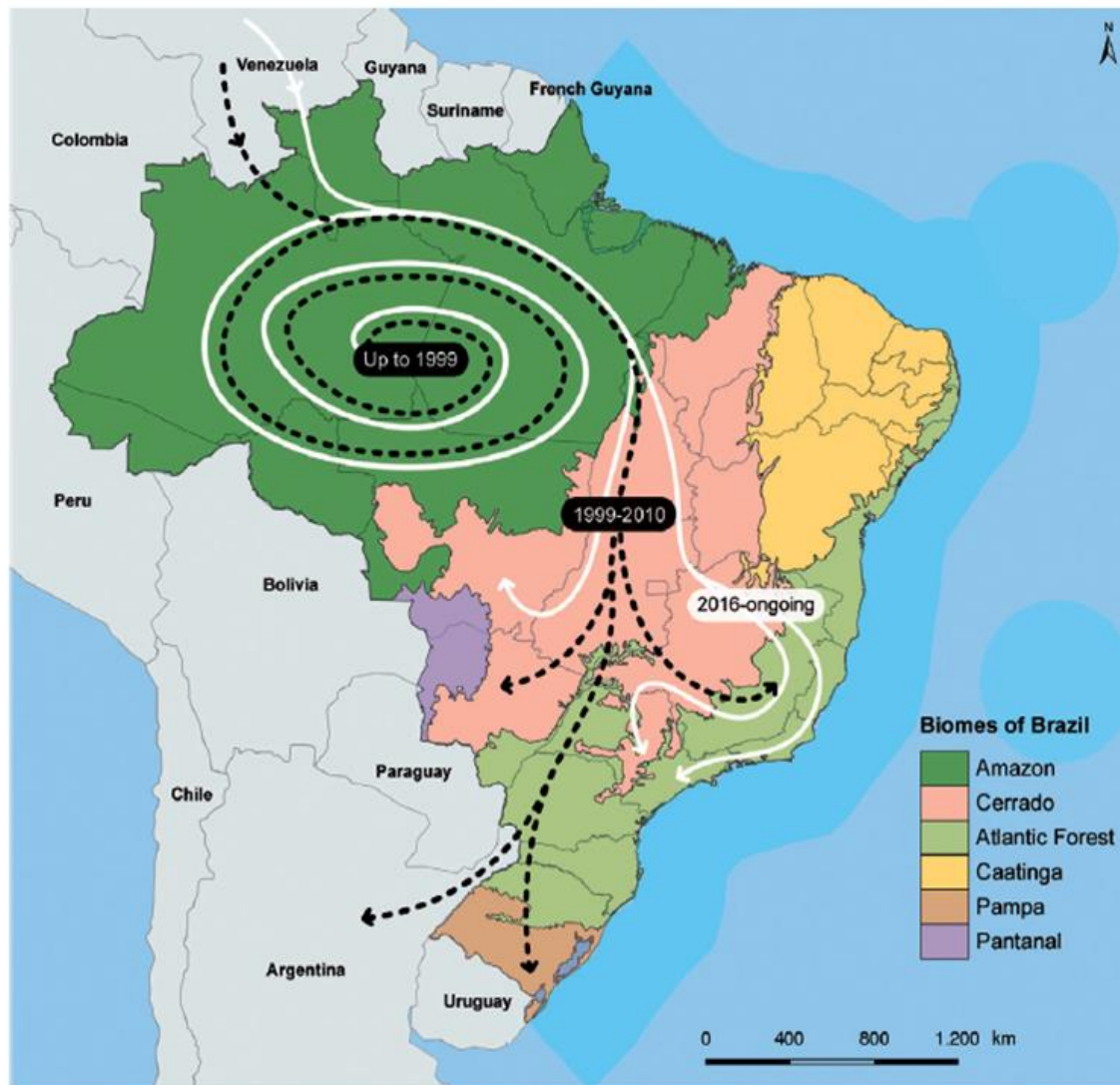


Fig. 2: yellow fever virus spread: rapid dislocation into and between Brazilian biomes. Black dashed line: viral spread from late 1980' until 2010; white line: viral spread from the first half of the 2010 decade onward, including the ongoing outbreak in the Southeast. Sources: IBGE/MMA 2004 for map of Brazilian biomes. Brazilian Ministry of Health//SVS, YF reports from 1999-2018 for epidemiological information on epizootic waves and human cases (<http://portalms.saude.gov.br/saude-de-a-z/febre-amarela-sintomas-transmissao-e-prevencao/situacao-epidemiologica-dados>).

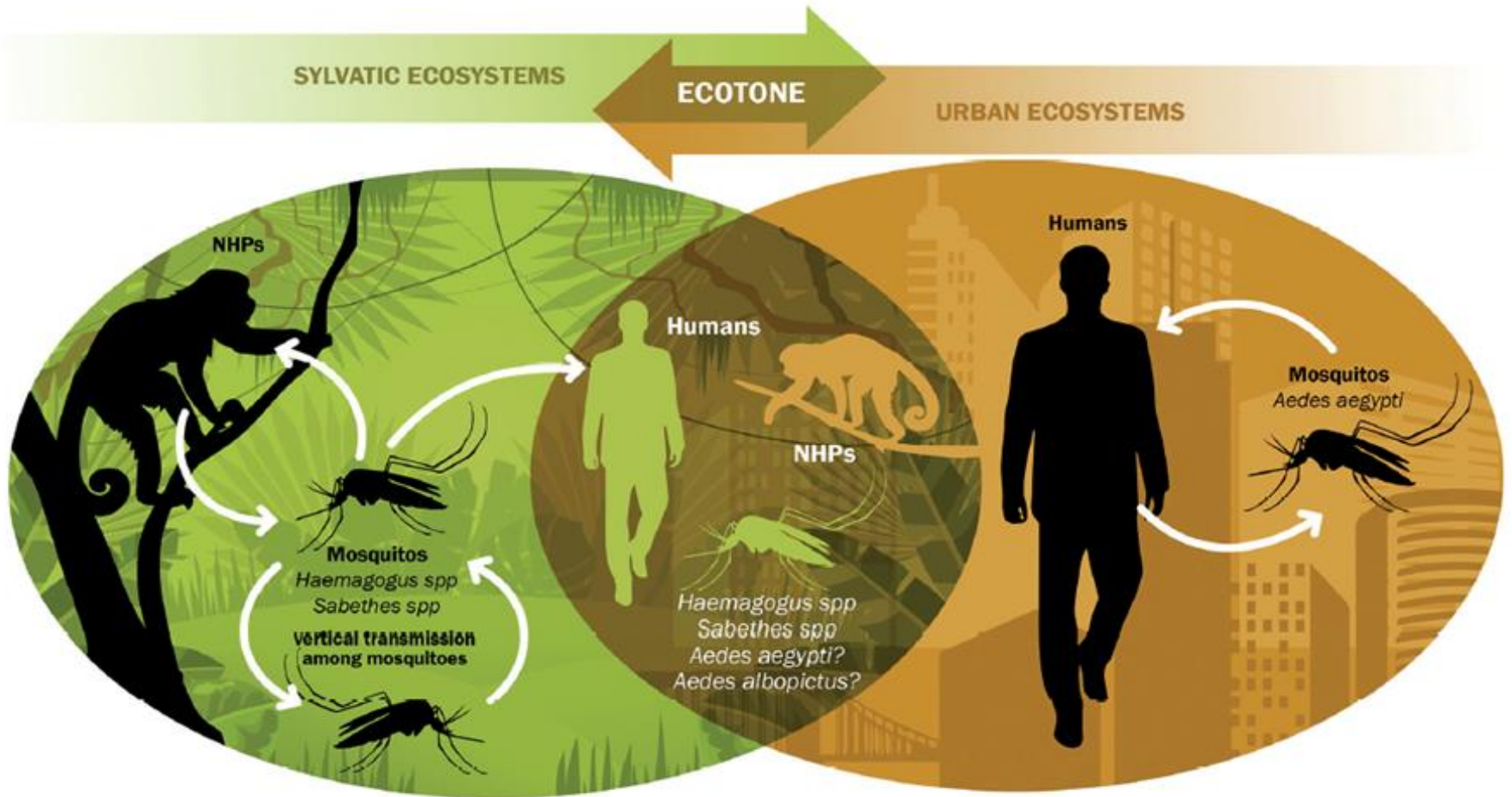


Fig. 4: yellow fever virus (YFV) transmission dynamics in Atlantic Forest biome: overlap of ecosystems and ecotone. In the last decades, the progressive combination of several factors has contributed to gradually expand the overlap of ecosystems (sylvatic and anthropic) and the ecotone as well as to imbricate the *Haemagogus*-vectored YFV cycle and the territory of synanthropic species, facilitating YFV expansion, human infections and increasingly jeopardised the reemergence of *Aedes* transmission in the urban areas. Among those factors are: (a) the augmentation of areas with environmental and ecological conditions to support mosquito and non-human primate (NHP) diversity and population growth due to the success of recent environmental policies; (b) the loss of some natural habitats forcing NHPs (e.g., marmosets, capuchins) to exploit the ecotone and the modified environments and their overpopulation of remaining forest fragments; (c) adoption of new life styles and practices by the contemporary man leading to an increasing approach to the woods; (d) rapid and intense human displacements; (e) the ecological plasticity of vectors, specially the liability of *Haemagogus* to span long distances beyond the forest limits and *Ae. albopictus* to colonise and disperse from the modified into the sylvatic ecosystem; (f) the crescent infestation rates by *Ae. aegypti* in expanding urban and peri-urban areas near the *Haemagogus*-transmitted YFV cycle.

81 years of Yellow Fever Vaccine production in Brazil

- 1937 March - H. Smith trouxe a cepa 17D e iniciou a produção da vacina no Brasil – Henrique de Azevedo Penna, o parceiro brasileiro
- ✓ Um ano depois > 60.000 pessoas foram vacinadas
- ✓ Smith, Penna e Paoliello, concluíram que “**existe um método seguro para produzir a vacina da FA em larga escalar**”.

-Bica, Alfredo, Anais Simpósio 50 aniversário da introdução da cepa 17 D no Brasil, 1988



Vaccination at Fazenda Pedra Preta, on Três Pontas, MG, August 15, 1937

- Formulation of vaccine
- Scale-up of production
- Seed-lot system
- Several production procedures
- Use of SPF chicken embryo

Production and use/supply YFV in Brazil



- Use - from 1937 to 1986 – 154.383.814 vaccinated
 - Rodopiano de Oliveira, A. *In Anais Simpósio 50 aniversário da introdução da cepa 17 D no Brasil, 1988*
- ✓ Supply to NIP
 - Last 30 decades, 690 million doses
- From 2011 to 2017- 190.857.195 doses
- Only in 2017 – 64.117.500 doses
- 2018 program: 40.523.100 doses - 18.500.000 doses already supplied
- Production expansion: CMO/Libbs – additional 30 million doses
- ✓ Exportation - since 2001 – PQ/WHO, 120 million doses exported

Source: Derem/Bio-Manguinhos, 2011



Fractioned dose was used to control the YF epidemic in Kinshasa/RDC in 2016 and in Brazil in 2018



Dose-response in adults 02

RESEARCH PAPER

Human Vaccines & Immunotherapeutics 9:4, 1–10; April 2013; © 2013 Landes Bioscience

17DD yellow fever vaccine

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

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Seroconversion rates – Nt Ab according to vaccine dosage*. All the participants seronegatives before vaccination N = 749

Grupo UI/dose	Total	Proporção	IC 95%
27.476 UI	131	97,7	93,5; 99,5
10.447 UI	115	99,1	95,3; 100,0
3.013 UI	132	97,7	93,5; 99,5
587 UI	131	96,9	92,4; 99,2
158 UI	122	88,5	81,5; 93,6
31 UI	118	66,9	57,7; 75,3

P = 0,000

* Serology 30 days after vaccination

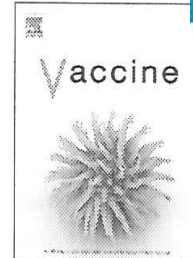
WHO – 1.000 IU minimal dose recommended



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

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Serology of dose-response study 8 years later

Vaccine dosage	Participants with YF Ab at protective level (>2,7 mUI/mL)			Total examined
	N	%	I.C.95%	N
27.476 UI	56	82,3	71,2 - 90,5	68
10.447 UI (1/3)	44	86,3	73,7 - 94,3	51
3.013 UI (1/9)	54	80,6	69,1 - 89,2	67
587 UI (1/58)	55	93,2	83,5 - 98,1	59
158 UI (1/173)	40	80,0	66,3 - 90,0	50
31 UI (1/886)	22	95,7	78,1 - 99,9	23
Total	271	85,2	80,8 - 88,9	318

P = 0,159 Fisher



Obrigado!
Muchas Gracias!
Thank you!

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<http://www.bio.fiocruz.br/>