Yellow Fever Update

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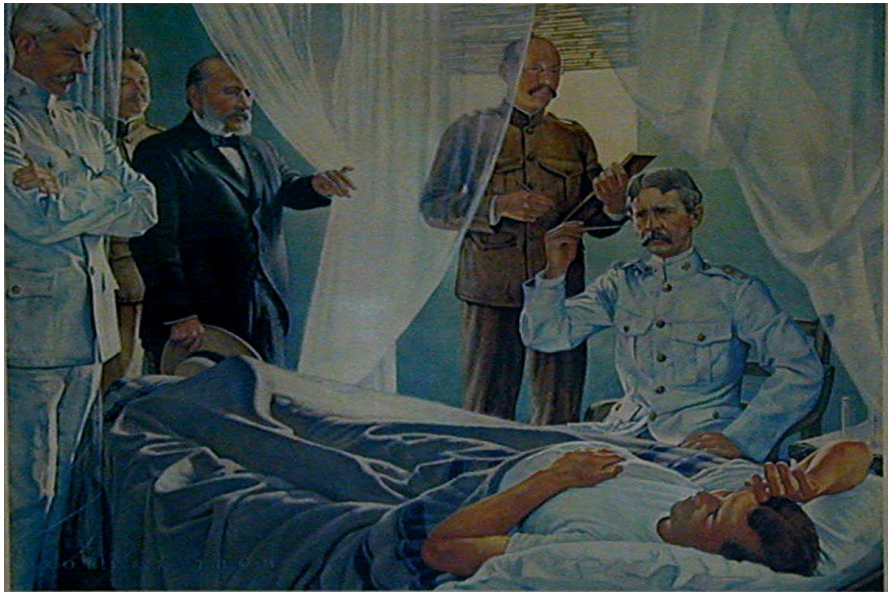
Disclosure

- No conflict regarding YF Vaccine
- Hold a patent regarding pharmacological treatment of YF using MAP Kinases inhibitors
- Financial payments or grant support regarding dengue vaccine from: Sanofi-Pasteur and/or Butantan-NIH Vaccine
- Thanks to Marcos Freire, PhD FIOCRUZ for sharing some data used in this presentation

BASIC YF DATA COMES FROM EARLY XX CENTURY

In 1881, Carlos Juan Finlay, a physician in Havana, first proposed that yellow fever was a mosquito-borne illness, which subsequently was proven by Walter Reed and colleagues.

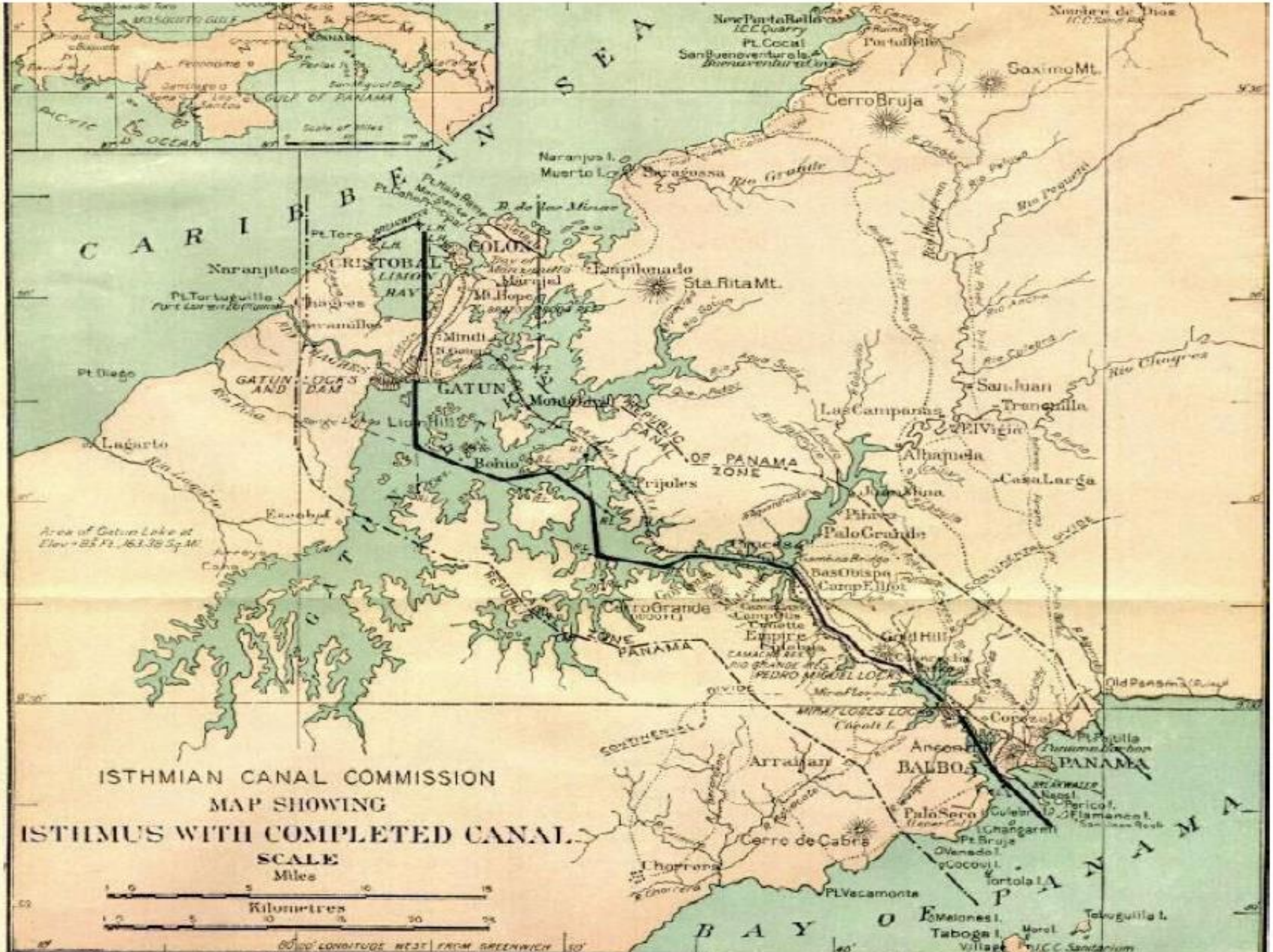
U.S. Army doctor Discovered the Cause of Yellow Fever
August 27, 1900



“I THANK GOD that I did not accept anybody’s opinion on this subject, but determined to put it to a through test with human beings in order to see what would happen… actual trial proven that I was right…” - Walter Reed

“The Etiology of Yellow Fever an Additional Note,” read before the Pan-American Medical Congress at Havana, in February, 1901

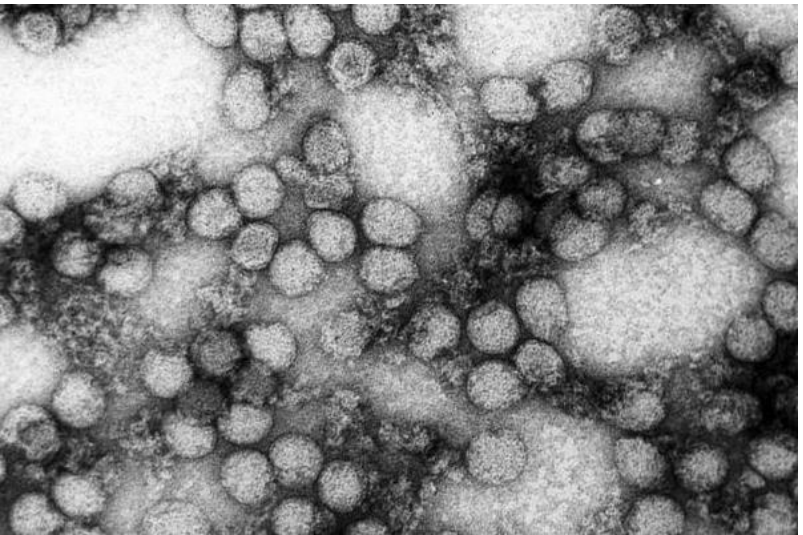
“1. The mosquito – C. facciatus – serves at the intermediate host for the parasite of yellow fever. “2. Yellow fever is transmitted to the nonimmune individual by means of the bite of the mosquito that has previously fed on the blood of those sick with this disease. “5. Yellow fever can also be experimentally produced by the subcutaneous injection of blood taken from the general circulation during the first and second days of this disease. “8. Yellow fever is not conveyed by fomites, and hence disinfection of articles of clothing, bedding, or merchandise, supposedly contaminated by contact with those sick with this disease, is unnecessary. “10. The spread of yellow fever can be most effectually controlled by measures directed to the destruction of mosquitoes and the protection of the sick against the bites of these insects.”


ISTHMIAN CANAL COMMISSION
MAP SHOWING
ISTHMUS WITH COMPLETED CANAL
SCALE
Miles
Kilometres
CARIBBEAN SEA
BAY OF PANAMA
GULF OF PANAMA
PACIFIC OCEAN
COLON
CRISTOBAL
LIMON BAY
GATUN
GATUN LOCKS AND DAM
REPUBLIC OF PANAMA
CANAL ZONE
PEDRO MIGUEL LOCKS
MIRAFLORES LOCKS
BALBOA
PANAMA
Naranjitos
Chagres
Pt. Toro
Mt. Hope
Sta. Rita Mt.
Cerro Bruja
Saxino Mt.
Portobello
Pt. Cocal
Lagarto
Lion Hill
Bohio
Frijoles
Las Campanas
San Juan
Alhajuela
Casa Larga
Palo Grande
Bas Obispo
Camp Elliot
Cerro Grande
Empire
Gold Hill
Corozal
Ancon
Old Panama
Arraijan
Palo Seco
Cerro de Cabra
Chorrera
Pt. Vacamonte
Taboga I.
Tabeguilla I.
Area of Gatun Lake at Elev. + 85 Ft. 163.38 Sq. Mi.
80°00' LONGITUDE WEST FROM GREENWICH

Nobel Prize in Physiology or Medicine

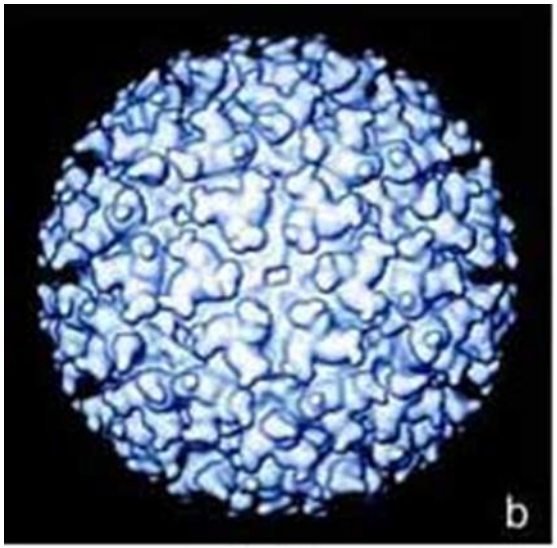
- **Max Theiler –** 1951 - "for his discoveries concerning yellow fever and how to combat it“

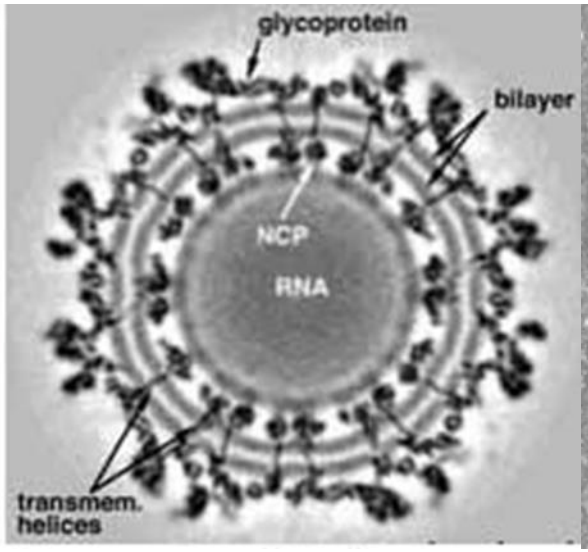
Yellow Fever

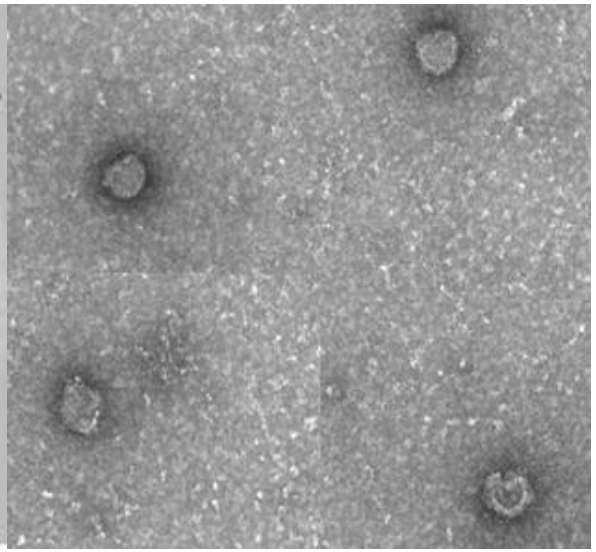


YELLOW FEVER VIRUS

Etiological agent:







Transmission Cycles of yellow fever

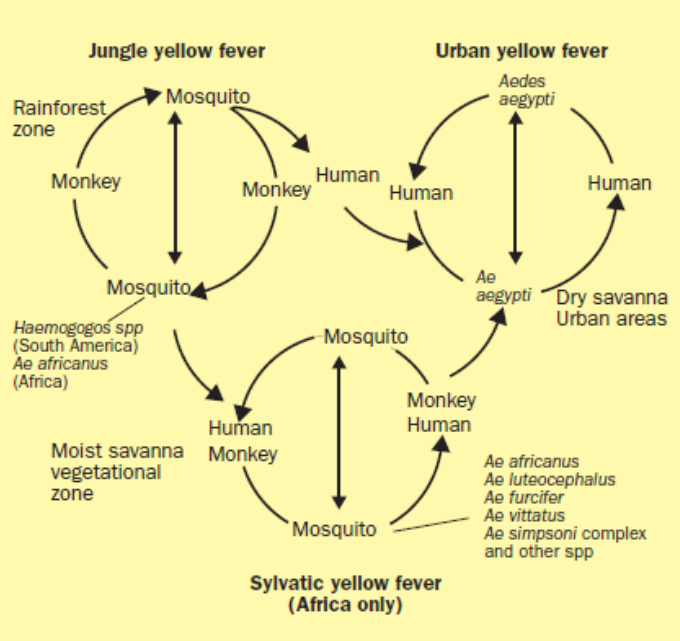
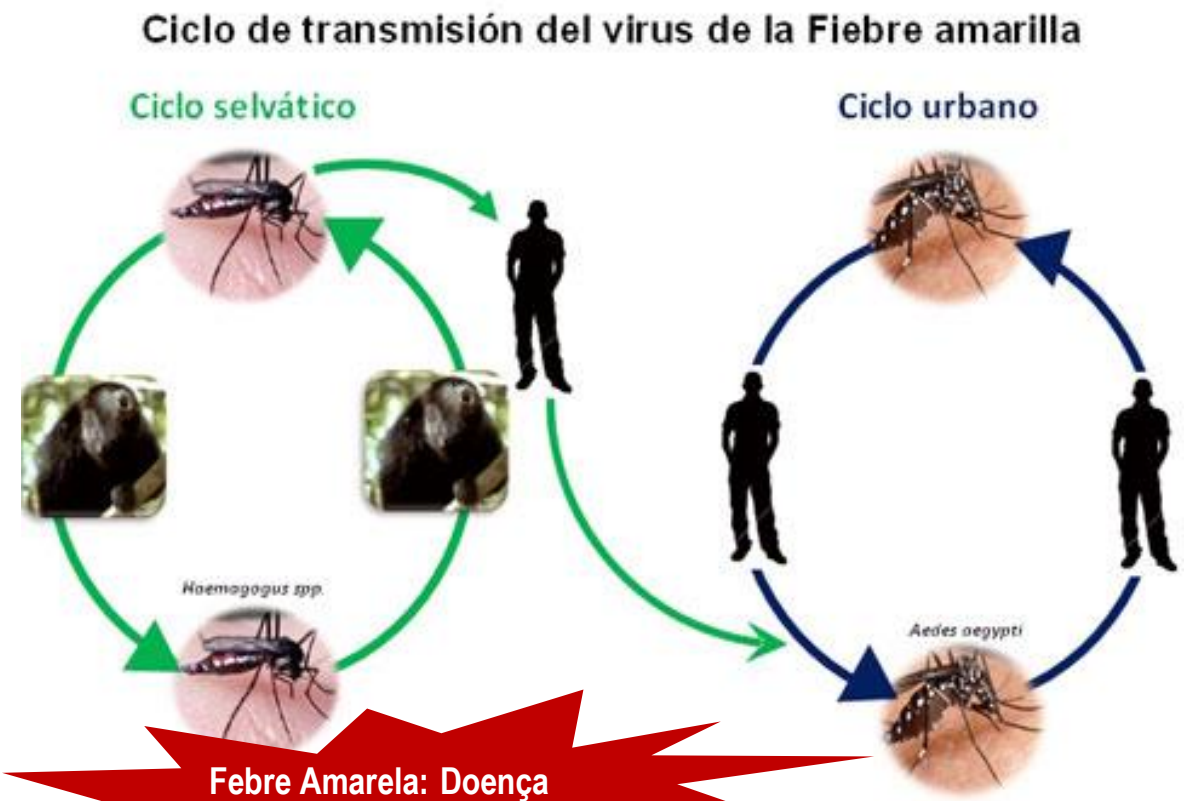


Figure 3. The transmission cycles of yellow fever. The virus is maintained by transmission between monkeys and tree-hole breeding mosquitoes. Human beings acquire "jungle yellow fever" when exposed to the bite of mosquitoes that have previously fed on an infected monkey. The vectors and ecology differ in Africa and South America. In Africa, tree-hole breeding Aedes spp reach high densities in the moist savanna vegetational zone and transmit the virus between people. In both continents, Ae aegypti, which breeds in and around houses in man-made containers, is responsible for interhuman transmission of "urban" yellow fever virus.



Febre Amarela: Doença não erradicável!

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Instituto de Tecnologia em Imunobiológicos
Bio-Manguinhos
40 anos

Fonte: SVS/MS

Hosts

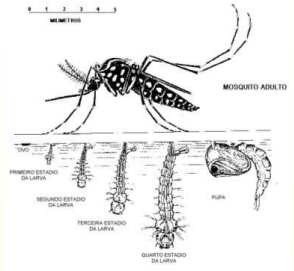
Cebus sp
(macaco prego)

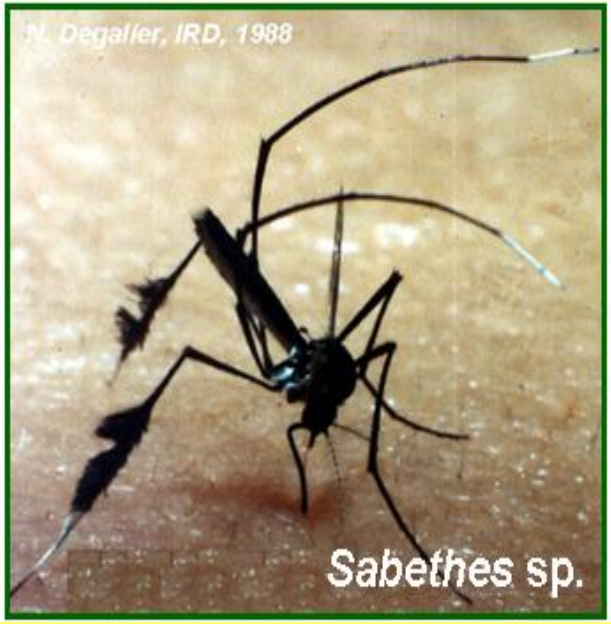
Alouatta sp
(guariba, bugio)

Callithrix sp
(mico, soim)

Host — Amplify — Disseminate

Vectors





Vectors — Reservoirs — Dissemination

THE DISEASE

Figure 5. Yellow fever patient during the period of infection. The patient febrile and acutely ill, with prominent conjunctival congestion. During th pre-icteric phase, the illness is difficult to differentiate from many other infectious diseases. Virus is present in the blood and the patient is infectious for blood-feeding mosquitoes.

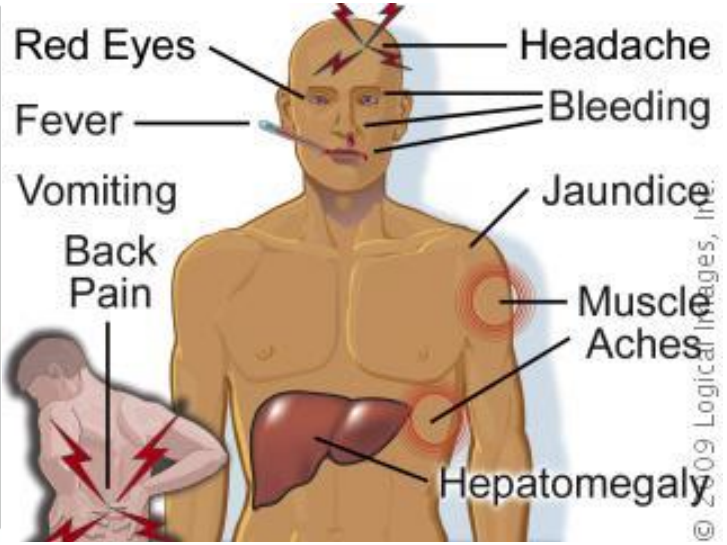


Figura 6 - O "iceberg" da febre amarela. Distribuição das formas clínicas.

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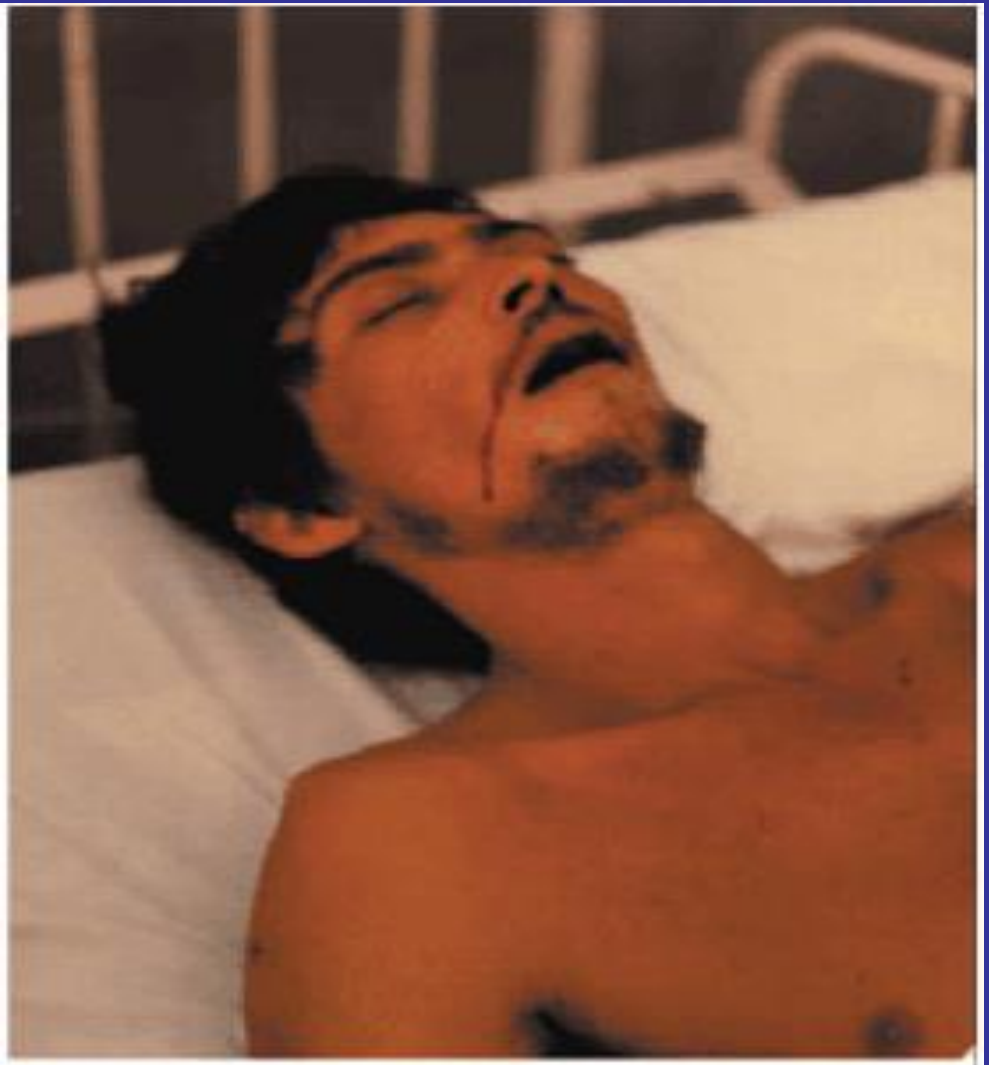


Figura 7- Febre amarela. Paciente em coma com quadro maligno. Notar hemorragia.

Pedro Fernando da Costa Vasconcelos. Rev. Soc. Bras. Med. Trop. vol.36 no.2 Uberaba Mar./Apr. 2003

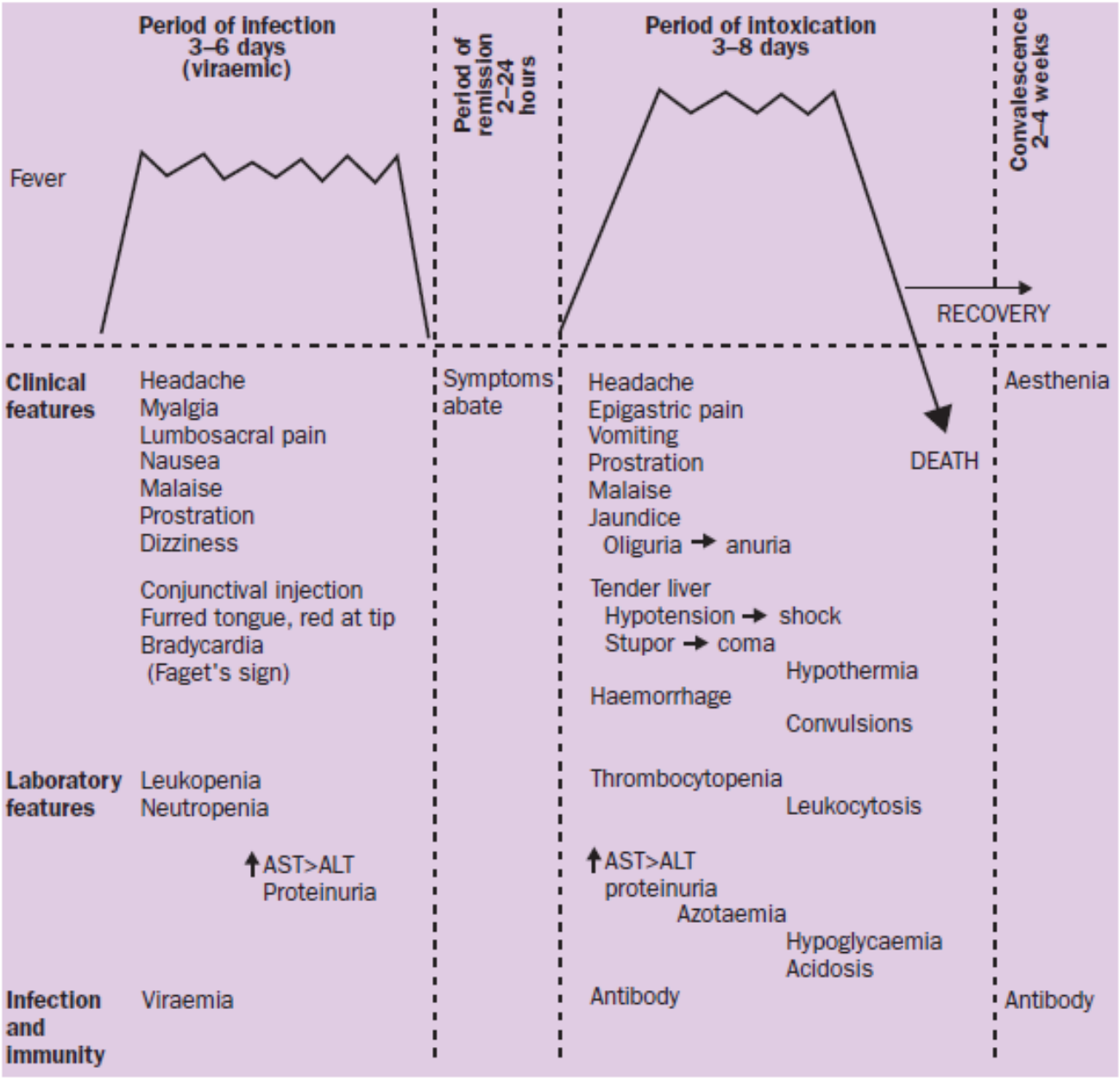
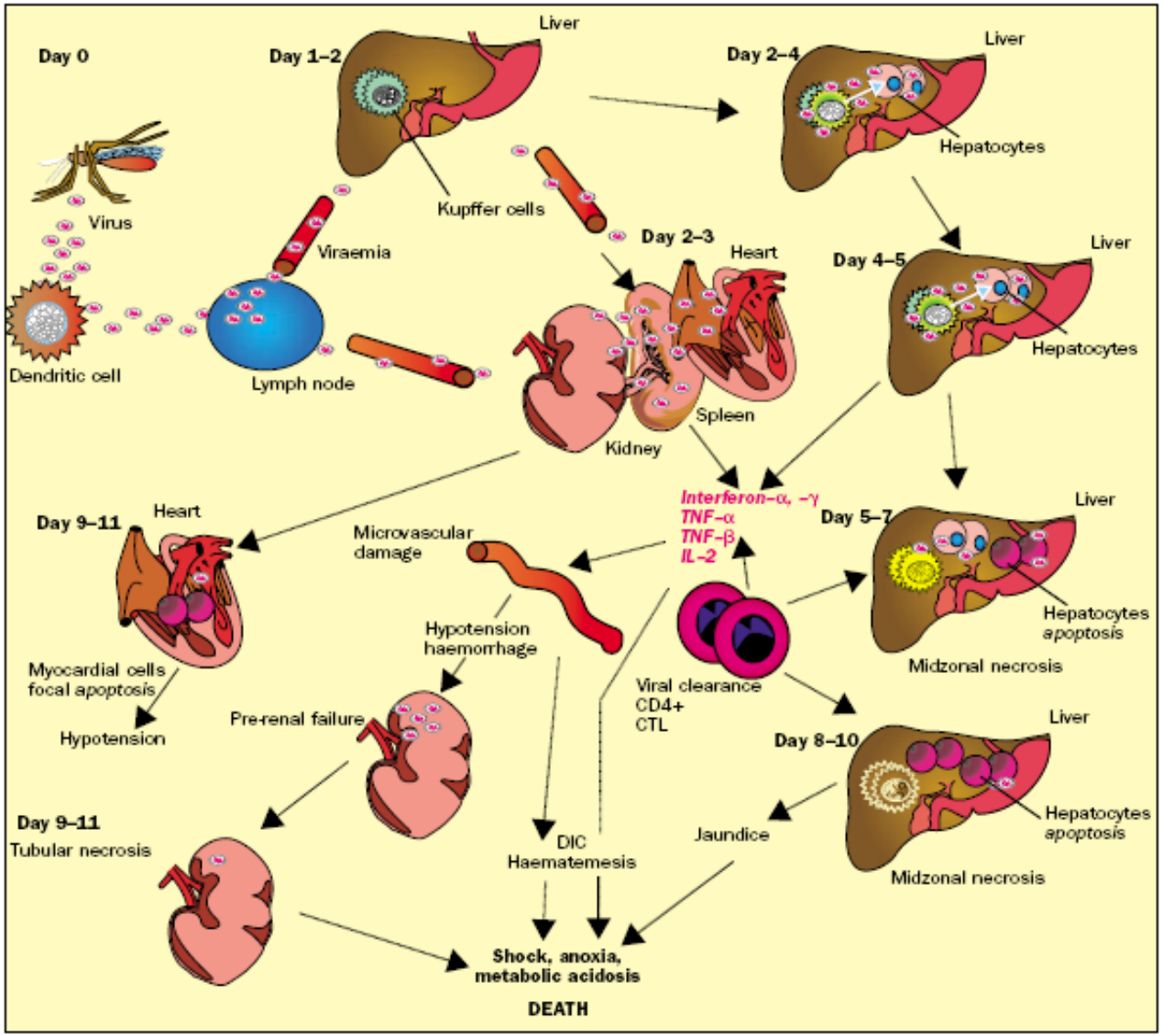


Figure 4. Stages of yellow fever infection, showing the major clinical and laboratory features of the disease.

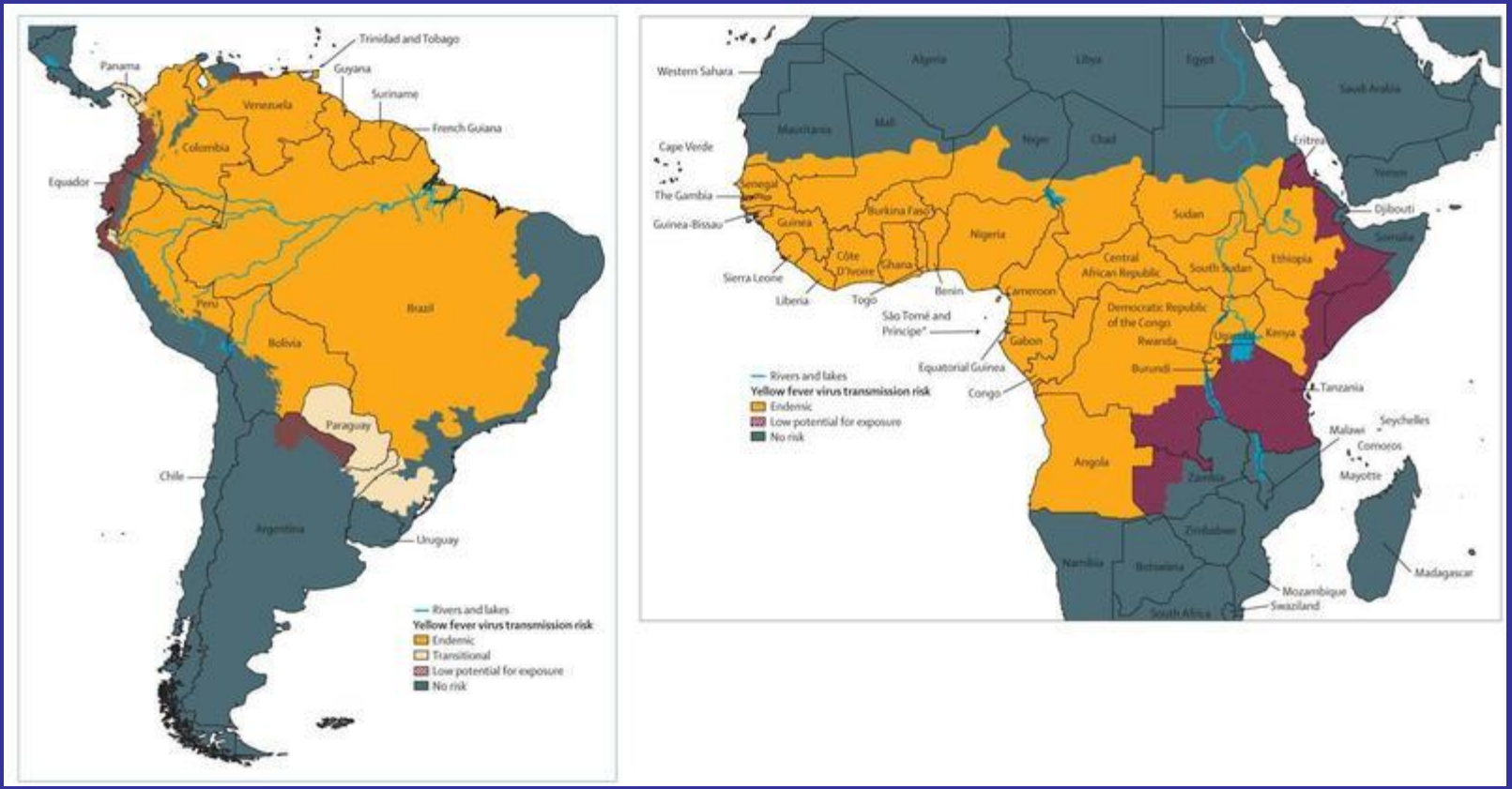
YF Pathogenesis



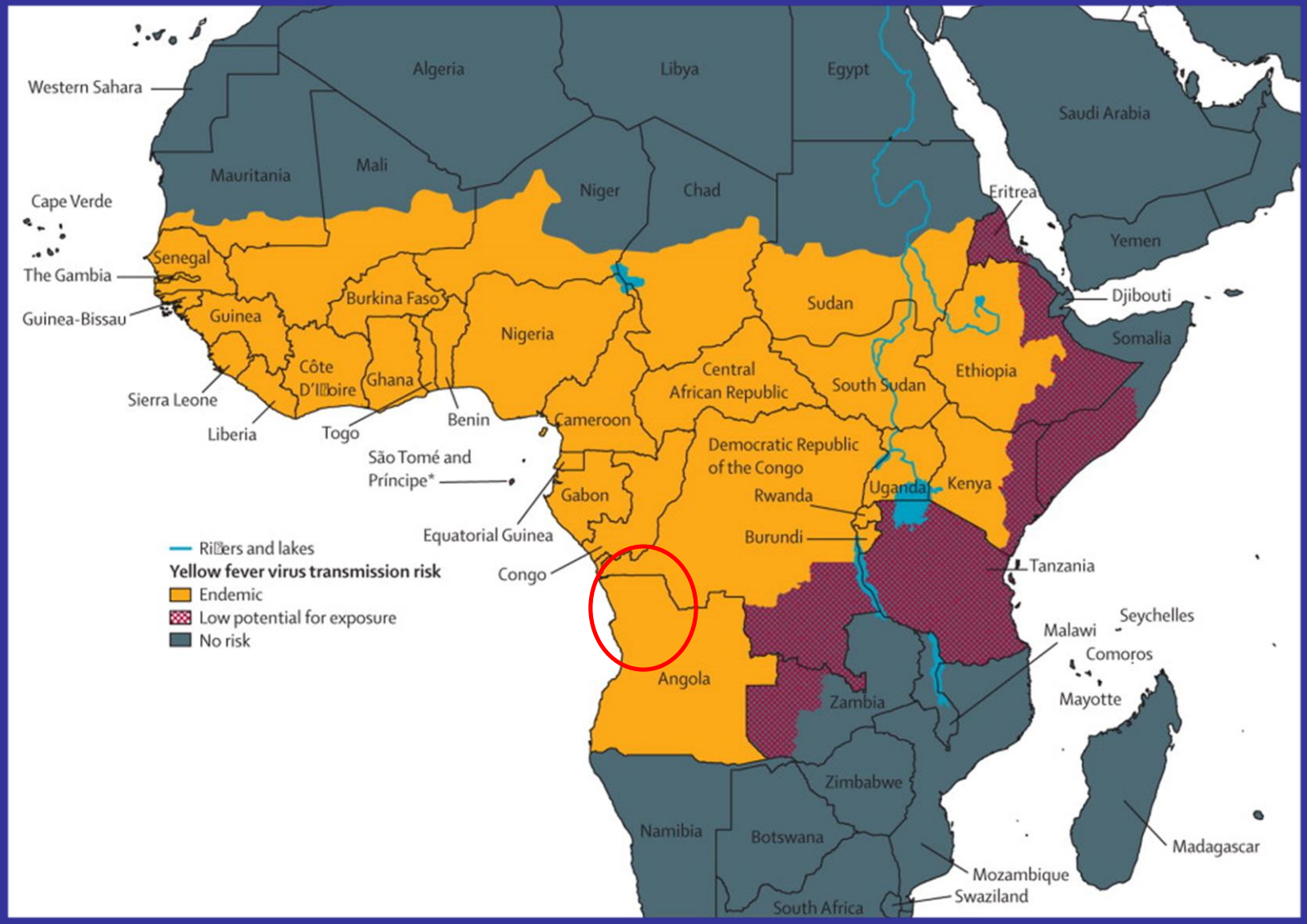
THE LANCET Infectious Diseases Vol 1 August 2001

CURRENT SITUATION OF YFV

YELLOW FEVER VIRUS TRANSMISSION RISK



EPIDEMIC IN AFRICA
2016



EPIDEMIC IN AFRICA (DEMOCRATIC REPUBLIC OF THE CONGO AND ANGOLA) 2016

Angola
884 confirmed cases
121 deaths among confirmed cases (case fatality rate, 13.7%)
4347 suspected cases
377 deaths among suspected cases (case fatality rate, 8.7%)

Kenya
2 confirmed cases

China
11 confirmed cases

DR Congo
78 confirmed cases (57 imported from Angola, 8 sylvatic, 13 autochthonous)
16 deaths among confirmed cases (case fatality rate, 21.1%)
2987 suspected cases
121 deaths among suspected cases (case fatality rate, 4.0%)

Approximately 30 million people were vaccinated in the two countries.

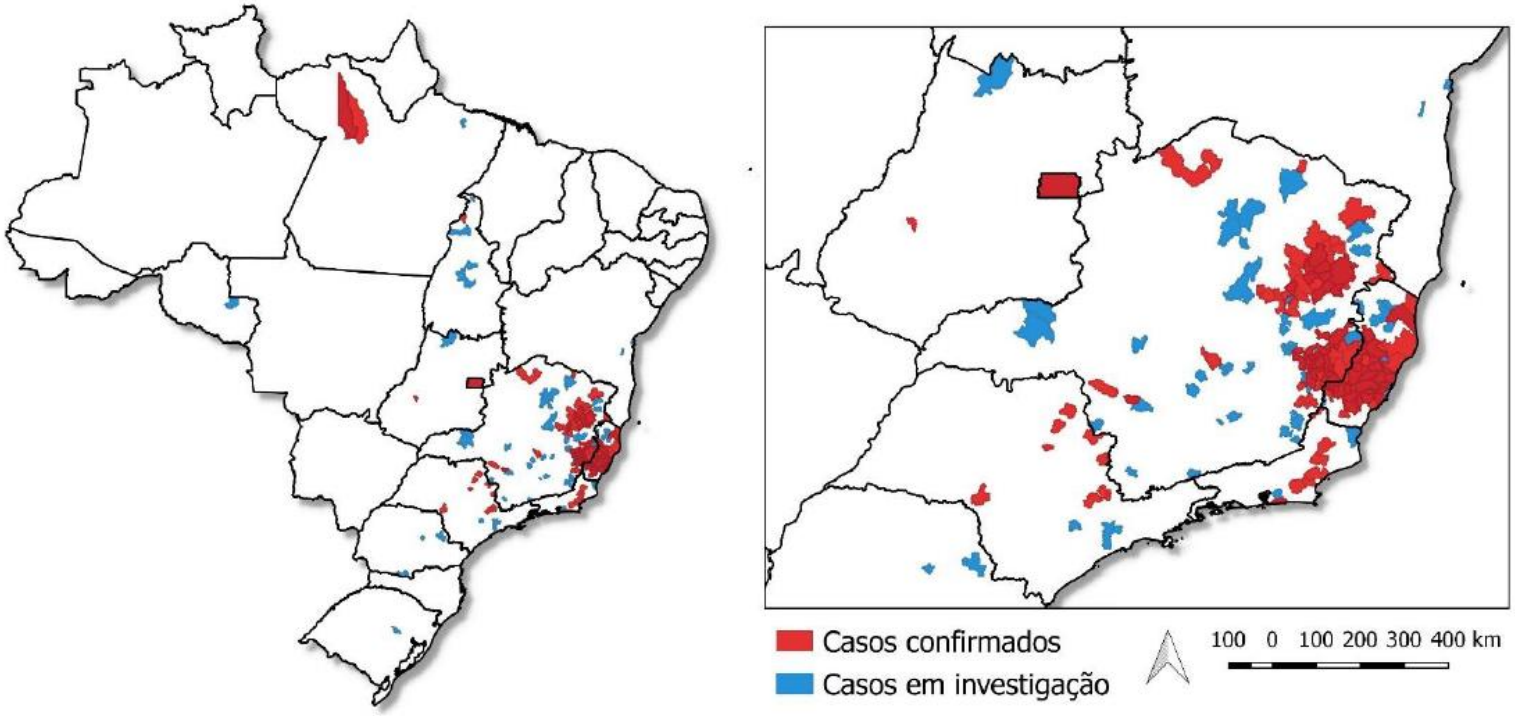
This depleted the WHO/UNICEF and Brazilian stocks

YELLOW FEVER IN THE AMERICAS

YELLOW FEVER CASES IN BRAZIL

01/12/16 -31/05/17

Figura 1 - Distribuição geográfica dos casos suspeitos de febre amarela notificados à SVS/MS até 31 de maio de 2017, com início dos sintomas a partir de 01 dezembro de 2016, por município do LPI e classificação.



CASES OF YELLOW FEVER IN BRAZIL
2016 - 2017

Tabela 1- Distribuição dos casos de febre amarela notificados à SVS/MS até 31 de maio de 2017, com início dos sintomas a partir de 01 dezembro de 2016, por UF do Local Provável de Infecção (LPI) e classificação.

REGIÃO	UF do LPI	Municípios com casos notificados	Classificação dos casos			
			Casos Confirmados	Casos em Investigação	Casos Descartados	Total de casos notificados
CENTRO OESTE	Goiás	19	1	9	65	75
	Distrito Federal	1	1	4	49	54
	Mato Grosso do Sul	3	0	1	8	9
	Mato Grosso	2	1	0	11	12
NORTE	Amapá	1	0	1	4	5
	Tocantins	9	1	10	19	30
	Rondônia	1	0	3	6	9
	Pará	11	4	12	29	45
NORDESTE	Bahia	12	0	6	20	26
	Maranhão	2	0	2	13	15
SUDESTE	Espírito Santo	59	260	180	390	830
	Minas Gerais	173	487	223	885	1595
	Rio de Janeiro	18	17	9	56	82
	São Paulo	67	20	37	313	370
SUL	Rio Grande do Sul	11	0	4	20	24
	Santa Catarina	7	0	2	14	16
	Paraná	11	0	16	15	31
Descartados por outras UF´s[1]		-	0	0	12	12
Total[2]		**407**	**792**	**519**	**1929**	**3240**

[1] Casos descartados por outras UF´s (AM, CE, RR, RN e PI)

[2] Excluídas as duplicidades de registros na base de dados nacional

SUS MINISTÉRIO DA SAÚDE BRASIL GOVERNO FEDERAL

Ministério da Saúde FIOCRUZ Fundação Oswaldo Cruz

Instituto de Tecnologia em Imunobiológicos Bio-Manguinhos 40 anos

FATAL CASES OF YELLOW FEVER IN BRAZIL

2016 -2017

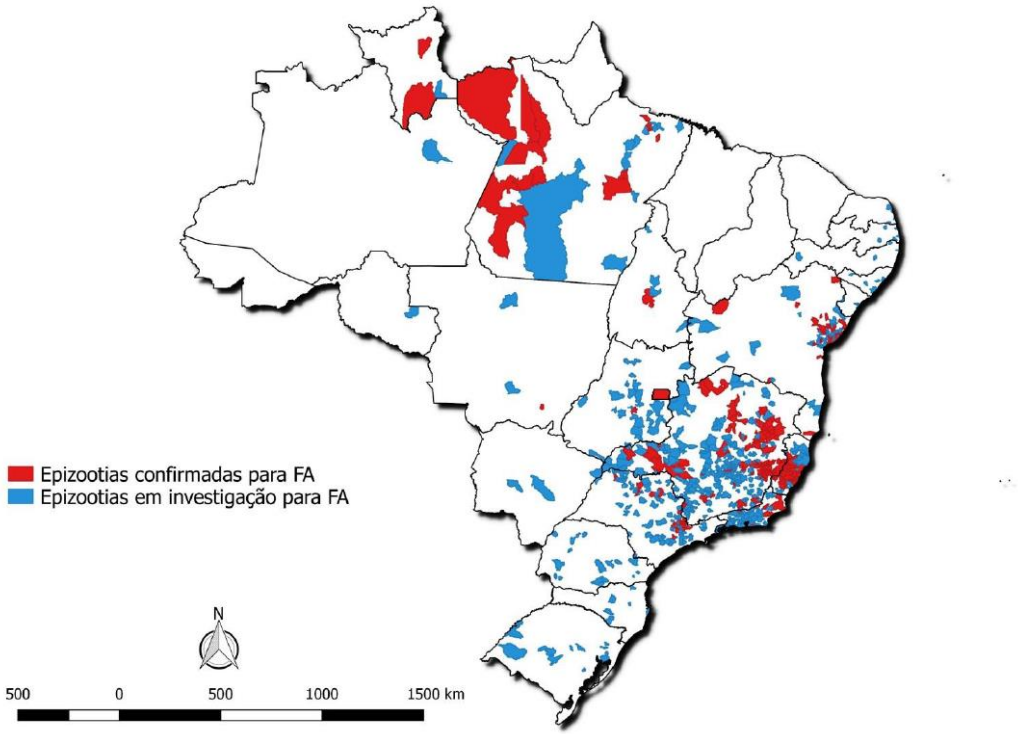
Tabela 2 - Distribuição dos óbitos suspeitos de febre amarela entre o total de casos notificados à SVS/MS até 31 de maio de 2017, com início dos sintomas a partir de 01 dezembro de 2016, por UF do Local Provável de Infecção (LPI) e classificação.

Região	UF do LPI	Municípios com óbitos	Classificação dos óbitos			
			Óbitos Confirmados	Óbitos em Investigação	Óbitos Descartados	Total de óbitos notificados
NORTE	Pará	3	4	0	2	6
	Tocantins	1	0	1	0	1
CENTRO OESTE	Goiás	3	1	1	4	6
	Distrito Federal	1	1	1	6	8
	Mato Grosso	1	1	0	1	2
SUDESTE	Espírito Santo	33	85	17	20	122
	Minas Gerais	61	165	15	44	224
	Rio de Janeiro	7	7	1	3	11
	São Paulo	15	10	0	37	47
SUL	Paraná	1	0	1	0	1
Descartados por outras UF´s[1]		-	0	0	7	7
Total		**126**	**274**	**37**	**124**	**435**

[1] **Óbitos descartados por outras UF´s (AM, AP, BA, MA, RS e SC)**

GEOGRAPHICAL DISTRIBUTION OF EPIZOOTICS IN BRAZIL

Figura 5 - Distribuição geográfica das epizootias em primatas não humanos suspeitas de febre amarela notificadas à SVS/MS até 31 de maio de 2017, com data de ocorrência a partir de 01 dezembro de 2016, por município do Local Provável de Infecção (LPI) e classificação.



YELLOW FEVER VACCINE

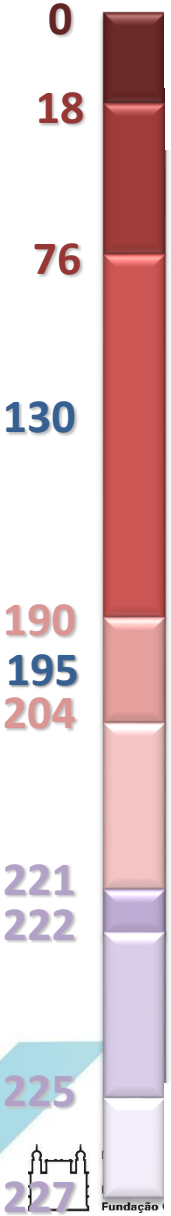
History of Virus Attenuation of Wild Yellow Fever Asibi Strain

30/06/1927

ASIBI virus,

Mahaffi & Bauer

54 passages in rhesus monkeys



December 1933. Minced tissue were inoculated with monkey sera infected with Asibi strain

18 passages in minced mouse embryo tissue

58 passages in minced whole chick embryo

designated 17D strain

114 passages using chick embryo without nervous tissues

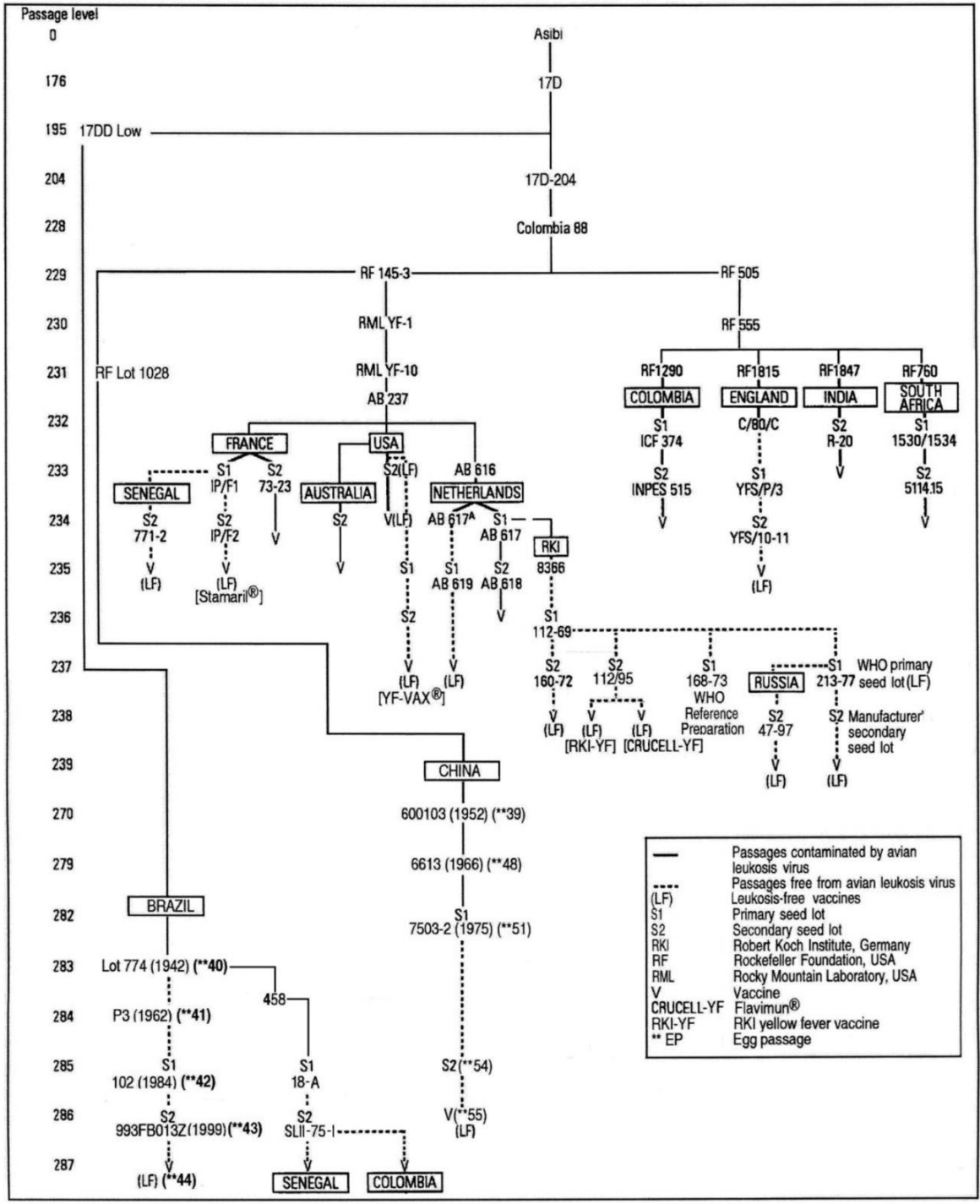
begin the 17DD strain

passages using chick embryo tissues without head and spinal cord and normal monkey or human serum

1936 - At 227th and 229th passages – experimental vaccination in Rockefeller Foundation employees. *Acceptable tolerability, development of neutralizing antibodies*

Yellow Fever` seed virus passage in different Manufacturers

Genealogy of yellow fever vaccine strains. All strains are derived from the Asibi strain and the 176 strain derived from it by passage. The divergence of the different seed strains is shown.



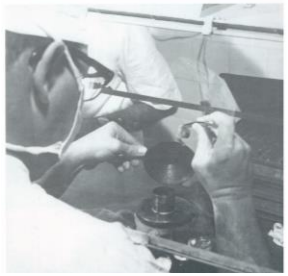
https://doi.org/10.1016/j.virol.2015.03.032

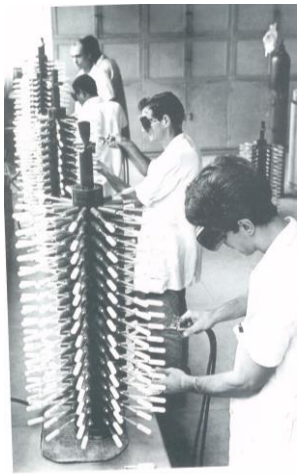
PASSAGE HISTORY OF 17DD SUBSTRAIN

In vitro subcultures	Egg passages	Brazil	Senegal
243	0		
283	40	EP 774	
284	41	S1 M3 / S1 458	
285	42	S2 / S2	S1 18-A
286	43	V / V	S2 75-1
287	44		V

Figure 38-19 Passage history of the 17DD substrain (derivation shown in Figure 38-17) to prepare seed viruses and vaccines in Brazil and Senegal. From Brès P, Koch M. Production and testing of the WHO yellow fever primary seed lot 213-77 and reference batch 168-73.WHO Expert Committee on Biological Standardization, 36th Report. Geneva: World Health Organization; 1987, with permission.

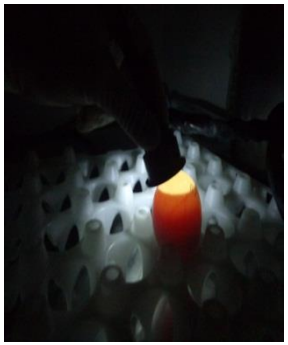
VACCINE PRODUCTION PROCESS (1942)

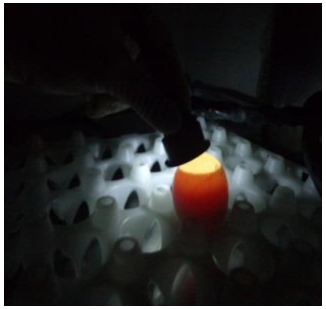




Fechamento das ampolas nas "arvores" ou "cachos".
Rio de Janeiro, 1950.
Album: LAFA/Bio-Manguinhos/Fiocruz

VACCINE PRODUCTION PROCESS (2017).





Suspensão viral (IFA)

Tri

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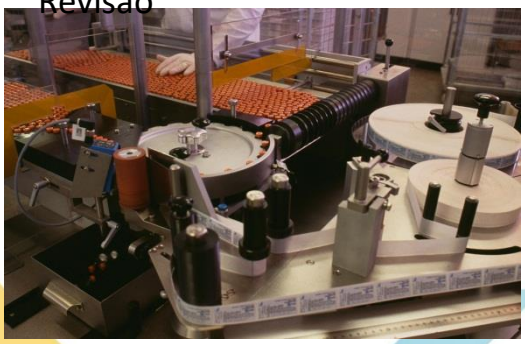
Instituto de Tecnologia em Imunobiológicos
Bio-Manguinhos
40 anos

VACCINE PRODUCTION PROCESS (2017).

Revisão



RESEARCH PAPER

Human Vaccines & Immunotherapeutics 12:2, 491–502; February 2016; Published with license by Taylor & Francis Group, LLC

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Previous years

Statements

Notes for the media

Commentaries

Events

Yellow fever vaccination booster not needed

News release

17 MAY 2013 | GENEVA - The yellow fever 'booster' vaccination given ten years after the initial vaccination is not necessary, according to WHO. An article published in WHO's Weekly Epidemiological Record (WER) reveals that the Organization's Strategic Advisory Group of Experts on immunization (SAGE) has reviewed the latest evidence and concluded that a single dose of vaccination is sufficient to confer life-long immunity against yellow fever disease.

Since yellow fever vaccination began in the 1930s, only 12 known cases of yellow fever post-vaccination have been identified, after 600 million doses have been dispensed. Evidence showed that among this small number of "vaccine failures", all cases developed the disease within five years of vaccination. This demonstrates that

Related links

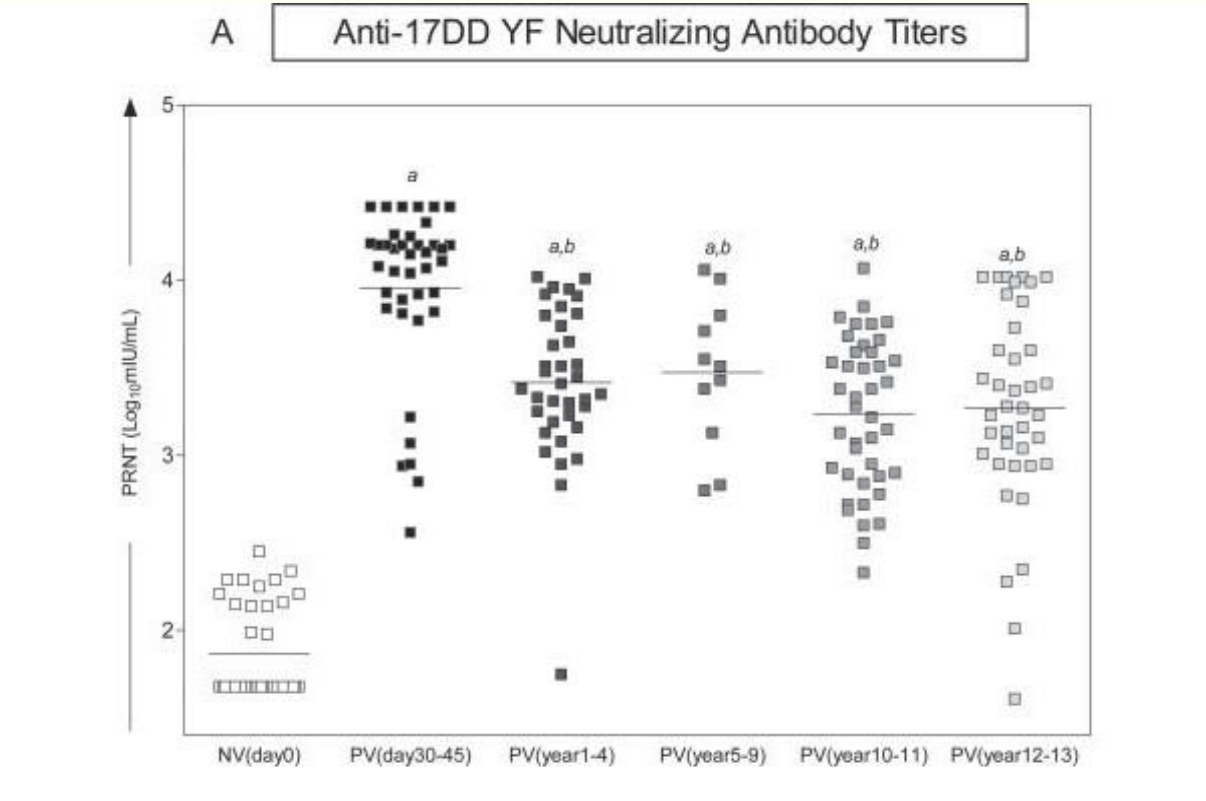
Weekly Epidemiological Record (WER)

About SAGE

Yellow fever fact sheet

More on yellow fever

DURATION OF IMMUNITY



Rev Saúde Pública 2004;38(5):671-8
www.fsp.usp.br/rsp

Immunogenicity of WHO-17D and Brazilian 17DD yellow fever vaccines: a randomized trial

Imunogenicidade das vacinas contra febre amarela WHO-17D e 17DD: ensaio randomizado

Luiz Antonio Bastos Camacho[a], Marcos da Silva Freire[b], Maria da Luz Fernandes Leal[b], Savitri Gomes de Aguiar[b], Jussara Pereira do Nascimento[b], Takumi Iguchi[a], José de Azevedo Lozana[a], Roberto Henrique Guedes Farias[c] and Collaborative Group for the Study of Yellow Fever Vaccines*

[a]Escola Nacional de Saúde Pública. Fundação Oswaldo Cruz (Fiocruz). Rio de Janeiro, RJ, Brasil.
[b]Instituto de Tecnologia em Imunogiológicos. Bio-Manguinhos. Fiocruz. Rio de Janeiro, RJ, Brasil.
[c]Instituto de Biologia do Exército. Rio de Janeiro, RJ, Brasil

Successful Use of Fractioned Doses (1/5th)

- Backed up by SAGE
- Strong political buy-in
- 2 months from decision to implementation
- Technical, Operational & Logistical challenges
  - Syringe supply, vaccine reconstitution, training of HCW, social mobilization…
- Coordinated effort among multiple partners (MoH, NGOs, National and International PH agencies, donors, community)
- INRB/CDC immunogenicity study ongoing on 742 individuals
- SAGE will meet mid-October to provide recommendations on FD

~7, 5 m people >2y vaccinated in Kinshasa

SERIOUS ADVERSE EVENTS OF YF VACCINE

Case	Place, year	Age, years	Sex	Time after vaccination days	Clinical and laboratory summary	Outcome

Virology 290, 309–319 (2001)
doi:10.1006/viro.2001.1168, available online at http://www.idealibrary.com on IDEAL®

Phenotypic and Molecular Analyses of Yellow Fever 17DD Vaccine Viruses Associated with Serious Adverse Events in Brazil

R. Galler,*,[1] K. V. Pugachev,† C. L. S. Santos,‡ S. W. Ocran,† A. V. Jabor,* S. G. Rodrigues,§ R. S. Marchevsky,¶ M. S. Freire,¶ L. F. C. Almeida,¶ A. C. R. Cruz,§ A. M. Y. Yamamura,¶ I. M. Rocco,‡ E. S. Travassos da Rosa,§ L. T. M. Souza,‡ P. F. C. Vasconcelos,§ F. Guirakhoo,† and T. P. Monath†

*Instituto Oswaldo Cruz and ¶Instituto de Tecnologia em Imunobiológicos, Fundação Oswaldo Cruz, 21045-900, Rio de Janeiro, RJ, Brazil; †Acambis, Inc, Cambridge, Massachusetts; ‡Instituto Adolpho Lutz, São Paulo, SP, Brazil; and §Instituto Evandro Chagas/Fundação Nacional de Saúde, Belém, PA, Brazil

Received July 6, 2001; returned to author for revision August 20, 2001; accepted August 31, 2001

					Coagulation disorder.	
6	Rio Grande do Sul, 2001	4	M	4	Fever, prostration, petechiae. Lymphadenopathy. AST and ALT 20 x; Bilirubin 7,01. Leukopenia with left shift. Renal failure.	Death 10th day
7	Rio de Janeiro, 2003	67	M	4	Fever, asthenia, myalgia, cephalea and prostration. AST: 2572; TGP: 2525. Leukopenia. Respiratory failure. Yellow fever neutralizing antibodies: 3533 mUI/mL (10 days after vaccination); 43875 mUI/mL (23 days after vaccination).	Recovered 48th day

SERIOUS ADVERSE EVENTS OF YF VACCINE

❖ Dados internacionais

- Eventos adversos severos: eventos viscerotrópicos (0,3/100.000 doses)
- Eventos neurológicos (0,4/100.000 doses)
- Anafilaxia (0,8/100.000 doses)

Source: Hayes EB, 2007

YELLOW FEVER VACCINE: TECHNOLOGICAL IMPROVEMENT

PRODUCTION OF YF 17DD VACCINE IN CEF

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Available online at www.sciencedirect.com

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Vaccine 23 (2005) 2499–2510

Vaccine

www.elsevier.com/locate/vaccine

Production of yellow fever 17DD vaccine virus in primary culture of chicken embryo fibroblasts: yields, thermo and genetic stability, attenuation and immunogenicity

Marcos S. Freire[a], George F. Mann[a,*,1], Renato S. Marchevsky[a], Anna M.Y. Yamamura[a], Luiz F.C. Almeida[a], Alfredo V. Jabor[c], José M.N. Malachias[a], Evandro S.F. Coutinho[b], Ricardo Galler[c]

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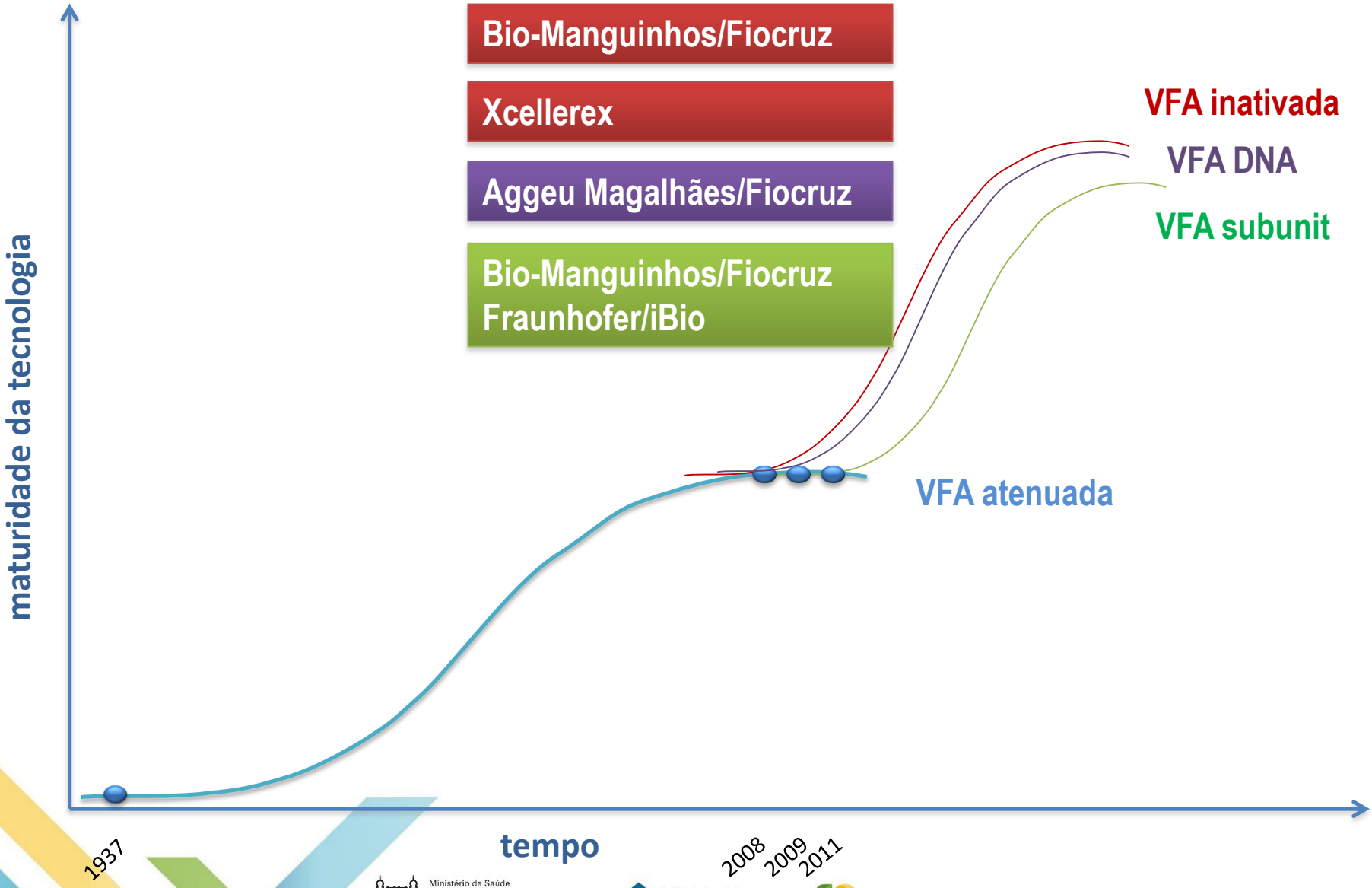
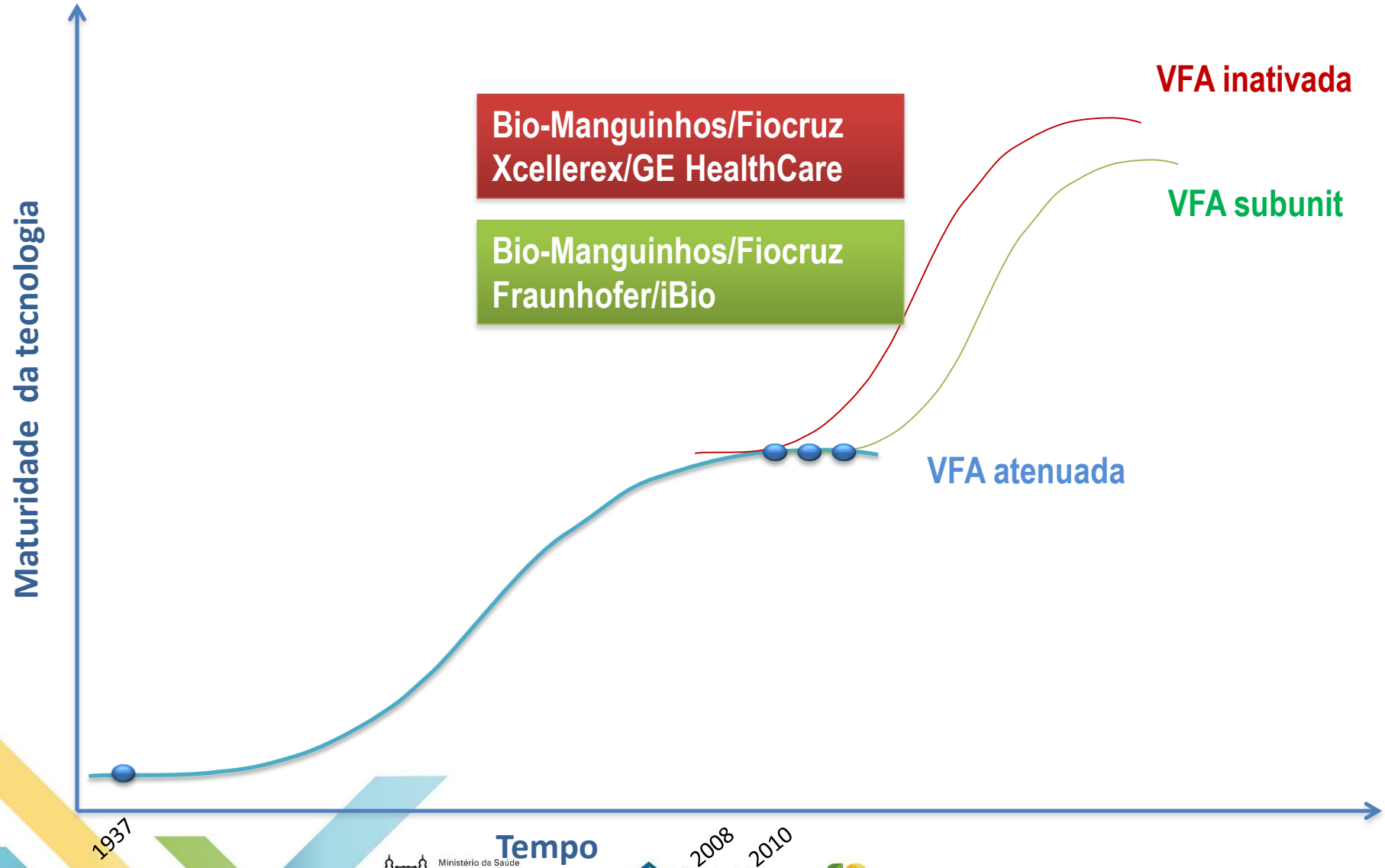
YELLOW FEVER VACCINE: TECHNOLOGICAL IMPROVEMENT



YELLOW FEVER VACCINE: TECHNOLOGICAL IMPROVEMENT



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Bio-Manguinhos
40 anos

AN INACTIVATE VACCINE AGAINST YF

Contents lists available at ScienceDirect

Journal of Virological Methods

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

Pressure-inactivated yellow fever 17DD virus: Implications for vaccine development

Luciane P. Gaspar[a,*], Ygara S. Mendes[b], Anna M.Y. Yamamura[a], Luiz F.C. Almeida[a], Elena Caride[a], Rafael B. Gonçalves[b,1], Jerson L. Silva[b], Andréa C. Oliveira[b], Ricardo Galler[a], Marcos S. Freire[a]

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[b] Programa de Biologia Estrutural, Instituto de Bioquímica Médica and Centro Nacional de Ressonância Magnética Nuclear de Macromoléculas Jiri Jonas, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ 21941-590, Brazil

Bio-Manguinhos/Fiocruz

AN INACTIVATE VACCINE AGAINST YF

The NEW ENGLAND JOURNAL of MEDICINE

From Xcellerex, Marlborough, MA (T.P.M., E.F., M.J.M., M.S., D.W.T.); Johnson City Clinical Trials, Lenexa, KS (C.T.J.); and Veristat, Holliston, MA (J.B.). Address reprint requests to Dr. Monath at Kleiner, Perkins, Caufield, and Byers, 2750 Sand Hill Rd., Menlo Park, CA 94025, or at tmonath@kpcb.com.

N Engl J Med 2011;364:1326-33.

ORIGINAL ARTICLE

An Inactivated Cell-Culture Vaccine against Yellow Fever

Thomas P. Monath, M.D., Elizabeth Fowler, Ph.D., Casey T. Johnson, D.O., John Balser, Ph.D., Merribeth J. Morin, Ph.D., Maggie Sisti, B.S., and Dennis W. Trent, Ph.D.

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40 anos

DNA VACCINE AGAINST YF

Anais da Academia Brasileira de Ciências (2009) 81(4): 663-669
(Annals of the Brazilian Academy of Sciences)
ISSN 0001-3765
www.scielo.br/aabc

Membrane and envelope virus proteins co-expressed as lysosome associated membrane protein (LAMP) fused antigens: a potential tool to develop DNA vaccines against flaviviruses

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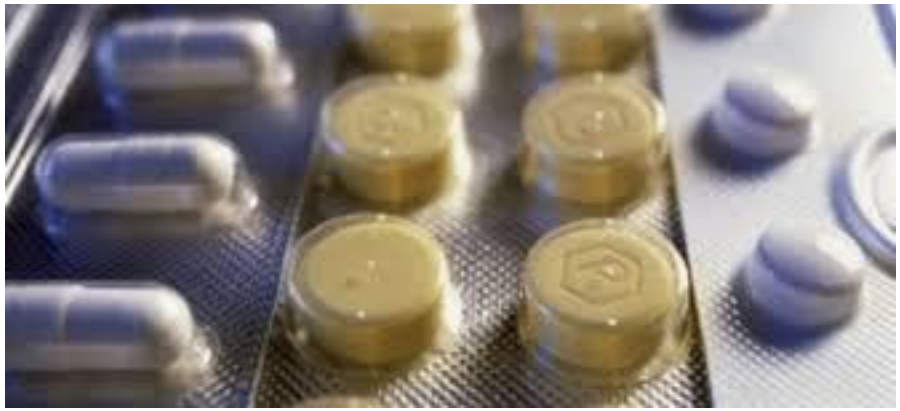
Manuscript received on August 5, 2008; accepted for publication on March 3, 2009;
presented by JERSON L. SILVA

Aggeu Magalhães/Fiocruz

HOW TO DO A CLINICAL TRIAL OF YF VACCINE?



DRUGS?

Journal of proteome research

Article

pubs.acs.org/jpr

Systems Biology Reveals NS4B-Cyclophilin A Interaction: A New Target to Inhibit YFV Replication

Alessandra Vidotto,[†] Ana T. S. Morais,[†] Milene R. Ribeiro,[†] Carolina C. Pacca,[†] Ana C. B. Terzian,[†] Laura H. V. G. Gil,[‡] Ronaldo Mohana-Borges,[§] Philippe Gallay,[∥] and Mauricio L. Nogueira*[,†]

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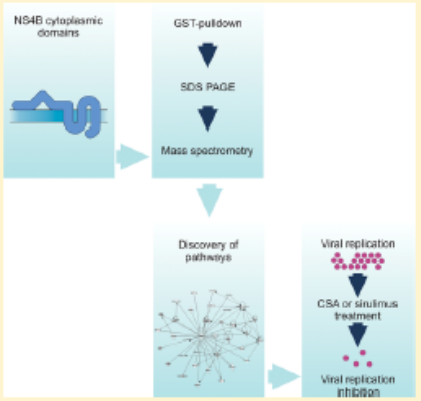
Supporting Information

ABSTRACT: Yellow fever virus (YFV) replication is highly dependent on host cell factors. YFV NS4B is reported to be involved in viral replication and immune evasion. Here interactions between NS4B and human proteins were determined using a GST pull-down assay and analyzed using 1-DE and LC−MS/MS. We present a total of 207 proteins confirmed using Scaffold 3 Software. Cyclophilin A (CypA), a protein that has been shown to be necessary for the positive regulation of flavivirus replication, was identified as a possible NS4B partner. 59 proteins were found to be significantly increased when compared with a negative control, and CypA exhibited the greatest difference, with a 22-fold change. Fisher's exact test was significant for 58 proteins, and the *p* value of CypA was the most significant (0.000000019). The Ingenuity Systems software identified 16 pathways, and this analysis indicated sirolimus, an mTOR pathway inhibitor, as a potential inhibitor of CypA. Immunofluorescence and viral plaque assays showed a significant reduction in YFV replication using sirolimus and cyclosporine A (CsA) as inhibitors. Furthermore, YFV replication was strongly inhibited in cells treated with both inhibitors using reporter BHK-21-rep-YFV17D-LucNeoIres cells. Taken together, these data suggest that CypA-NS4B interaction regulates YFV replication. Finally, we present the first evidence that YFV inhibition may depend on NS4B-CypA interaction.



KEYWORDS: *yellow fever virus, NS4B, proteomics, protein interactions, systems biology, cyclophilin A, cyclosporine A, sirolimus*

Antiviral Research 111 (2014) 82–92

Contents lists available at ScienceDirect

Antiviral Research

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

MEK/ERK activation plays a decisive role in yellow fever virus replication: Implication as an antiviral therapeutic target

Jonas D. Albarnaz [a,b,1], Leonardo C. De Oliveira [a,b,1], Alice A. Torres [a,b,1], Rafael M. Palhares [a,b], Marisa C. Casteluber [a,b], Claudiney M. Rodrigues [a,b], Pablo L. Cardozo [a,b], Aryádina M.R. De Souza [a,b], Carolina C. Pacca [c], Paulo C.P. Ferreira [b], Erna G. Kroon [b], Maurício L. Nogueira [c], Cláudio A. Bonjardim [a,b,*]

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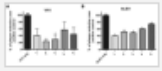
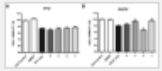
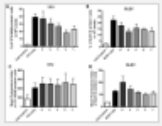
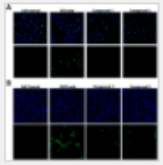
Figures and tables

Biomedicine & Pharmacotherapy

Volume 87, March 2017, Pages 381–387

Thiosemicarbazones and Phthalyl-Thiazoles compounds exert antiviral activity against yellow fever virus and Saint Louis encephalitis virus

Carolina Colombelli Pacca[a, b, 1], Rafael Elias Marques[c, 1], José Wanderlan P. Espindola[d], Gevânio B.O.Oliveira Filho[d], Ana Cristina Lima Leite[d], Mauro Martins Teixeira[c], Mauricio L. Nogueira[a]

Show more

http://doi.org/10.1016/j.biopha.2016.12.112

Abstract

Arboviruses, ***arthropod-borneviruses***, are frequency associated to human outbreak and represent a serious health problem. The genus Flavivirus, such as Yellow Fever Virus (YFV) and Saint Louis Encephalitis Virus (SLEV), are important pathogens with high morbidity and mortality worldwide. In Brazil, YFV is maintained in sylvatic cycle, but many cases are notified annually, despite the efficiency of vaccine. SLEV causes an acute encephalitis and is widely distributed in the Americas. There is no specific antiviral drugs for these viruses, only supporting treatment that can alleviate symptoms and prevent complications. Here, we evaluated the potential anti-YFV and SLEV activity of a series of thiosemicarbazones and phthalyl-thiazoles. Plaque reduction assay, flow cytometry, immunofluorescence and cellular viability were used to test the compounds *in vitro*. Treated cells showed efficient inhibition of the viral replication at concentrations that presented minimal toxicity to cells. The assays showed that phthalyl-thiazole and phenoxymethyl-thiosemicarbazone reduced 60% of YFV replication and 75% of SLEV replication.

Keywords

Virus Genes
DOI 10.1007/s11262-009-0328-3

RNA interference inhibits yellow fever virus replication in vitro and in vivo

Carolina C. Pacca · Adriana A. Severino · Adriano Mondini · Paula Rahal · Solange G. P. D'avila · José Antonio Cordeiro · Mara Correa Lelles Nogueira · Roberta V. M. Bronzoni · Maurício L. Nogueira

Received: 18 September 2008 / Accepted: 9 January 2009

Abstract RNA interference (RNAi) is a process that is induced by double stranded RNA and involves the degradation of specific sequences of mRNA in the cytoplasm of the eukaryotic cells. It has been used as an antiviral tool against many viruses, including flaviviruses. The genus *Flavivirus* contains the most important arboviruses in the world, i.e., dengue (DENV) and yellow fever (YFV). In our study, we investigated the in vitro and in vivo effect of RNAi against YFV. Using stable cell lines that expressed RNAi against YFV, the cell lines were able to inhibit as much as 97% of the viral replication. Two constructions (one against NS1 and the other against E region of YFV genome) were able to protect the adult Balb/c mice against YFV challenge. The histopathologic analysis demonstrated an important protection of the central nervous system by RNAi after 10 days of viral challenge. Our data suggests that RNAi is a potential viable therapeutic weapon against yellow fever.

Keywords RNAi · Yellow fever · Flaviviridae · Arboviruses

Virus Genes
DOI 10.1007/s11262-009-0328-3

RNA interference inhibits yellow fever virus replication in vitro and in vivo

Carolina C. Pacca · Adriana A. Severino · Adriano Mondini · Paula Rahal · Solange G. P. D'avila · José Antonio Cordeiro · Mara Correa Lelles Nogueira · Roberta V. M. Bronzoni · Maurício L. Nogueira

BUT NO CLINICAL DEVELOPMENT

Received: 18 September 2008 / Accepted: 9 January 2009

Abstract RNA interference (RNAi) is a process that is induced by double stranded RNA and involves the degradation of specific sequences of mRNA in the cytoplasm of the eukaryotic cells. It has been used as an antiviral tool against many viruses, including flaviviruses. The genus *Flavivirus* contains the most important arboviruses in the world, i.e., dengue (DENV) and yellow fever (YFV). In our study, we investigated the in vitro and in vivo effect of RNAi against YFV. Using stable cell lines that expressed RNAi against YFV, the cell lines were able to inhibit as much as 97% of the viral replication. Two constructions (one against NS1 and the other against E region of YFV genome) were able to protect the adult Balb/c mice against YFV challenge. The histopathologic analysis demonstrated an important protection of the central nervous system by RNAi after 10 days of viral challenge. Our data suggests that RNAi is a potential viable therapeutic weapon against yellow fever.

Keywords RNAi · Yellow fever · Flaviviridae · Arboviruses

Take Home Lesson

a) YFV is re-emerging in South America and Africa with higher than usual number of cases

b) There is a good vaccine

c) There is not enough vaccine available. The stocks are in record low

d) There is technology for new vaccines.

e) No drug available

LPV-FAMERP

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