Academia Brasileira de Ciências
Simpósio – Doenças Negligenciadas

Viroses negligenciadas

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ARBOVIRUSES IN BRAZIL

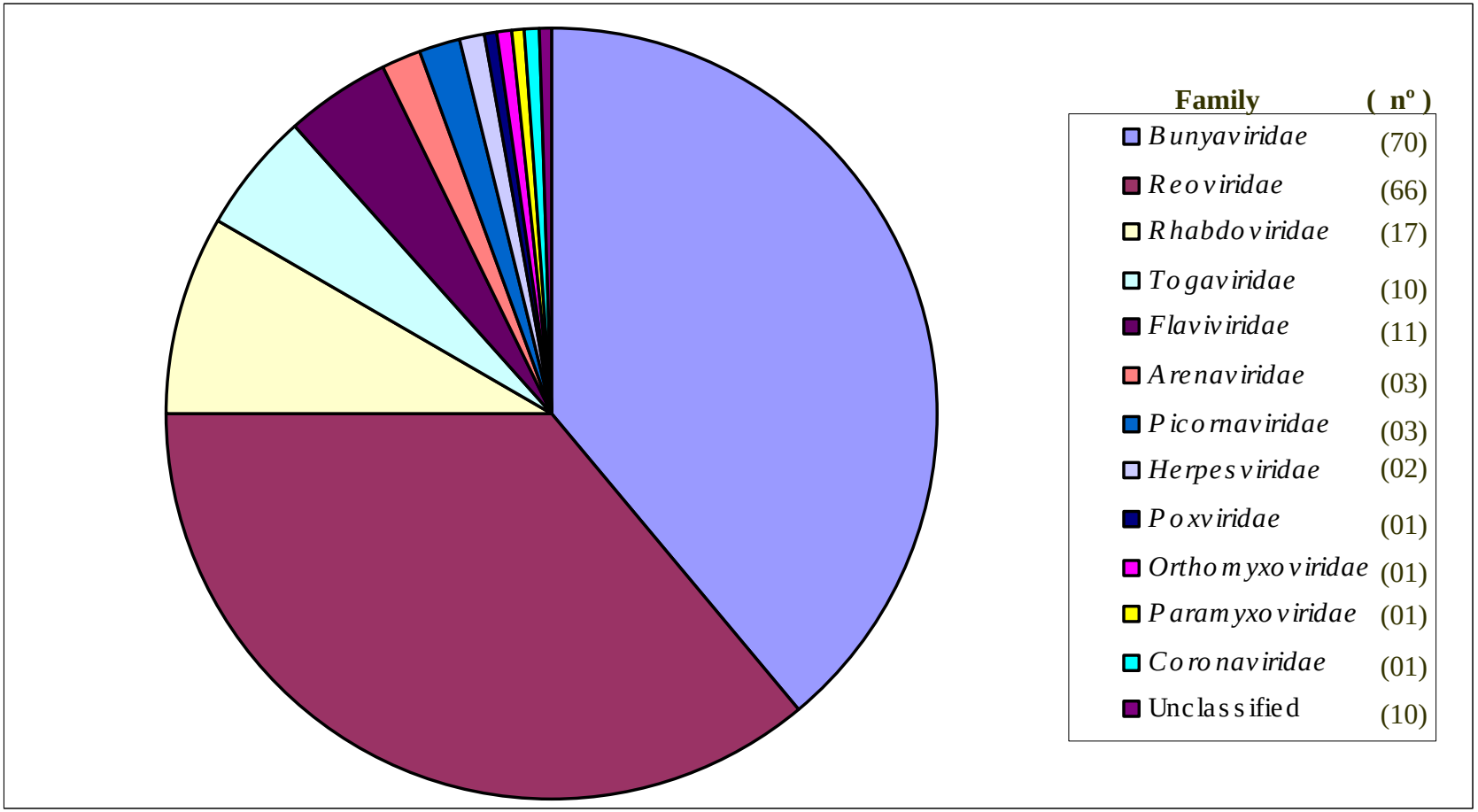
- In Brasil at least 210 arboviruses have been isolated.
- The Amazon forest is one of the most important, perhaps the more rich, natural eco-system reservoir for arboviruses in ther world, probably due its biodiversity.
- In the ***International Catalogue of Arbovirus and Certain Other Viruses of Vertebrates***, presently, 535 arboviruses including certain other viruses of vertebrates are registered.
- Approximately, 1/3 of all arboviruses registered in the world have been found in the Brazilian Amazon.

The IEC research activities Brazilian Amazon region

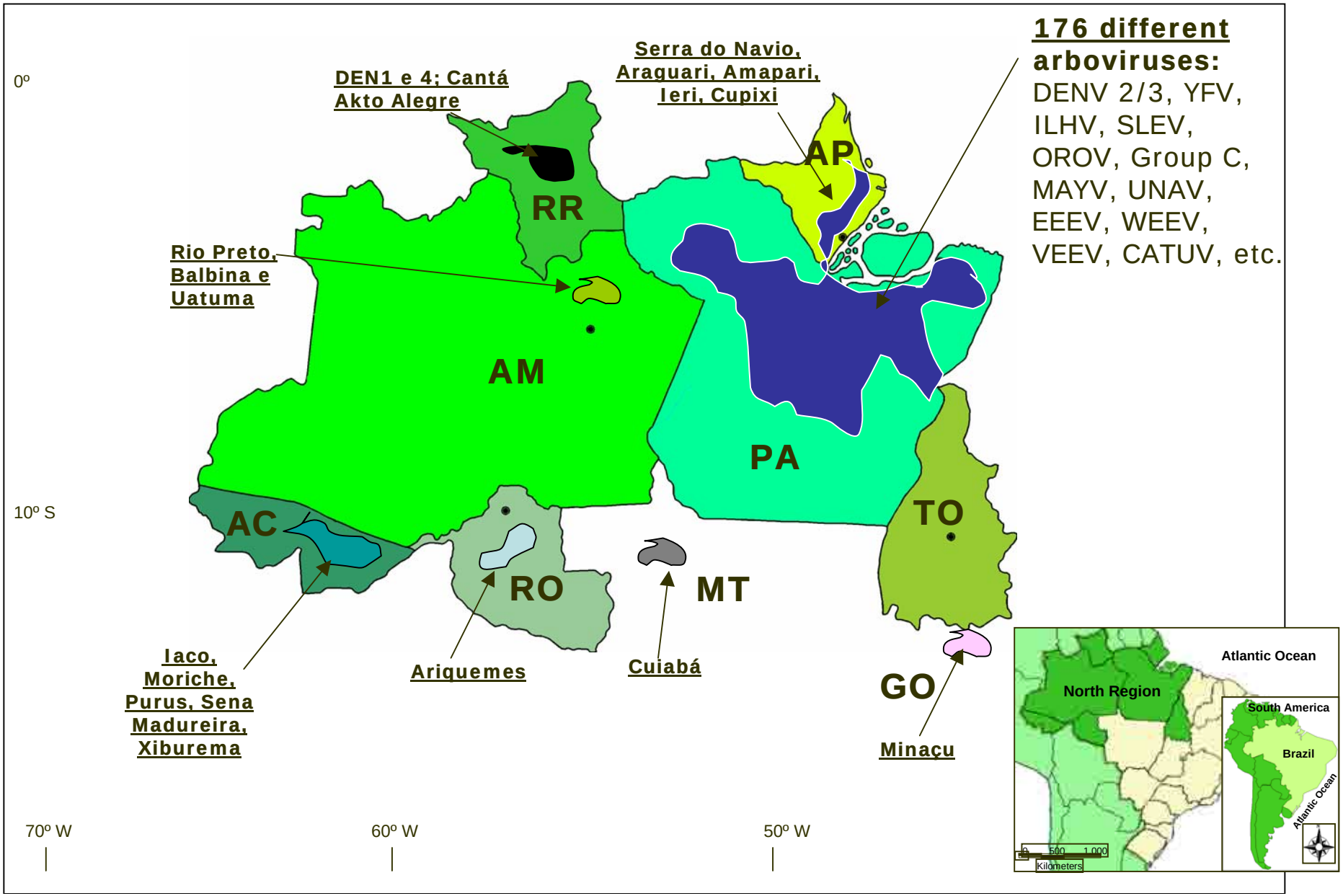
1954/2007:

- **Over 12,000 isolates of 196 types of arboviruses recognized**
- **163 isolated for the first time in Brasil**
- **At least 110 new to the science**
- **34 associated with disease in humans**
- **Five associated with epidemics or outbreaks: dengue, Mayaro, Oropouche, Rocio and yellow fever**

Distribution of 196 different types of arboviruses isolated in the Brazilian Amazon region according of the virus family



Place of isolation of 196 Arboviruses in the Brazilian Amazon, 1954-2006.



Factors associated in the emergence of arboviruses in the Amazon region of Brazil

- Growth of Amazonian population;
- Uncontrolled (unplanned) urbanization;
- Mining
- Construction of highways in the forest;
- Construction of hydroelectric (dams);
- Cut of forest for several purposes.

Surveillance of Arboviruses. Eco-epidemiologic studies in the Brazilian Amazon



Belem-Brasilia



Santarem- Cuiaba

1960: Belem-Brasilia highway.

1964: Serra do Navio/AP - ICOMI.

1970 - Construction of other highways.

1980: Construction of the Hydro-electric of Tucuruí/Pa.



Serra do Navio

During decades several other areas have been surveied for the circulation of arboviruses (Balbina, Jari, Cachoeira Porteira, Porto Trombetas, Carajás, etc) or are being studied (Salobo, Juruti, Santarem-Cuiaba Highway, etc) .



Itaituba-Jacareacanga



Porto Trombetas



Transamazon Highway -1972

Table 3. Arboviruses and serogroups emergents in Brazilian Amazon region, their probable factor(s) of emergence, and association with human disease.

Virus/groups	Probable factors for(s) emergence	Disease in man
Viruses		
Dengue	Poor mosquito control; increased urbanization in tropics.	Yes, epidemic
Gamboa	Flooding of dam *, Migrating birds.	Not yet
Guaroa	Flooding of dam *	Yes, sporadic cases
Mayaro	Deforestation	Yes, limited outbreak
Oropouche	Deforestation; increased of colonization and urbanization in Amazon.	Yes, epidemic
Triniti	Flooding of dam *	Not yet
Yellow fever	Urbanization in tropics; deforestation; lack of widespread immunization.	Yes, epidemic
Serogroups		
Anopheles A [1]	Flooding of dam *	Not yet
Changuinola [2]	Flooding of dam *, deforestation, use of subsoil.	Not yet

* During construction of dam in Tucurui, Pará State, millions of hematophagous insects were obtained in a few days, from which several strains of knwon and new viruses were obtained;

1 In this serogroup of family *Bunyaviridae*, the new virus species Arumateua, Caraipé and Tucurui were isolated, and occurred increase in circulation of Lukuni, Tacaiuma and Trombetas viruses.

2 In this serogroup of family *Reoviridae* 27 new virus species were isolated in Tucurui, 4 in Carajas (use of subsoil) and 8 in Altamira (deforestation for several purposes) from phlebotominae sandflies.

Vasconcelos et al., 2001

Oropouche

- Explosive epidemics in the Brazilian Amazon 1960 - 2009;
- Over 30 epidemics in the Brazilian Amazon; and in Peru and Panama;
- Approximately 500,000 infections;
- Large epidemics in Belém, Manaus, etc.;
- Febrile disease and Meningitis;
- Vector: *Culicoides parensis*;
- Silent and complexe mantainance cycle;
- Urban cyicle: midge-man;
- Four genotypes. Detection of reassortant OROV in nature.

Sylvatic cycle of Oropouche fever virus



Monkeys, birds, sloths, rodents

Vertebrate Host

Hematophagous Arthropod

Vertical transmission

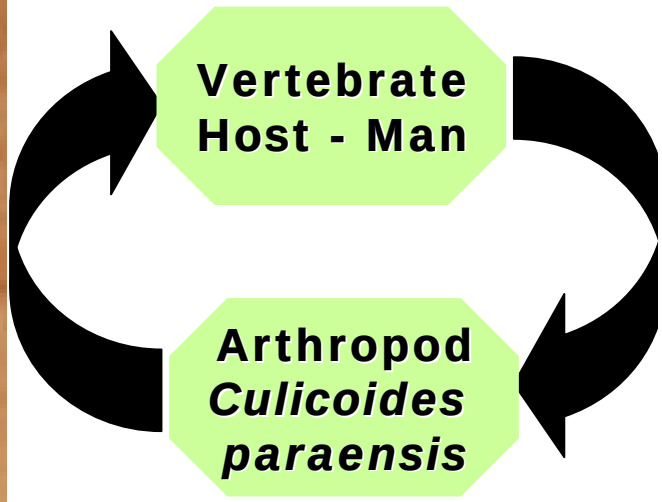
Aedes serratus, Coquilletidia venezuelensis

Hematophagous Arthropod

Pinheiro et al., Am. J. Trop. Med. Hyg., 1981

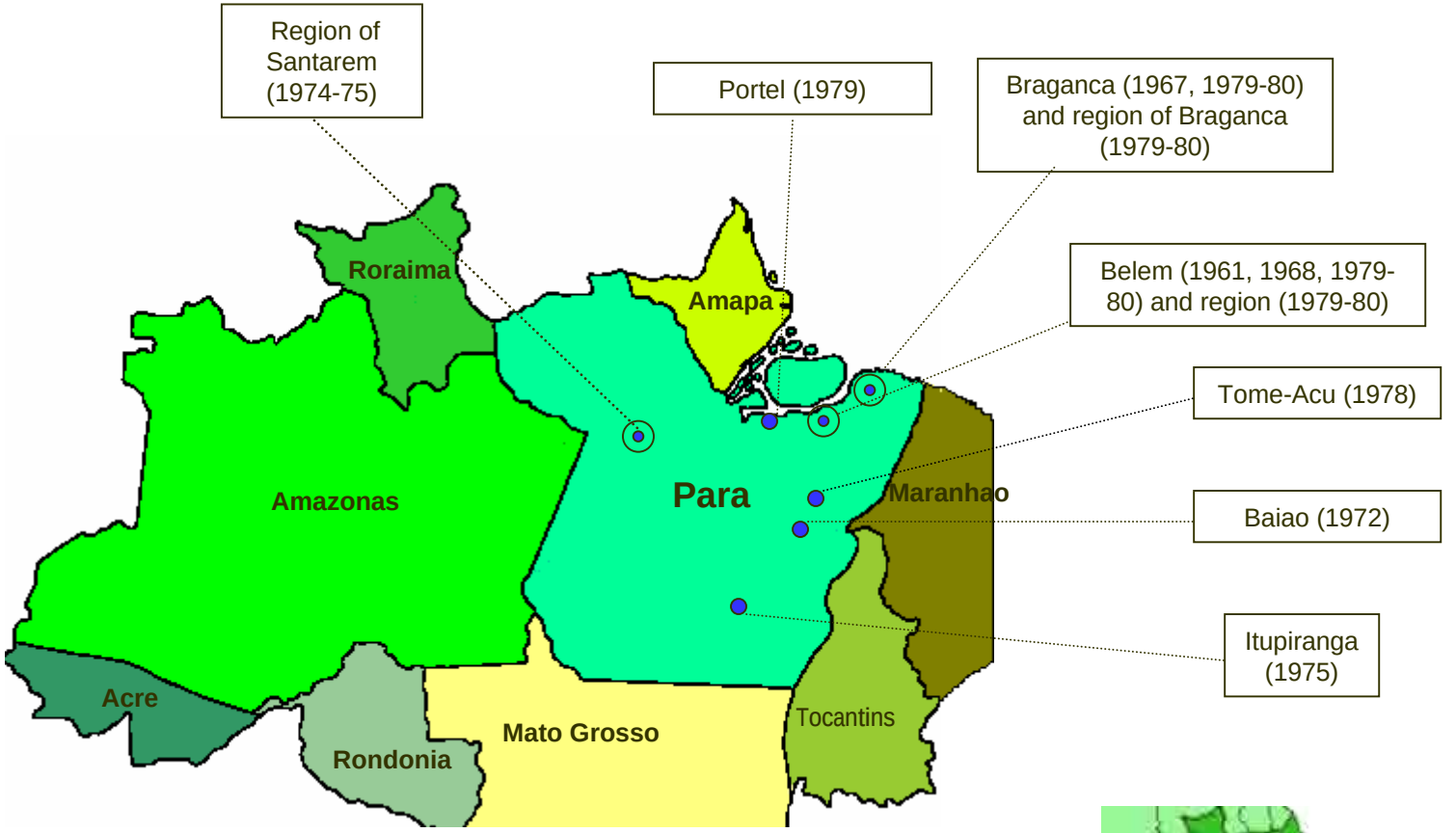
Oropouche: Urban vector *Culicoides paraensis*



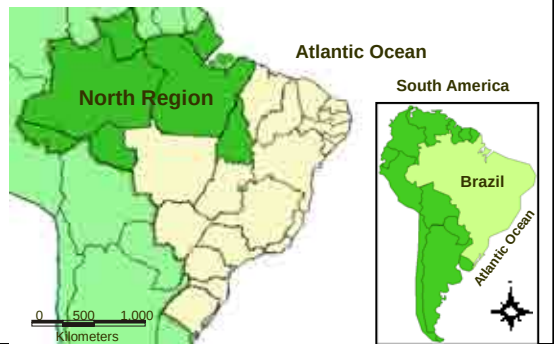


Pinheiro et al., Am. J. Trop. Med. Hyg., 1981;
Pinheiro et al., Science, 1982

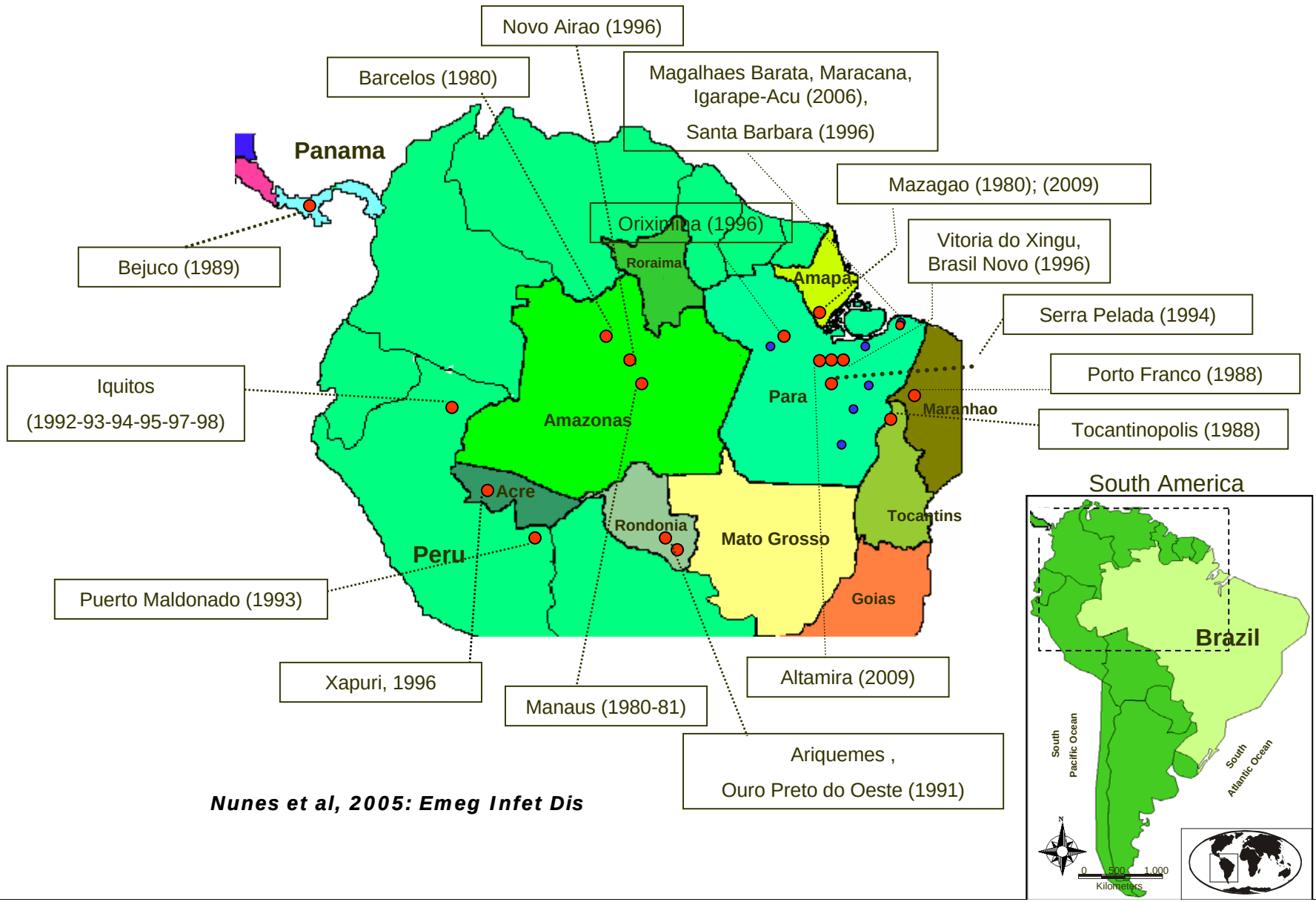
OROPOUCHE OUTBREAKS BETWEEN 1961 - 1980



Nunes et al, 2005: Emeg Infet Dis

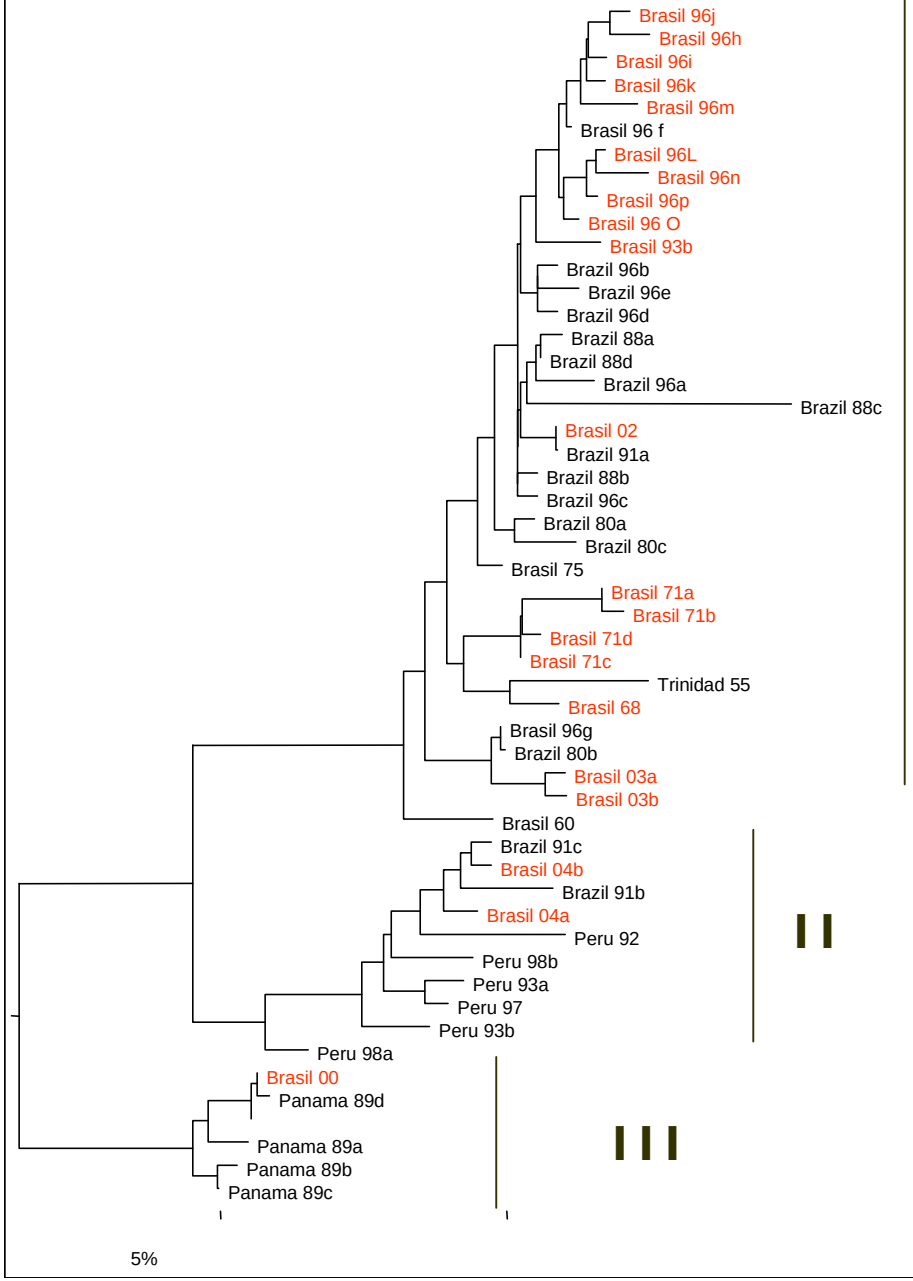


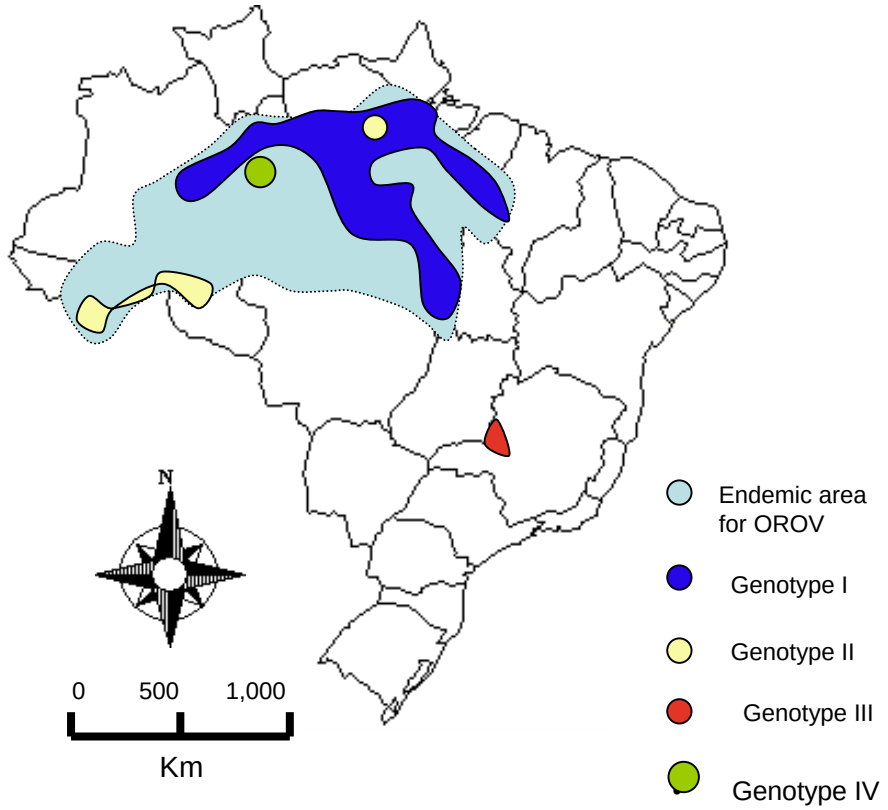
OROPOUCHE OUTBREAKS BETWEEN 1980 - 2009



Nunes et al, 2005: Emeg Infet Dis

Phylogeny of Oropouche virus based on Nucleocapsid gene (693nt), 1955-2005





Saeed *et* al., J Gen Virol, 2000

Nunes *et al* Emerg Infect Dis, 2005

Azevedo *et al* Emerg Infect Dis, 2007

Vasconcelos et al., 12010 PLoS Pathogens - Submitted

Mayaro Fever

•Mayaro fever virus belongs to genus A*lphavirus* (*Togaviridae).* It is transmitted by *Haemagogus janthinomys*;

•1954 – First isolations of MAY virus occurred in Trinidad, South America, from five febrile patients (Anderson et al. 1957);

•1955 – Isolation of MAY virus in Brasil from febrile patients in a small village near Guamá River, about 200 Km east of Belém;

•1955 – First Epidemic reported in Santa Cruz, Bolivia;

•1978 – A large epidemic (800 cases) is reported in Belterra, in Pará state;

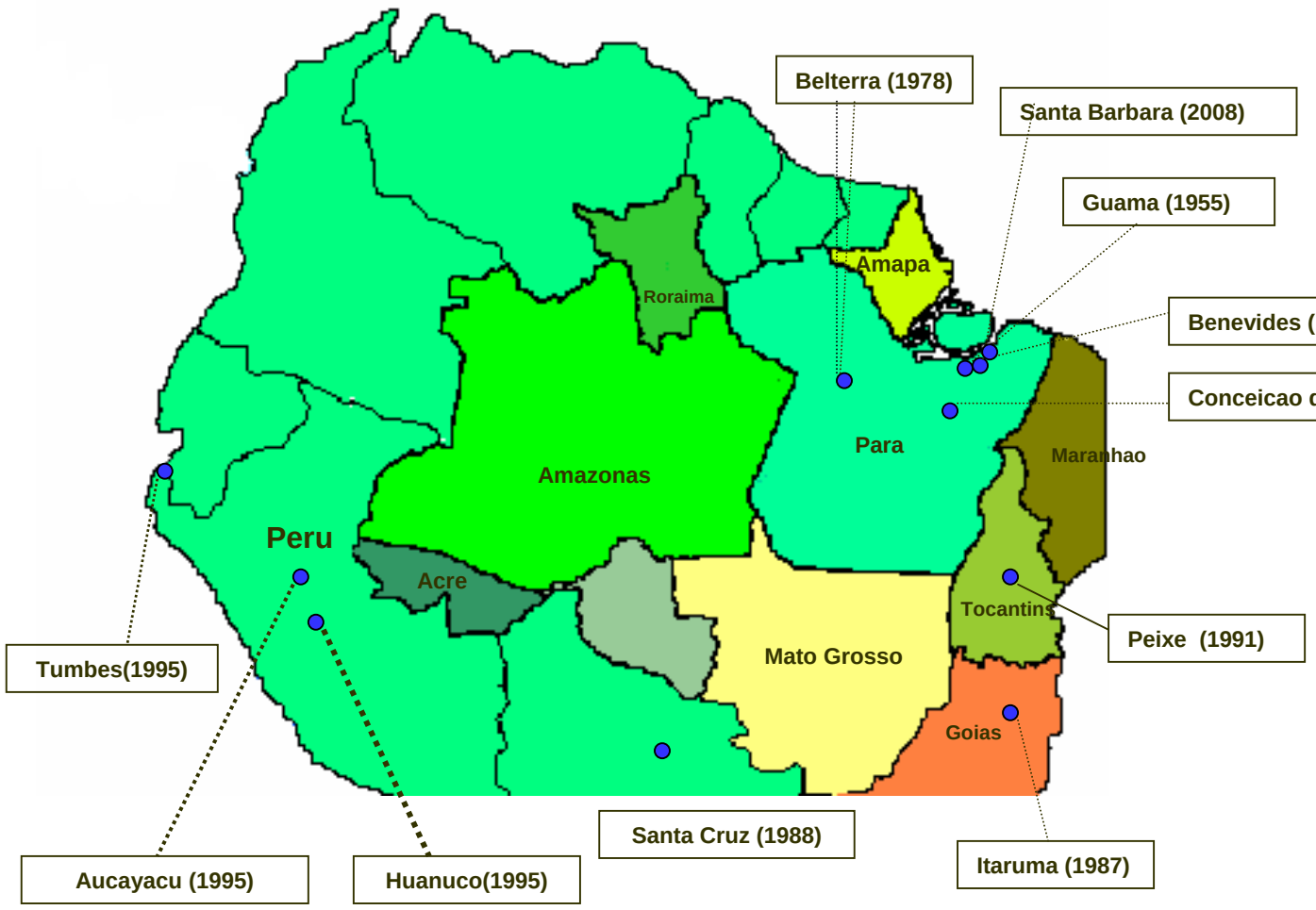
•1981 – An outbreak in several small villages, Goiás State;

•1991 – Two small outbreaks reported in Peixe (Tocantins State) and Benevides (Pará State);

•2008 – An outbreak was registered in Santa Barbara, Parã State.

MAJOR MAYARO OUTBREAKS IN THE AMAZON REGION

1955-2008

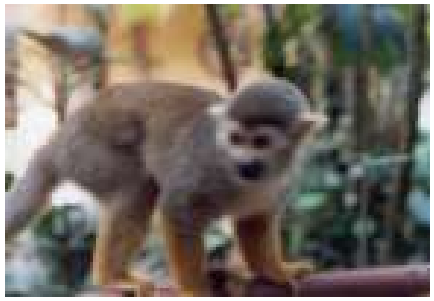




Azevedo et al, 2009: Emeg Infet Dis

Transmission cycle

VERTEBRATE HOST



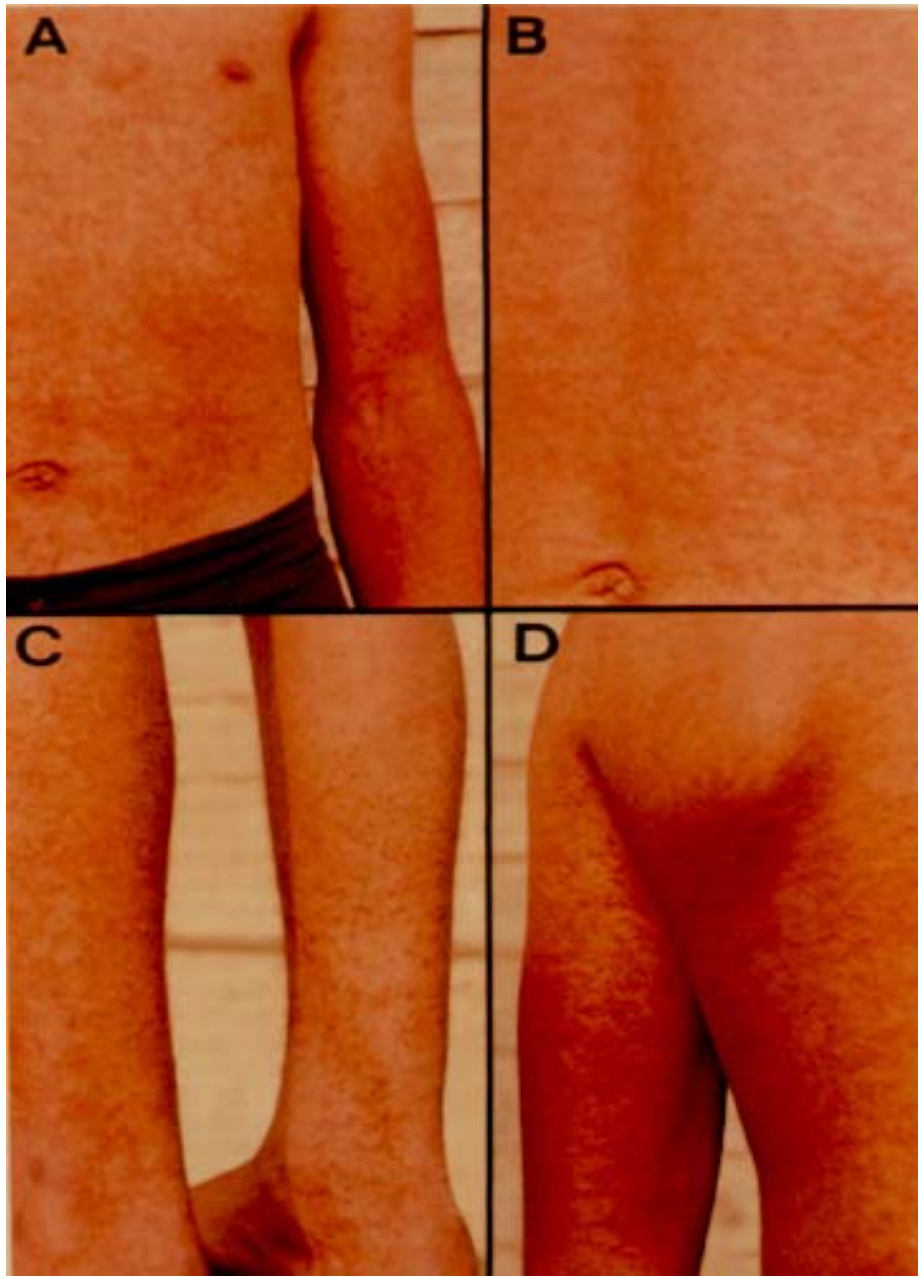
MONKEYS AND BIRDS



HAEMAGOGUS JANTHINOMYS



MAN -ACIDENTAL HOST



Pinheiro et al., Am. J. Trop. Med. Hyg., 1981

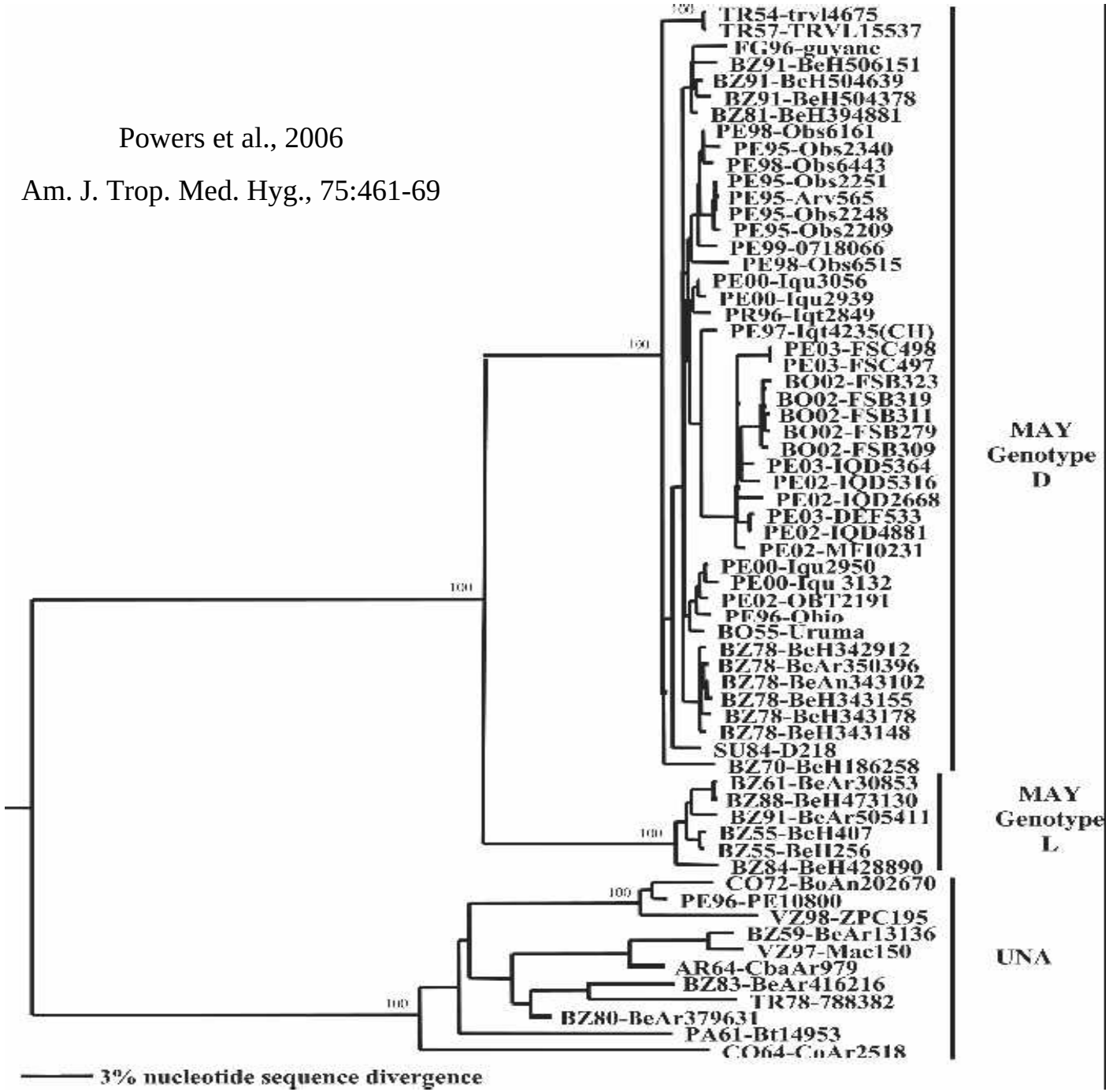


Powers et al., 2006

Am. J. Trop. Med. Hyg., 75:461-69

Powers et al., 2006

Am. J. Trop. Med. Hyg., 75:461-69



Arboviruses with potential to cause encephalitis in Brazilian Amazon

Family-genus-Antigenic group	Virus	Source of isolation			
		Man	Wild Host	Sentinel Animal	Arthropod
Togaviridae-Alphavirus - A	EEEV	-[1]	+	+	+
	WEEV	-[1]	+	-	+
	VEEV (MUCV)	+	+	-	+
	VEEV (PIXV)	+[2]	+	-	+
Flaviviridae-Flavivirus – B	SLE	+	+	+	+
Bunyaviridae-Orthobunyavirus-Bunyamwera	Tucunduba	+	-	-	+

+ isolation, - without isolation, [1]serologic evidence, [2]laboratory infection

Transmission Cycles



Conopophagidae-*Conopophaga aurita*
WEEV



Culex mosquito

EEEV, WEEV, SLEV& ROCV



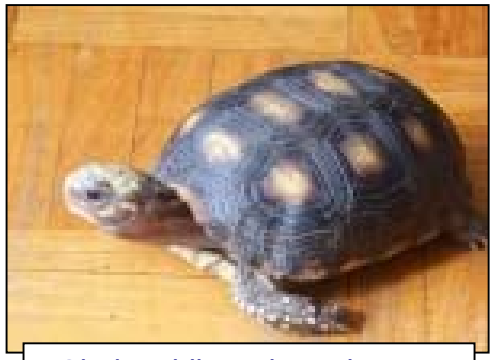
Formicariidae-*Hylophylax poecilonota*
SLEV



Thamnophilidae-
Phlegopsis nigromaculata
WEEV, EEEV

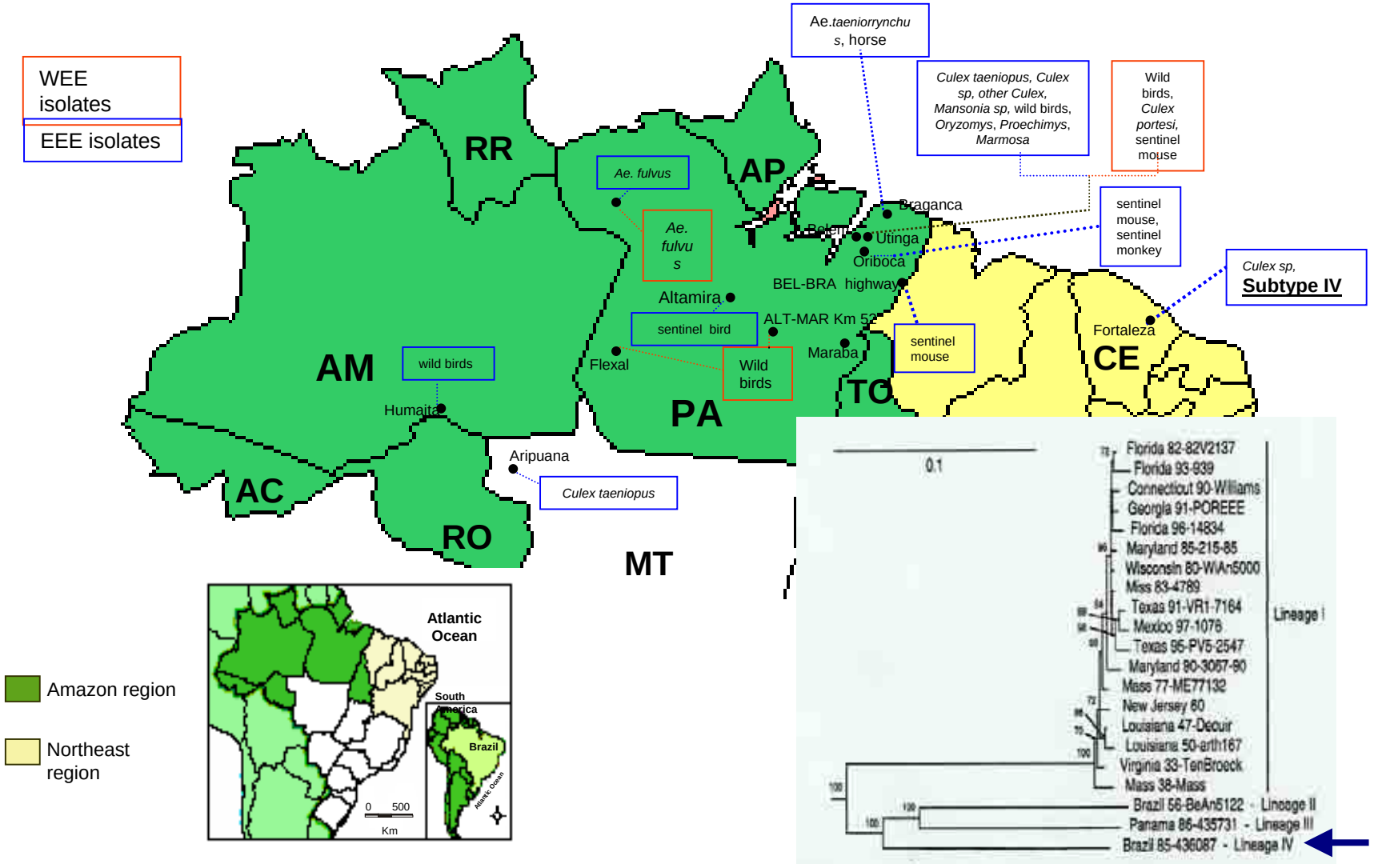


Fringillidae-*Cacicus cela*
EEEV

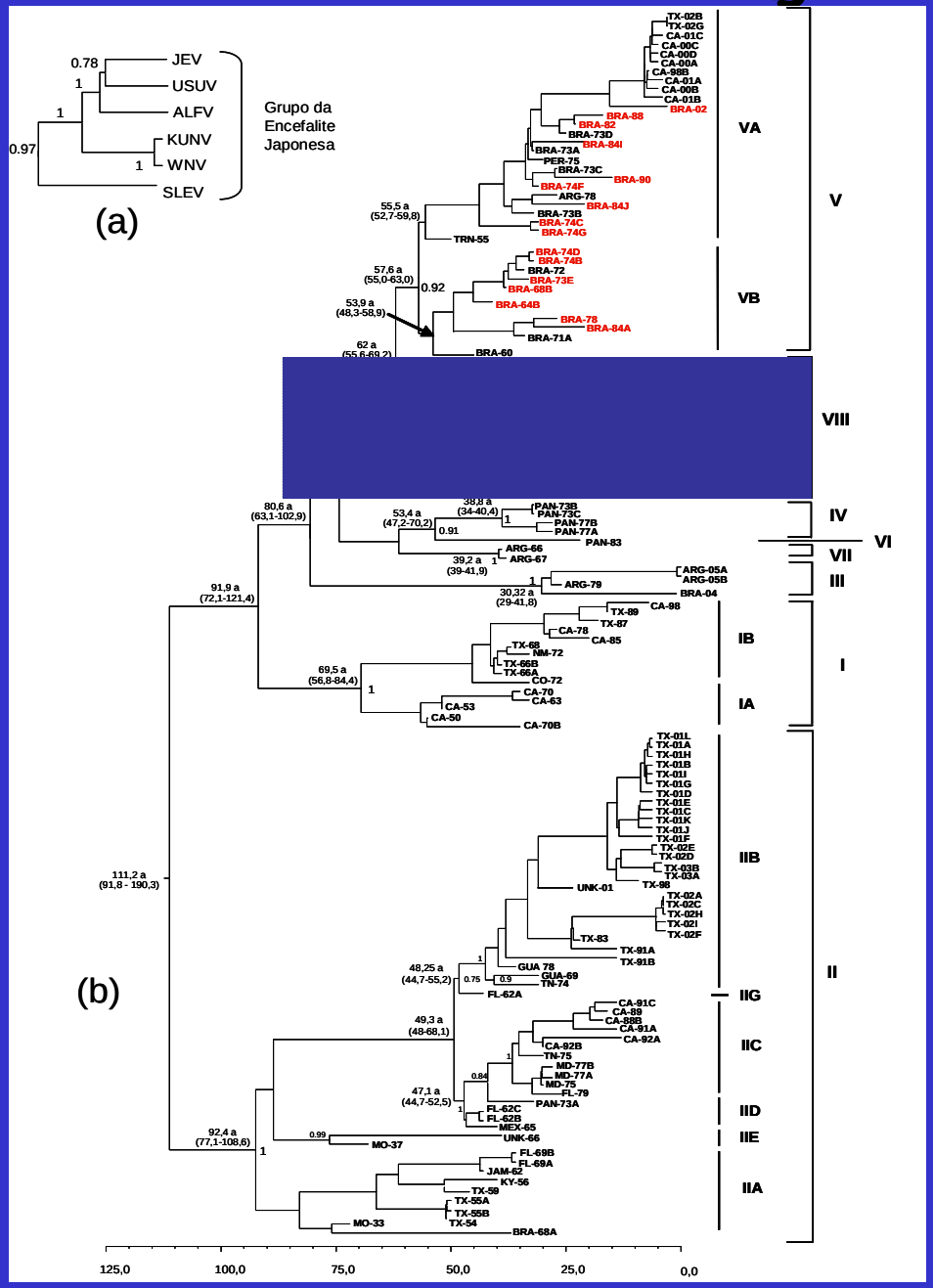


Chelonoidis carbonaria (Jabuti)
SLEV

EEEV e WEEV: Place of where strains were isolated in Amazon and Northeast regions



SLEV: genetic divergence and dispersion



SLEV: ANÁLISE FILOGENÉTICA E EVOLUÇÃO

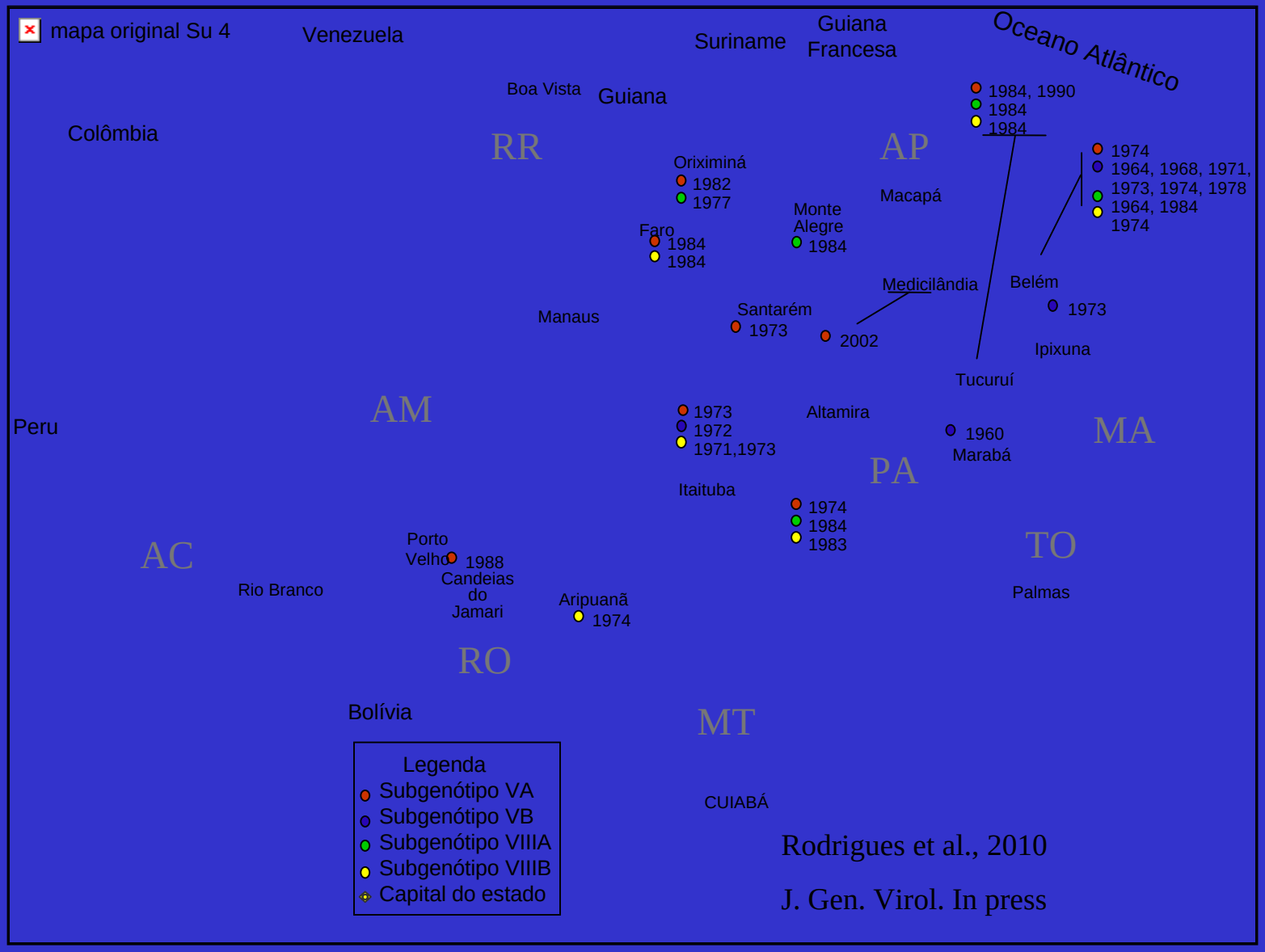
(a) Método Bayesiano, para membros do complexo da Encefalite japonesa; e

(b) Métodos Bayesiano e do relógio molecular relaxado, com base no gene E de 133 cepas do SLEV, sendo 30 cepas sequenciadas neste estudo (amostras em vermelho) e 103 disponíveis no *GenBank*.

Os isolados foram nomeados de acordo com a localização e ano de isolamento: ARG (Argentina), BRA (Brasil), CA (Califórnia), CO (Colorado), FL (Florida), GUA (Guatemala), JAM (Jamaica), KY (Kentucky), MD (Maryland), MEX (México), NM (New México), MO (Missouri), PAN (Panamá), PER (Peru), TN (Tennessee), TRIN (Trinidad), TX (Texas) e *UNK (Localização desconhecida nos EUA)*.

Rodrigues et al., 2010; J. Gen. Virol. In press

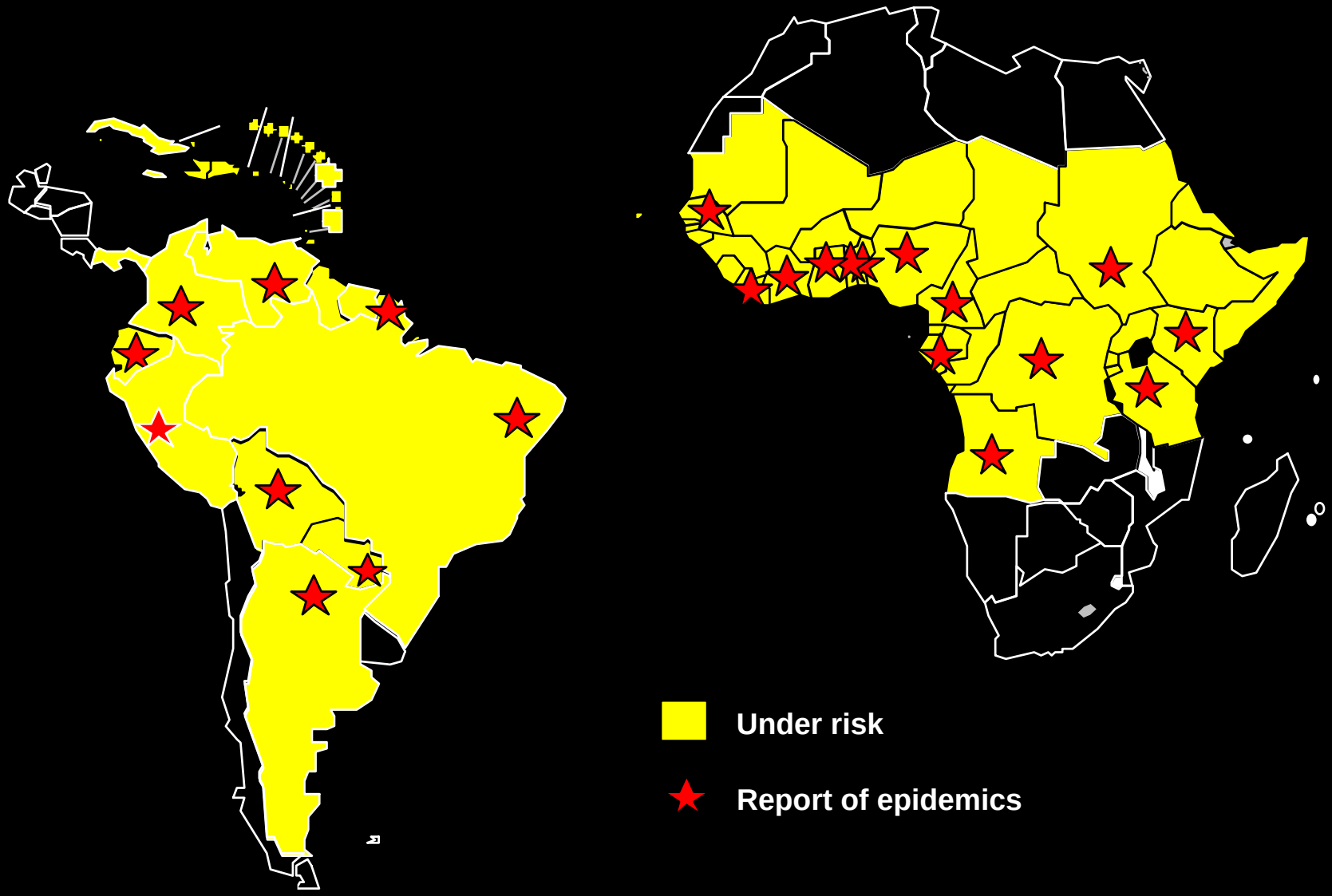
SLEV: DISTRIBUIÇÃO NA AMAZÔNIA BRASILEIRA



Yellow Fever in South America

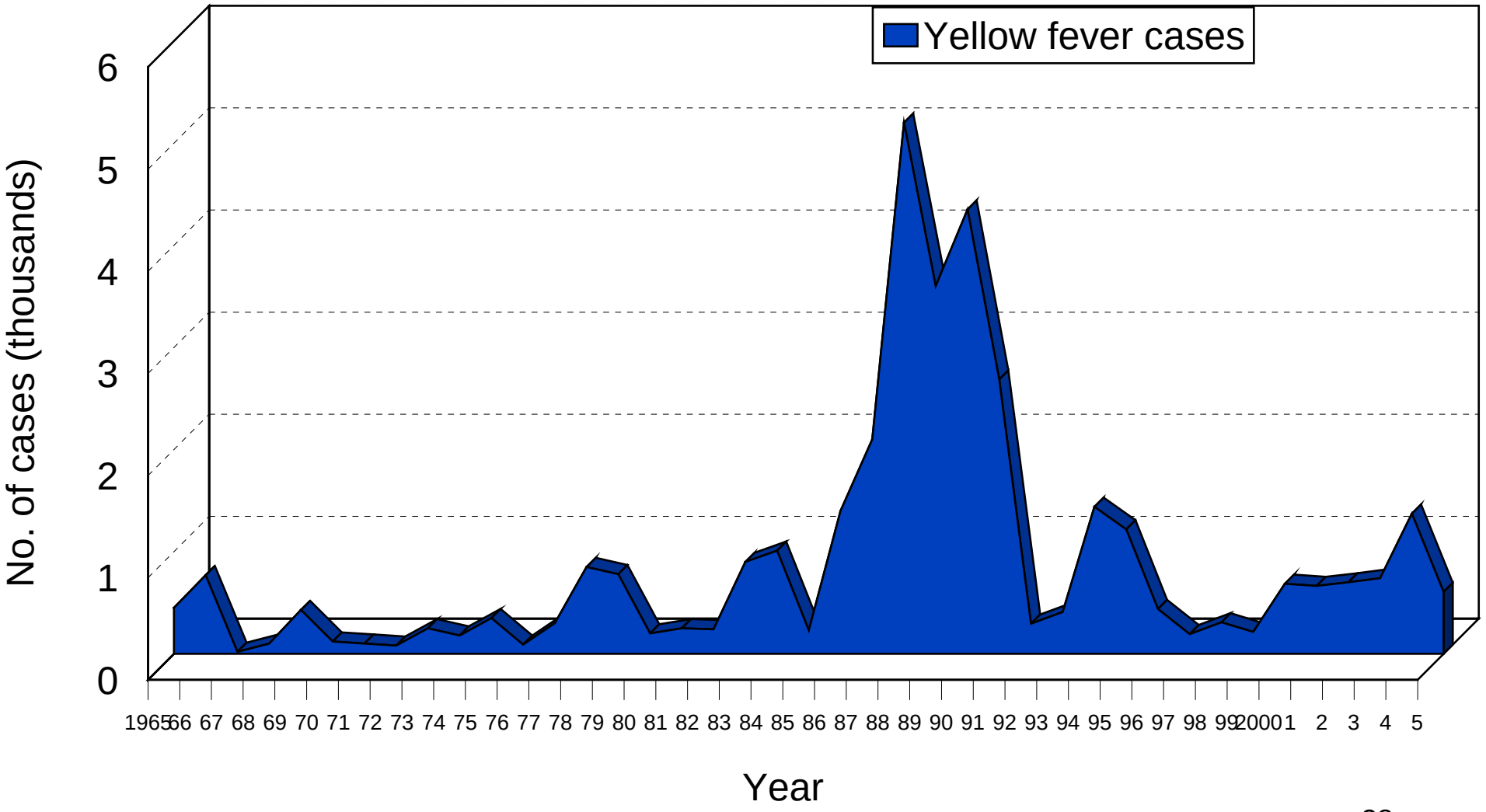
- More than 90% of cases reported in four countries: Bolivia, Brazil, Colombia and Peru;
- Last large urban outbreak in the Americas in 1929, Rio de Janeiro-Brazil;
- Last urban cases in Brazil, 1942 in Acre State, and in the America, 1954 in Trinidad;
- High case-fatality rate (33%-79%);
- 1/3 are asymptomatic or mild forms, while severe pictures are responsible for 10% of cases;
- At least 50% of severe pictures have fatal outcome;
- Severe presentation is responsible for at least 70% of reported cases

Countries under risk of yellow fever in Africa and in the Americas, 1985-2008.



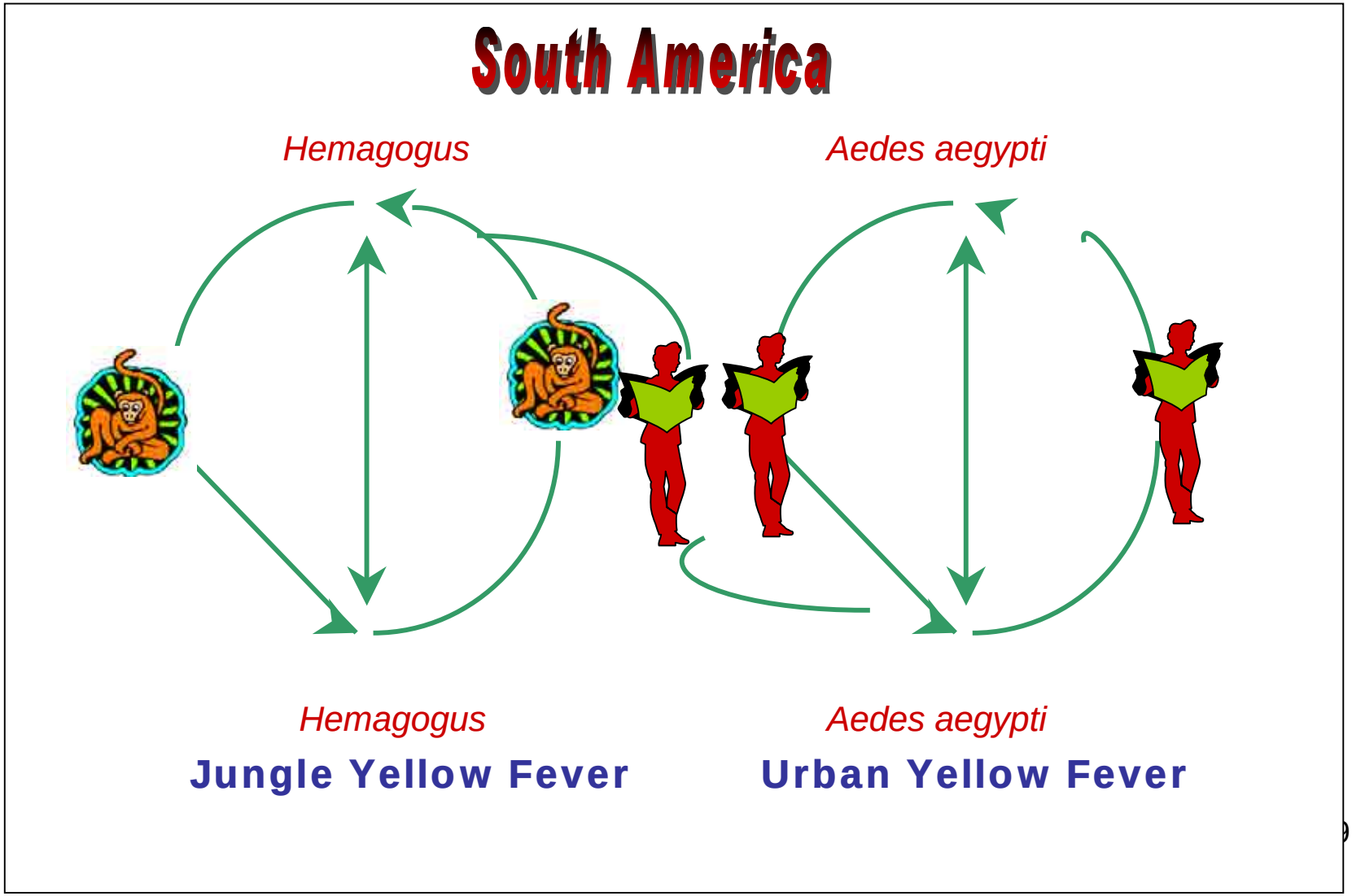
The designation employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Yellow fever cases reported to the WHO, 1965-2005

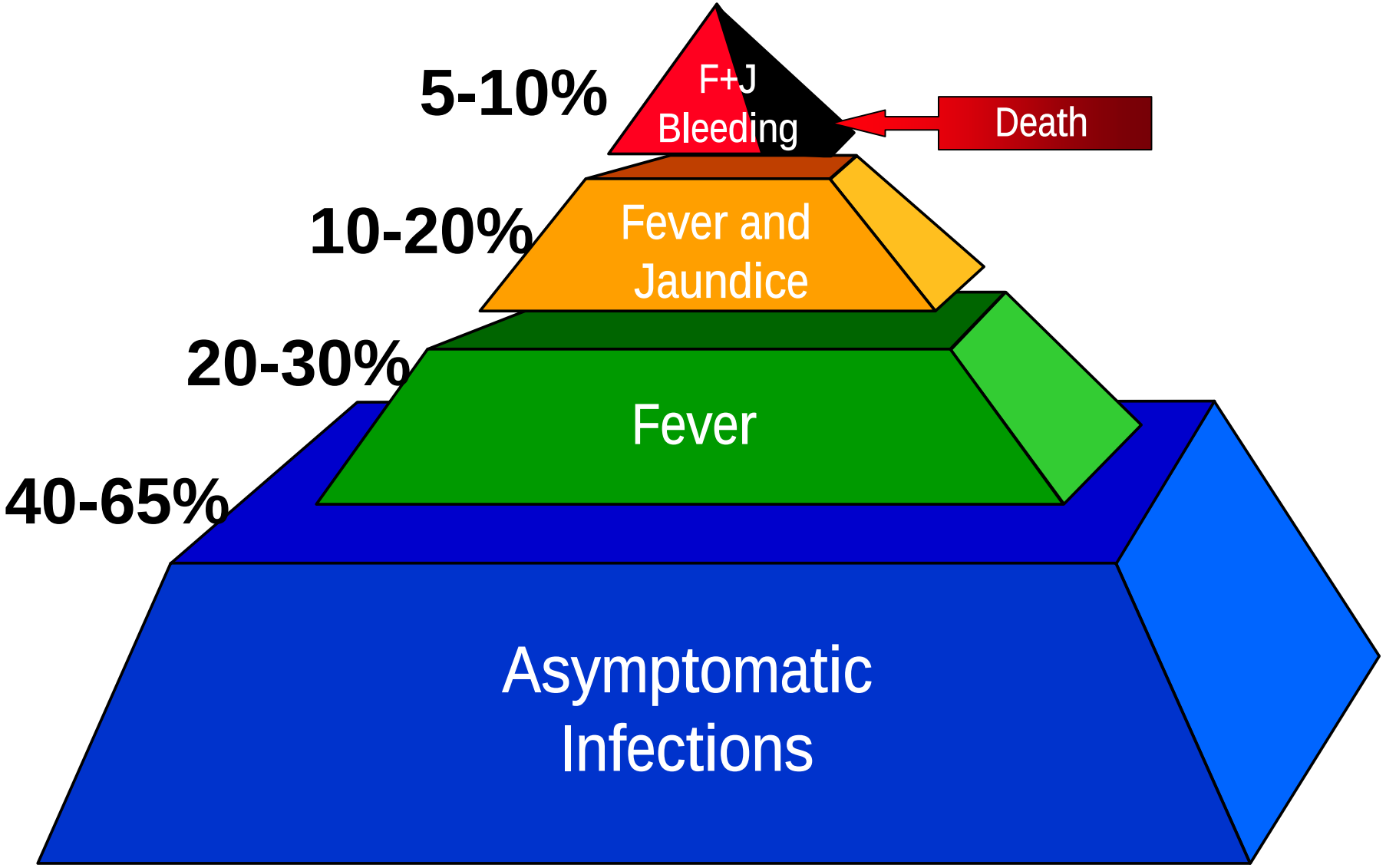


Source:WHO

- Main vectors are *Haemagogus* mosquitoes. *Sabethes* are secondary vectors;
- Monkeys are vertebrate (primary) hosts;
- Complex jungle cycles that are not well understood.



Yellow Fever Clinical Manifestation

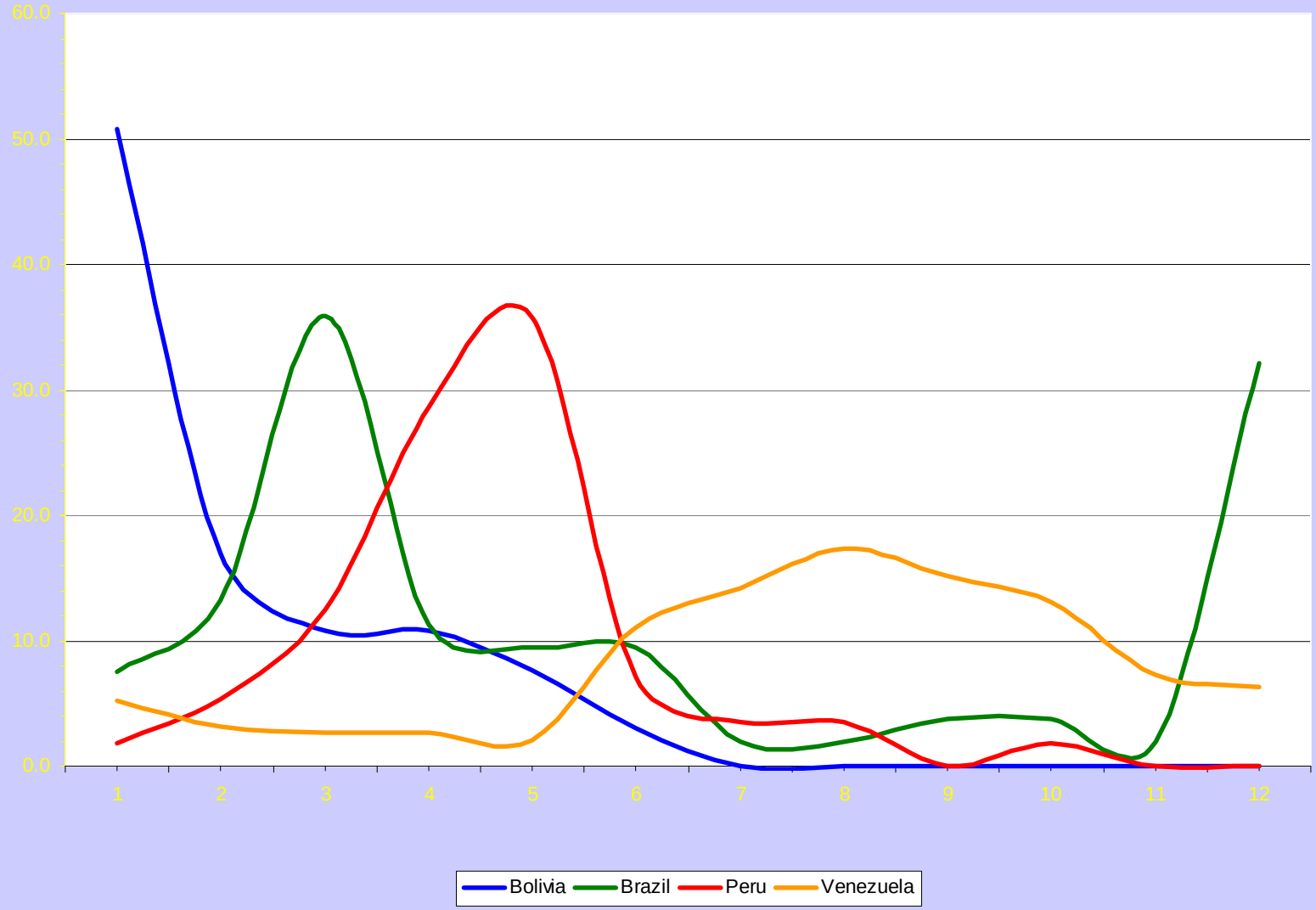


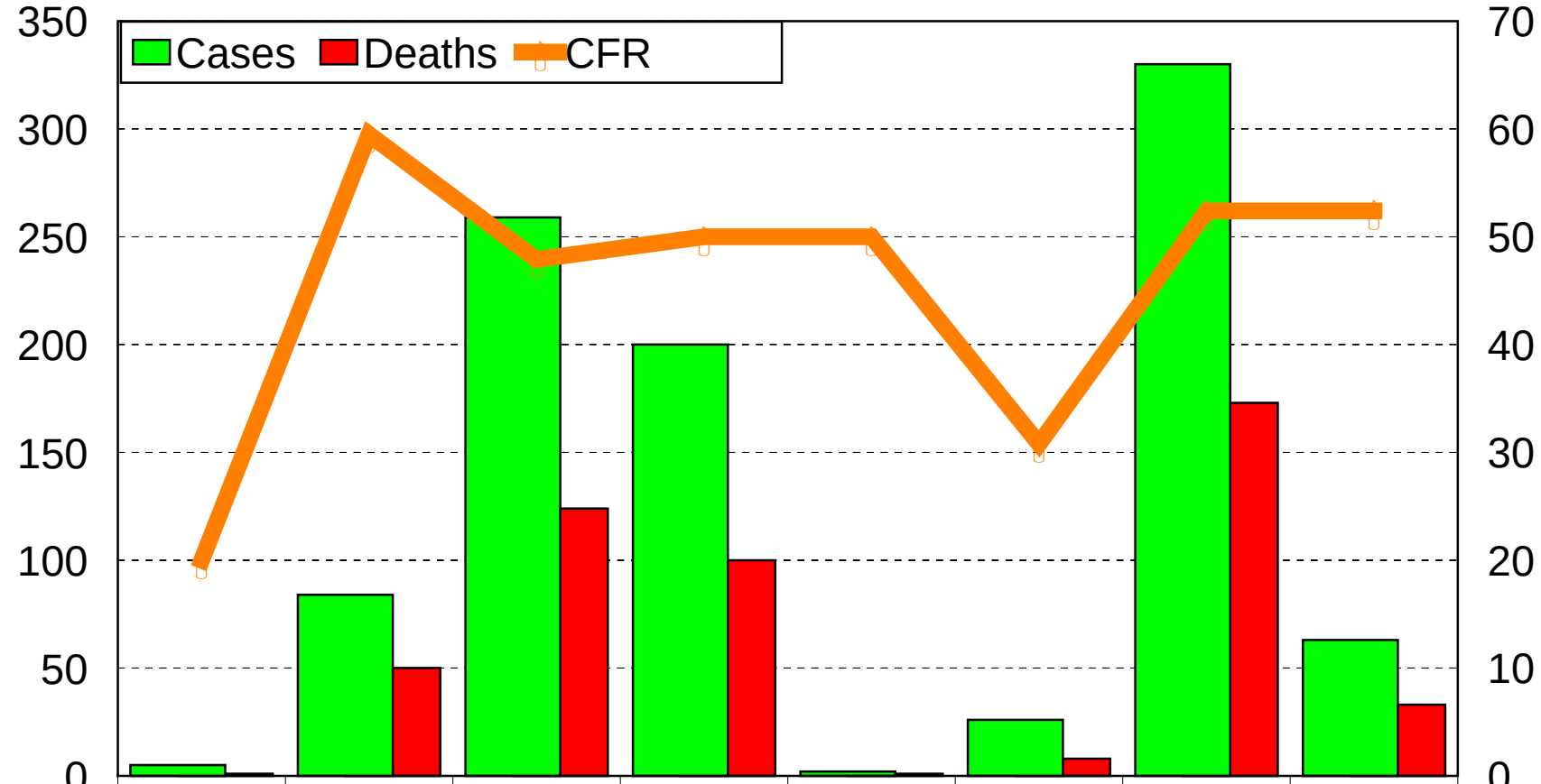
Vasconcelos, RSBMT, 2003

“The Iceberg”

Jungle yellow fever in the Americas: monthly distribution of cases.

- More than 90% of cases occurring between December and April (rainy season);





	Argentina	Bolivia	Brasil	Colombia	Ecuador	Paraguay	Peru	Venezuela
Cases	5	84	259	200	2	26	330	63
Deaths	1	50	124	100	1	8	173	33
CFR	20	59,5	47,9	50	50	30,8	52,4	52,4

Figure 4. Yellow fever cases, deaths and case-fatality rate by country in South America,2000 to 2008.

Source: PAHO/WHO


Afua

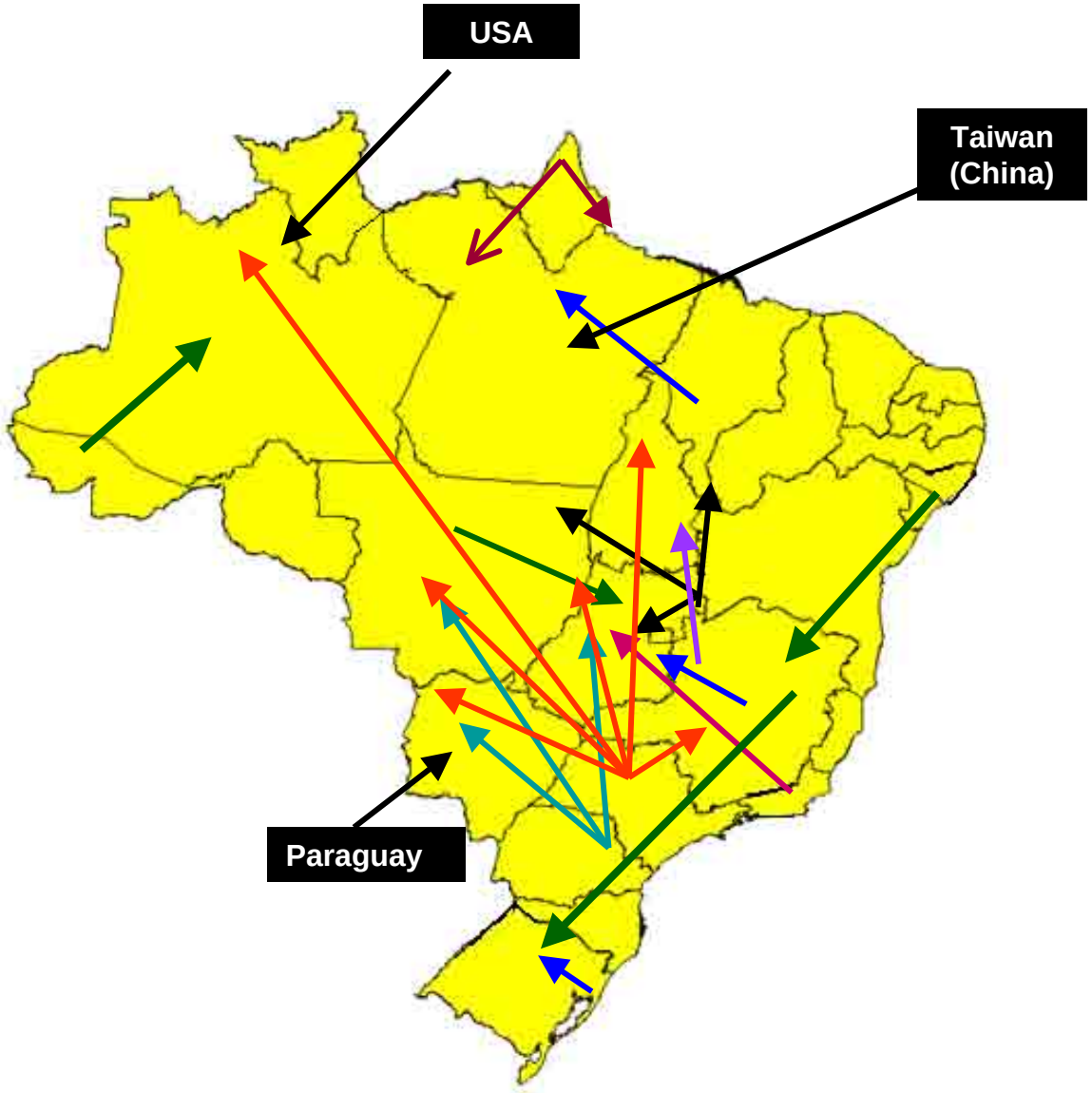

Altamira


C. Araguaia


Altamira

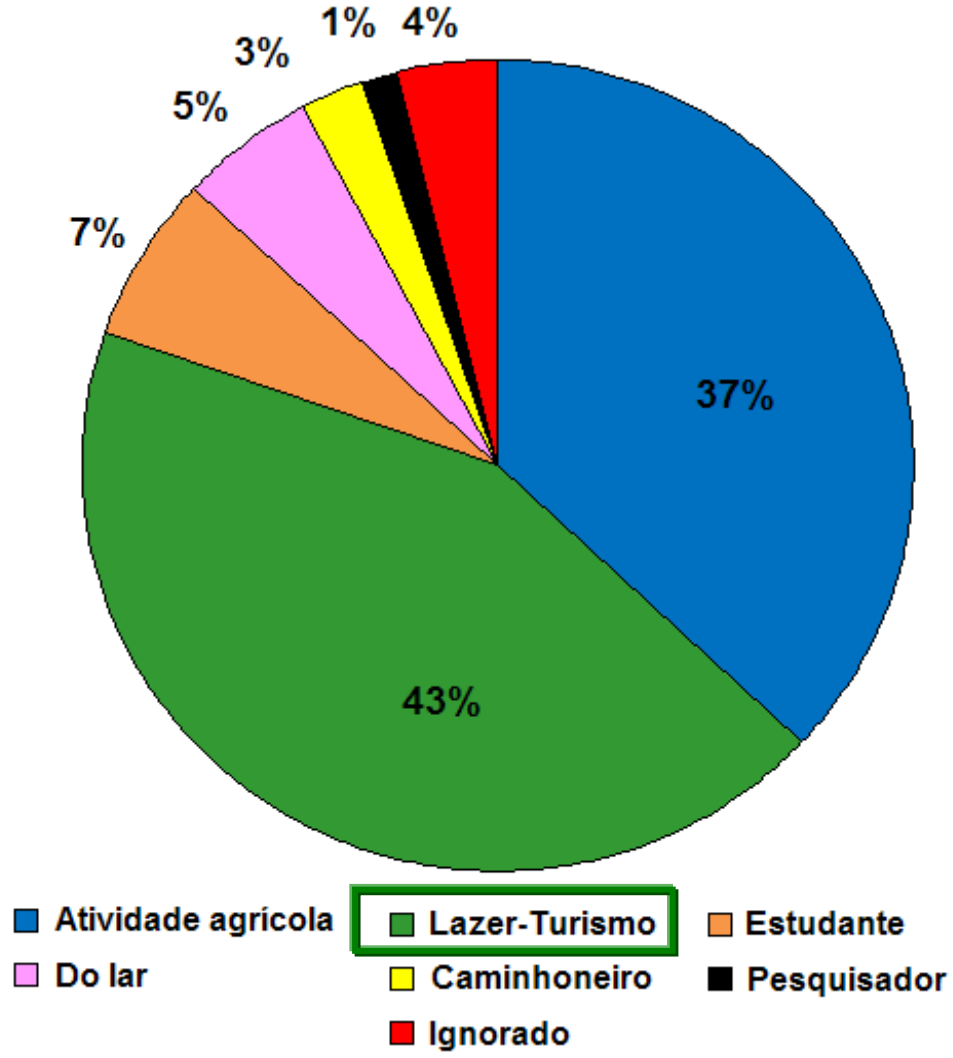
Destiny of travelers which became infected with yellow fever

- GO: 60% (44/73)
- MS: 11% (8/73)
- PA 7% (5/73)
- TO: 5,5% (4/73)
- AM: 5,5% (4/73)
- MG: 5,5% (4/73)
- MT: 4% (3/73)
- RS: 1% (1/73)



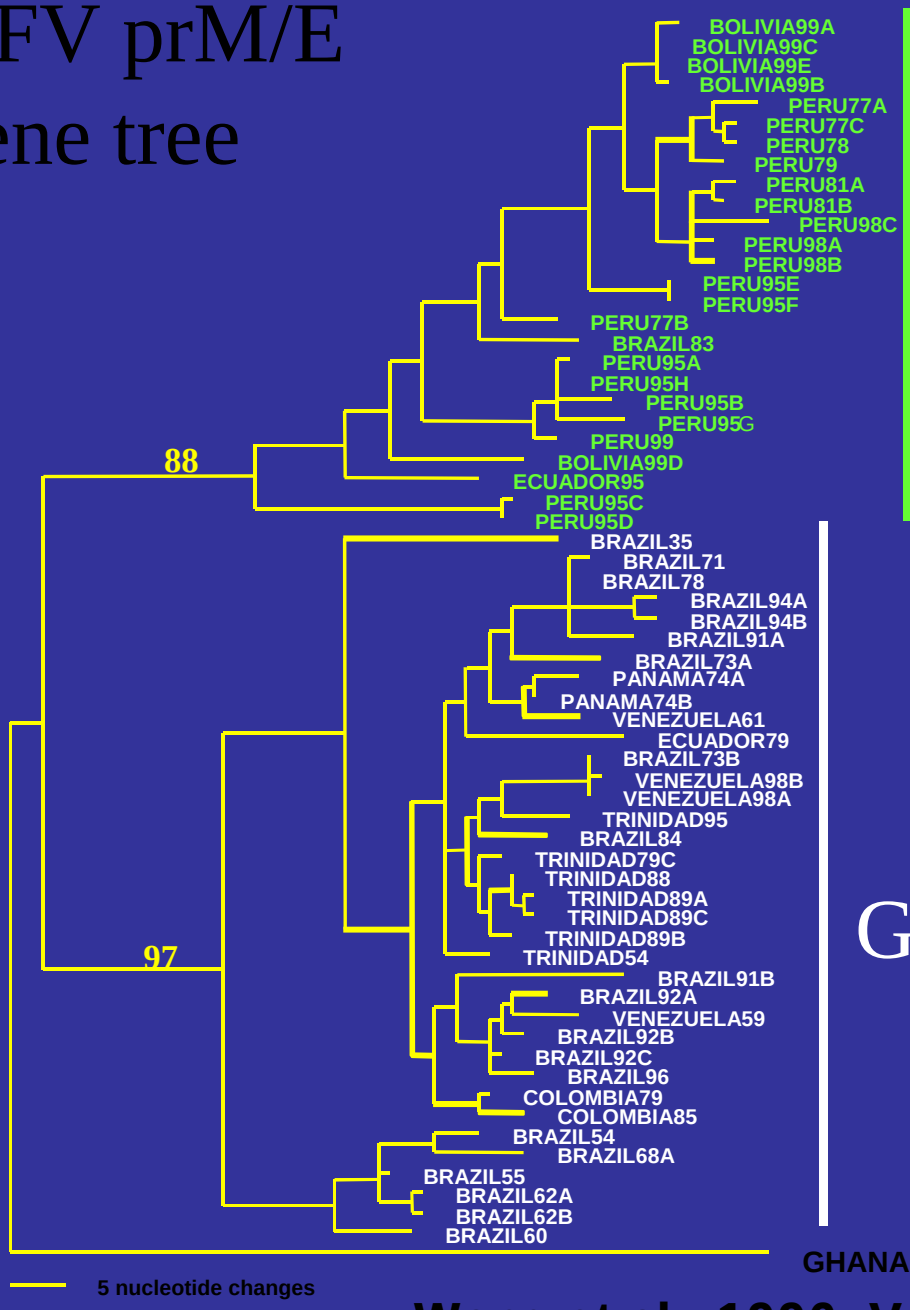
Fonte: SINAN

Casos de febre amarela em viajantes segundo atividade no momento da exposição. Brasil, 1999 – 2009*



Fonte: SINAN * Dados provisórios

YFV prM/E gene tree



Genotype II

Genotype I



Wang et al., 1996; Vasconcelos et al., 2004

① **Amazon region**

AC – Acre
AM – Amazonas
AP – Amapá
AL – Alagoas
PA – Pará
RO – Rondônia
RR – Roraima
TO – Tocantins

② **Northeastern**

BA – Bahia
CE – Ceará
MA – Maranhão
PB – Paraíba
PE – Pernambuco
PI – Piauí
RN – Rio G. do

③ **Central-west**

DF – Distrito Federal
GO – Goiás
MT – Mato Grosso
MS – Mato G. do Sul

④ **Southeastern**

ES – Espírito Santo
MG – Minas Gerais
RJ – Rio de Janeiro
SP – São Paulo

⑤ **Southern**

PR – Paraná
RS – Rio G. do Sul
SC – Santa Catarina

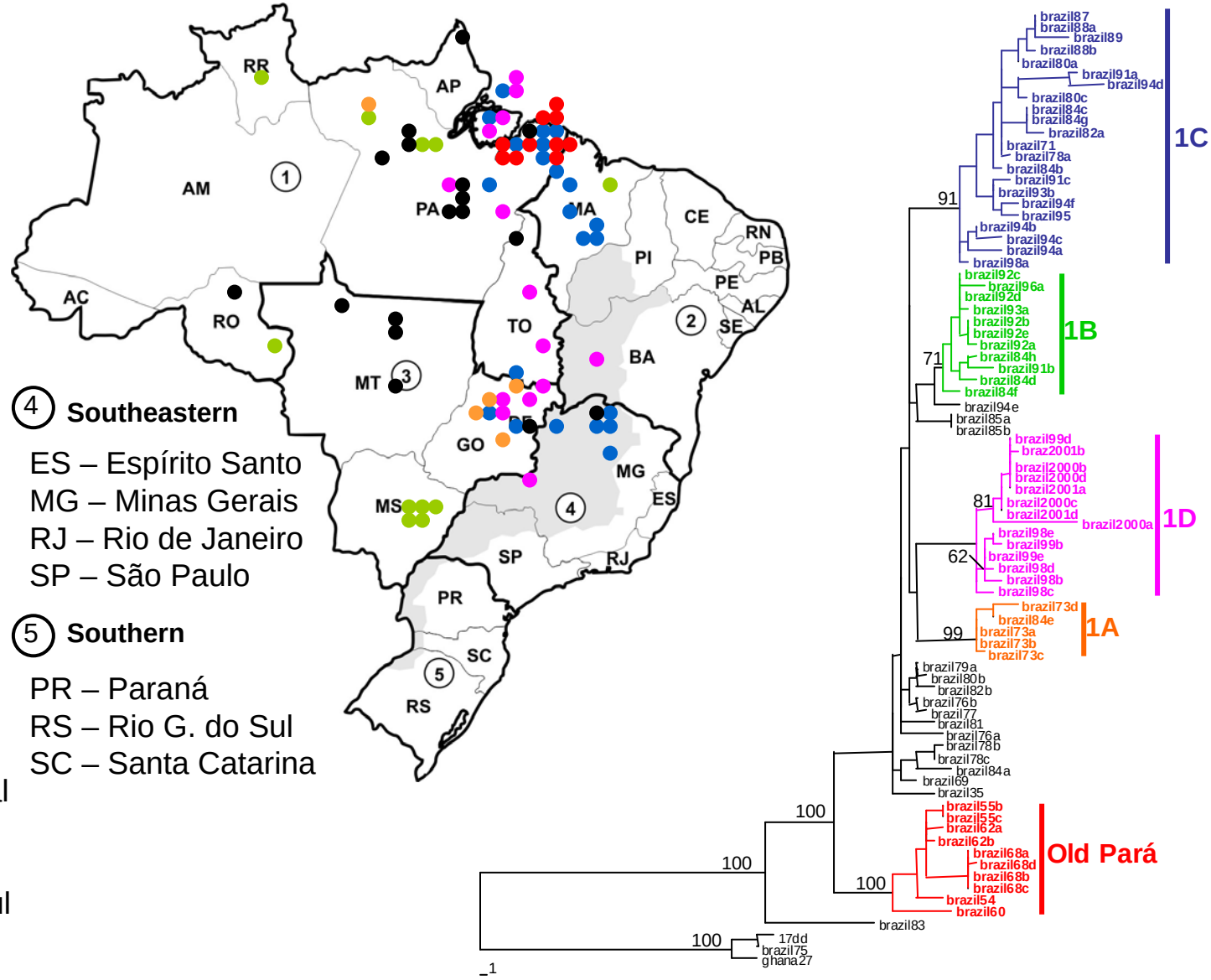
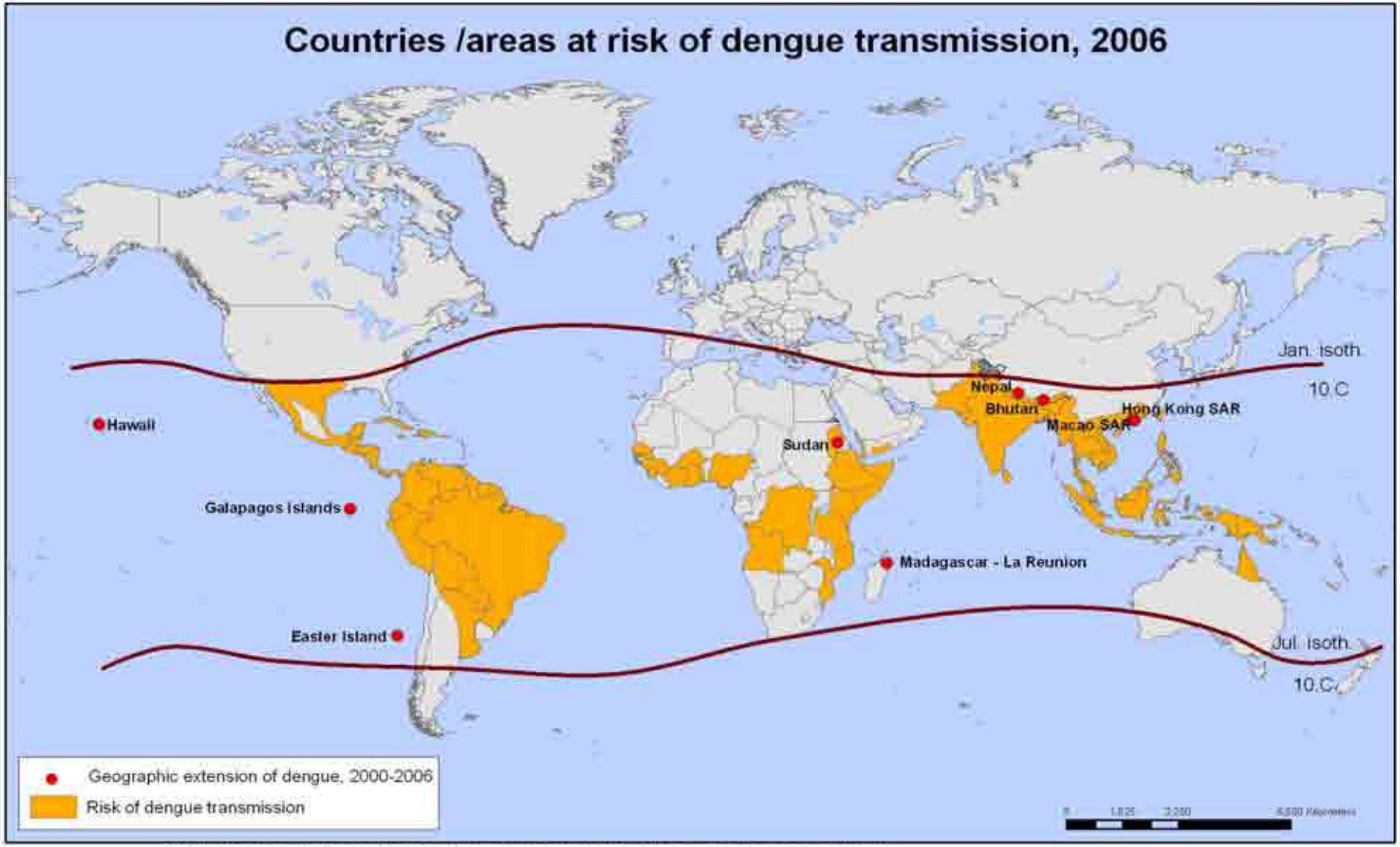


Figure 2. Brazilian NS5/3'NCR phylogeny (576 nts) based on yellow fever isolates (neighbor joining tree, Kimura2-P distance correction, midpoint rooted). Geographic origin of isolates is indicated on map figure. Colors correspond to genetic clade structure. Black dots refer to isolates with unresolved phylogenetic position.

Vasconcelos et al., EID, 10:1578-84, 2004.

Dengue Pandemic



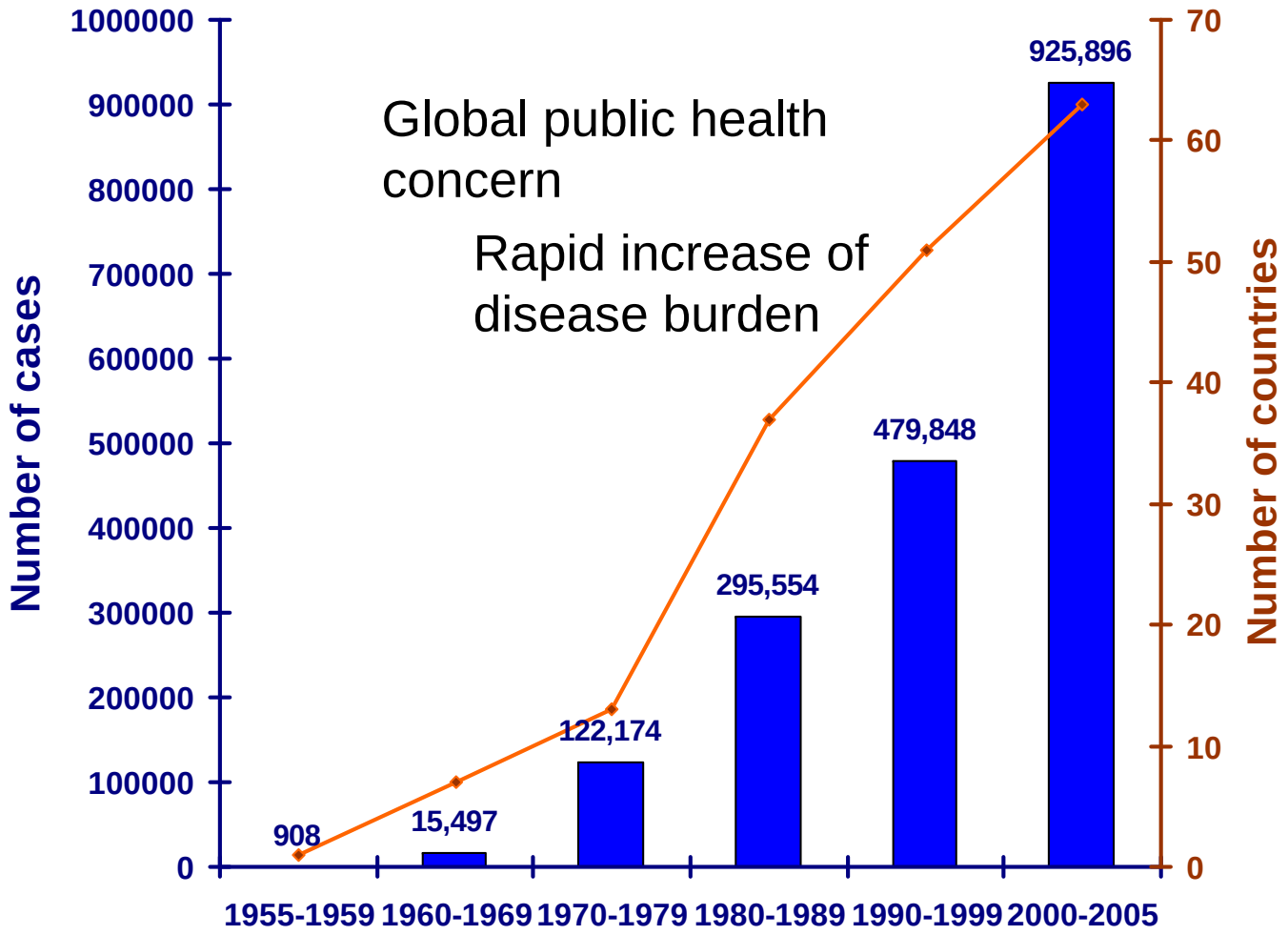
World Health Organization

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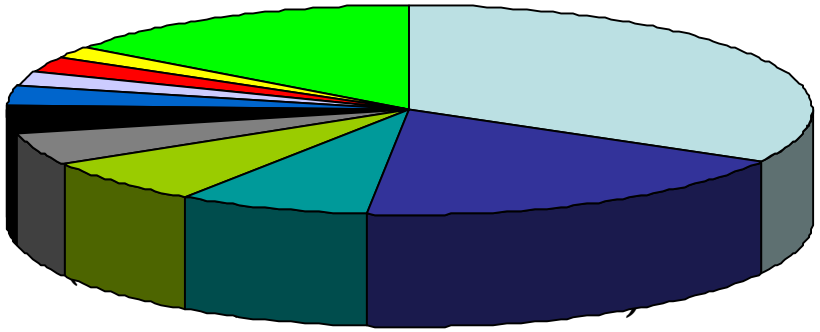
Data Source: WHO
Map Production: Public Health Mapping and GIS
Communicable Diseases (CDS) World Health Organization

Average annual number of DF/DHF cases reported to WHO & of countries reporting dengue



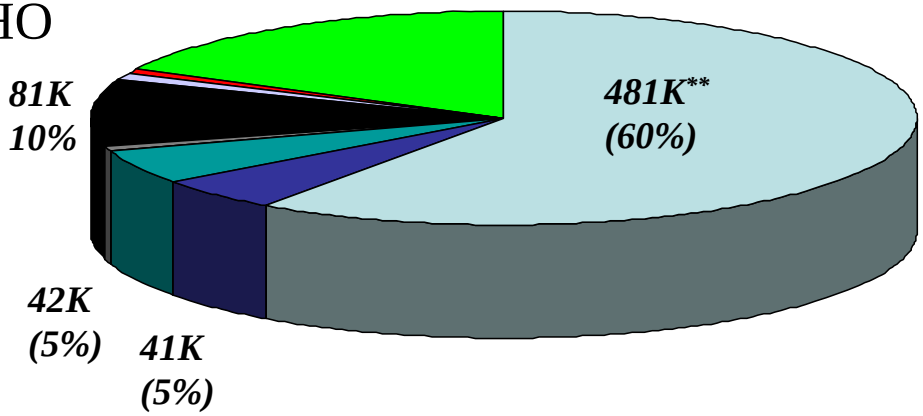
PAHO countries population and reported dengue 2007

Population
(559* Million)



- Brasil
- Mexico
- Colombia
- Argentina
- Peru
- Venezuela
- Chile
- Ecuador
- Guatemala
- Cuba
- Others

DF+DHF Cases
Reported to PAHO
Jan 2008
(806,000)



*not including U.S
** as of week 39

Evolution of DHF in the Americas

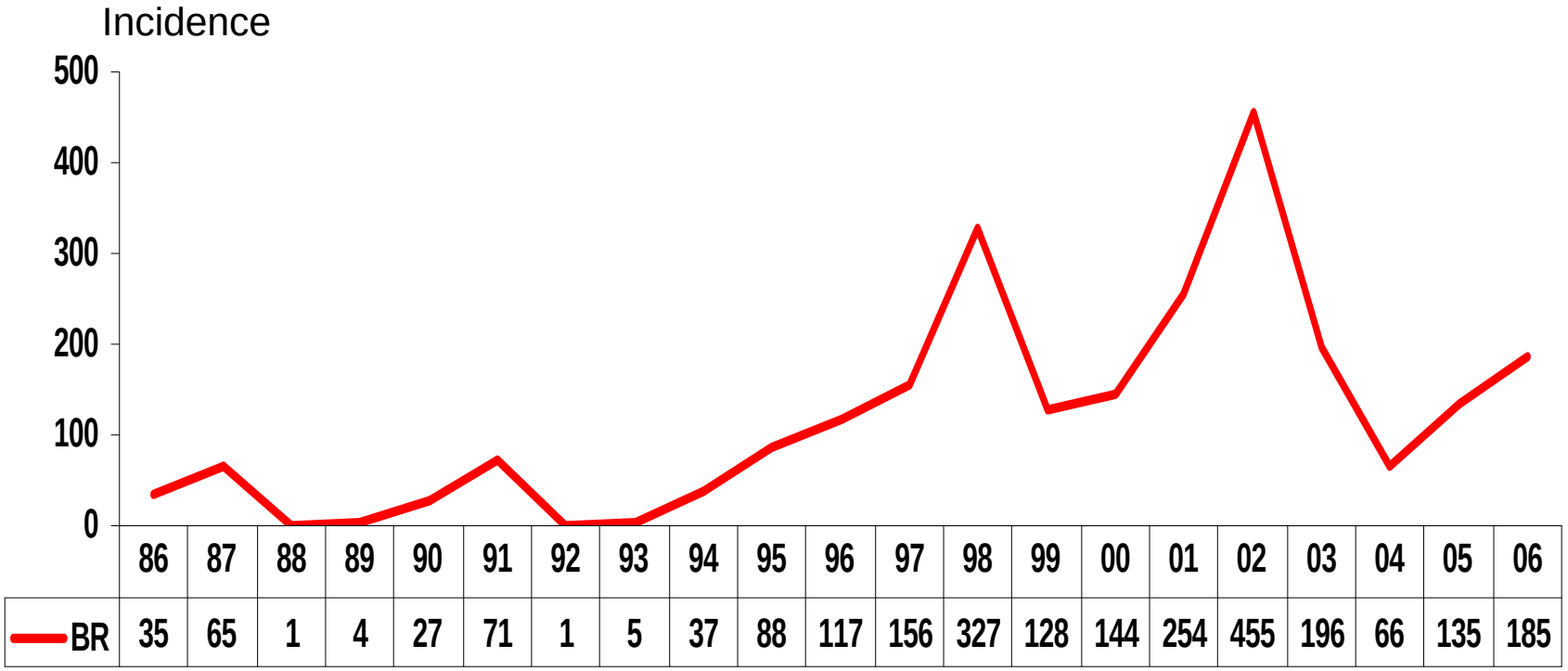
1968 - 1980
5 countries: 60 Cases



1981 - 2005
28 countries: >139,000 Cases



Dengue: incidence (1)
Brasil, 1986-2006*

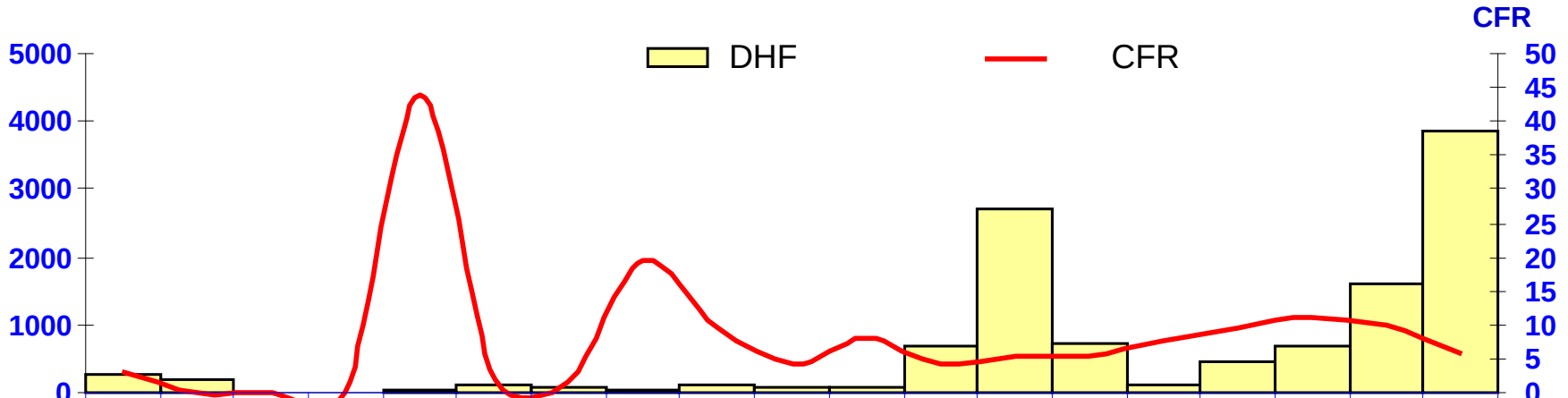


	86	87	88	89	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05	06
BR	35	65	1	4	27	71	1	5	37	88	117	156	327	128	144	254	455	196	66	135	185

(1) Cases x 100,000 inhabitants

*Provisional figure for December 2006

Confirmed DHF cases, deaths and case-fatality rate (CFR) in Brazil, 1990 – 2008*

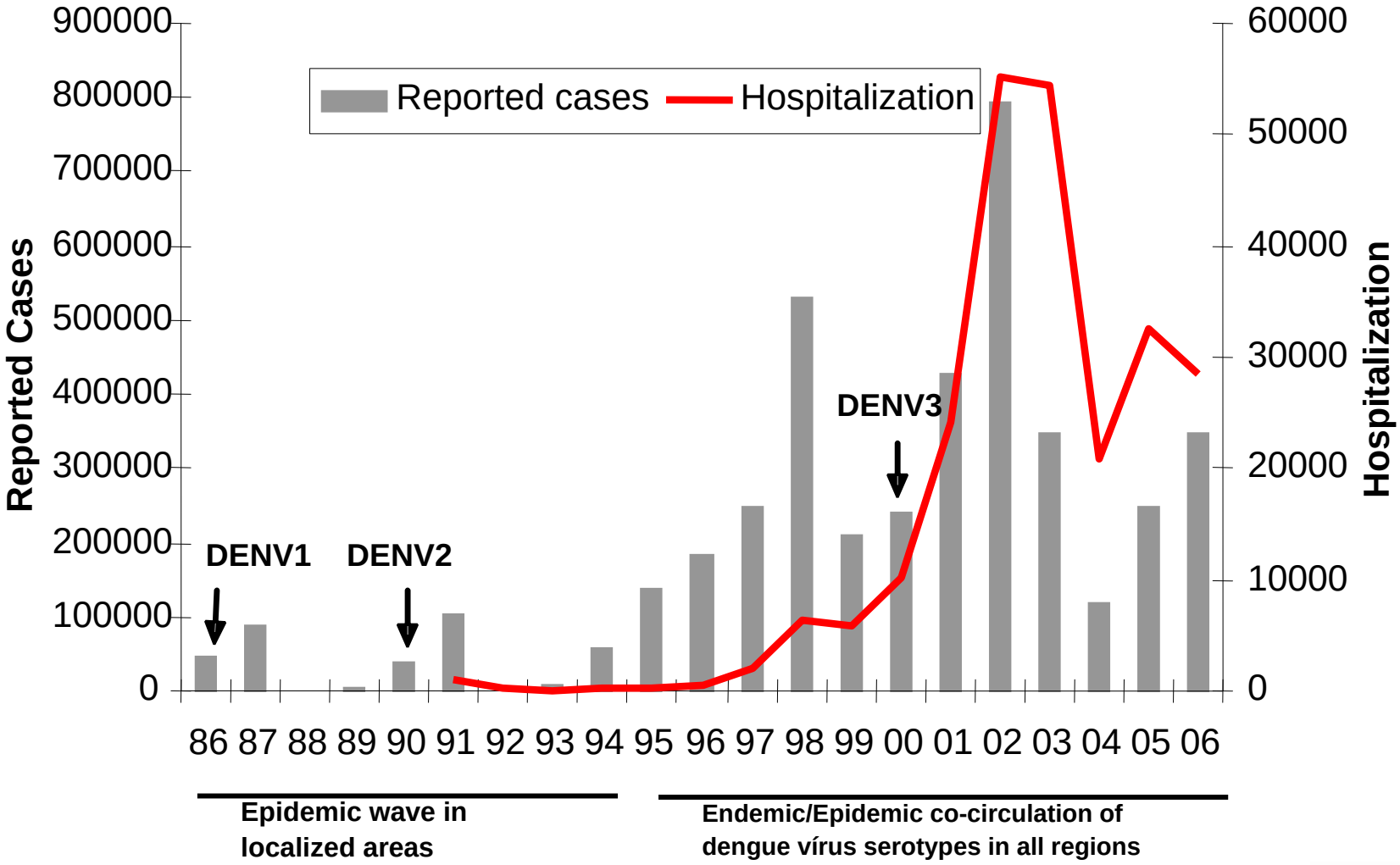


	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
DHF	274	188	0	0	25	114	69	46	105	72	62	682	2714	727	103	463	682	1586	3848
Deaths	8	0	0	0	11	2	1	9	10	3	5	29	150	38	8	45	76	159	213
CFR	2,92	0,00	0,00	0,00	44,00	1,75	1,45	19,57	9,52	4,17	8,06	4,25	5,53	5,23	7,77	9,72	11,14	10,03	5,54

*Data up to WE 39

Reported Cases and Hospitalization by Dengue

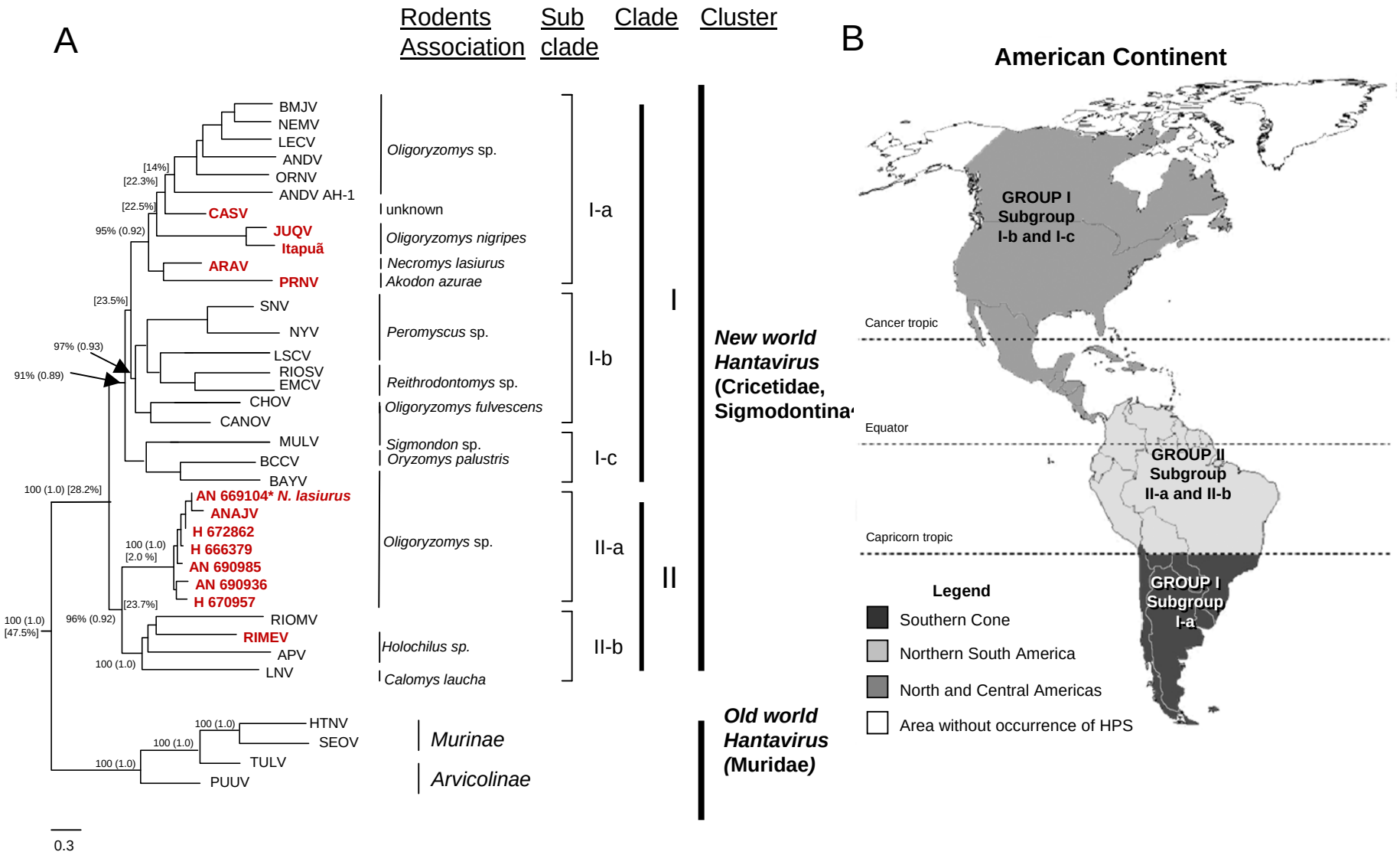
Brasil, 1986-2006*



*Information of dengue hospitalized patients. Provisional data, October/2006

Ministério da Saúde

HANTAVIRUSES



Travassos da Rosa et al., 2010; Emerg. Infect. Dis. In press

RAIVA

Ciclo Epidemiológico da Raiva



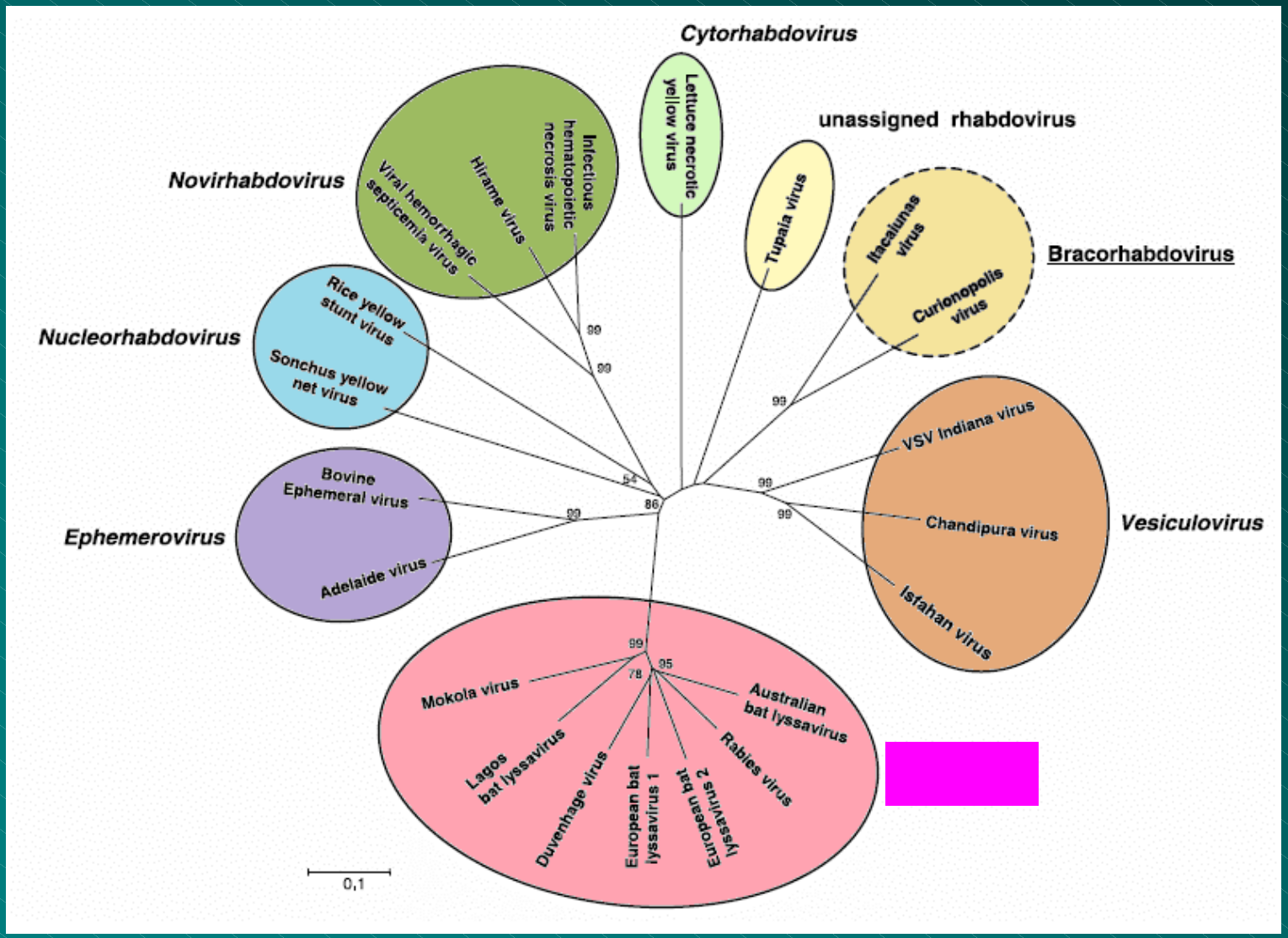
TAKAOKA et al, 2003

Distribuição Geográfica Mundial segundo agente transmissor



Fonte: Adaptado de Rupprecht *et al.*, 2002.

Rhabdoviridae

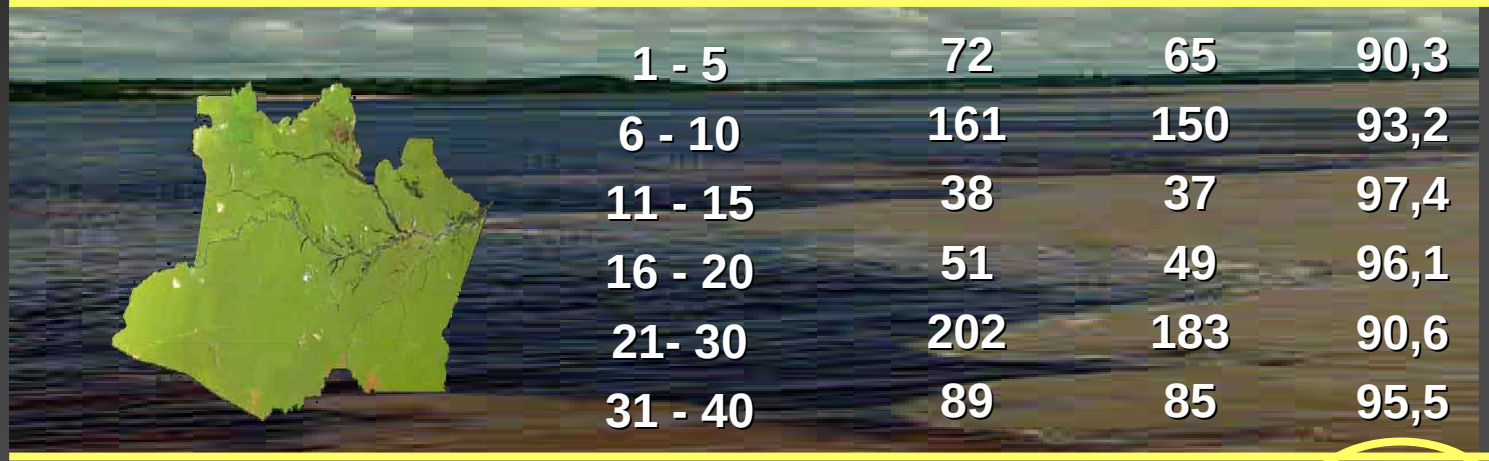


Diniz et al., 2006

HEPATITES VIRAIS

SOROPREVALÊNCIA DE INFECÇÃO PELO HAV NA AMAZÔNIA

Clemens SAC & Fonseca JCF, 2000

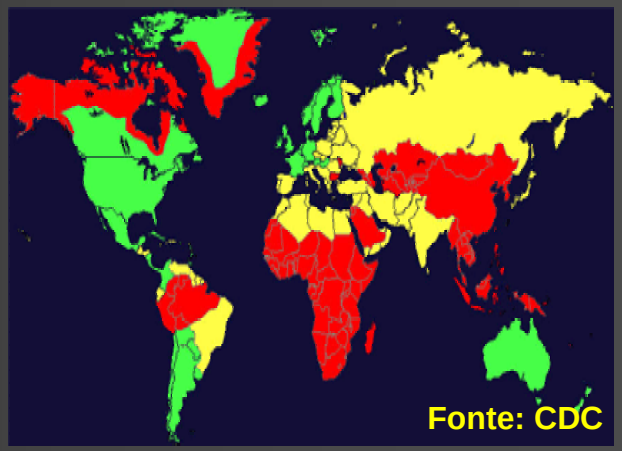


Faixa etária	amostras	nº+	%
1 - 5	72	65	90,3
6 - 10	161	150	93,2
11 - 15	38	37	97,4
16 - 20	51	49	96,1
21- 30	202	183	90,6
31 - 40	89	85	95,5
Total	613	569	92,8

Alta endemicidade: soroprevalência de 92,8% (média nacional 64,7%).

HEPATITE B

- A OMS estima a existência de 350 milhões de portadores crônicos do HBV no mundo
- No Brasil ± 15% da população já teve contato com o HBV.



HORIZONTAL
+ 5 ANOS/
ADULTOS

CURA
90-95%

<1%
FULMINANTE

5-10%
CRONICIDADE

10%

CIRROSE

3-5%

CARCINOMA HEPATOCELULAR

VERTICAL
PERINATAL/
ATÉ 5 ANOS

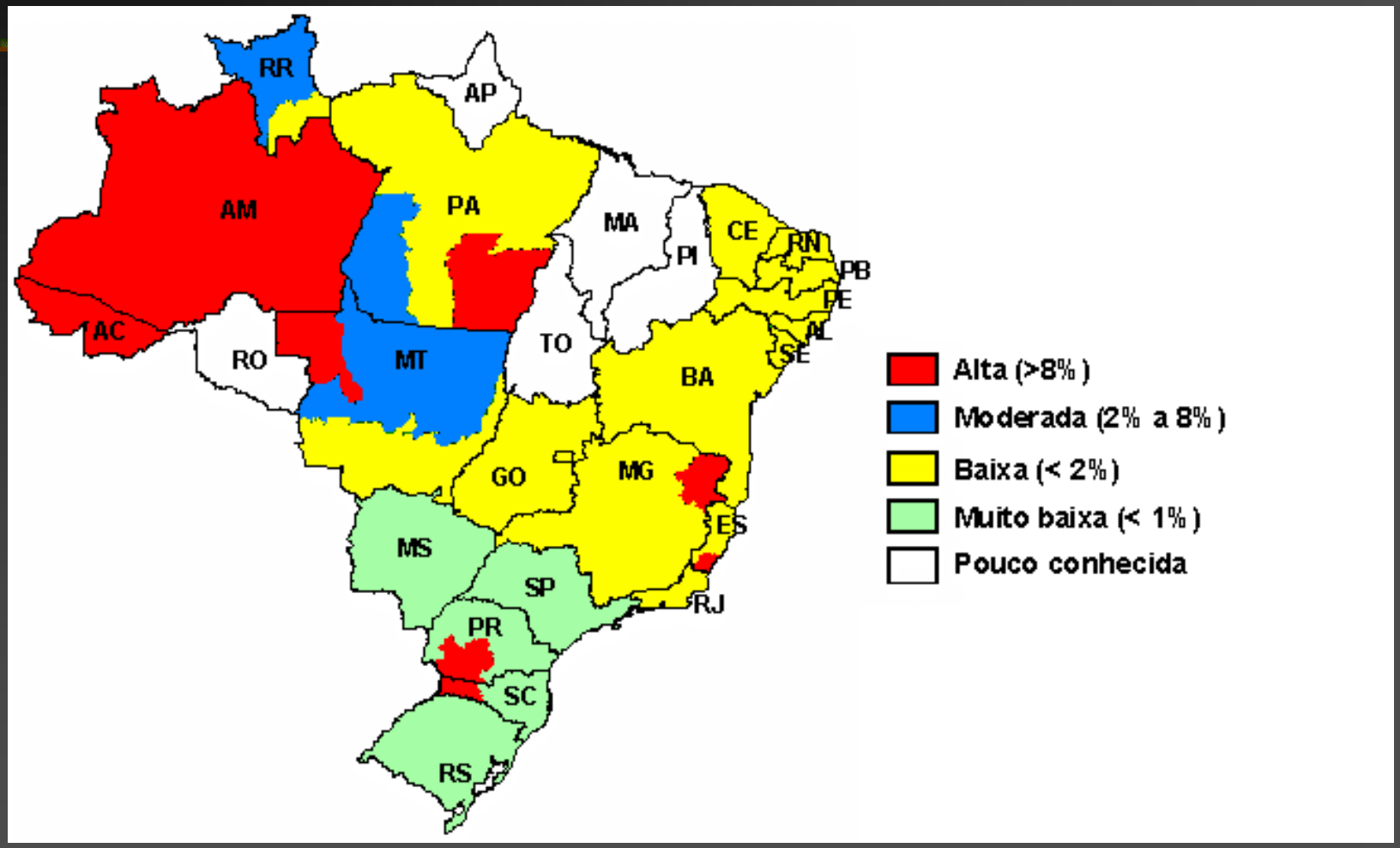
90-95%

CRONICIDADE

25%

ÓBITO POR DOENÇA HEPÁTICA NA FASE ADULTA

Distribuição do HBV no Brasil



* Adaptado de Souto 1999

HEPATITE D NA AMÉRICA DO SUL

ESTUDOS DE PREVALÊNCIA EM PAÍSES DA AMÉRICA DO SUL

Na década de 1940: "Hepatite Fulminante de Santa Marta". (BUITRAGO *et al.*, 1986).

Em 1998, surto de hepatite D na população indígena Waorani. (MANOCK *et al.*, 2000).

Entre 1992-1993, surto de hepatite D em militares da bacia Amazônica peruana (CASEY *et al., 1996*).



Entre 1979 e 1982: "Hepatite Fulminante da Tribo Yucpa (HADLER *et al.*, 1984).

Desde a década de 1950: "Febre Negra de Lábrea". (BENSABATH; DIAS, 1983; BENSABATH; SOARES, 1986; BENSABATH *et al.*, 1987 e FONSECA *et al.*, 1988).

Em 2001, rios Purus e Acre: altas prevalências de HBV e HDV. (PAULA *et al.*, 2001).

DISTRIBUIÇÃO GEOGRÁFICA DO HDV

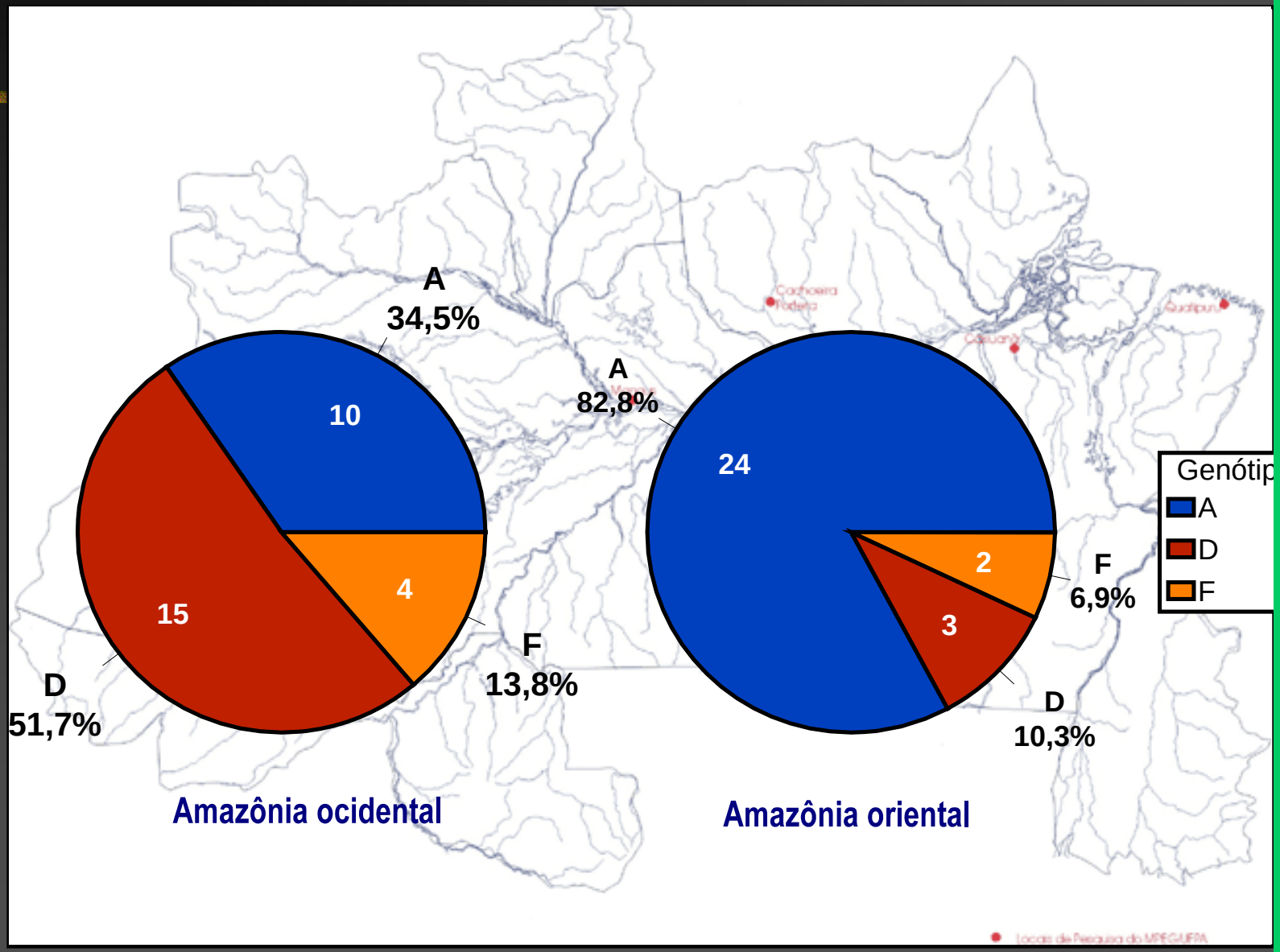
Genótipo I – Cosmopolita

Genótipo II – Ásia

Genótipo III –Norte da América do Sul

Alguns dados sugerem a correlação entre os genótipos do HBV e HDV e severidade de doença (Genótipo III do HDV e Genótipo F do HBV).

Distribuição geral da freqüência de genótipos do HBV na Amazônia ocidental e oriental



Conselho Nacional
De Desenvolvimento
Científico e Tecnológic

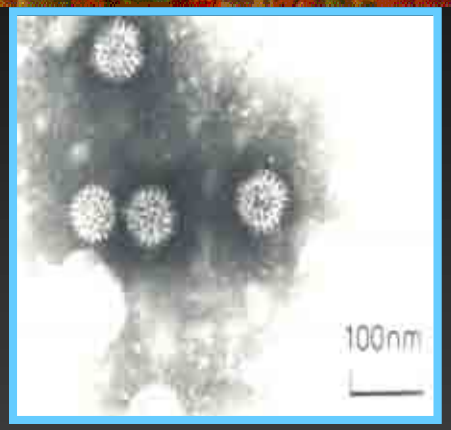
Instituto
Evandro Chagas

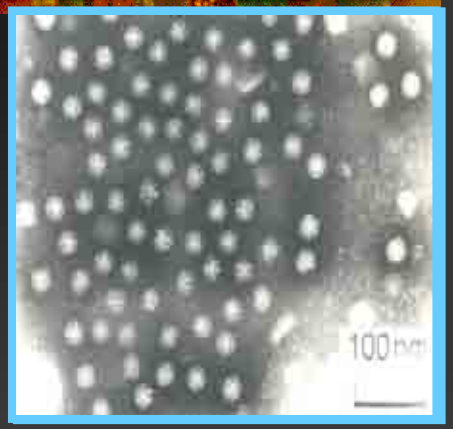
Secretaria de
Vigilância em Saúde

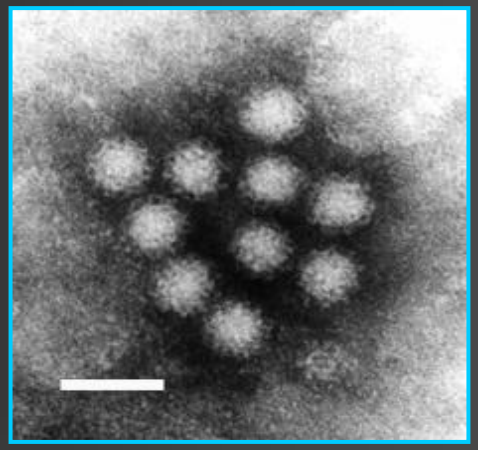
Ministério da Saúde

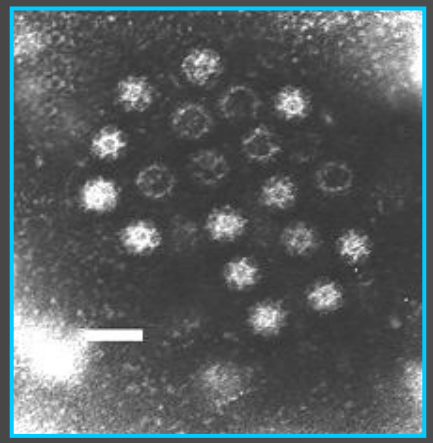
Etiologia viral das diarréias

- Rotavirus
- Astrovirus
- Norovírus
- Sapovírus

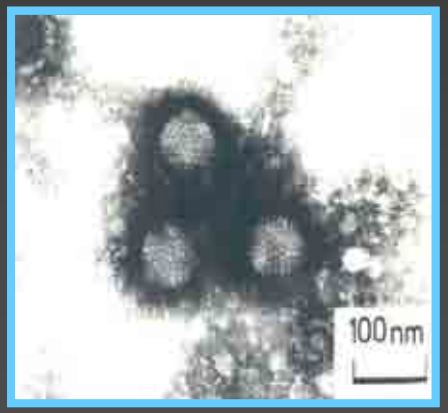


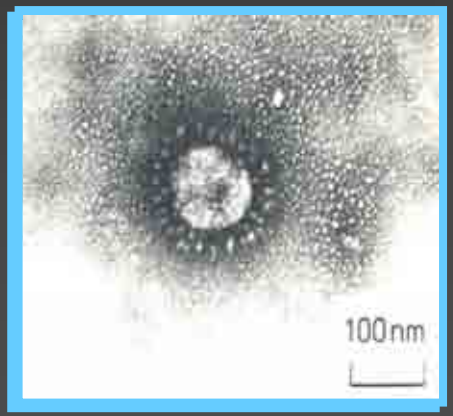


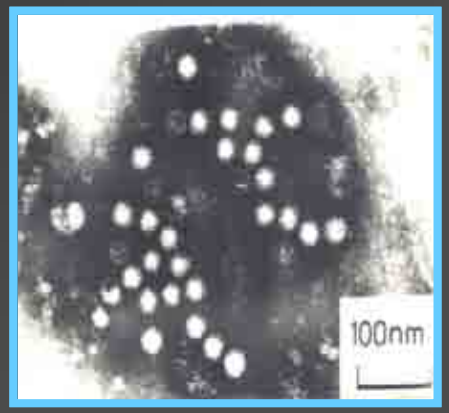




- Adenovirus
- Torovirus
- Enterovirus



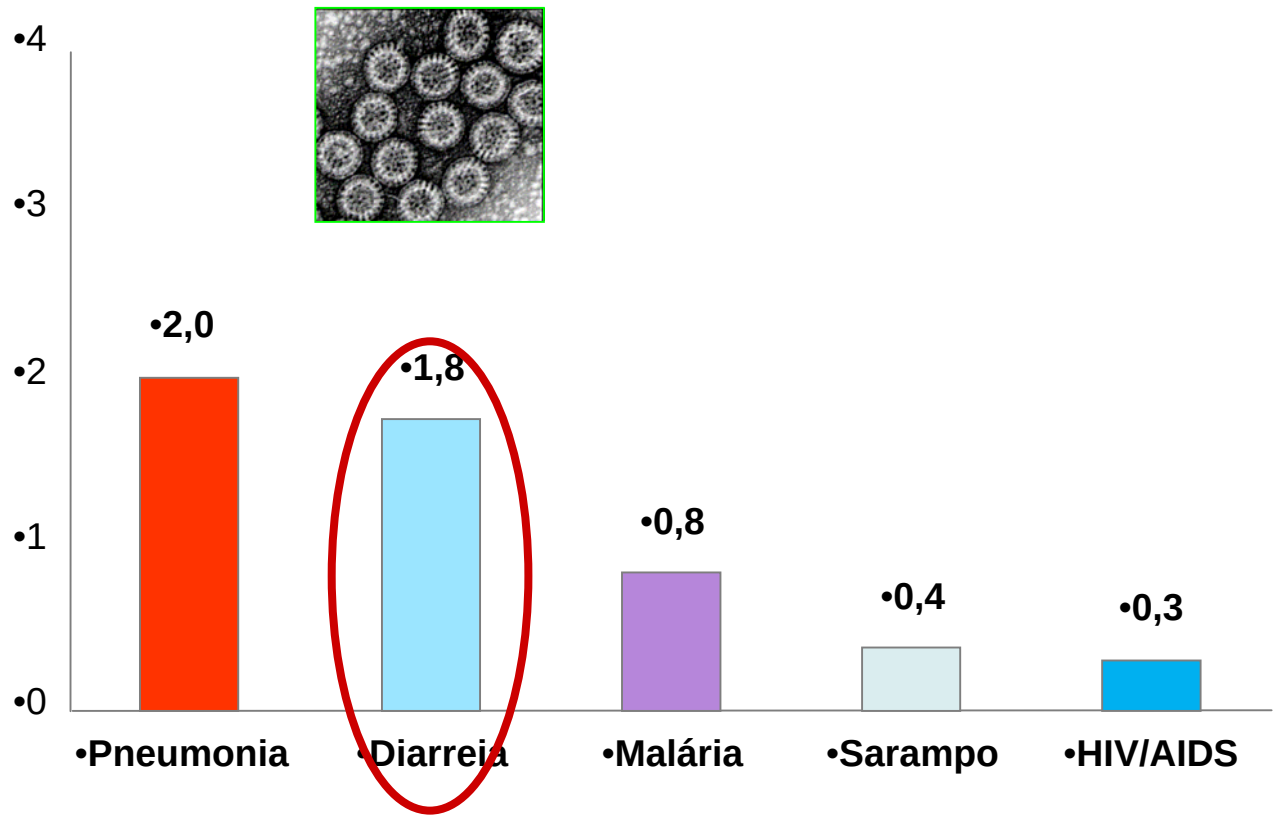




- **Fonte: Atlas da *The Electron Microscopy Unit*, *Public Health Laboratory*, Bristol, UK**

•Mundo: Crianças <5 anos

•Mortes por diarréia >2x mortes por malária!



•Bryce J, *et al. Lancet* 2005; 365: 1147–52.

Norovirus

► >90% dos surtos de diarréia não bacteriana são causados pelos NoV

► Cada ano ocorrem 64.000 episódios de diarréia por NoV que requerem hospitalização – países industrializados

► 900.000 visitas clínicas entre crianças de países industrializados

►200.000 mortes em crianças <5a em países em desenvolvimento

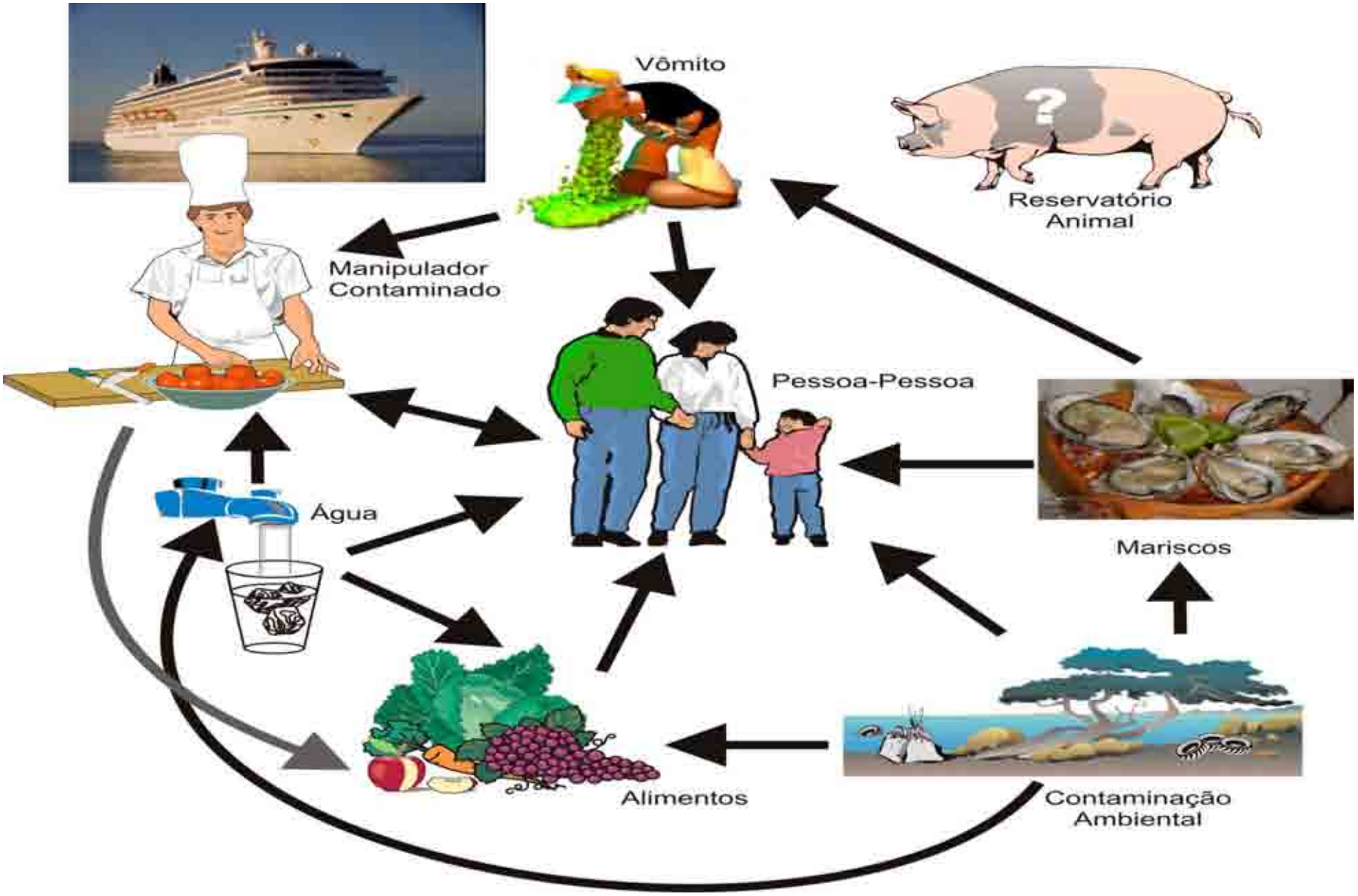
►Metodologia só disponível nos lab. de referência. Ainda permanece desconhecida a real prevalência e o impacto econômico da doença causada por esses vírus

►NoV responsável por 12% dos casos gastroenterite grave entre crianças <5a- tanto em países industrializados como em desenvolvimento.

►NoV responsável 12% diarréias leves/moderadas- pessoas de todas as idades

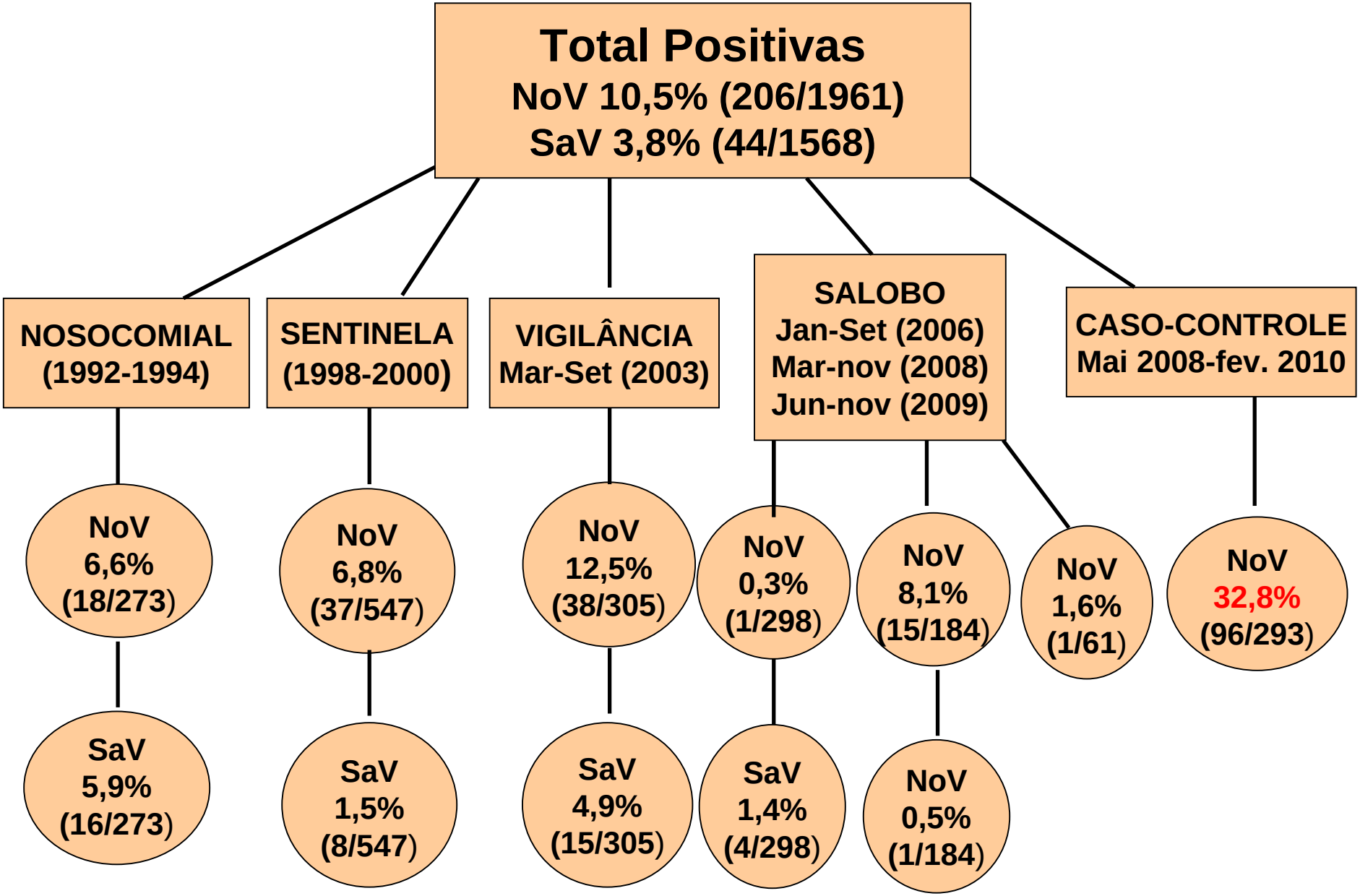
Patel et al., 2008

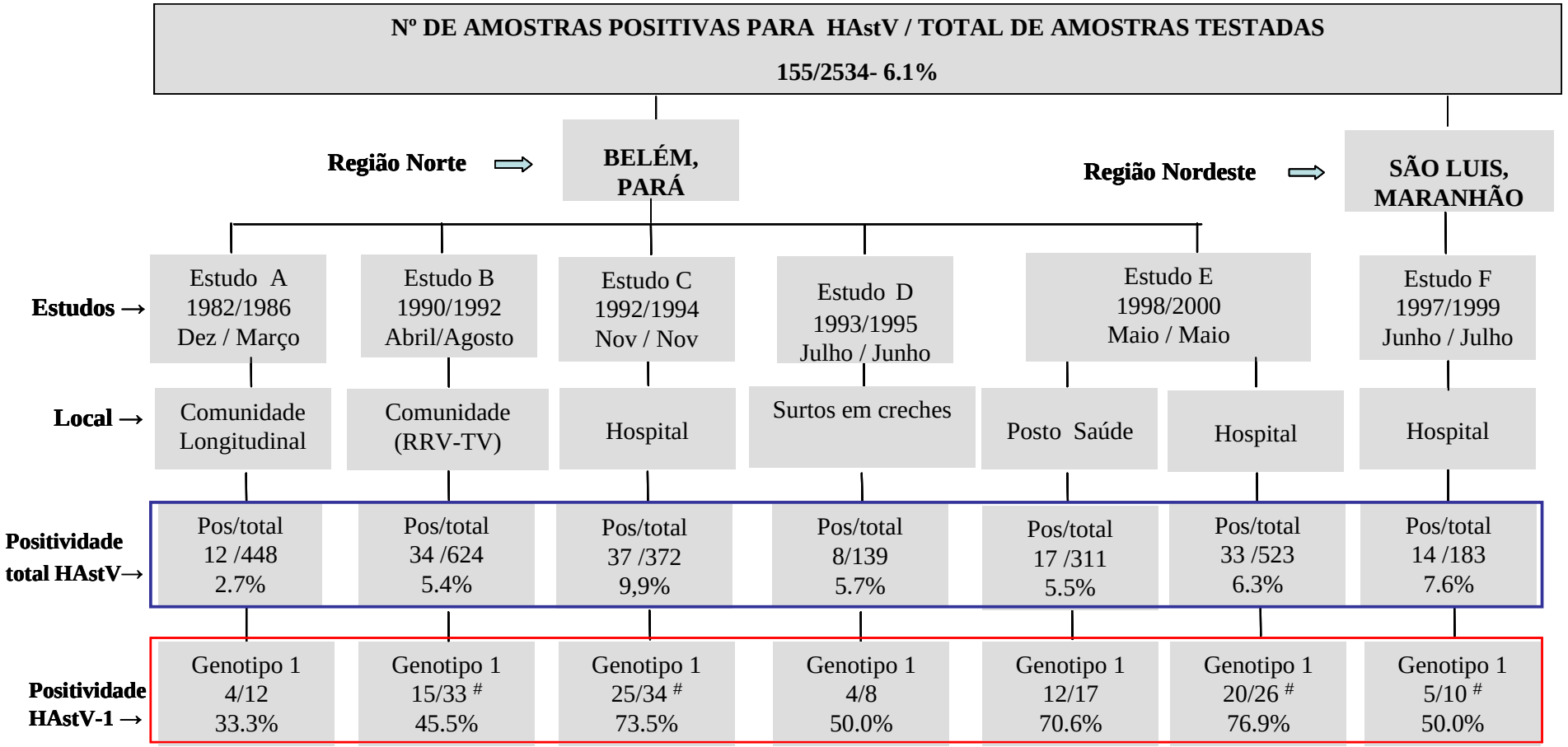
Calicivírus humanos e astrovírus: rotas de transmissão



Adaptado de Moreno-Espinosa *et al*., 2004

Amostras fecais provenientes de diversos projetos realizados no Instituto Evandro Chagas testadas quanto a presença dos norovírus e sapovírus



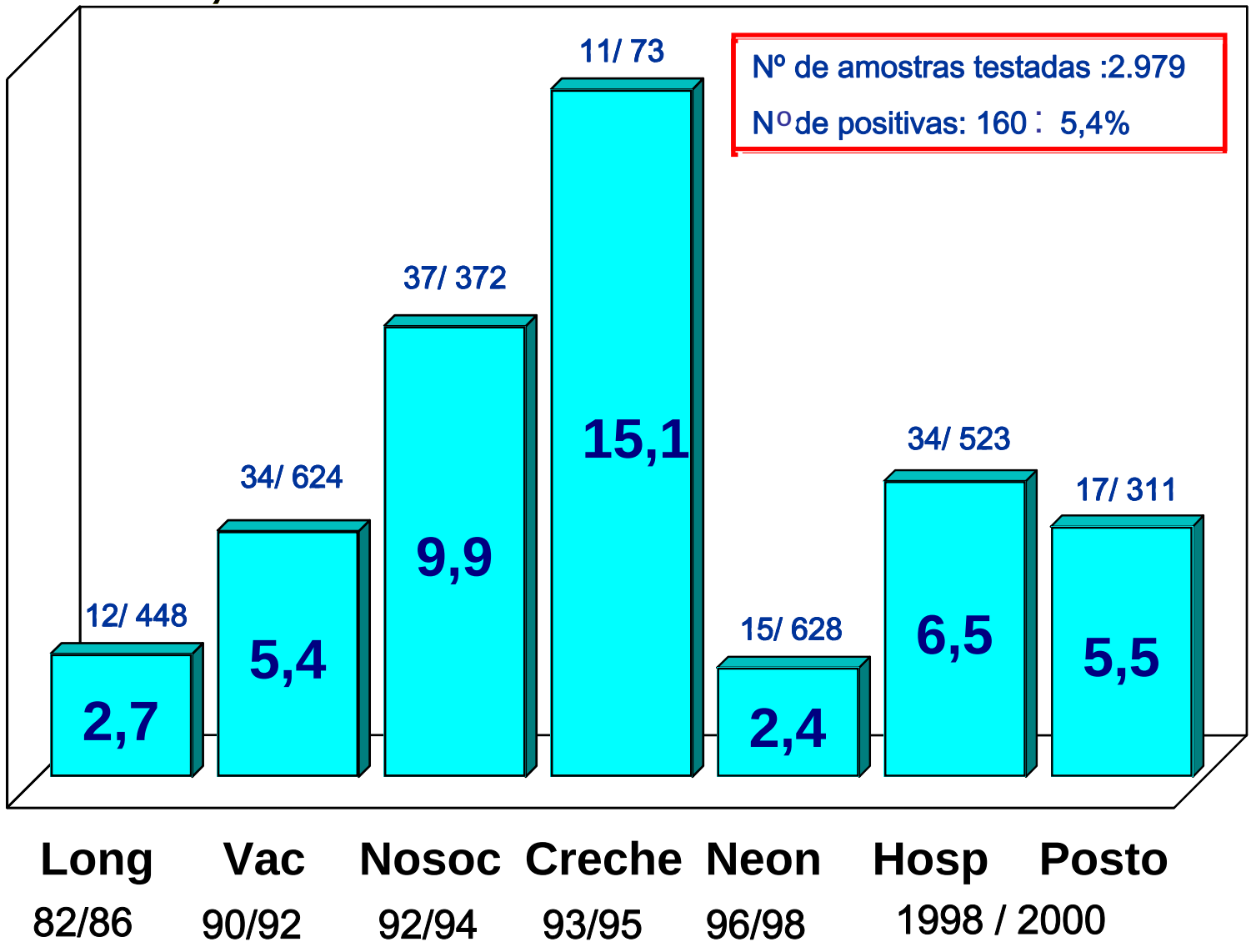


Algumas amostras foram positivas para HAstV pelo EIA e negativas pelo RT-PCR

⇒ Um total de 140 amostras foram positivas para HAstV pelo RT-PCR: 60.7% (85/140) para HAstV-1, 23.6% (33/140) para HAstV-2, 4.3% (6/140) para HAstV-3, 5.0% 7/140) para HAstV-4, 2.1% (3/140) para HAstV-5, 0.7% (1/140) para HAstV-6 e 8, 1.4% (2/140) para HAstV-7 e 1.4% (2/140) amostras não foram genotipadas

➡ **Surto tribo indígena Maxakali, Minas Gerais, em janeiro de 2004**

Frequência de astrovírus em espécimes fecais de crianças diarréicas oriundas de diversos estudos. Belém, Pará. Dezembro/1982 a maio/2000









New Campus of Instituto Evandro Chagas in Ananindeua/Pará.

• OBRIGADO

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