V Fórum de Leishmaniose Visceral do Estado de São Paulo

Leishmaniose visceral: conheça, apoie, atue.

Centro de Convenções Rebouças, São Paulo-SP

07h às 17h de 08 de agosto de 2017

Leishmaniose Visceral

Epidemiologia, Clínica e Tratamento

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Instituto de Infectologia Emilio Ribas-SES-SP

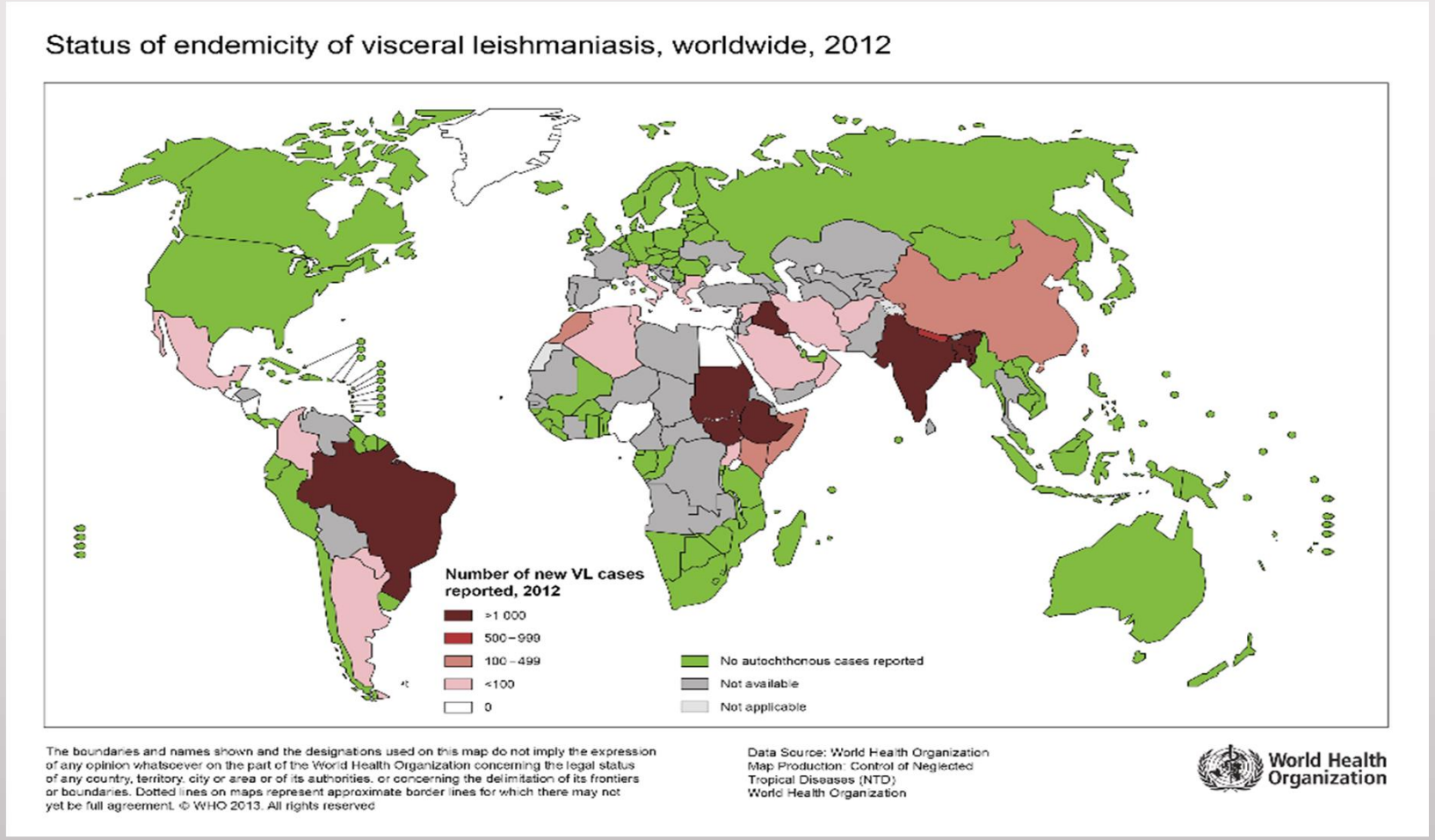
Laboratório de Investigação Médica-HC-FMUSP

Instituto de Medicina Tropical-USP

Instituto de Infectologia EMÍLIO RIBAS

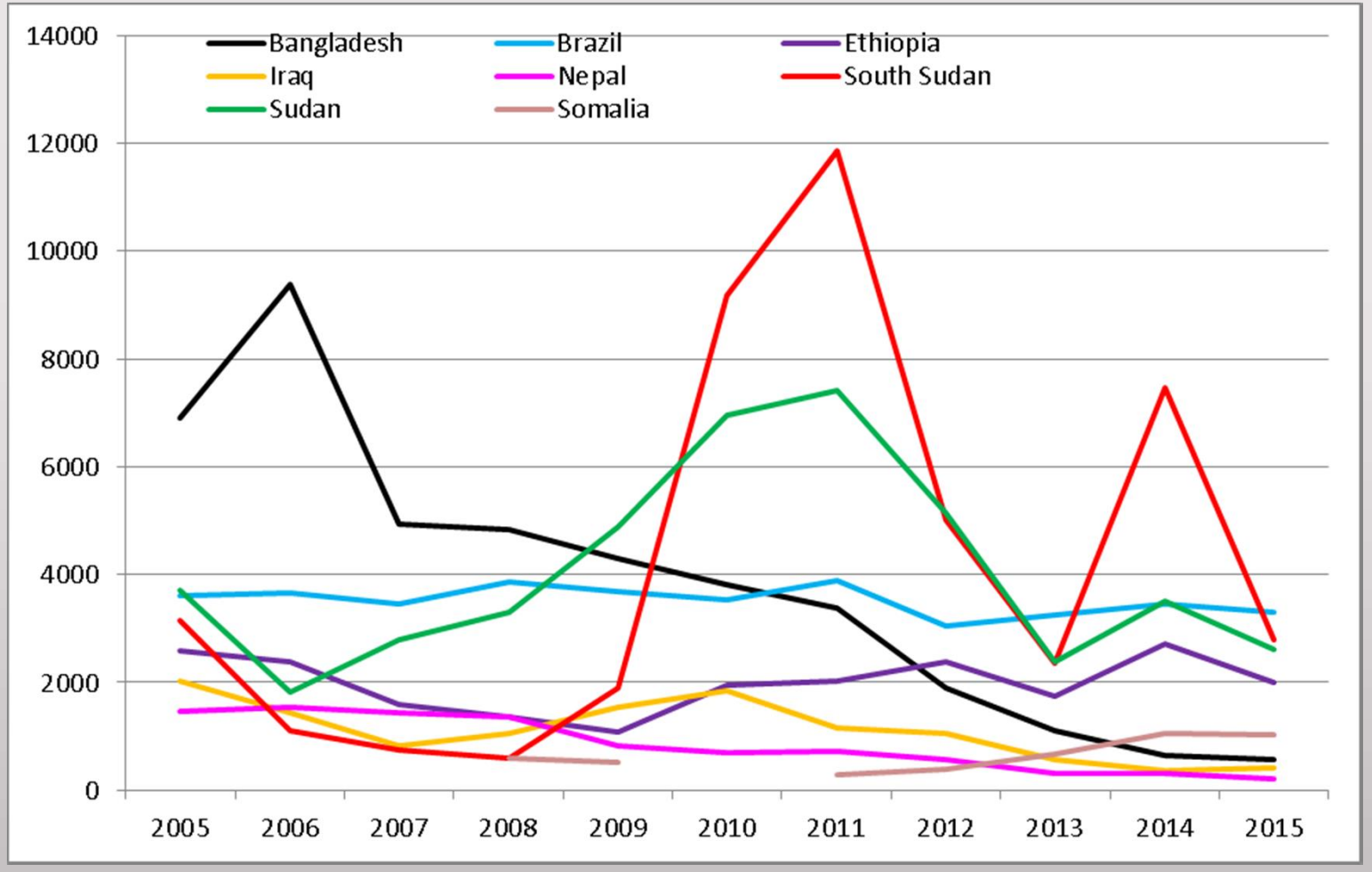
INSTITUTO DE MEDICINA TROPICAL DE SÃO PAULO – BRASIL

Leishmaniose Visceral



90% dos casos: **Brasil**, Etiopia, Nepal, Índia, Sudão e Bangladesh

LV nos oito países mais afetados
(exceto Índia)



LV nas Americas

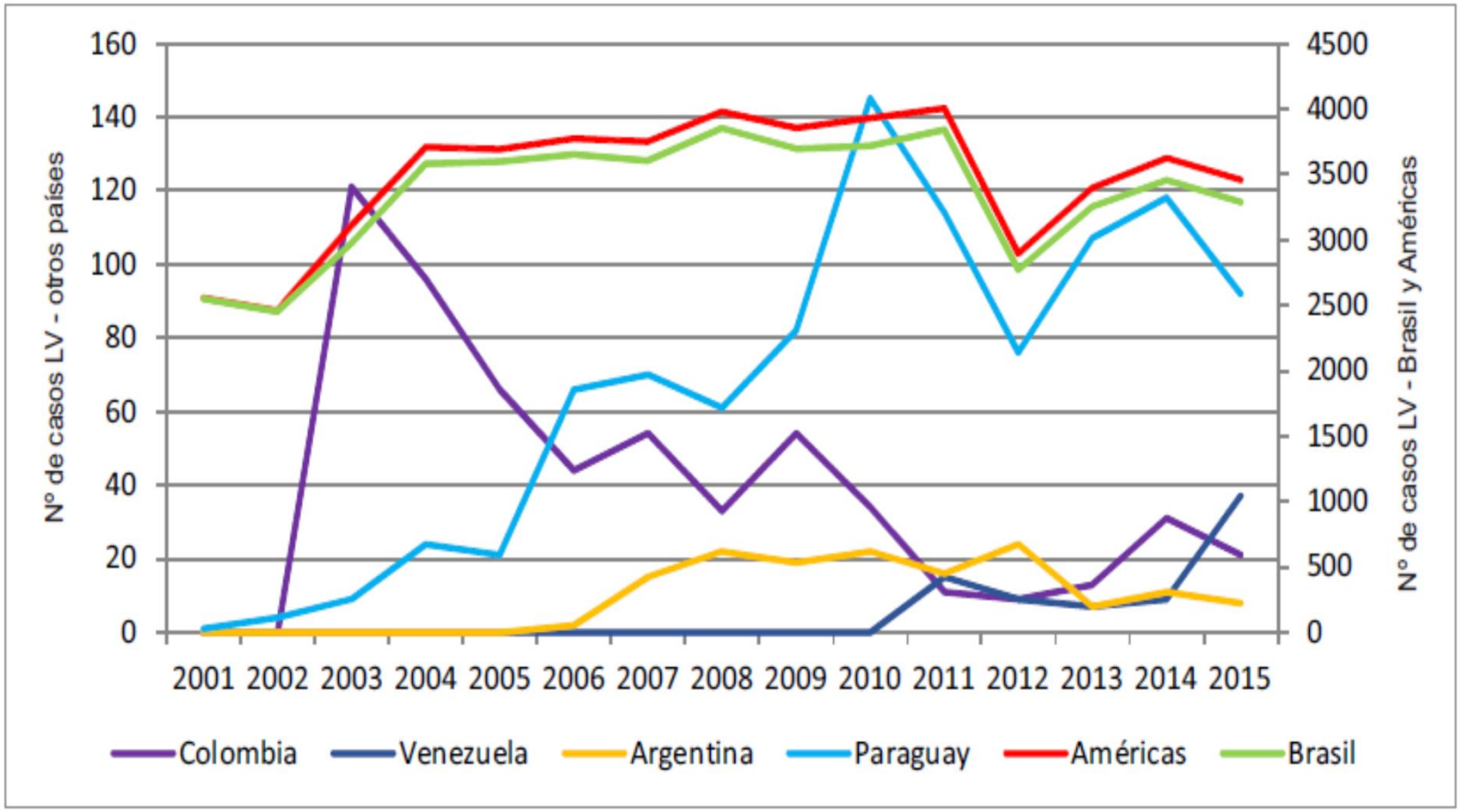


Figura 9. Casos de leishmaniasis visceral, en los países con el mayor número de casos, Américas, 2001 -2015.
Fuente: SisLeish-OPS/OMS: Datos reportados por los Programas Nacionales de Leishmaniasis/Vigilancia. Datos disponibles en el 20 de febrero 2017.

LV nas Américas

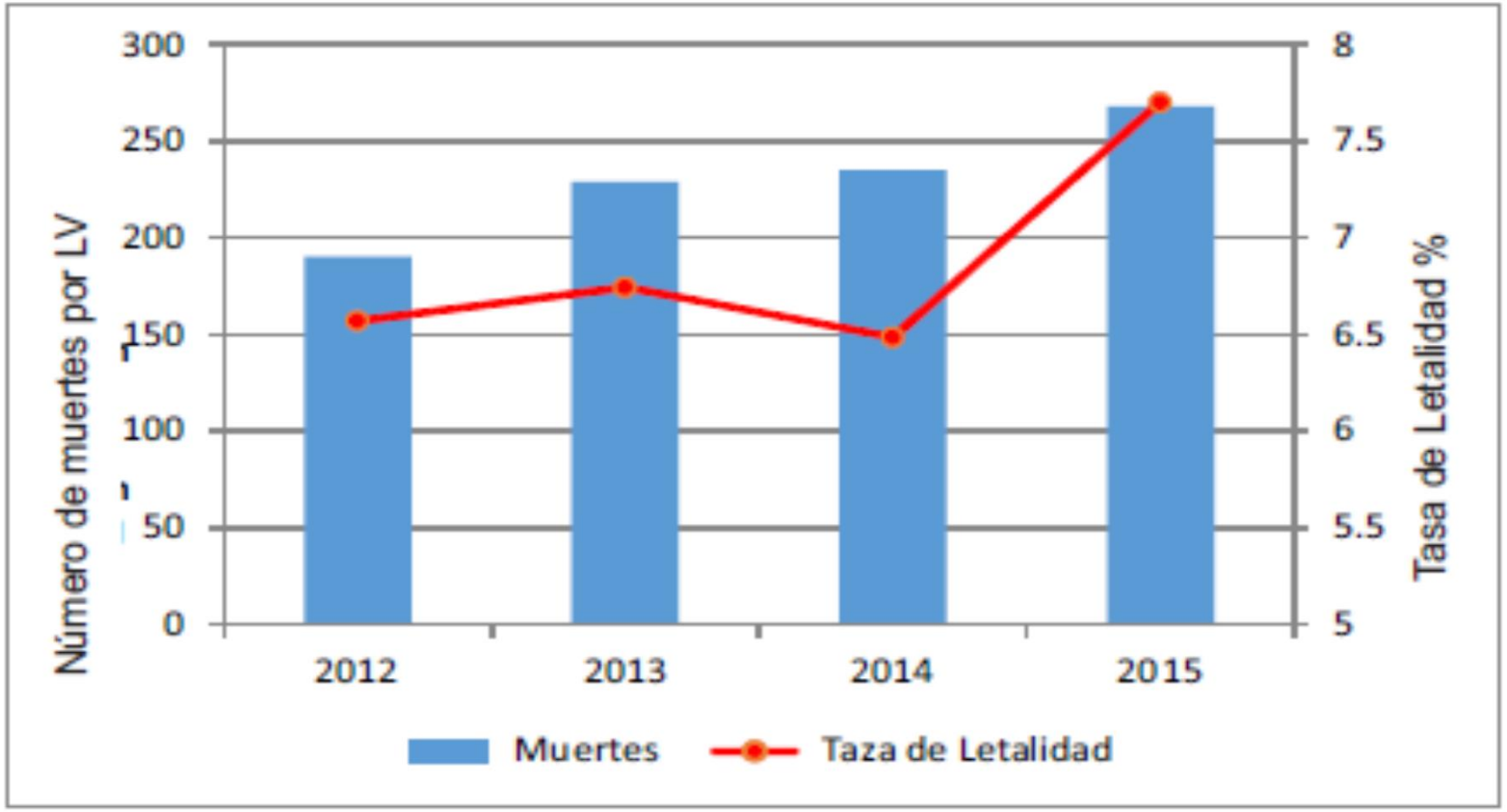


Figura 10. Número de muertes y letalidad de la leishmaniasis visceral, Américas, 2012 -2015.
Fuente: SisLeish-OPS/OMS: Datos reportados por los Programas Nacionales de Leishmaniasis/Vigilancia. Datos disponibles en el 20 de febrero 2017.

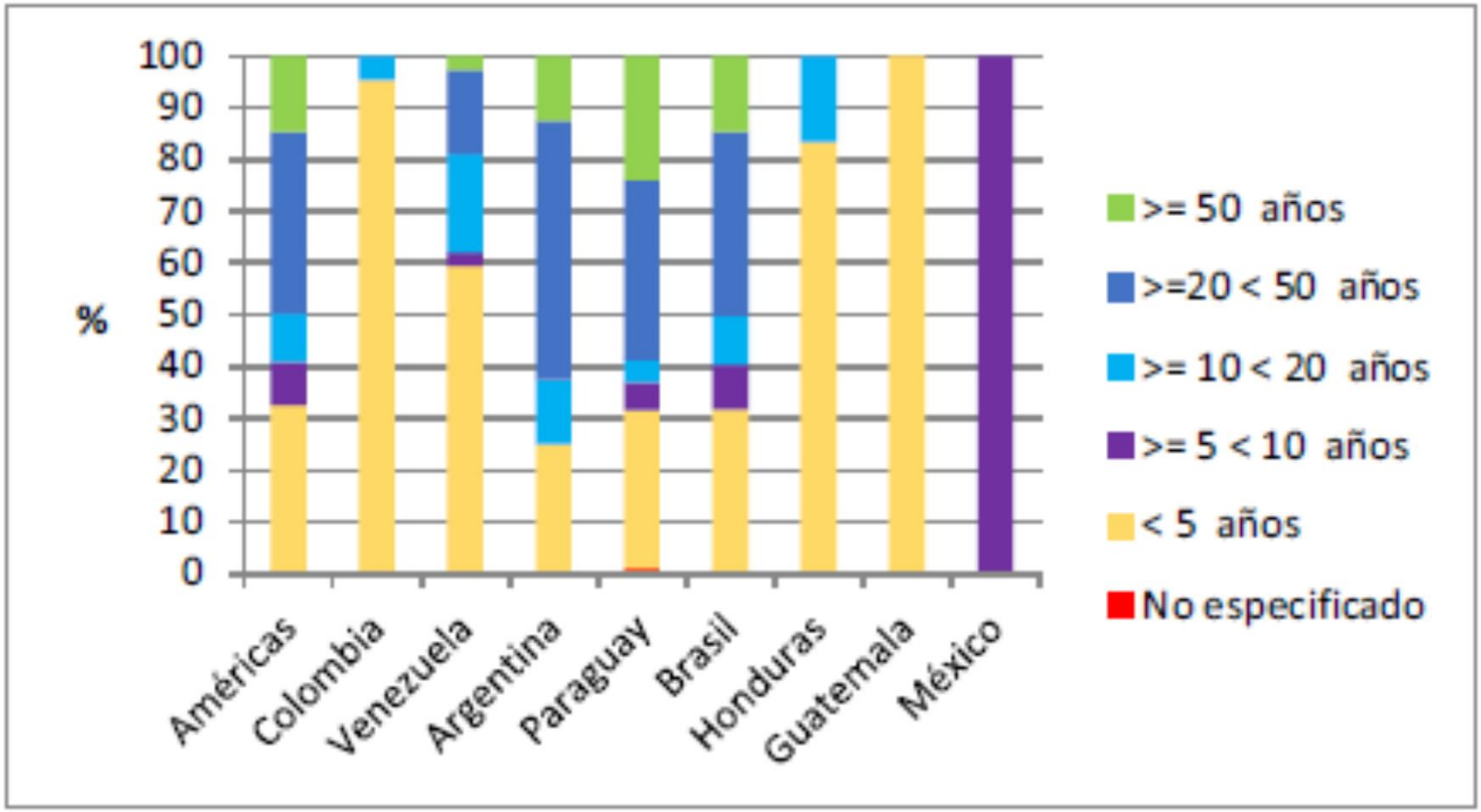


Figura 11. Proporción de casos de leishmaniasis visceral por grupos de edad y país, Américas, 2015.

Fuente: SisLeish-OPS/OMS: Datos reportados por los Programas Nacionales de Leishmaniasis/Vigilancia.

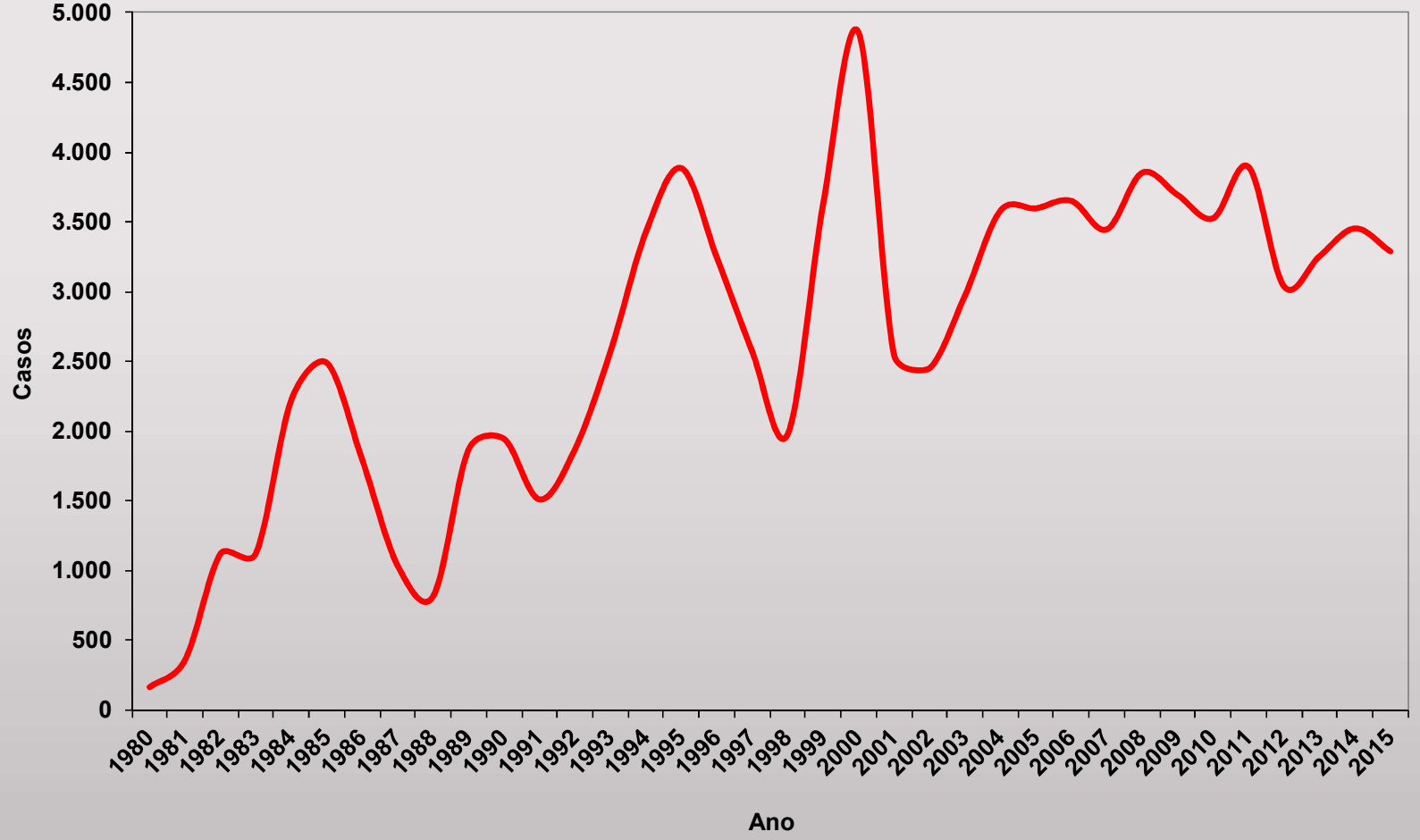
Datos disponibles en el 20 de febrero 2017

Situação Epidemiológica da LV no Brasil 2015

- 3.289 casos
- Coeficiente de incidência – 1,61 casos/100.000 habitantes
- 21 UF – 5 Regiões brasileiras
- 64,8% sexo masculino
- 54,9% Região Nordeste
- 40,2% dos casos em crianças 0-9 anos
- Letalidade: 7,8%
- 2.447 internações e média de permanência de 13,8 dias
- 7,4 % de coinfectados *Leishmania*/HIV

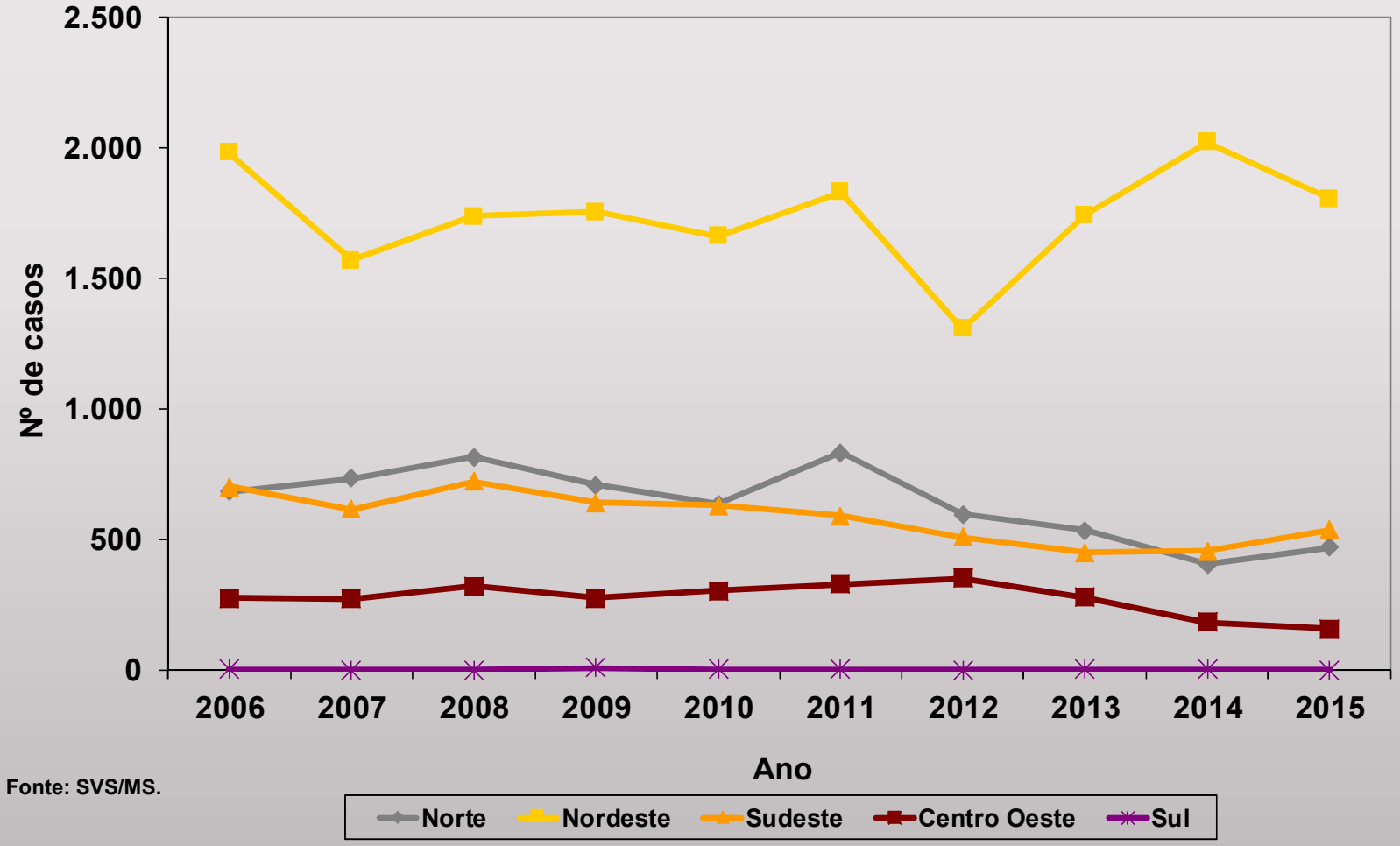
Fonte: SVS/MS.

Casos de leishmaniose visceral no Brasil 1980 a 2015



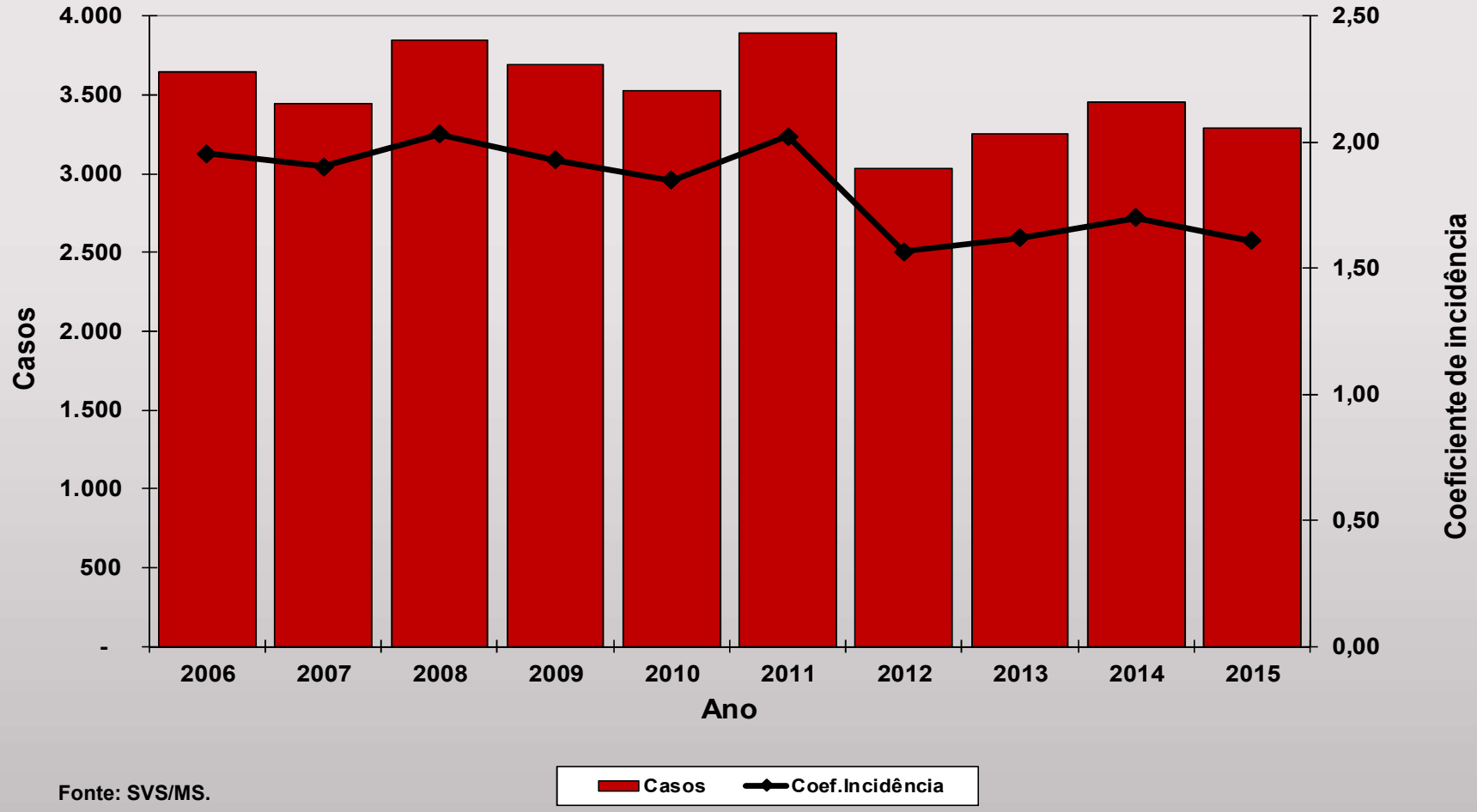
Fonte: SVS/MS.

Casos de leishmaniose visceral por regiões brasileiras, 2006 a 2015



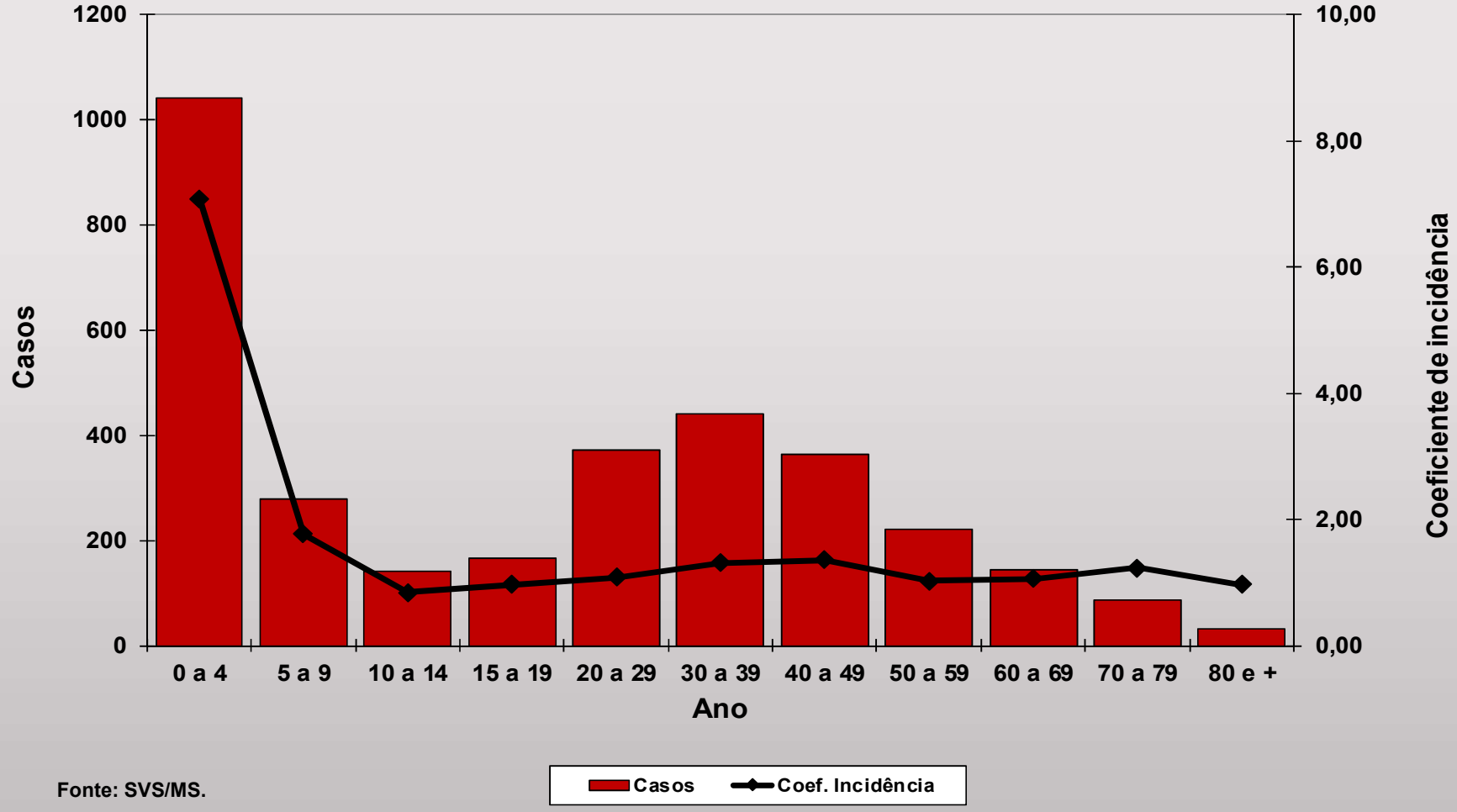
Fonte: SVS/MS.

Casos e coeficiente de incidência LV no Brasil 2005 a 2015



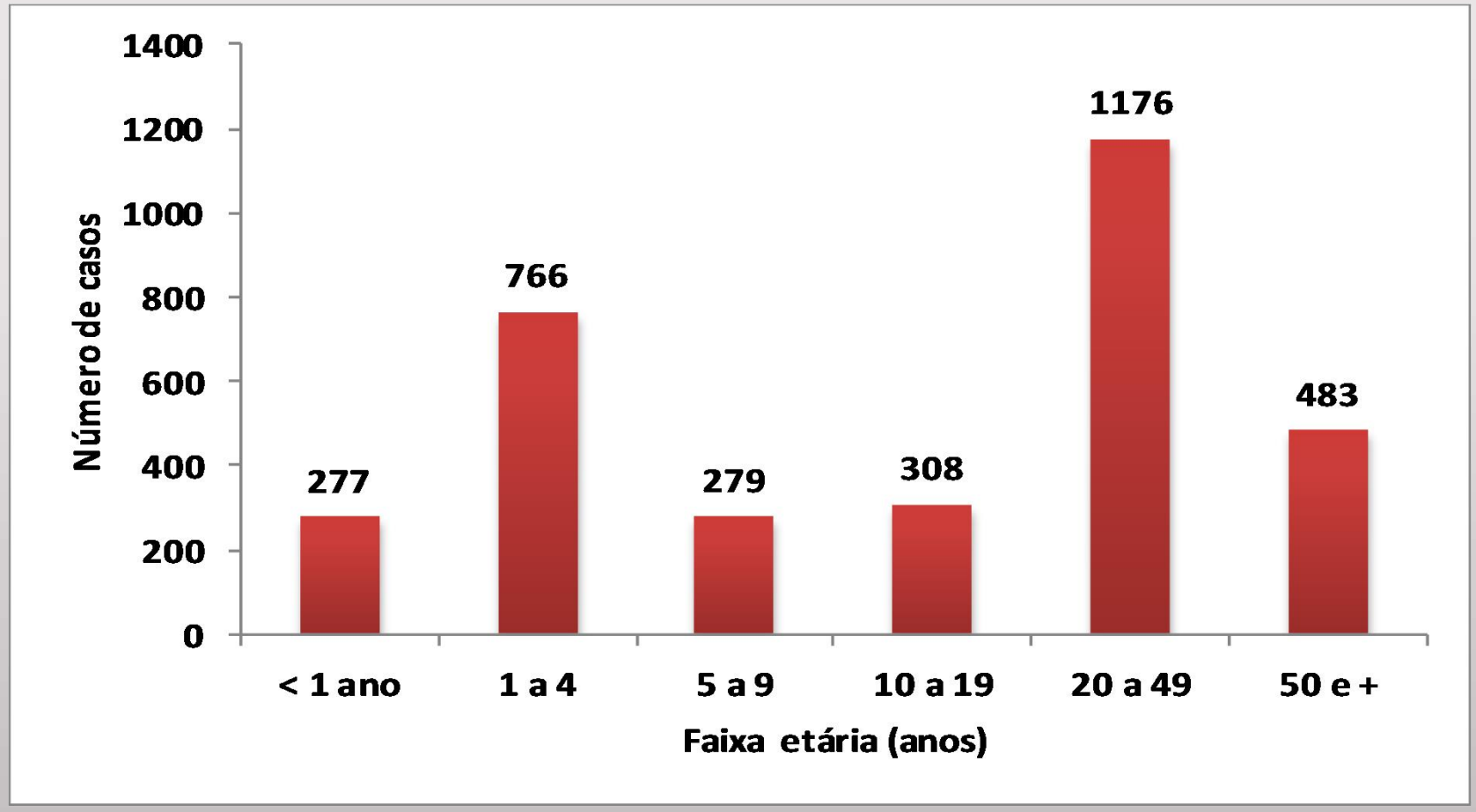
Fonte: SVS/MS.

Casos e coeficiente de incidência de LV faixa etária, Brasil, 2015



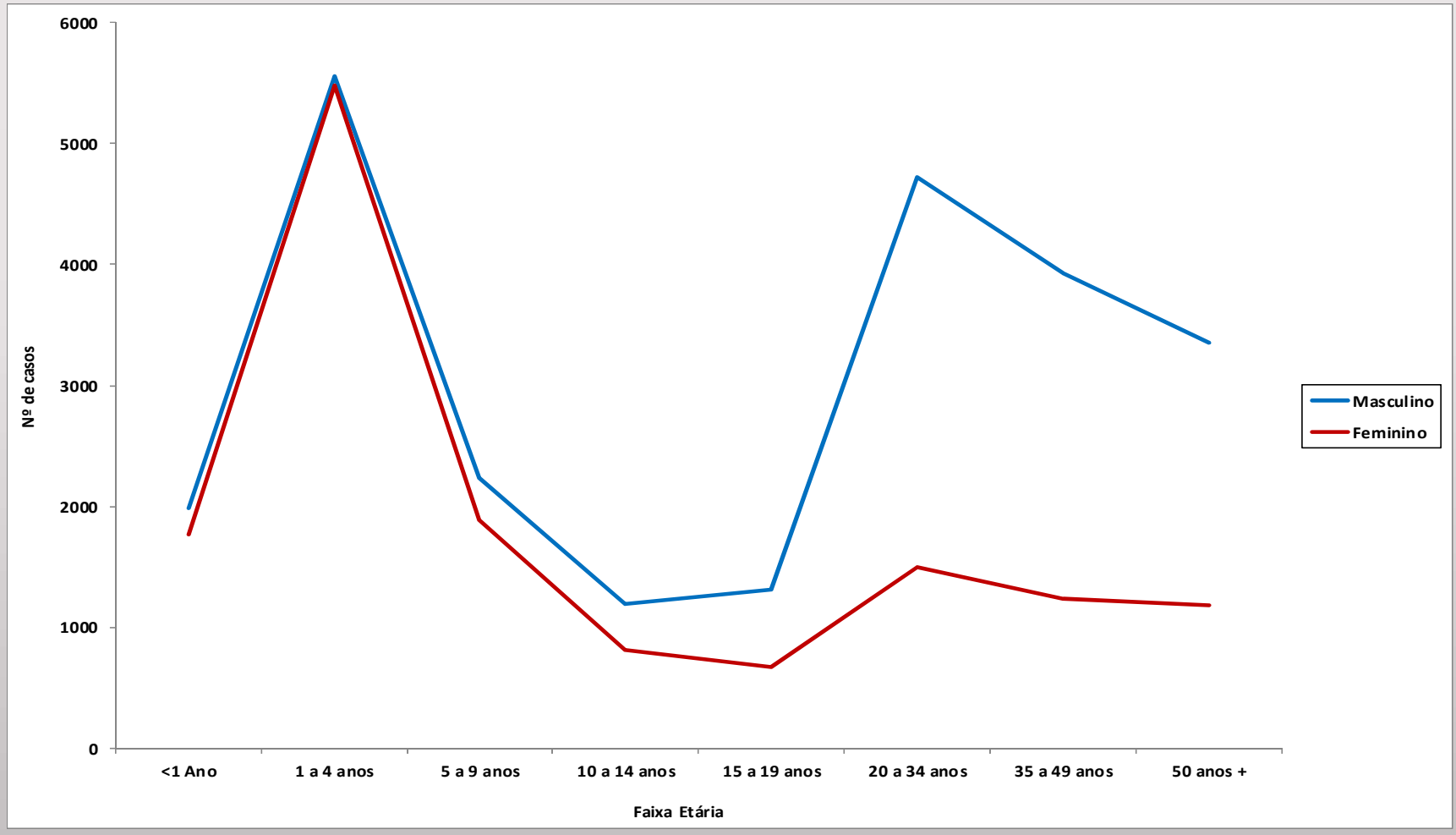
Fonte: SVS/MS.

Casos de leishmaniose visceral faixa etária, Brasil, 2015



Fonte: SVS/MS.

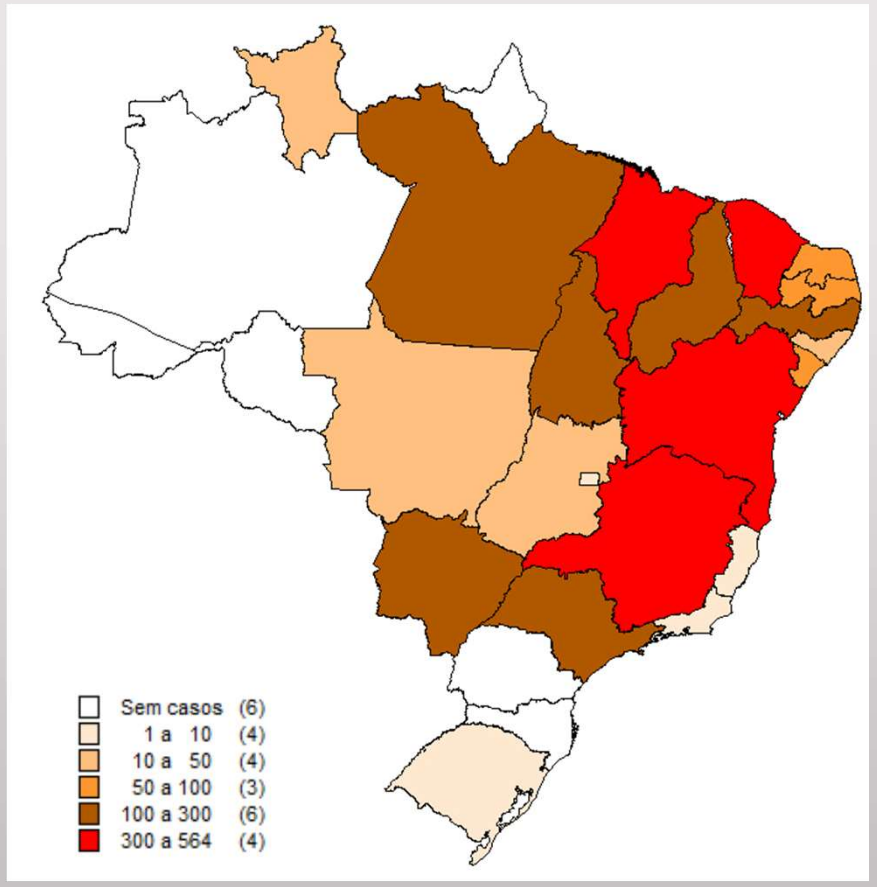
Casos de leishmaniose visceral segundo sexo e faixa etária, Brasil, 2005 a 2015



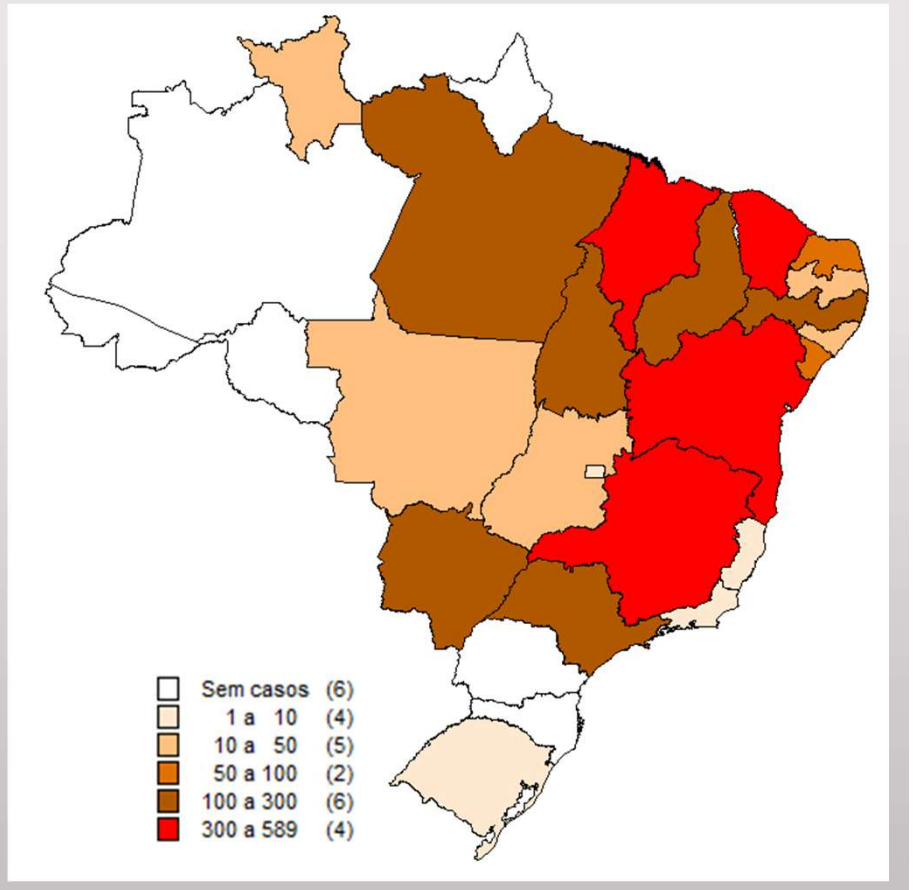
Fonte: SVS/MS.

Casos de LV por UF de infecção, Brasil, 2014 e 2015

2014



2015



Fonte: SVS/MS.

Casos de LV por UF, Brasil, 2003 a 2015

2003-2005

2006-2008

2009-2011

2012-2014

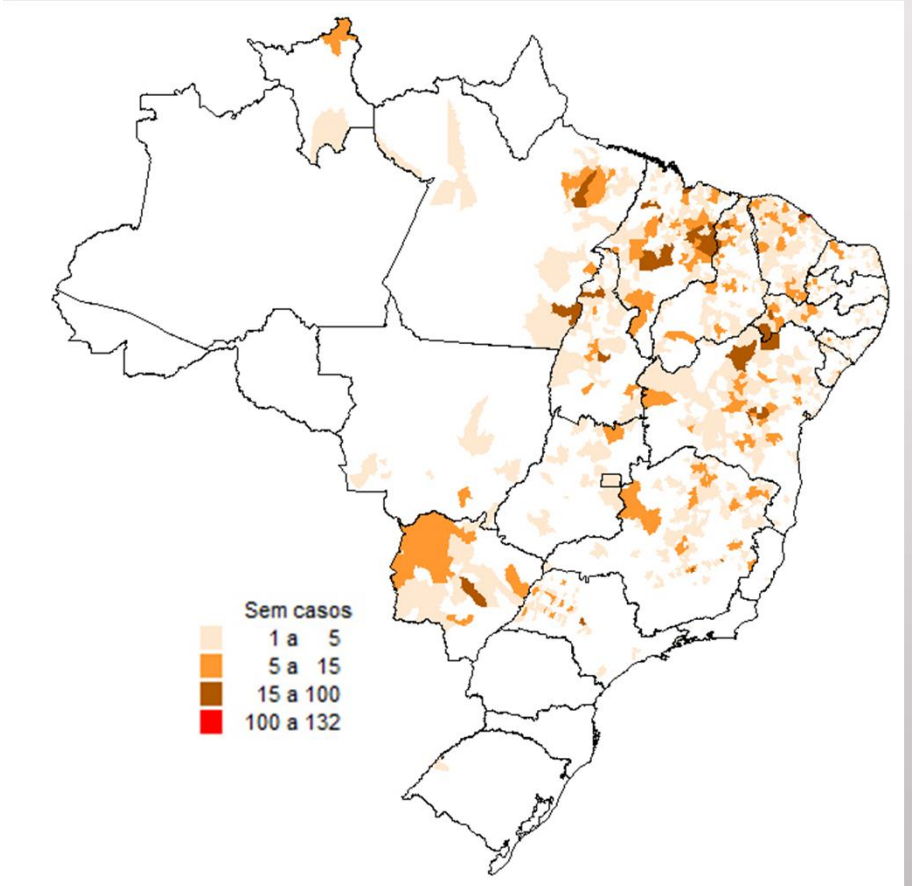
2015

1 Ponto = 1 Caso

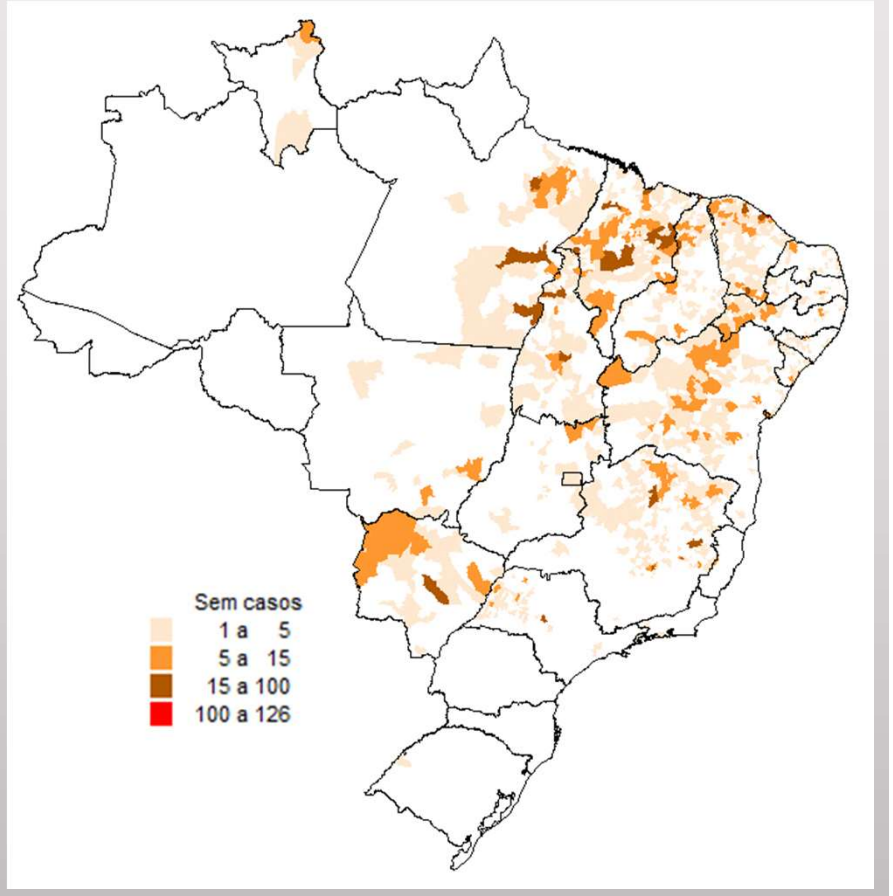
Fonte: SVS/MS.

Casos de LV por Município de infecção, Brasil, 2014 e 2015

2014

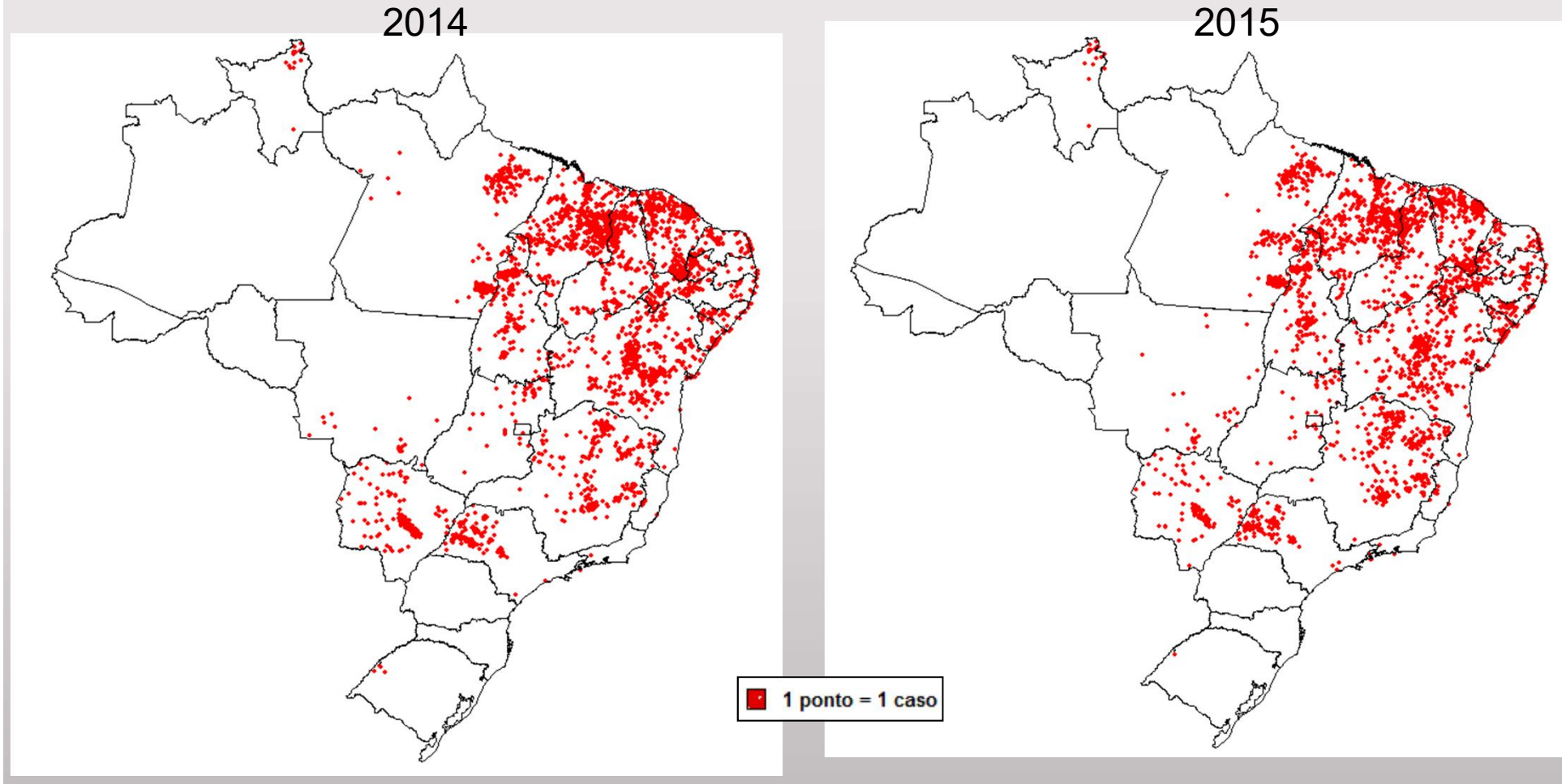


2015



Fonte: SVS/MS.

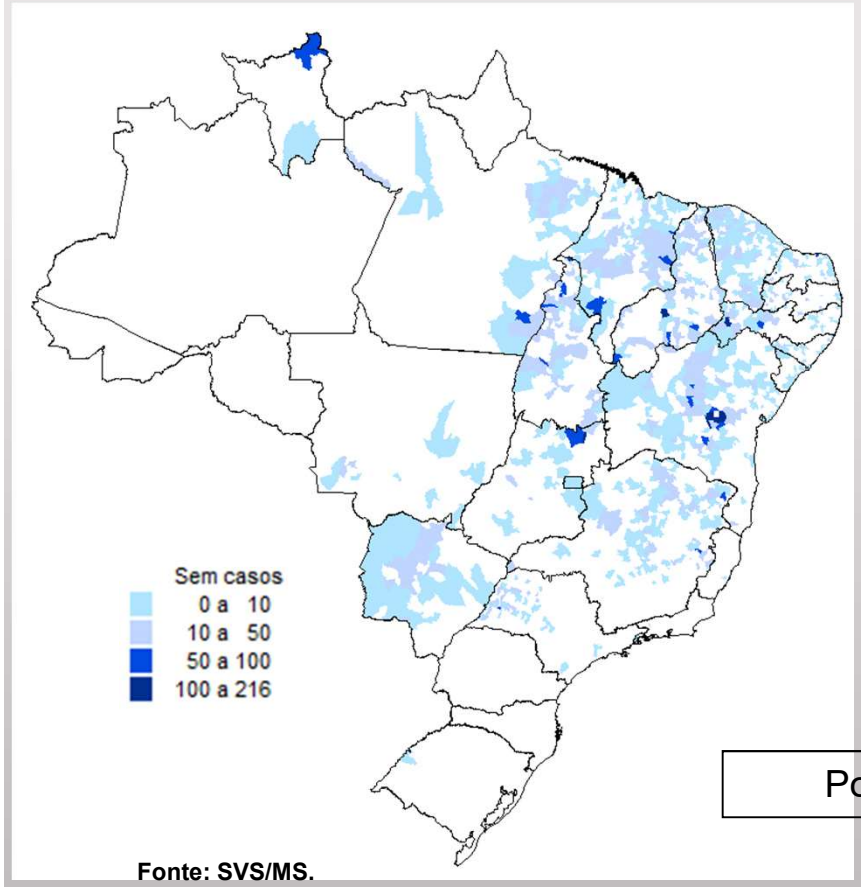
Casos de LV por Município de infecção, Brasil, 2014 e 2015



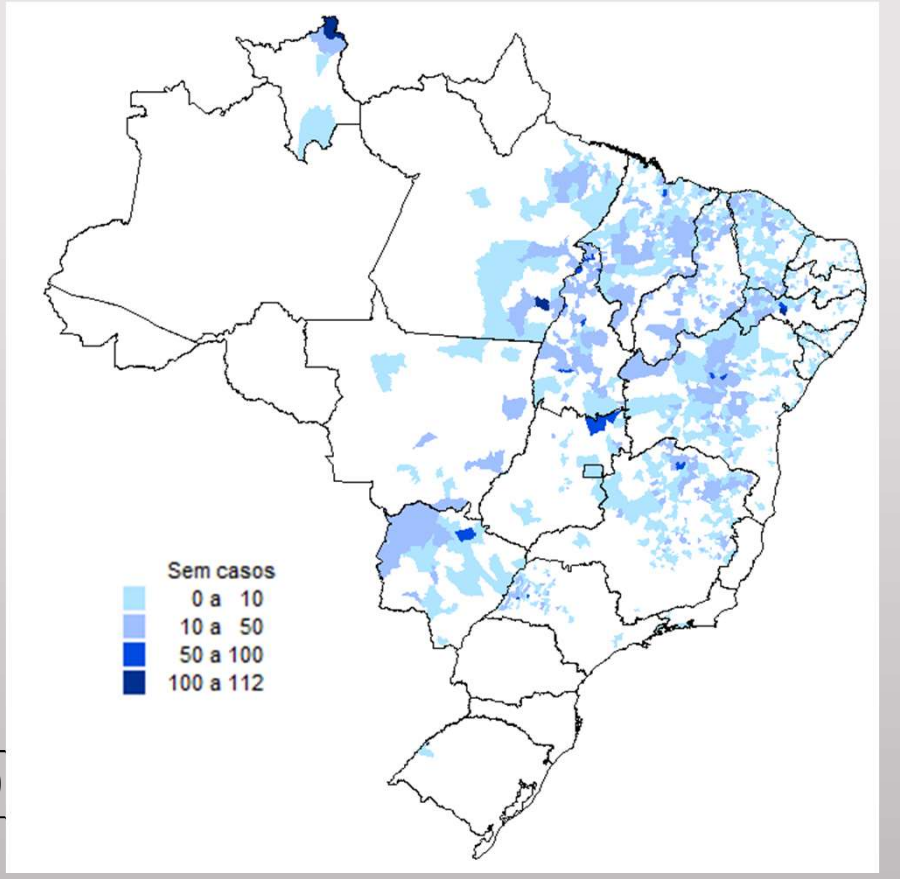
Fonte: SVS/MS.

Incidência de casos de LV por Município de infecção, Brasil, 2014 e 2015

2014



2015

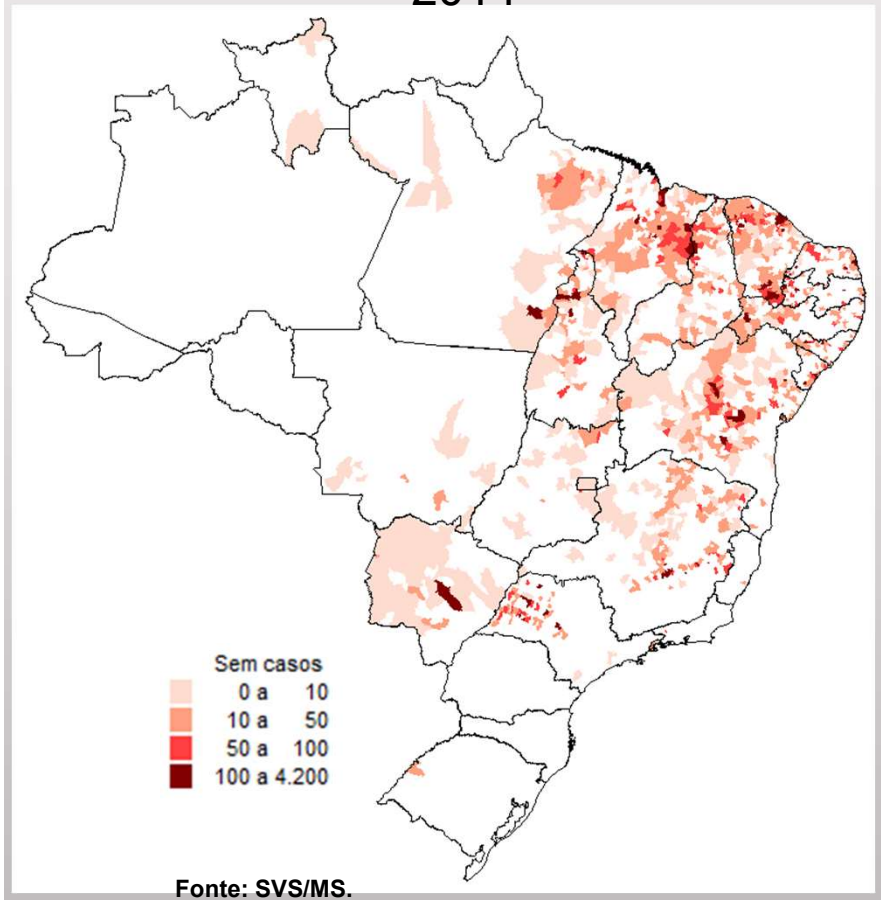


Por 100.000

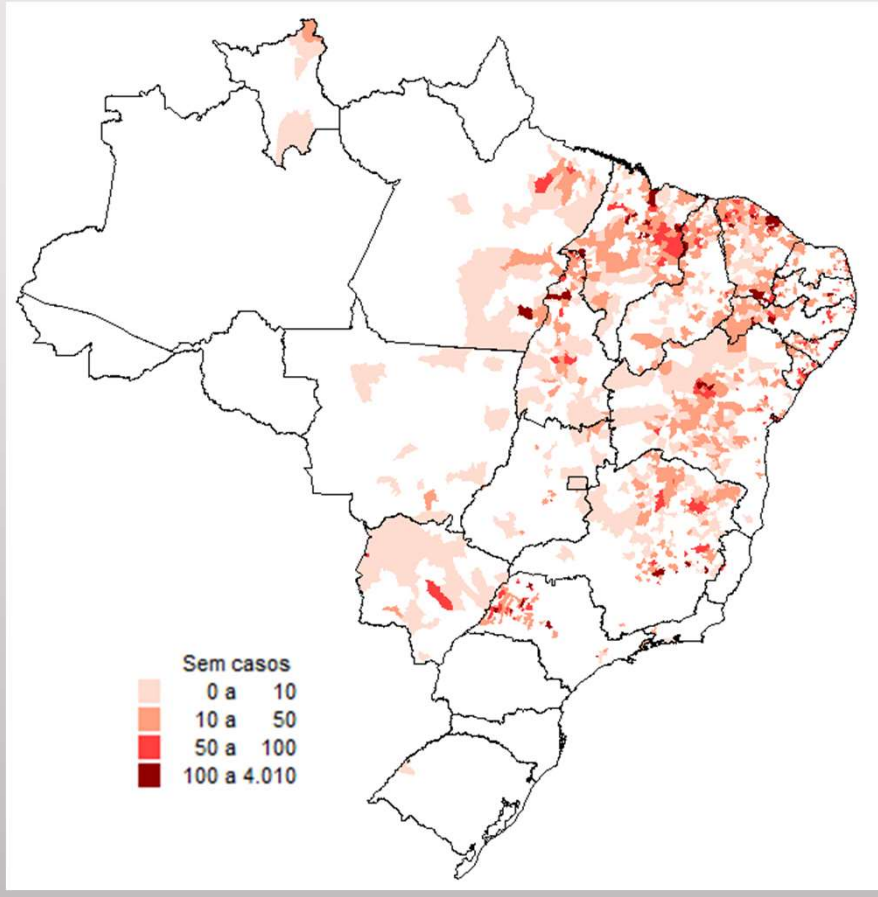
Fonte: SVS/MS.

Densidade de casos de LV por Município de infecção, Brasil, 2014 e 2015

2014

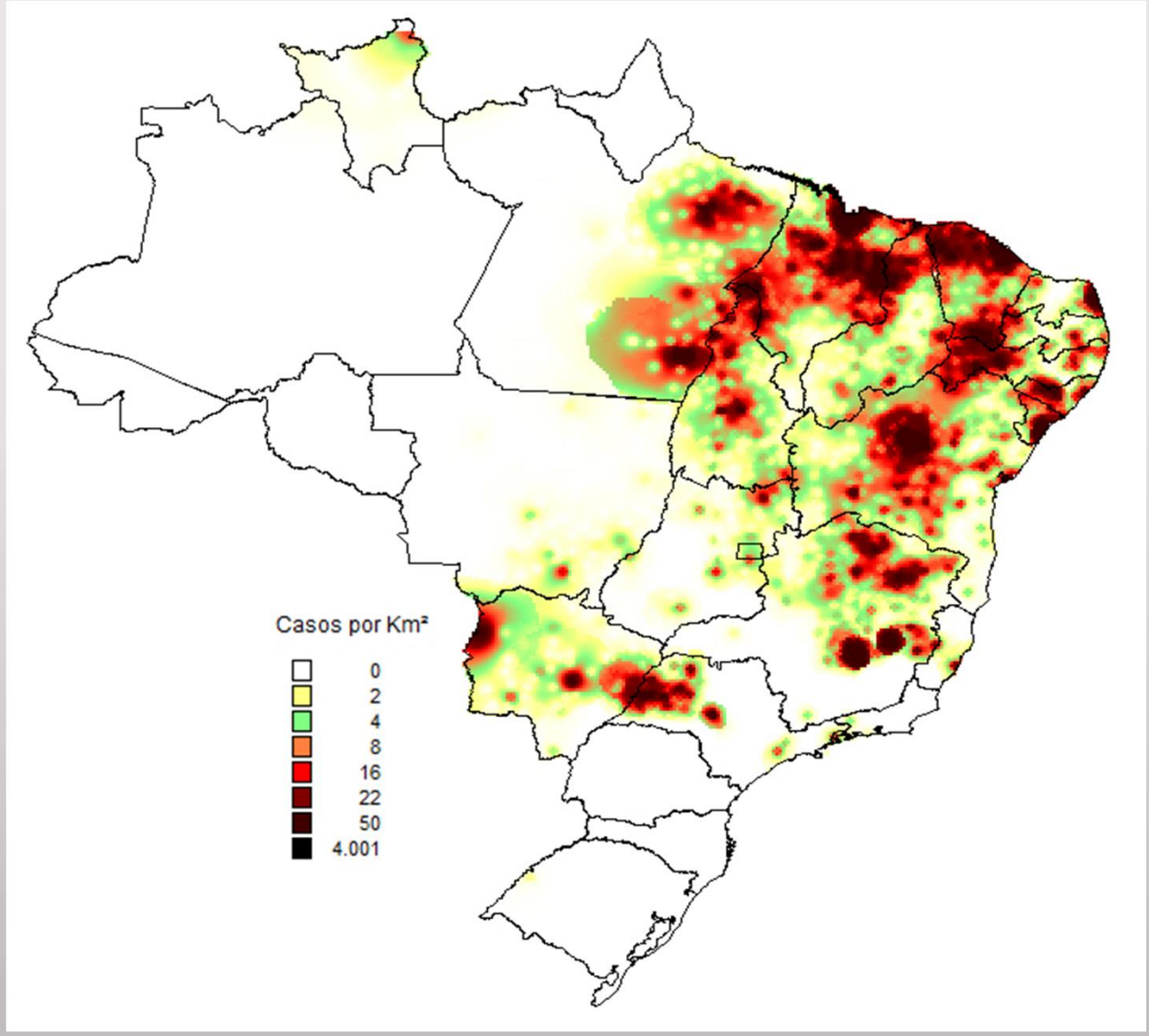


2015



Fonte: SVS/MS.

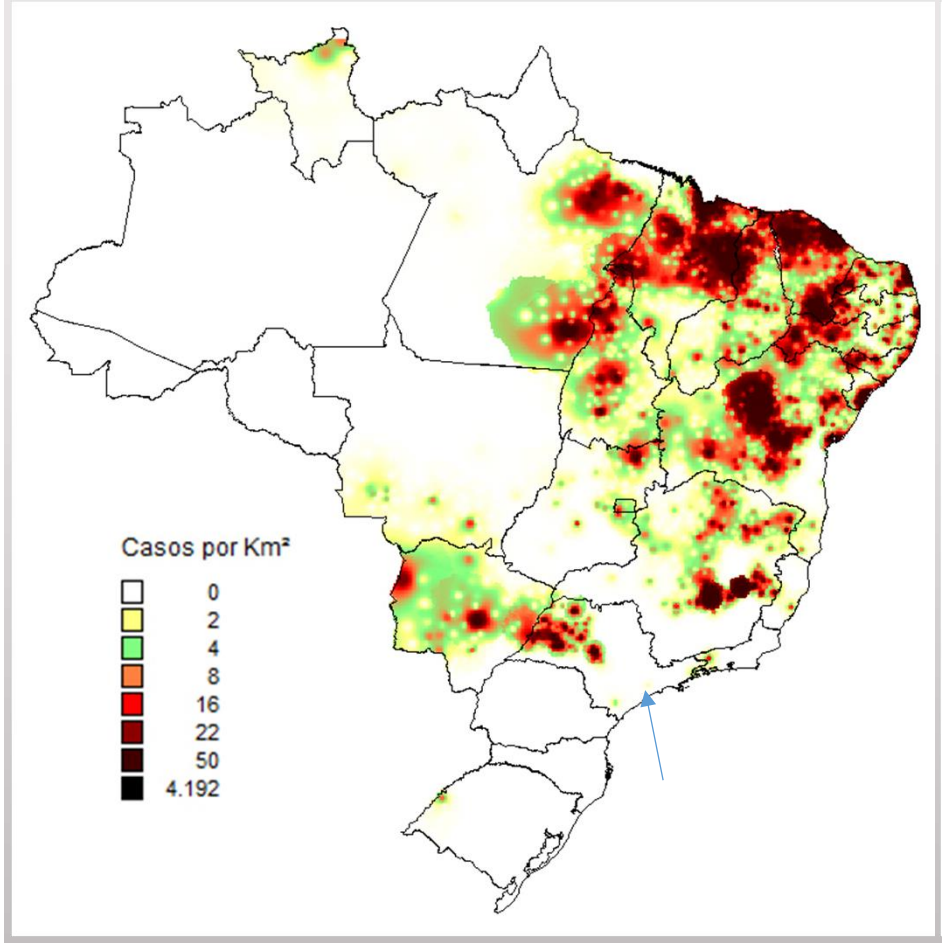
Áreas com maior concentração de casos de LV, Brasil, 2015



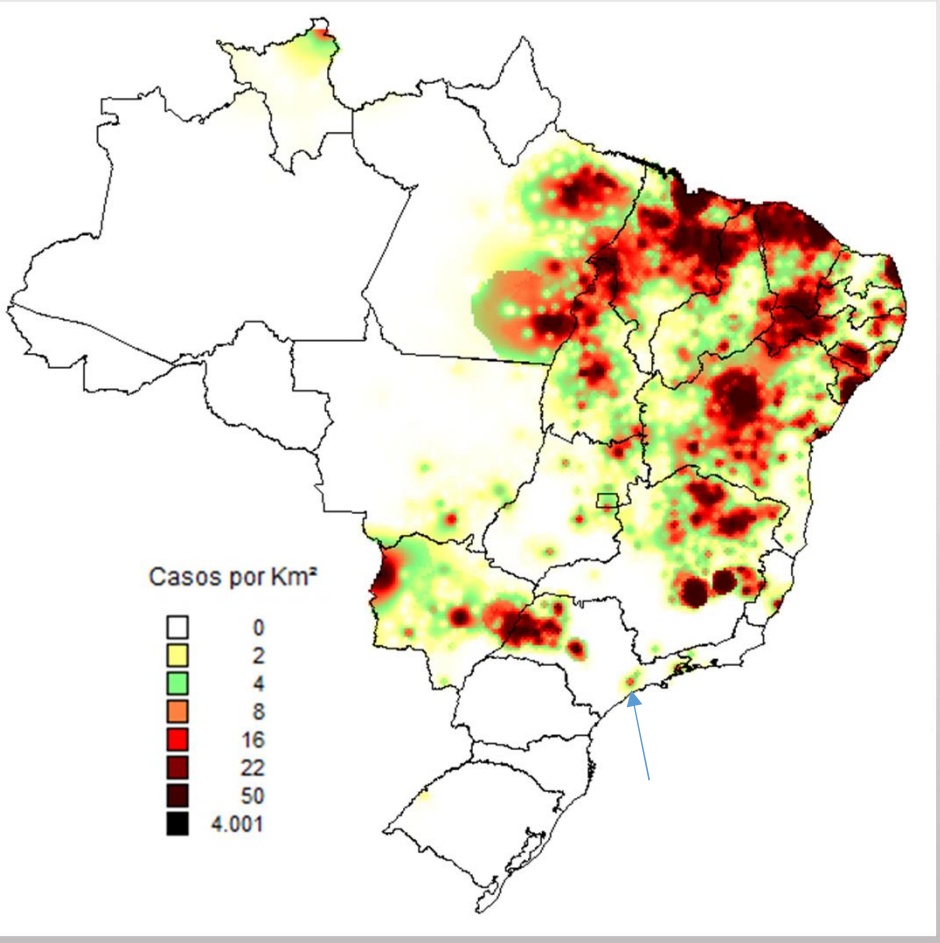
Fonte: SVS/MS.

Mapa de Grid da densidade de casos de LV 2014 e 2015

2014

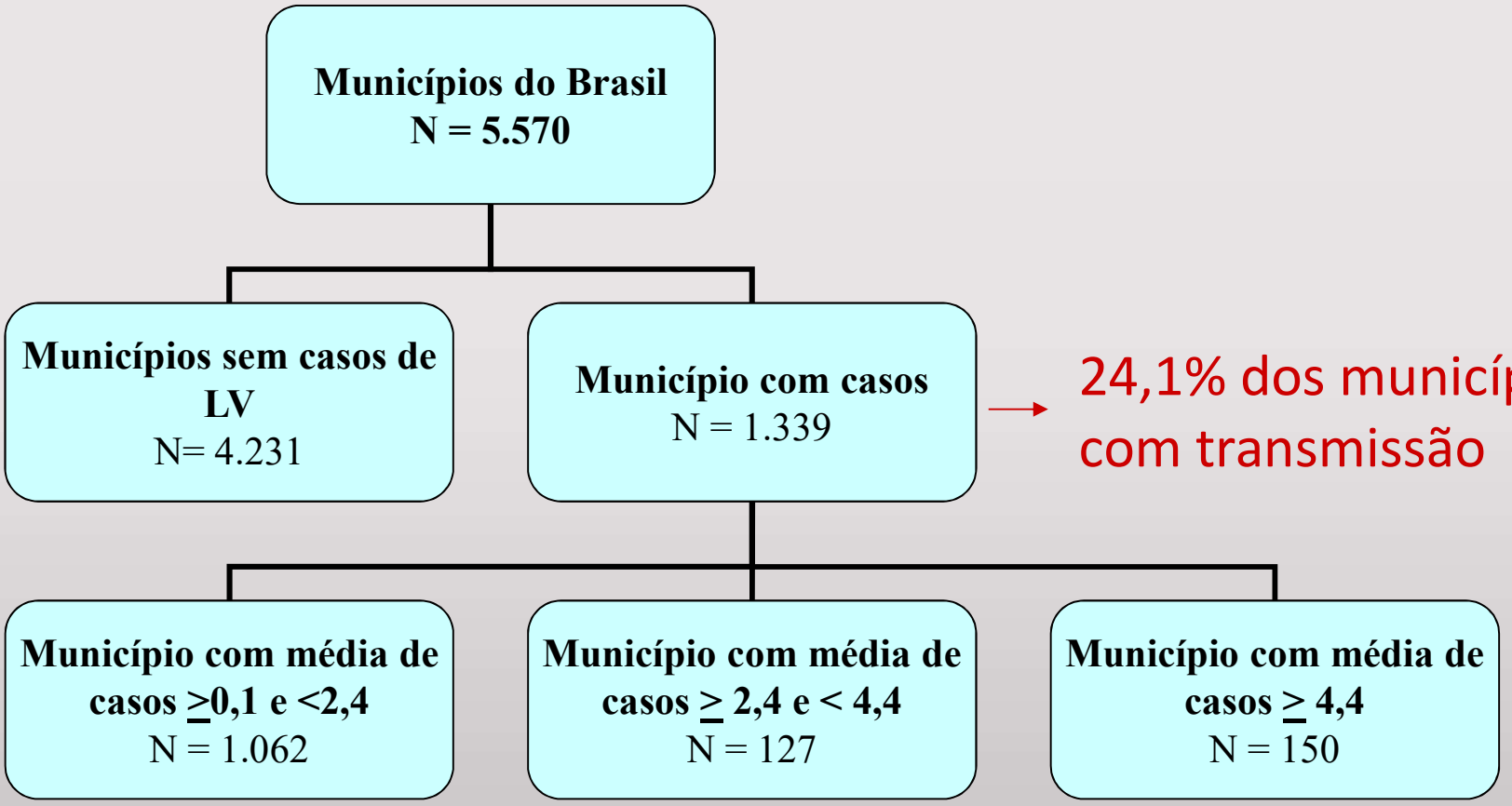


2015



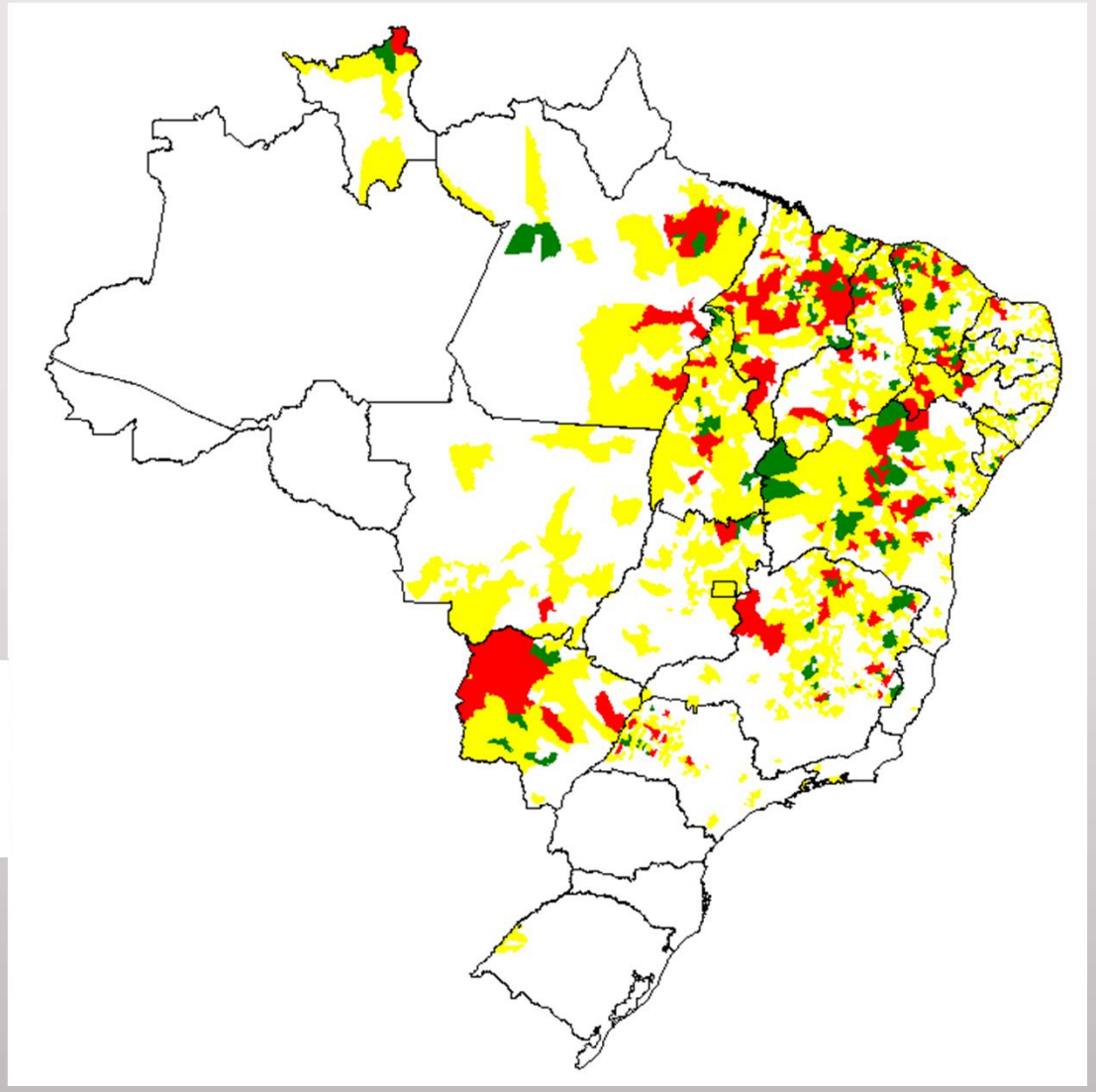
Fonte: SVS/MS.

Estratificação dos municípios: média de casos de 2013 a 2015



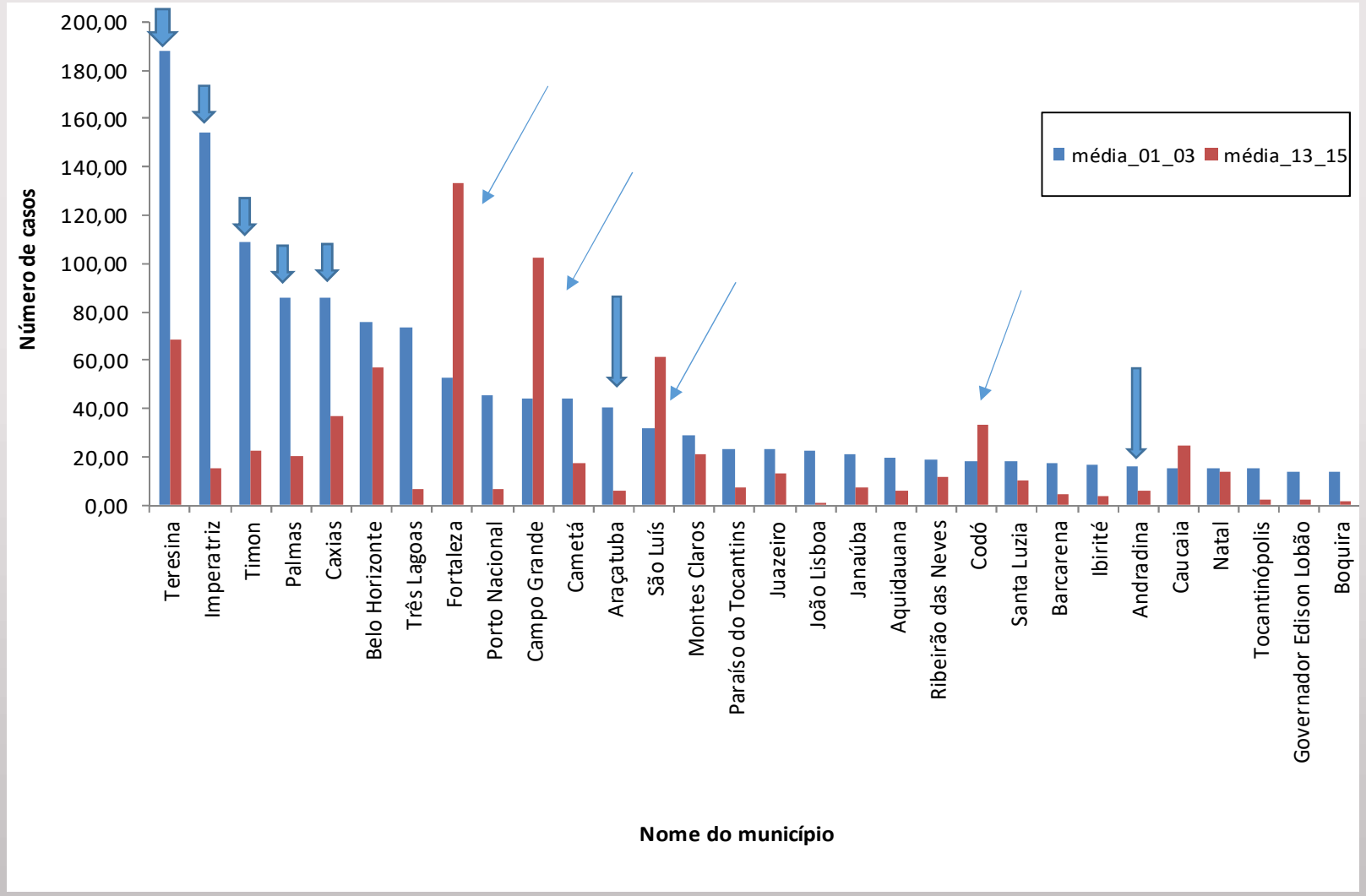
Fonte: SVS/MS.

Estratificação dos municípios: média de casos de LV, 2013 a 2015



Fonte: SVS/MS.

Situação atual dos 30 municípios com maior número de casos na média de 2001 a 2003, Brasil, 2001 a 2015



Fonte: SVS/MS.

Urbanização da LV no Brasil

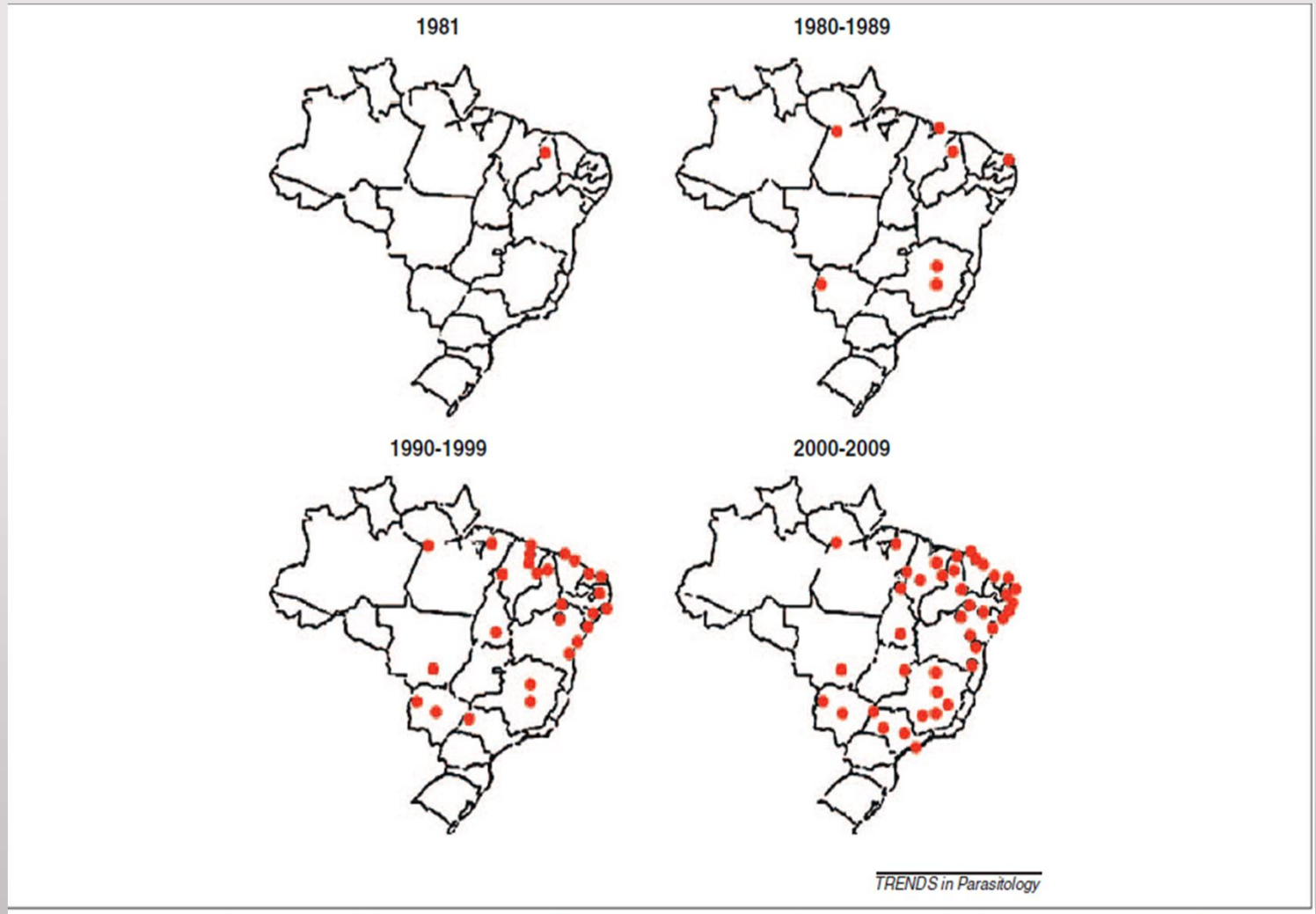


Figure 2. Spread of urban visceral leishmaniasis in Brazil, 1981–2009. Dots indicate cities with >100,000 inhabitants with >10 cases of visceral leishmaniasis per year.

Harhay et al. Trends in Parasitology 2011

Situação Epidemiológica dos casos humanos de Leishmaniose Visceral no Estado de São Paulo

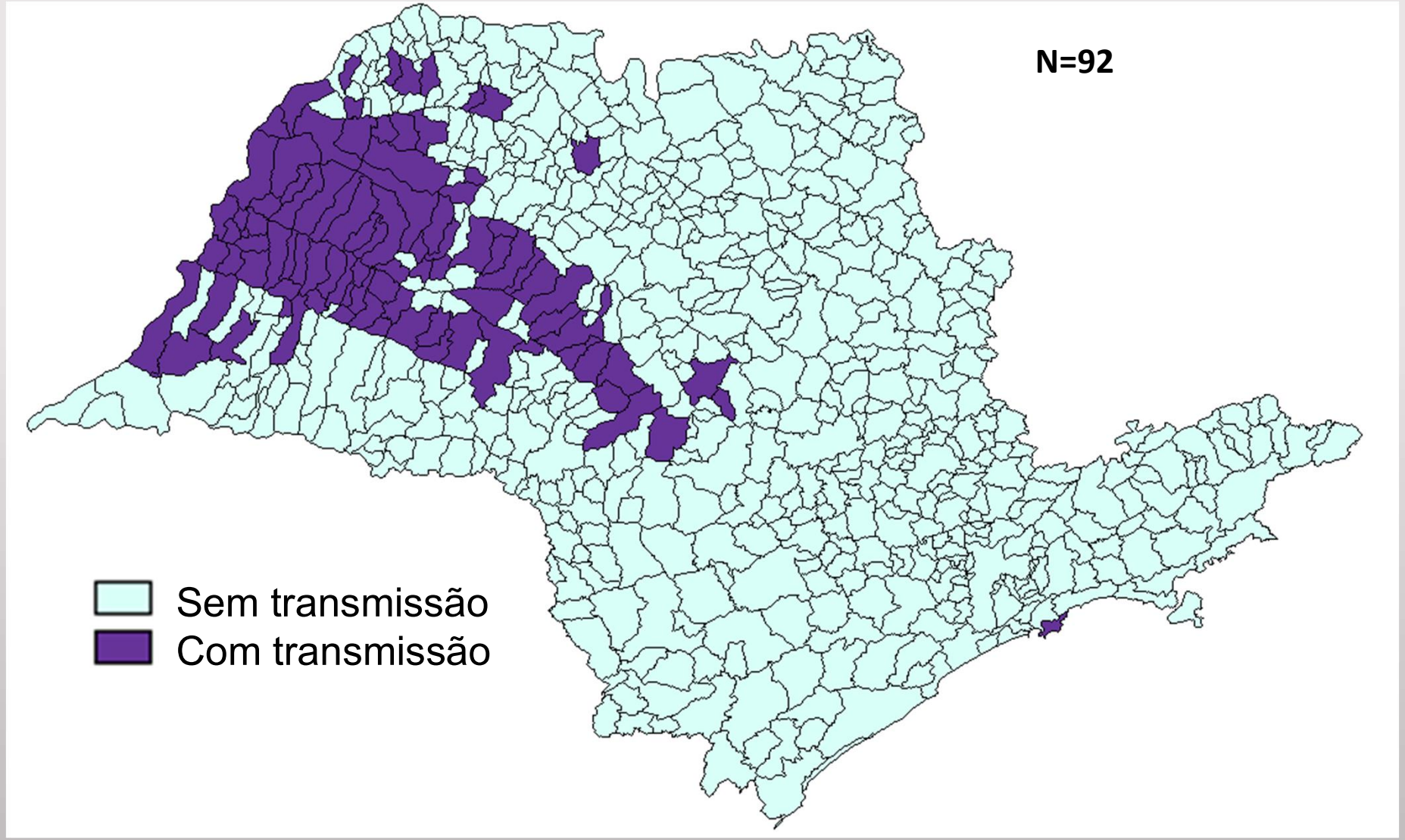
Epidemiologia de casos humanos de LV no Estado de São Paulo

1999 a 2016

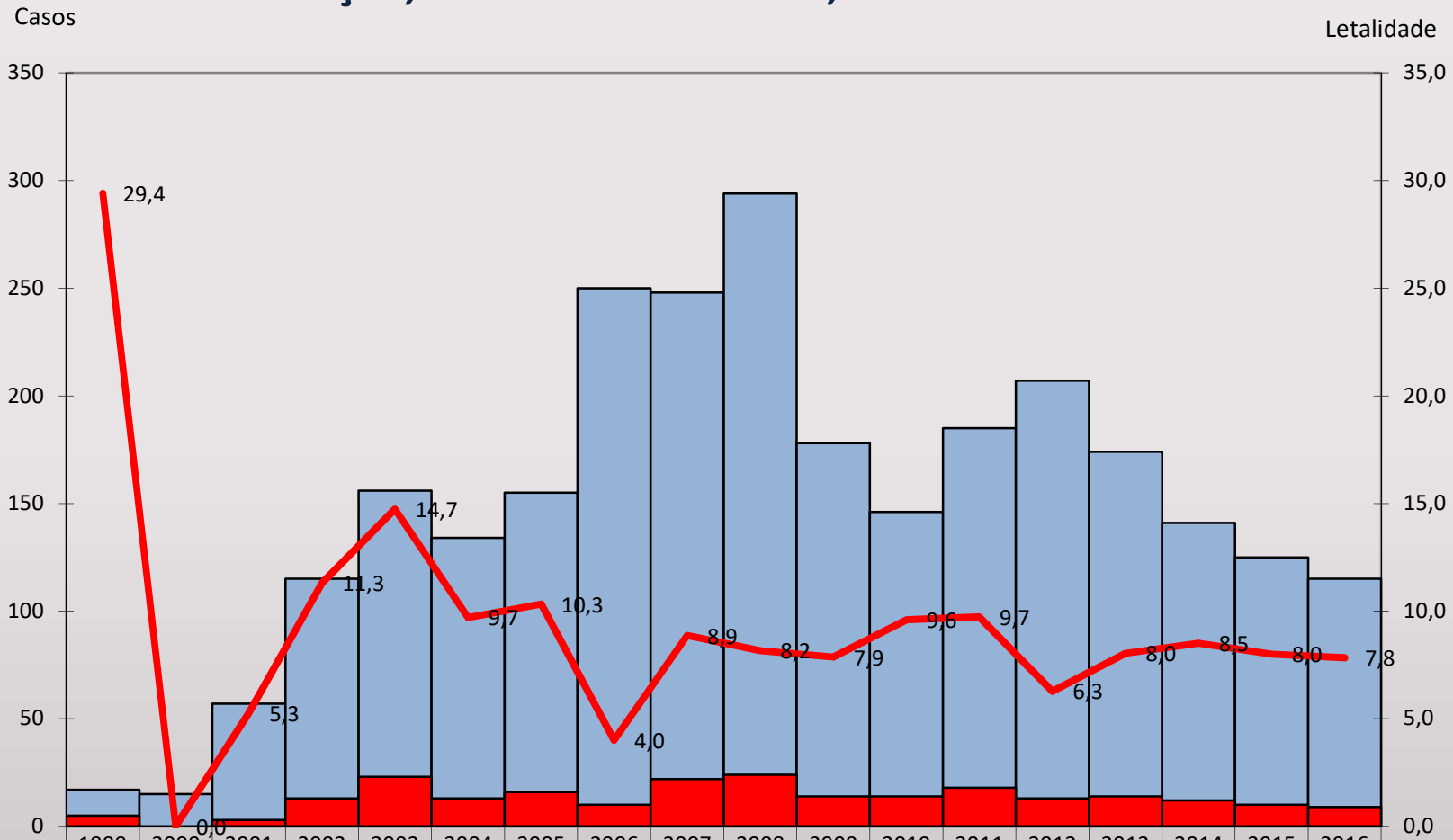
- 6.705 notificações - média anual 372,5 casos
  - 2.467 confirmados como autóctones do ESP
    - média anual – 150,7 casos
    - 233 óbitos – letalidade de 8,6%
    - municípios com transmissão
      - 2012 – 76 municípios
      - 2017 – 92 municípios

↑ 21% no período

Distribuição de casos humanos de LV no Estado de São Paulo, 1999 a 2016



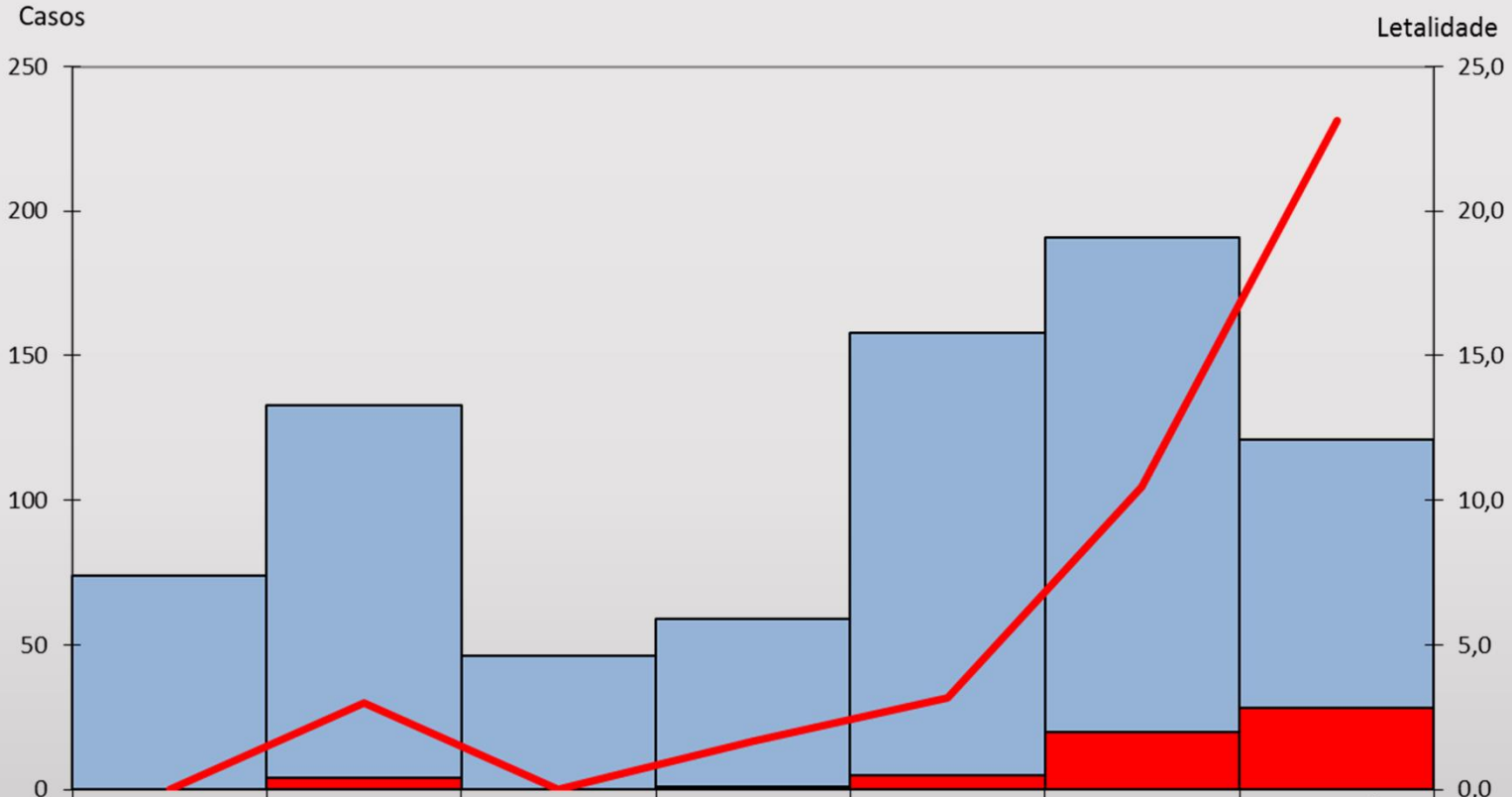
Casos autóctones e óbitos por Leishmaniose visceral segundo ano de notificação, Estado de São Paulo, 1999 a 2016



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Confirmado	17	15	57	115	156	134	155	250	248	294	178	146	185	207	174	141	125	115
Óbitos	5	0	3	13	23	13	16	10	22	24	14	14	18	13	14	12	10	9
Letalidade	29,4	0,0	5,3	11,3	14,7	9,7	10,3	4,0	8,9	8,2	7,9	9,6	9,7	6,3	8,0	8,5	8,0	7,8

Fonte: Sinan-W e Sinan-Net

Casos, óbitos e letalidade por LV segundo faixa etária, residentes do SP, 2012 a 2016



	1	1 - 4	5 - 9	10 - 19	20 - 39	40 - 59	60 e mais
Confirmado	74	133	46	59	158	191	121
Óbitos	0	4	0	1	5	20	28
Letalidade	0,0	3,0	0,0	1,7	3,2	10,5	23,1

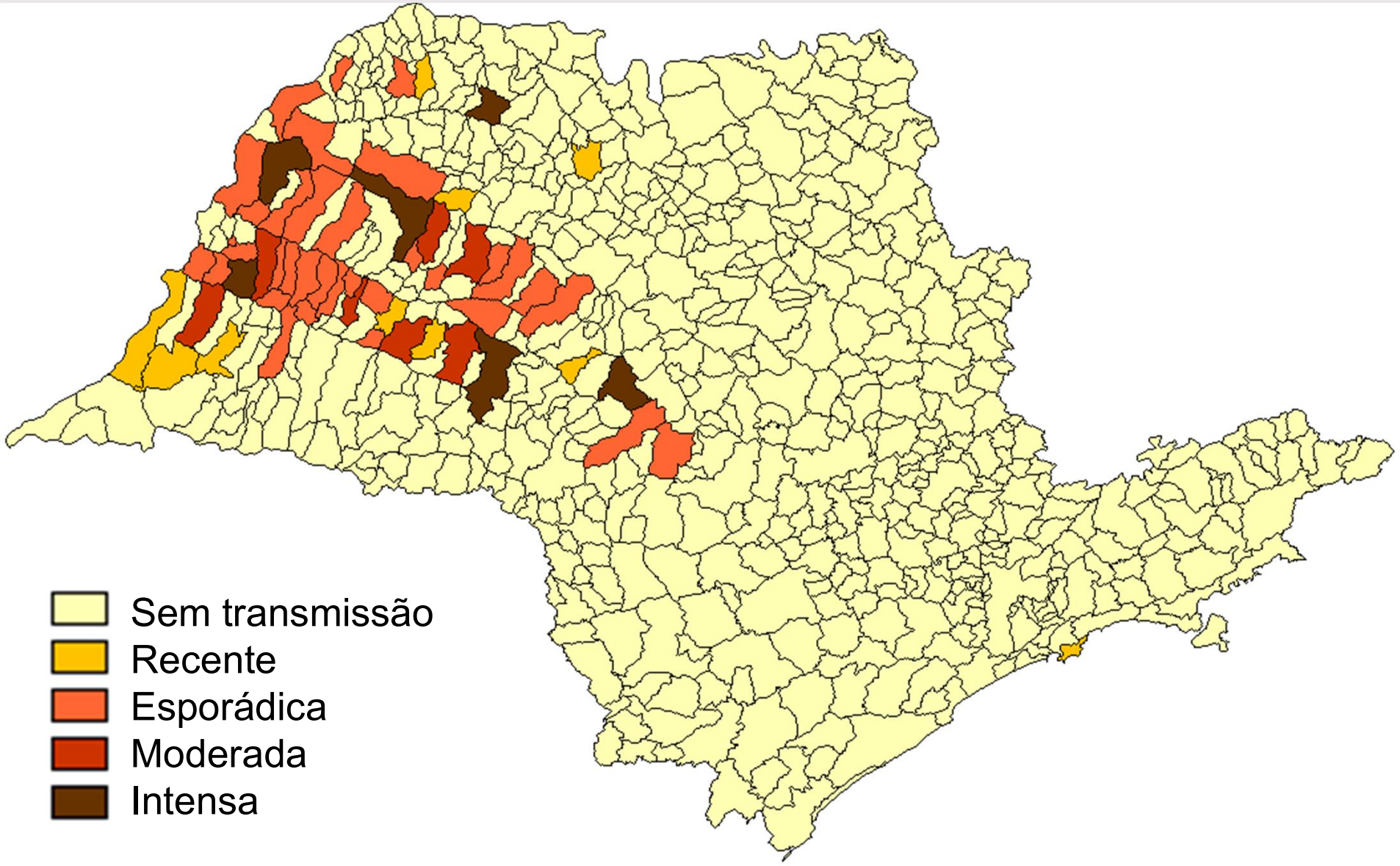
Fonte: Sinan-W e Sinan-Net

Leishmaniose visceral – Epidemiologia no ESP

Triênio 2014 a 2016

- 381 casos
  - 67,4% do sexo masculino
  - 95,2% da zona urbana
  - 18,5% HIV positivo
  - distribuídos em 57 municípios com transmissão de casos humanos
    - Recente: 10 (17,5%)
    - Esporádica: 34 (59,6%)
    - **Moderada**: 7 (12,3%)
    - **Intensa**: 6 (10,5%)

Classificação dos municípios com transmissão humana de Leishmaniose Visceral , Estado de São Paulo, triênio 2014 a 2016



Fonte: Sinan-net

Municípios prioritários com população ≥50.000 – ações devem ser realizadas considerando divisão em Área de Trabalho Local (ATL), triênio 2014 - 2016

GVE	Município	Total de casos de 2014 a 2016	Média de 2014 a 2016	Estratificação quanto a transmissão de casos humanos de LV"	Categoria quanto a prioridade para as ações de VE	População 2016 (Estimativa IBGE)	CI/100.000 hab em 2016	Divisão ATL (Municípios com TM e TI: pop. > 50 mil hab.)
	Andradina	18	6	Intensa	Prioritário	57.300	5,24	Definir ATL
	Araçatuba	16	5,3	Intensa	Prioritário	193828	0,52	Definir ATL
	Birigui	13	4,3	Moderada	Prioritário	119.536	1,67	Definir ATL
Araçatuba	Penápolis	12	4,0	Moderada	Prioritário	62.409	3,20	Definir ATL
Bauru	Bauru	73	24,3	Intensa	Prioritário	369.368	5,96	Definir ATL
	Marília	14	4,7	Intensa	Prioritário	233.639	4,28	Definir ATL
Marília	Tupã	11	3,7	Moderada	Prioritário	65.705	4,57	Definir ATL
São José do Rio Preto	Votuporanga	22	7,3	Intensa	Prioritário	92.032	2,17	Definir ATL

Municípios com ocorrência de 1º caso humano, Estado de São Paulo, triênio 2014 a 2016

- **2014**
  - Iacri /GVE Marília
  - Marabá Paulista / GVE Presidente Prudente
  - Presidente Epitácio / GVE Presidente Venceslau

- **2015**
  - Buritama /GVE Araçatuba
  - Presidente Alves/ GVE Bauru
  - Santo Anastácio/ GVE Presidente Prudente

- **2016**
  - Herculândia /GVE Marília
  - Estrela d' Oeste/ GVE Bauru
  - Santo Anastácio/ GVE Presidente Prudente
  - São José do Rio Preto / GVE São José do Rio Preto
  - **Guarujá / GVE Santos**

Casos confirmados de Leishmaniose Visceral segundo LPI, Estado de São Paulo, triênio 2014 a 2016

Mun infec SP	Média de 2014 a 2016	Estratificação quanto a transmissão de casos humanos de LV"	Categoria quanto a prioridade para as ações de VE
GVE XI ARAÇATUBA	**28,3**	**Intensa**	**Prioritário**
ANDRADINA	6,0	Intensa	Prioritário
ARACATUBA	5,3	Intensa	Prioritário
AVANHANDAVA	0,7	Esporádica	Não prioritário
BILAC	0,3	Esporádica	Não prioritário
BIRIGUI	4,3	Moderada	Prioritário
BRAUNA	0,7	Esporádica	Não prioritário
BURITAMA	1,0	Recente	
CASTILHO	0,7	Esporádica	Não prioritário
GUARACAI	0,3	Esporádica	Não prioritário
ILHA SOLTEIRA	0,3	Esporádica	Não prioritário
MIRANDOPOLIS	2,0	Esporádica	Não prioritário
NOVA INDEPENDENCIA	0,3	Esporádica	Não prioritário
PENAPOLIS	4,0	Moderada	Prioritário
PEREIRA BARRETO	1,0	Esporádica	Não prioritário
SANTO ANTONIO DO ARACANGUA	0,3	Esporádica	Não prioritário
VALPARAISO	1,0	Esporádica	Não prioritário
GVE XV BAURU	**30,3**	**Intensa**	**Prioritário**
AGUDOS	1,3	Esporádica	Não prioritário
BAURU	24,3	Intensa	Prioritário
CAFELANDIA	0,7	Esporádica	Não prioritário
GETULINA	0,3	Esporádica	Não prioritário
LENCOIS PAULISTA	0,7	Esporádica	Não prioritário
LINS	2,3	Esporádica	Não prioritário
PRESIDENTE ALVES	0,3	Recente	
PROMISSAO	0,3	Esporádica	Não prioritário

Casos confirmados de Leishmaniose Visceral segundo LPI, Estado de São Paulo, triênio 2014 a 2016

Mun infec SP	Média de 2014 a 2016	Estratificação quanto a transmissão de casos humanos de LV"	Categoria quanto a prioridade para as ações de VE
GVE XIX MARÍLIA	**29,3**	**Intensa**	**Prioritário**
ADAMANTINA	2,3	Esporádica	Não prioritário
BASTOS	2,7	Esporádica	Não prioritário
FLORIDA PAULISTA	2,3	Esporádica	Não prioritário
HERCULANDIA	0,7	Recente	
IACRI	1,7	Recente	
LUCELIA	2,3	Esporádica	Não prioritário
MARIAPOLIS	0,7	Esporádica	Não prioritário
MARILIA	4,7	Intensa	Prioritário
OSVALDO CRUZ	3,0	Moderada	Prioritário
PACAEMBU	1,0	Esporádica	Não prioritário
POMPEIA	2,7	Moderada	Prioritário
RINOPOLIS	0,7	Esporádica	Não prioritário
SALMOURAO	1,0	Esporádica	Não prioritário
TUPA	3,7	Moderada	Prioritário
GVE XXI PRES.PRUDENTE	**3**	**Moderada**	**Prioritário**
ESTRELA D'OESTE	0,3	Recente	
PRESIDENTE PRUDENTE	1,3	Esporádica	Não prioritário
SANTO ANASTACIO*	1,3	Recente	

Casos confirmados de Leishmaniose Visceral segundo LPI, Estado de São Paulo, triênio 2014 a 2016

Mun infec SP	Média de 2014 a 2016	Estratificação quanto a transmissão de casos humanos de LV"	Categoria quanto a prioridade para as ações de VE
GVE XXII PRES.VENCESLAU	**26**	**Intensa**	**Prioritário**
DRACENA	5,7	Intensa	Prioritário
FLORA RICA	0,7	Esporádica	Não prioritário
IRAPURU	1,0	Esporádica	Não prioritário
JUNQUEIROPOLIS	3,7	Moderada	Prioritário
MARABA PAULISTA	0,7	Recente	
NOVA GUATAPORANGA	1,0	Esporádica	Não prioritário
OURO VERDE	1,7	Esporádica	Não prioritário
PANORAMA	2,3	Esporádica	Não prioritário
PRESIDENTE EPITACIO	4,0	Recente	
PRESIDENTE VENCESLAU	3,7	Moderada	Prioritário
TUPI PAULISTA	1,7	Esporádica	Não prioritário
GVE XXV SANTOS	**0,7**	**Recente**	
GUARUJA	0,7	Recente	
GVE XXIX S J DO RIO PRETO	**7,7**	**Intensa**	**Prioritário**
SAO JOSE DO RIO PRETO	0,3	Recente	
VOTUPORANGA	7,3	Intensa	Prioritário
GVE XXX JALES	**1,7**	**Esporádica**	**Não prioritário**
JALES	1,3	Esporádica	Não prioritário
SANTA FE DO SUL	0,3	Esporádica	Não prioritário
ESTADO DE SÃO PAULO	127,0	Intensa	Prioritário

Consolidado de solicitações de anfotericina b lipossomal liberadas para tratamento de paciente de LV, Estado de São Paulo, 2014* a 2017**

Critério		2014*				2015				2016				2017**			
		Tratamento		Profilaxia 2ª		Tratamento		Profilaxia 2ª		Tratamento		Profilaxia 2ª		Tratamento		Profilaxia 2ª	
		Pedidos	frascos	Pedidos	frascos	Pedidos	frascos	Pedidos	frascos	Pedidos	frascos	Pedidos	frascos	Pedidos	frascos	Pedidos	frascos
MS	HIV	31	992	9	314	28	763	21	575	30	880	46	1194	10	442	10	373
	Não HIV	43	1023	0	0	62	1426	0	0	88	2060	6	104	25	599	1	24
SES	Não HIV	13	98	1	70	30	262	3	63	36	223	2	42	21	164	2	10
Total		87	2113	10	384	120	2451	24	638	154	3163	54	1340	56	1205	13	407

Fonte: Planilha de solicitações de anfotericina b lipossomal recebidas na Divisão de Zoonoses com emissão de fatura pela CCTIES

* liberações a partir de 04/2014

** até 04/08/2017

Educação em Saúde

- Oficina para implantação do teste rápido para LV – parceria CVE e IAL
- Participação de treinamento para equipes assistenciais
- Planejamento de ações para municípios de diferentes situações epidemiológicas – parceria CVE, IAL, SUCEN
- Produção de documentos técnicos
- “Semana Nacional de Controle e Combate à Leishmaniose” (Lei nº 12.604, 2012) - Realização de “Fórum de LV do Estado de São Paulo”

DOENÇA MULTIFATORIAL

Agente Etiológico

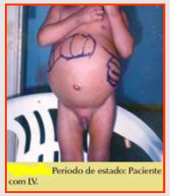
Vetor

Reservatório

Raposa: reservatório silvestre da *Leishmania chagasi*

Cão com emagrecimento, ceratoconjuntivite, lesões de face e orelha.

Hospedeiro susceptível



Período de estado: Paciente com LV.

Alterações Geográficas

Fatores

físicos

humanos ou sociais

biológicos

Risk Factors for Visceral Leishmaniasis among Residents and Migrants in Kafta-Humera, Ethiopia

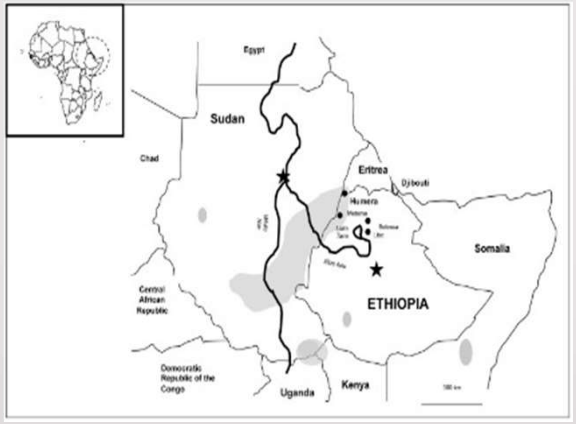


Table 5. Multivariable conditional logistic regression models for factors associated with risk of visceral leishmaniasis among residents and migrants in Humera, Tigray, Ethiopia.

Factor	Matched OR[1]	95% CI[1]	P
Residents			
Always slept under net in rainy season	0.24	0.12–0.48	<.0001
Slept under acacia at night	5.22	1.66–16.42	0.005
Usually slept on ground	2.96	1.20–7.30	0.02
Walls of thatched grass on wood frame	5.30	1.34–21.03	0.02
Monthly expenditure <100 birr per person	3.22	1.42–7.33	0.005
Head of house left school before class 5	2.78	1.17–6.59	0.02
Migrants			
HIV infection[2]	3.98	0.94–16.9	0.06
Ever slept under net	0.20	0.10–0.42	<0.0001
Slept under an acacia at night	4.74	1.88–11.99	0.001
Slept near dogs	6.79	1.83–25.16	0.004
Staple food is porridge (rather than injera)	4.65	2.33–9.29	<0.0001
No formal schooling	5.02	2.59–9.74	<0.0001

[1]Odds ratios (OR) and 95% confidence intervals (CI).
[2]Data on HIV status missing for at least one member of 21 case-control sets; these sets therefore excluded from analysis.
doi:10.1371/journal.pntd.0002543.t005

Citation: Argaw D, Mulugeta A, Herrero M, Nombela N, Teklu T, et al. (2013) Risk Factors for Visceral Leishmaniasis among Residents and Migrants in Kafta-Humera, Ethiopia. PLoS Negl Trop Dis 7(11): e2543. doi:10.1371/journal.pntd.0002543

Prediction of high-risk areas for visceral leishmaniasis using socioeconomic indicators and remote sensing data

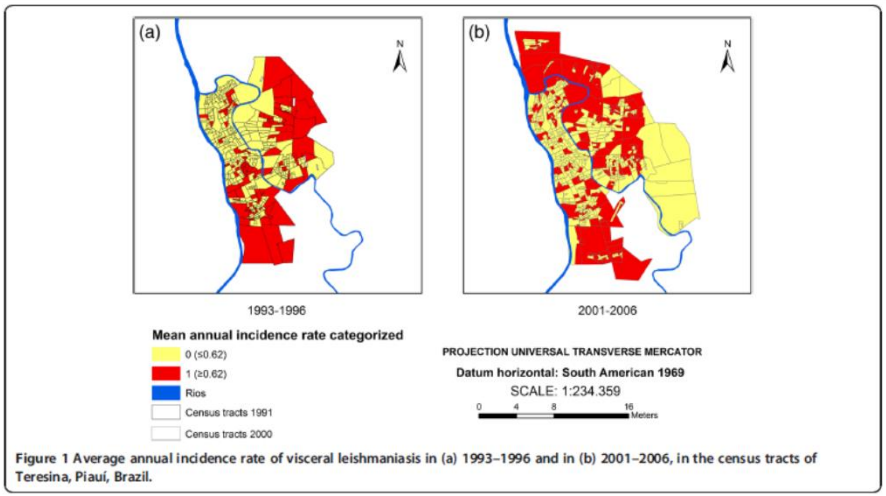


Figure 1 Average annual incidence rate of visceral leishmaniasis in (a) 1993–1996 and in (b) 2001–2006, in the census tracts of Teresina, Piauí, Brazil.

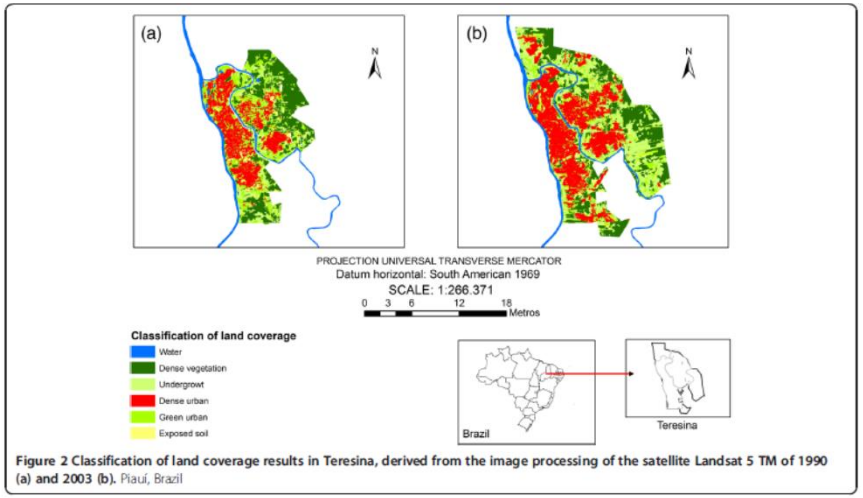


Figure 2 Classification of land coverage results in Teresina, derived from the image processing of the satellite Landsat 5 TM of 1990 (a) and 2003 (b). Piauí, Brazil

Abstract

Spatial heterogeneity in the incidence of visceral leishmaniasis (VL) is an important aspect to be considered in planning control actions for the disease. The objective of this study was to predict areas at high risk for visceral leishmaniasis (VL) based on socioeconomic indicators and remote sensing data. We applied classification and regression trees to develop and validate prediction models. Performance of the models was assessed by means of sensitivity, specificity and area under the ROC curve. The model developed was able to discriminate 15 subsets of census tracts (CT) with different probabilities of containing CT with high risk of VL occurrence. The model presented, respectively, in the validation and learning samples, sensitivity of 79% and 52%, specificity of 75% and 66%, and area under the ROC curve of 83% and 66%. Considering the complex network of factors involved in the occurrence of VL in urban areas, the results of this study show that the development of a predictive model for VL might be feasible and useful for guiding interventions against the disease, but it is still a challenge as demonstrated by the unsatisfactory predictive performance of the model developed.

Almeida and Werneck *International Journal of Health Geographics* 2014, **13**:13

Relative Risk of Visceral Leishmaniasis in Brazil: A Spatial Analysis in Urban Area

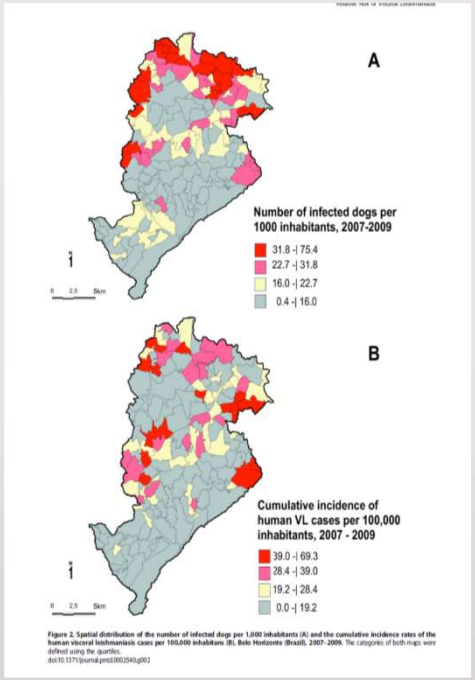


Figure 2. Spatial distribution of the number of infected dogs per 1,000 inhabitants (A) and the cumulative incidence rates of the human visceral leishmaniasis cases per 100,000 inhabitants (B), Belo Horizonte (Brazil), 2007-2009. The categories of both maps were defined using the quartiles.
doi:10.1371/journal.pntd.0002540.g002

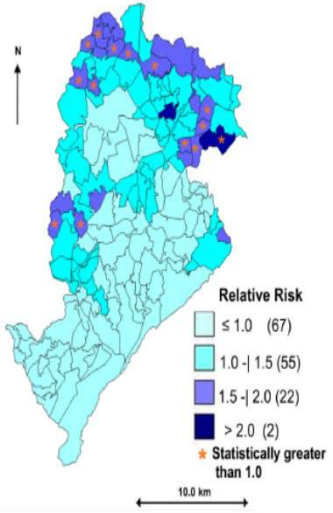


Figure 4. Spatial distribution of the smoothed estimates (mean) for the relative risk of visceral leishmaniasis (model 1), Belo Horizonte (Brazil), 2007-2009. The asterisks indicate the coverage areas whose relative risk is considered statistically greater than 1.0 (95% credibility interval).
doi:10.1371/journal.pntd.0002540.g004

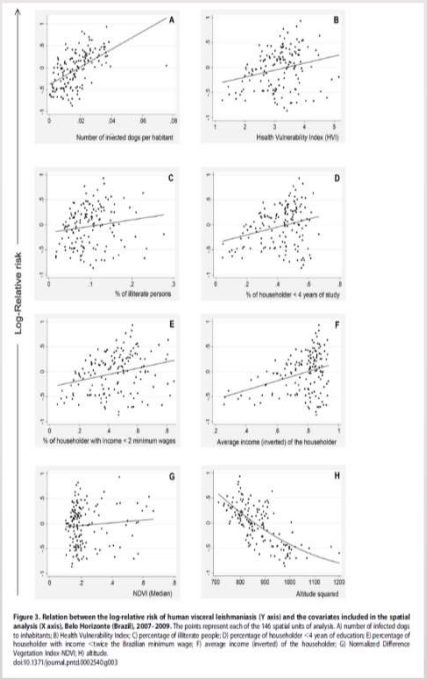


Figure 3. Relation between the log-relative risk of human visceral leishmaniasis (Y axis) and the covariates included in the spatial analysis (X axis), Belo Horizonte (Brazil), 2007-2009. The points represent each of the 146 spatial units of analysis. A) number of infected dogs to inhabitants; B) Health Vulnerability Index; C) percentage of illiterate people; D) percentage of householder <4 years of education; E) percentage of householder with income <twice the Brazilian minimum wage; F) average income (inverted) of the householder; G) Normalized Difference Vegetation Index NDVI; H) altitude.
doi:10.1371/journal.pntd.0002540.g003

Principal Findings: The relative risk of VL was shown to be correlated with income, education, and the number of infected dogs per inhabitants. The estimates of relative risk of VL were higher than 1.0 in 54% of the areas (79/146). The spatial modeling highlighted 14 areas with the highest relative risk of VL and 12 of them are concentrated in the northern region of the city.

Citation: de Araújo VEM, Pinheiro LC, de Mattos Almeida MC, de Menezes FC, Morais MHF, et al. (2013) Relative Risk of Visceral Leishmaniasis in Brazil: A Spatial Analysis in Urban Area. PLoS Negl Trop Dis 7(11): e2540. doi:10.1371/journal.pntd.0002540

Prevalence of malnutrition and associated risk factors among adult visceral leishmaniasis patients in Northwest Ethiopia: a cross sectional study

Table 2 Bivariate and multivariate analysis of possible risk factors with malnutrition among patients with VL in Northwest Ethiopia, 2012

Risk factors	Total	Severely Malnourished		COR (95% CI)	AOR (95%CI)	P-values
		Yes	No			
Eating breakfast						
Always	127 (31.5)*	97 (35.1)	179 (64.9)	1.00	1.00	0.07
Sometimes	276 (68.5)	53 (41.7)	74 (58.3)	1.32 (0.84 – 2.08)	1.56 (0.96 – 2.51)	
Domestic animal						
Present	218 (54.1)	85 (39.0)	133 (61.0)	1.00	1.00	0.48
Absent	185 (45.9)	65 (35.1)	120 (64.9)	0.85 (0.55 – 1.30)	0.99 (0.59 – 1.65)	
Private farm						
Present	168 (41.7)	70 (41.7)	98 (58.3)	1.00	1.00	0.14
Absent	235 (58.3)	80 (34.0)	155 (66.0)	0.72 (0.47 – 1.11)	0.65 (0.38 – 1.11)	
Family size						
≤5	212 (52.6)	79 (37.3)	133 (62.7)	1.00	1.00	0.98#
6-10	185 (45.9)	69 (37.3)	116 (62.7)	1.00 (0.65 – 1.54)	1.12 (0.18 – 6.67)	
≥11	6 (1.5)	2 (33.3)	4 (66.7)	0.84 (0.10 – 5.50)	1.19 (0.21 – 7.05)	
Anemia						
Mild	87 (21.6)	31 (35.6)	56 (64.4)	1.00	1.00	0.42
Moderate	205 (50.9)	72 (35.1)	133 (64.9)	0.98 (0.56 – 1.71)	1.38 (0.76 – 2.52)	
Severe	111 (27.5)	47 (42.3)	64 (57.7)	1.33 (0.71 – 2.47)	1.43 (0.88 – 2.32)	
HIV Status						
Negative	361 (89.6)	130 (36.0)	231 (64.0)	1.00	1.00	0.19
Positive	42 (10.4)	20 (47.6)	22 (52.4)	1.62 (0.81 – 3.21)	1.67 (0.34 – 3.32)	
Intestinal parasites						
Absent	211 (52.4)	50 (23.7)	161 (76.3)	1.00	1.00	0.00
Present	192 (47.6)	100 (52.1)	92 (47.9)	3.50 (2.24 – 5.48)	3.01 (2.20 – 5.11)	

*Figures in parenthesis indicate percentage, # Fisher exact.

Table 3 Intestinal parasites among adult VL patients in Northwest Ethiopia, 2012

Intestinal parasites	Total Number (%)	Severely malnourished	
		Yes Number (%)	No Number (%)
Protozoas			
Entamoeba histolytica/dispar	40 (9.9)	31 (77.5)	9 (22.5)
Giardia intestinalis	47 (11.7)	34 (72.3)	13 (27.7)
Helminthes			
Ascaris lumbricoides	41 (10.2)	29 (70.7)	12 (29.3)
Hook worm	85 (21.1)	50 (58.8)	35 (41.2)
Hymenolopsis nana	3 (0.7)	2 (66.7)	1 (33.3)
Schistosoma mansoni	4 (1.0)	4 (100)	0 (0.0)
Strongyloide stercolaris	23 (5.7)	14 (60.9)	9 (39.1)
Tanea species	4 (1.0)	4 (100)	0 (0.0)
Trichuris trichiura	4 (1.0)	3 (75.0)	1 (25.0)

Table 4 Multiple parasitic infections among severely malnourished adult VL patients in Northwest Ethiopia, 2012 (N = 48)

Multiple parasitic infections	Frequency
Ascaris lumbricoides + Hook worm	13
Entamoeba histolytica/dispar + *Giardia intestinalis*	7
Entamoeba histolytica/dispar + Hook worm	5
Hook worm + *Strongyloide stercolaris*	4
Giardia intestinalis + Hook worm	4
Giardia intestinalis + *Ascaris lumbricoides*	4
Giardia intestinalis + *Strongyloide stercolaris*	4
Schistosoma mansoni + *Entamoeba histolytica/dispar*	2
Ascaris lumbricoides + *Strongyloide stercolaris*	1
Hymenolopsis nana + *Entamoeba histolytica/dispar*	1
Giardia intestinalis + Hook worm + *Entamoeba histolytica/dispar*	2
Giardia intestinalis + Hook worm + *Strongyloide stercolaris*	1

Conclusions: The prevalence of malnutrition in VL patients was very high and it was associated with intestinal parasitic infections. Therefore, screening of severely malnourished VL patients for intestinal parasitic infections during admission is recommended.

Mengesha *et al. BMC Research Notes* 2014, **7**:75

DOENÇA MULTIFATORIAL

Agente Etiológico

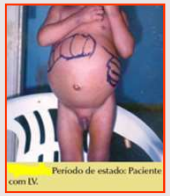
Vetor

Reservatório

Raposa: reservatório silvestre da *Leishmania chagasi*

Cão com emagrecimento, ceratoconjuntivite, lesões de face e orelha.

Hospedeiro susceptível



Período de estado: Paciente com LV.

Alterações Geográficas

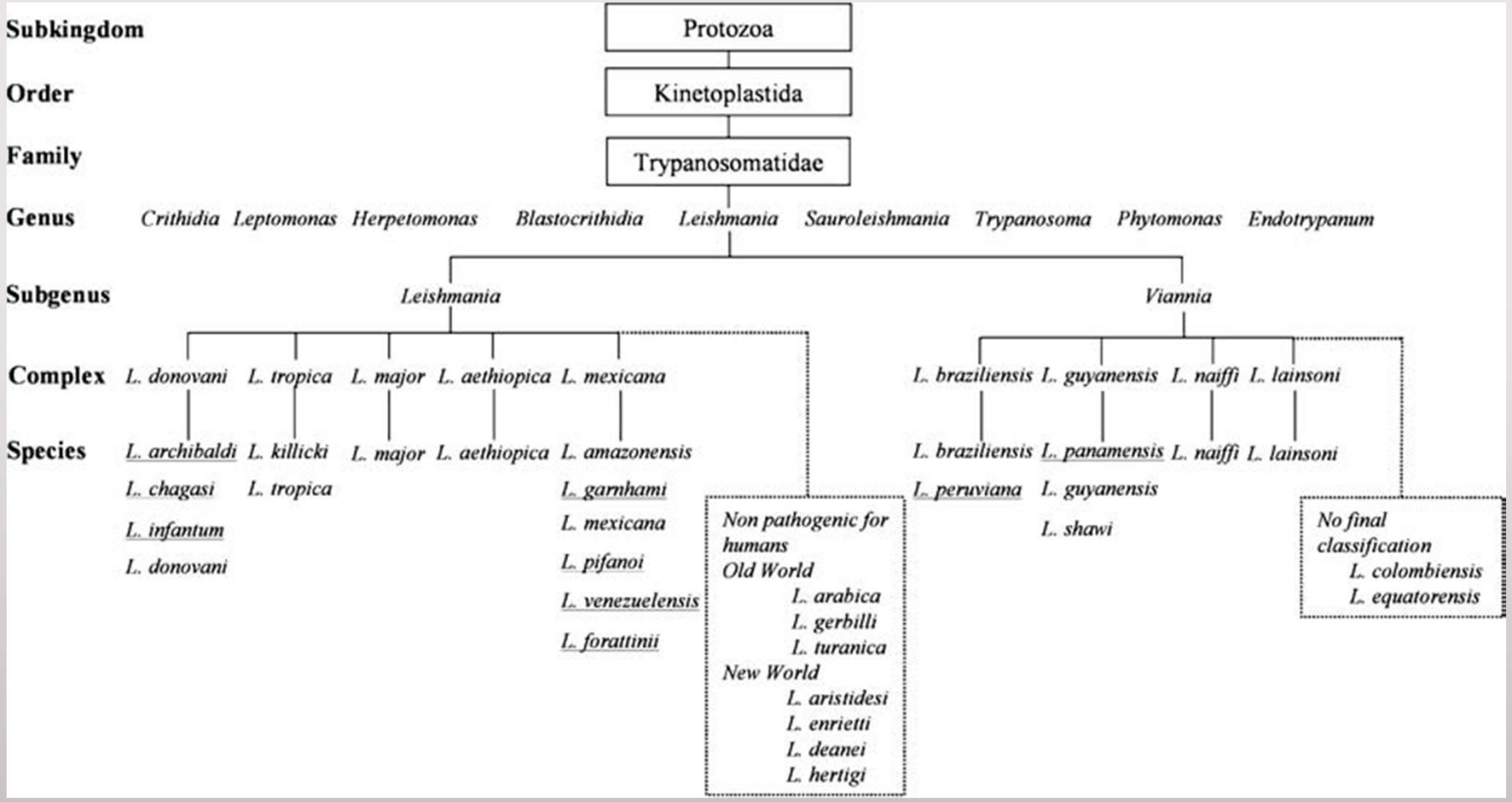
Fatores

físicos

humanos ou sociais

biológicos

Taxonomia

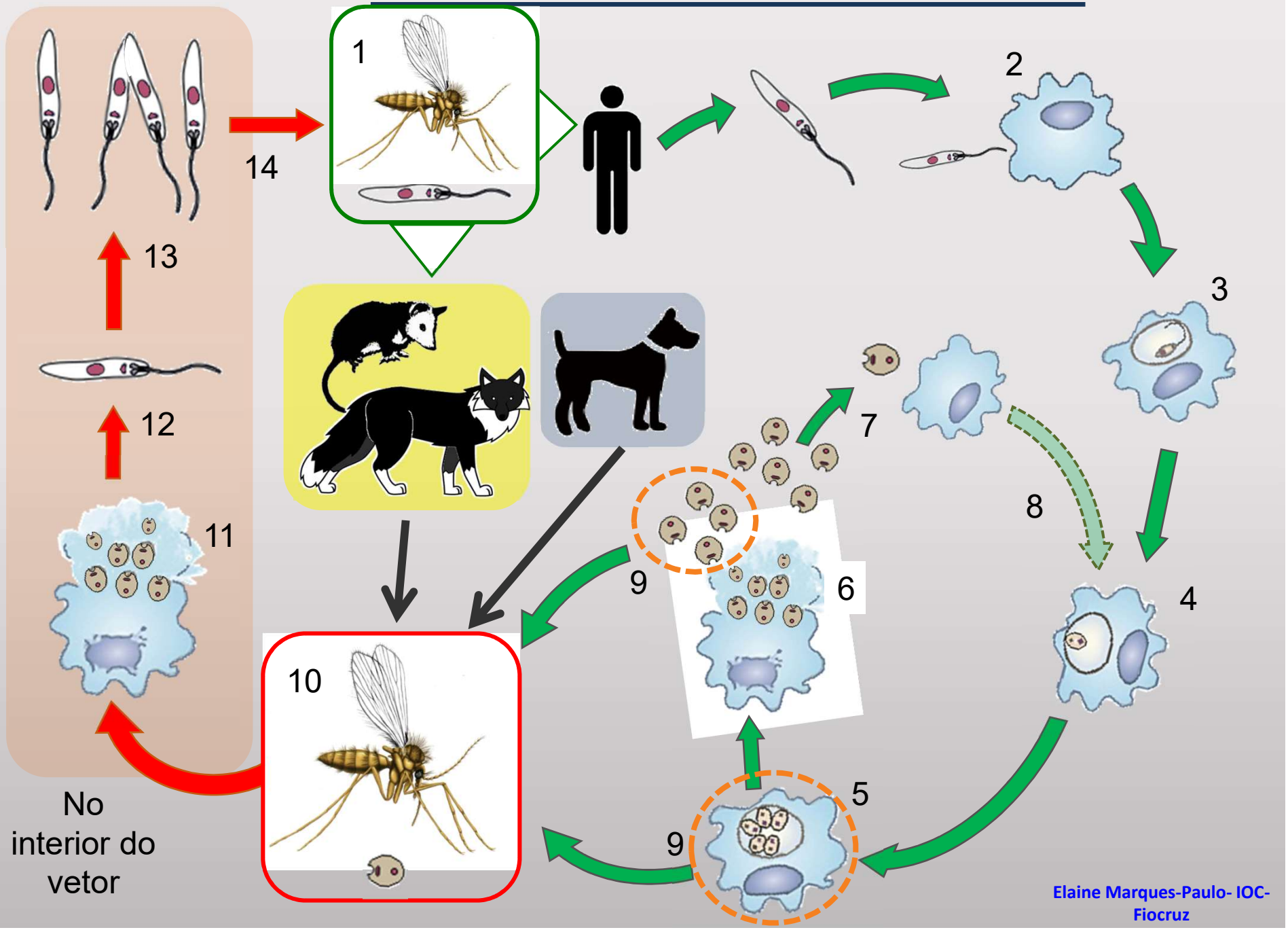


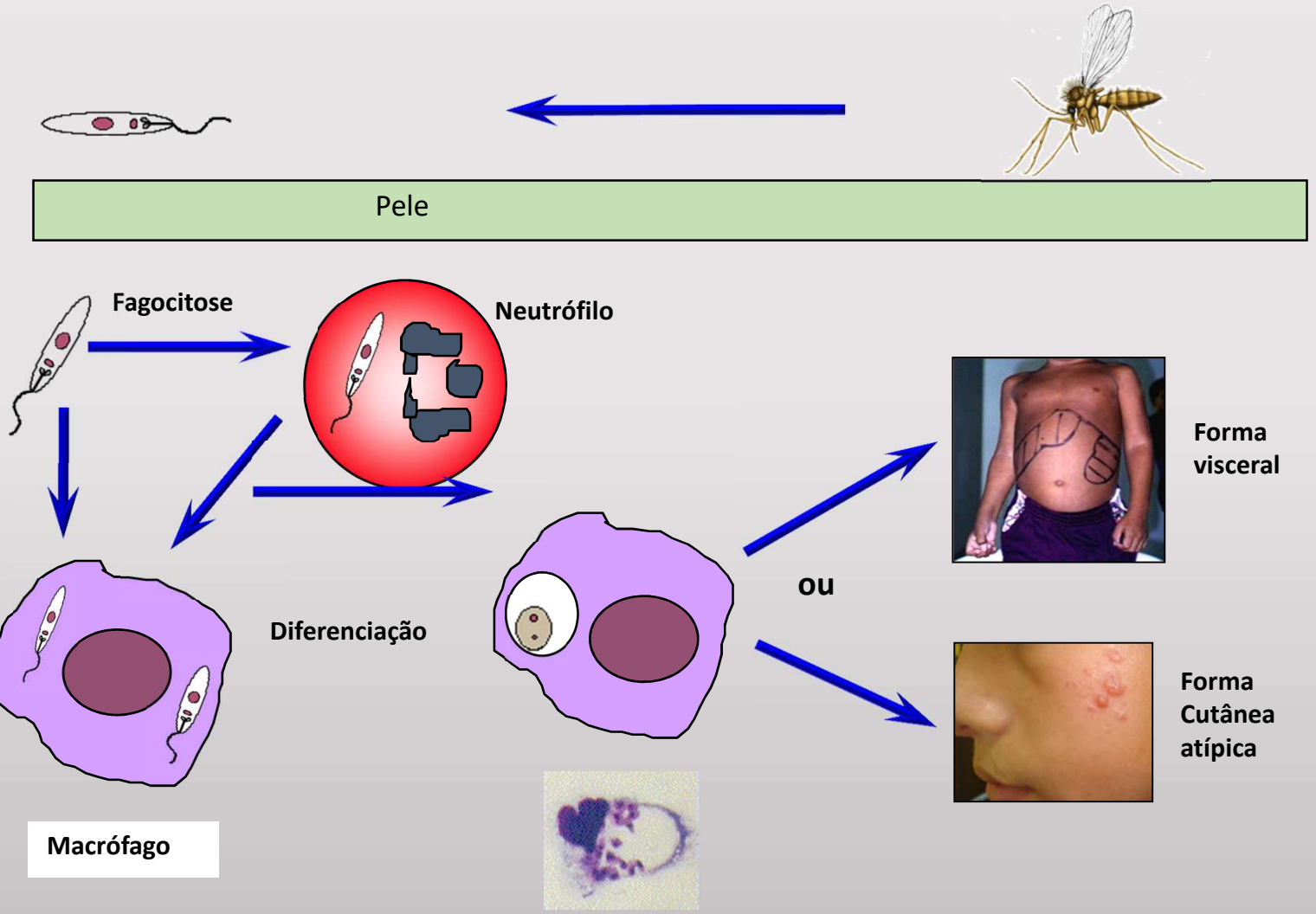
WHO and Bañuls et al, 2007

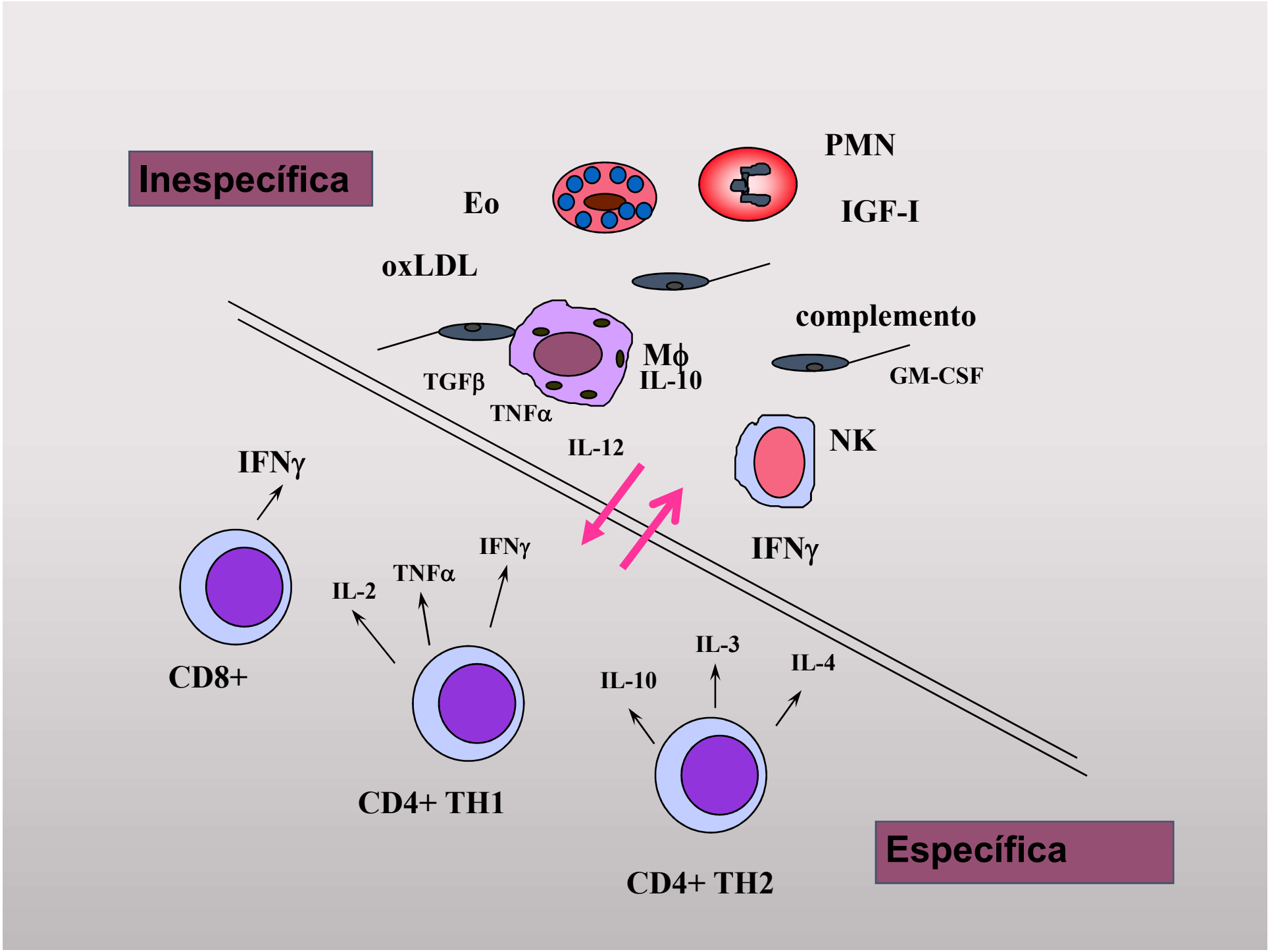
Leishmanias no mundo

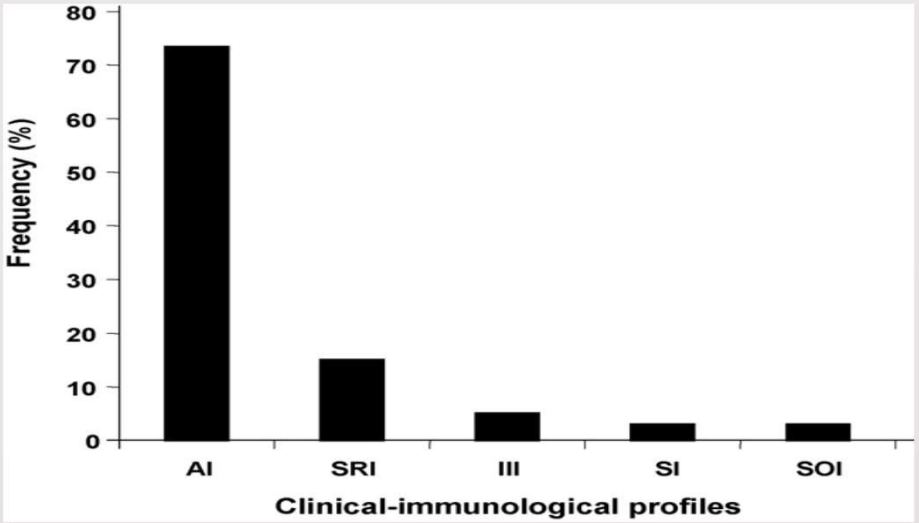
Subgenus	*L. (Leishmania)*	*L. (Leishmania)*	*L. (Viannia)*	*L. (Viannia)*
Old World	*L. donovani* *L. infantum*	*L. major* *L. tropica* *L. killicki*[a] *L. aethiopica* *L. infantum*		
New World	*L. infantum*	*L. infantum* *L. mexicana* *L. pifanoi*[a] *L. venezuelensis* *L. garnhami*[a] *L. amazonensis*	*L. braziliensis* *L. guyanensis* *L. panamensis* *L. shawi* *L. naïffi* *L. lainsoni* *L. lindenbergi* *L. peruviana* *L. colombiensis*[b]	*L. braziliensis* *L. panamensis*
Principal tropism	Viscerotropic	Dermotropic	Dermotropic	Mucotropic

Ciclo de vida *Leishmania infantum*




Pele
Fagocitose
Neutrófilo
Diferenciação
Macrófago
ou
Forma visceral
Forma Cutânea atípica


Inespecífica
Eo
PMN
IGF-I
oxLDL
complemento
Mϕ
TGFβ
IL-10
TNFα
GM-CSF
NK
IL-12
IFNγ
IFNγ
IL-2
TNFα
IFNγ
CD8+
CD4+ TH1
IL-10
IL-3
IL-4
CD4+ TH2
Específica



AI: asymptomatic infection=LST+/++++ and IFAT−
SRI: subclinical resistant infection= LST+/++ and IFAT+/++
III: indeterminate initial infection=LST−and IFAT+/++
SI: symptomatic infection=LST− and IFAT+++/++++
SOI: subclinical oligosymptomatic infection=LST− and IFAT+++/++++

Table 1 Clinical and immunological spectrum of human *Leishmania (L.) infantum chagasi* infection in the Amazon region, Brazil

Susceptible immunological pole		Resistant immunological pole
Symptomatic infection (AVL) LST− IFAT+++/++++	Indeterminate initial infection (III) LST− IFAT+/++	Asymptomatic infection (AI) LST+/++++ IFAT−
Subclinical oligosymptomatic infection (SOI) LST− IFAT+++/++++		Subclinical resistant infection (SRI) LST+/++ IFAT+/++

IFAT++++: 5120—10 240 (IgG); IFAT+++: 1280—2560 (IgG); IFAT++: 320—640 (IgG); IFAT+: 80—160 (IgG); IFAT−: negative reaction; LST: leishmanin skin test; LST++++: exacerbated reaction (≥16 mm); LST+++: strong reaction (13—15 mm); LST++: moderate reaction (9—12 mm); LST+: weak reaction (5—8 mm); LST−: negative reaction.

Crescente et al, AJTMH, 103, 2009

Perfil Clínico de LV

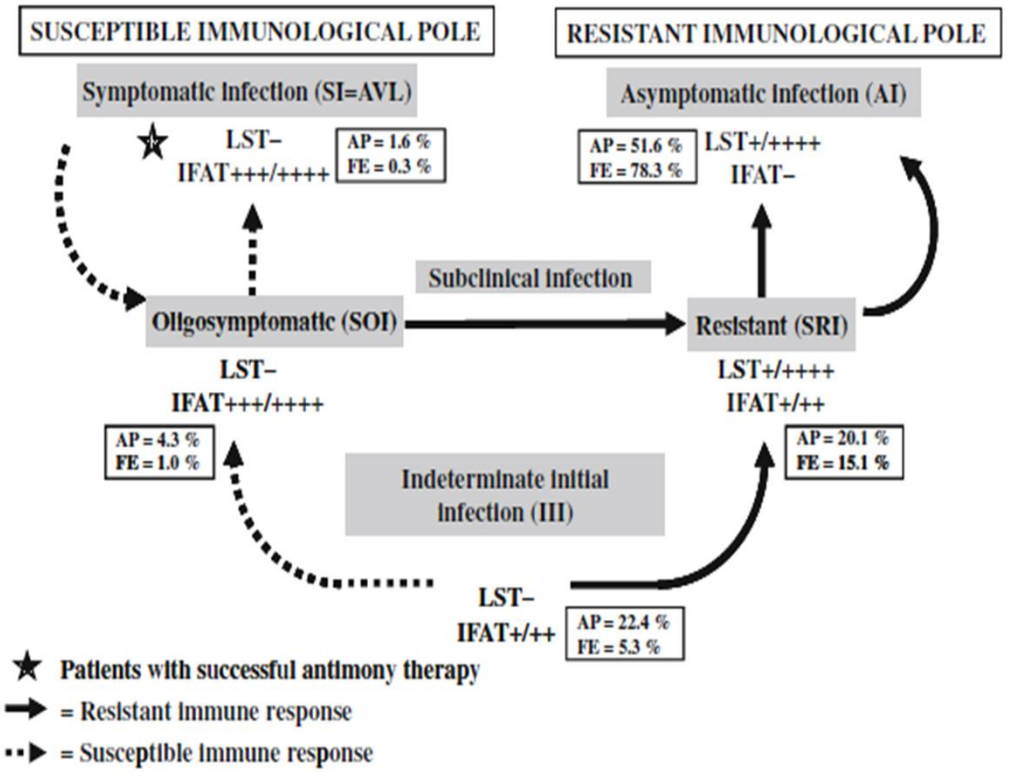
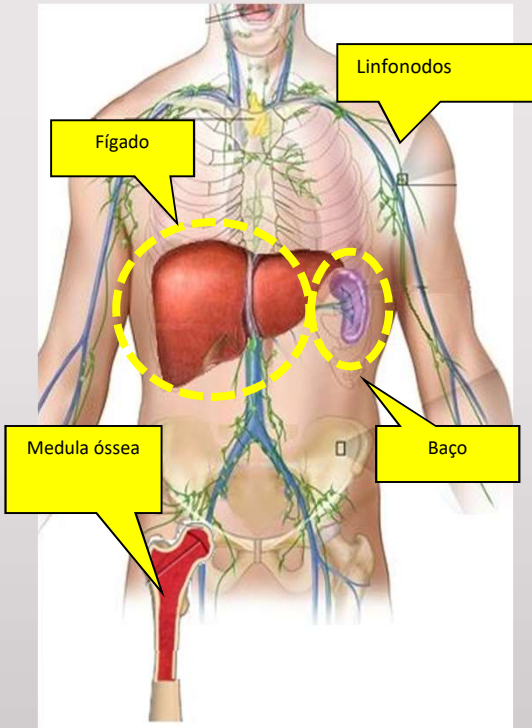


Fig. 2 Dynamics evolution of clinical-immunological profiles of human *Leishmania (L.) infantum chagasi*-infection in Amazonian Brazil. *IFAT* indirect fluorescent antibody test (IgG). *IFAT*++++ 5,120–10,240 (IgG). *IFAT*+++ 1,280–2,560 (IgG). *IFAT*++ 320–640 (IgG). *IFAT*+ 80–160 (IgG). *IFAT*– negative reaction. *LST* leishmanin skin test. *LST*++++ exacerbate reaction (≥16 mm). *LST*+++ strong reaction (13–15 mm). *LST*++ moderate reaction (9–12 mm). *LST*+ weak reaction (5–8 mm). *LST*– negative reaction. *AI* asymptomatic infection. *SI* symptomatic infection (=*AVL*). *SOI* sub-clinical oligosymptomatic infection. *SRI* sub-clinical resistant infection. *III* indeterminate initial infection. *AP* accumulated prevalence. *FE* final evolution of infection

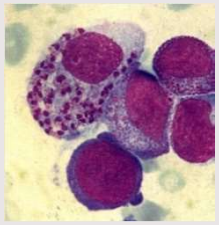
Silveira et al Parasitol Res (2010) 106:377–386

Aspectos imunopatogênicos da leishmaniose visceral

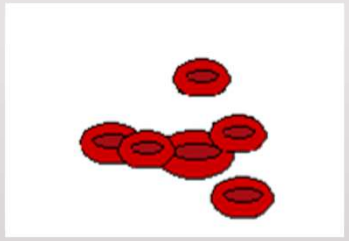
Órgãos alvo



Infecção de células do sistema reticulo endotelial

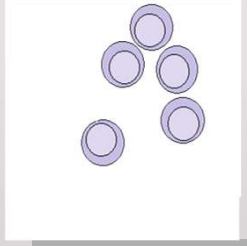


Comprometimento da medula óssea e desvio na produção de outros tipos celulares



Hemácias

Plaquetas



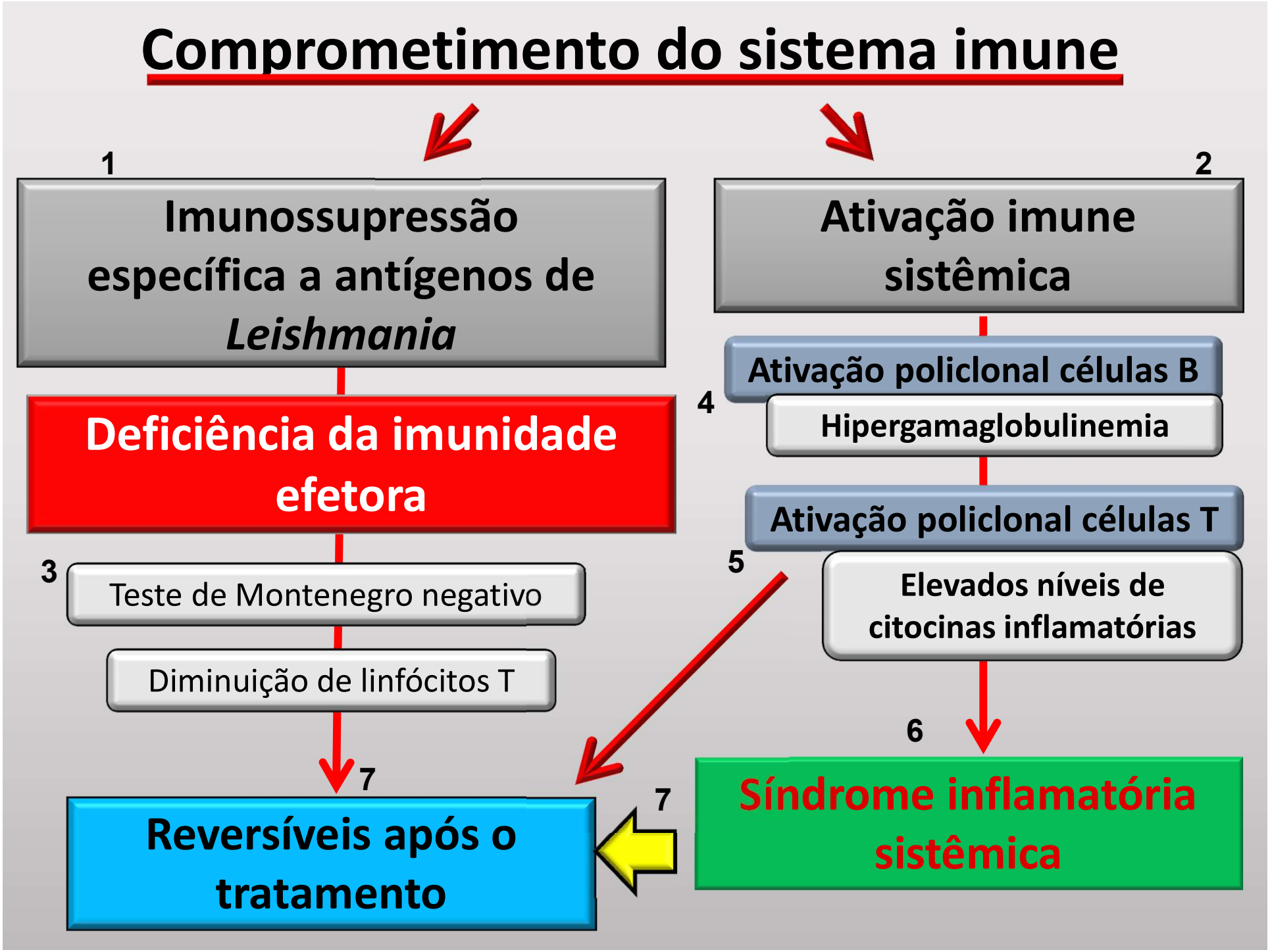
Neutrófilos

Monócitos

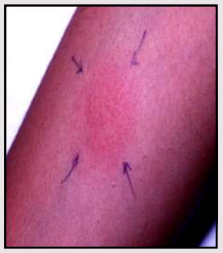
Triade clássica
- ✓Febre
- ✓Emagrecimento
- ✓Hepatoesplenomegalia

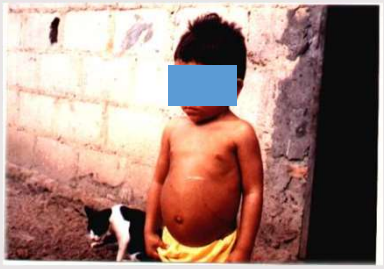
Diminuição na produção dos progenitores dos linfócitos T

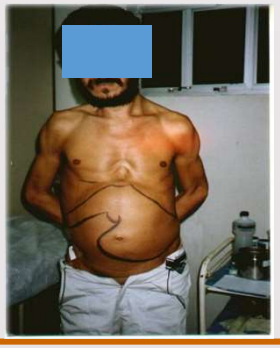
Alterações laboratoriais:
- ✓ Anemia
- ✓ Plaquetopenia
- ✓ Neutropenia
- ✓ Linfopenia


Comprometimento do sistema imune
1
Imunossupressão específica a antígenos de *Leishmania*
2
Ativação imune sistêmica
Deficiência da imunidade efetora
Ativação policlonal células B
4
Hipergamaglobulinemia
Ativação policlonal células T
3
Teste de Montenegro negativo
5
Elevados níveis de citocinas inflamatórias
Diminuição de linfócitos T
6
7
7
Reversíveis após o tratamento
Síndrome inflamatória sistêmica

Leishmaniose Visceral







Assintomática	Oligossintomática	Clássica

Sorologia

+	++	++++

Teste de Montenegro

+	+ ou -	-

Hepatoesplenomegalia

Ausente	Discreta	Volumosa

American Visceral Leishmaniasis: Factors Associated with Lethality in the State of São Paulo, Brazil

Table 3: Statistical analysis of factors associated with VL lethality, state of Sao Paulo, 1999–2005 (bivariate analysis).

Features	Outcome ($n = 376$)			OR (95% CI)	P value
	Death $n = 53$	Cured $n = 323$	Total $n = 376$		
Signs and symptoms					
Asthenia	44	191	235	3.38 (1.59–7.16)	0.0008
Cardiac abnormality	9	10	19	6.53 (2.28–18.65)	<0.0001
Dehydration	12	8	20	12.11 (4.66–31.47)	<0.0001
Diarrhea	20	52	72	3.16 (1.68–5.93)	0.0002
Dyspnea	12	22	34	4.00 (1.84–8.69)	0.0001
Edema	10	11	21	6.75 (2.7–16.86)	<0.0001
Hemorrhagic manifestation	18	22	40	7.24 (3.54–14.83)	<0.0001
Jaundice	10	6	16	12.88 (4.45–37.31)	<0.0001
Pallor	39	199	238	2.02 (1.02–4.01)	0.040
Dry Cough	29	127	156	1.86 (1.04–3.35)	0.035
Vomiting	13	35	48	2.67 (1.30–5.48)	0.006
Drowsiness	9	11	20	5.8 (2.27–14.79)	<0.0001
Laboratory analysis					
Total bilirubin ≥ 2.0	13	6	19	17.17 (6.18–47.7)	<0.0001
Hypoalbuminemia ≤ 3.0	15	37	52	3.05 (1.53–6.07)	0.0009
Thrombocytopenia ≤ 100.000	31	108	139	2.8 (1.55–5.08)	0.0004
Aspartate aminotransferase > 40	20	62	82	2.55 (1.37–4.74)	0.002
Comorbidities					
Liver disease	3	2	5	9.79 (1.59–60.11)	0.020
Diabetes	5	4	9	8.46 (2.19–32.62)	0.003
Peripheral vascular disease	7	5	12	9.86 (3.0–32.4)	<0.0001
Splenectomy	2	0	2	undefined	0.019
Congestive heart failure	4	2	6	13.33 (2.38–74.78)	0.004
Use of immunosuppressive drugs	3	0	3	undefined	0.002
Tuberculosis	3	1	4	19.65 (2.0–192.74)	0.009
Fever					
≥60 days	13	26	39	3.71 (1.76–7.80)	0.0002
≥30 days	26	79	105	2.97 (1.64–5.39)	0.0002
Age					
≥30 years	36	73	109	7.25 (3.85–13.66)	<0.0001
≥50 years	28	17	45	20.16 (9.74–41.73)	<0.0001
Complications	53	64	117	undefined	<0.0001
Opportunistic infections	21	43	64	4.27 (2.26–8.08)	<0.0001
Pneumonia	13	29	42	0.40 (0.18–0.89)	0.023
Bleeding	24	2	26	26.1 (5.77–117.78)	<0.0001
Sepsis	28	0	28	undefined	<0.0001
Antimicrobial use	34	59	93	8.71 (4.56–16.64)	<0.0001
Blood derivatives	36	95	131	5.61 (2.93–10.72)	<0.0001

Madalosso et al, Jounal of Trop. Med, 2012

American Visceral Leishmaniasis: Factors Associated with Lethality in the State of São Paulo, Brazil

Table 4: Final model of factors associated with VL lethality, state of Sao Paulo, 1999–2005 (multivariate analysis).

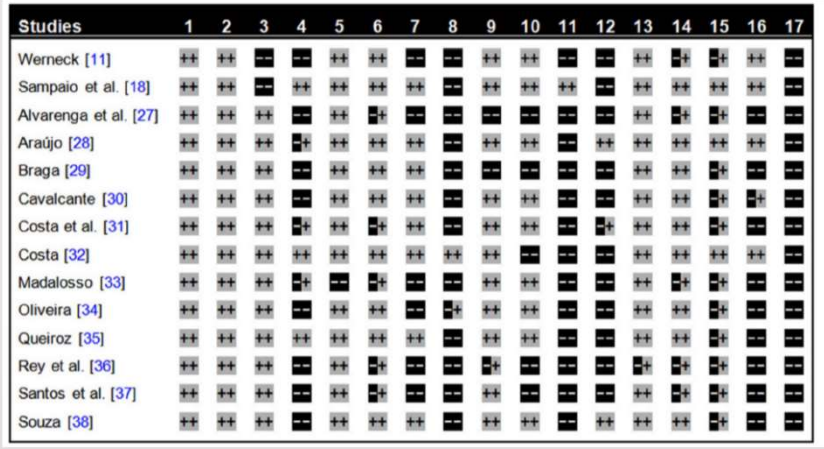
Variable	Clinical outcome			OR (95% CI)*	*P* value**
	Death $n = 53$	Cured $n = 323$	Total $n = 376$		
High total bilirubin					
Total Bilirubin ≥ 2.0 g/dL	13	6	19	7.36 (1.65–32.76)	<0.0001
Severe anemia					
Hemoglobin ≤ 5.0 g/dL	7	13	20	4.56 (1.17–17.48)	<0.0001
Antimicrobial agents	34	59	93	5.76 (2.27–14.64)	<0.0001
Age ≥ 50 years	28	17	45	29.54 (10.6–82.6)	
Length of illness (days)					
Fever >60 days	13	26	39	6.23 (2.05–18.92)	<0.0001
Hemorrhagic manifestations	18	22	40	2.62 (0.93–7.4)	0.0001
Cardiac abnormality	9	10	19	4.73 (1.3–17.23)	<0.0001
Diarrhea	20	52	72	2.76 (1.03–7.43)	<0.0001

*Odds ratio (95% confidence interval). **Likelihood ratio.

Madalosso et al, Jounal of Trop. Med, 2012

Risk Factors for Adverse Prognosis and Death in American Visceral Leishmaniasis: A Meta-analysis

1. Inclusion and exclusion criteria and selection of study population
2. Definition of VL cases selected to the study
3. Description of the treatment received by patients
4. Procedures for dealing with missing information in the medical records or in the SINAN, or losses/refusals of participants, in prospective studies
5. Measurement/confirmation of variables at the time of admission to hospital
6. Definition of variables
7. Methods of extraction of data from medical records or of measurement of variables performed in prospective studies
8. Criteria for analysis of continuous variables
9. Control of confounding factors or discriminant analysis
10. Methods of selection of variables in regression models or in discriminant analysis
11. Testing of interaction effects
12. Multicollinearity testing
13. Observance of the premises in statistical analysis
14. Description of the results (non-restriction to *P* values and/or to significant variables)
15. Sample size
16. Calibration and discrimination
17. External validation of predictive regression models

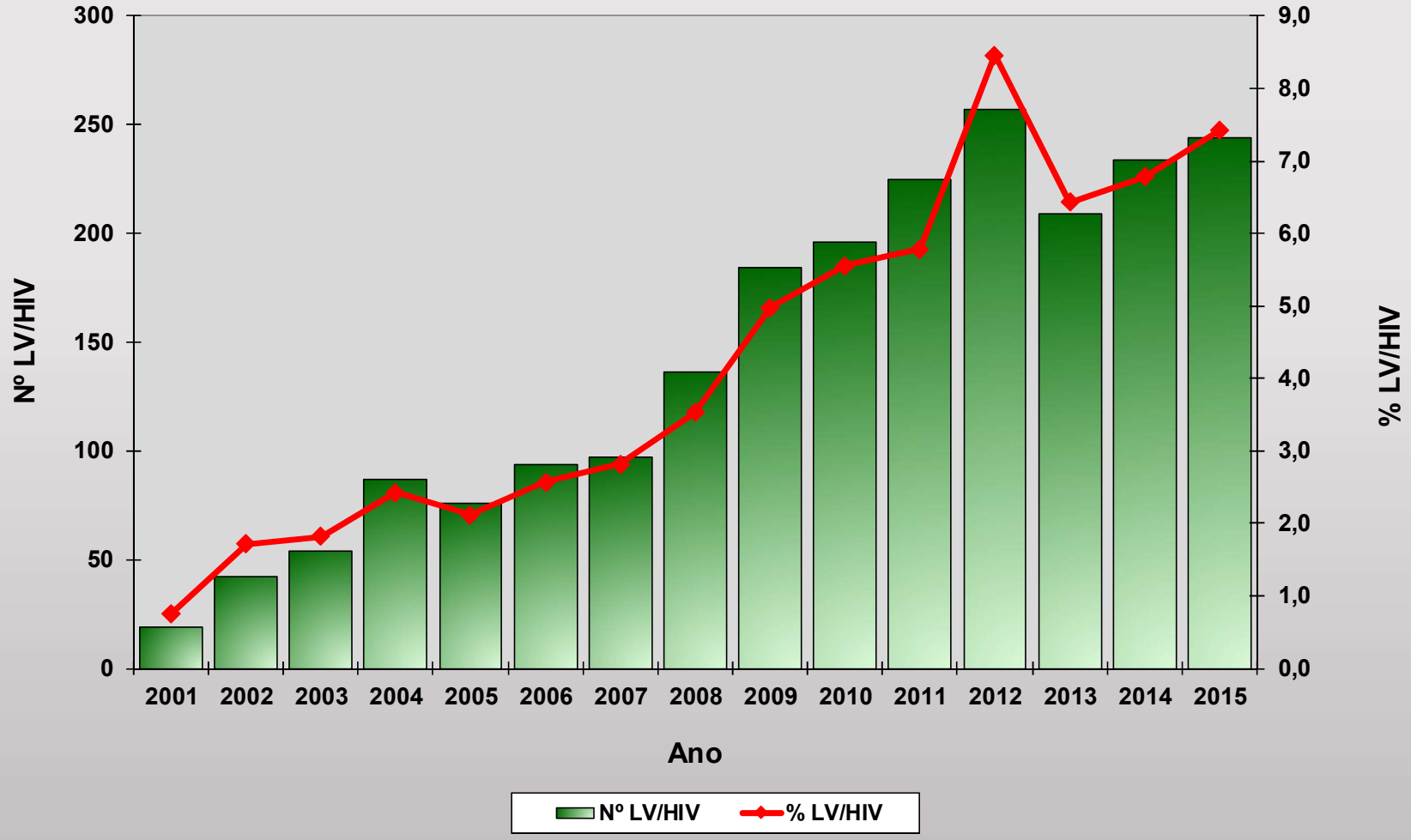


Methods/Principal Findings: The full texts of 14 studies conforming to the inclusion criteria were analyzed and their methodological quality examined by means of a tool developed in the light of current research tools. Information regarding prognostic variables was synthesized using meta-analysis. Variables were grouped according to the strength of evidence considering summary measures, patterns and heterogeneity of effect-sizes, and the results of multivariate analyses. The strongest predictors identified in this review were jaundice, thrombocytopenia, hemorrhage, HIV coinfection, diarrhea, age <5 and age >40–50 years, severe neutropenia, dyspnoea and bacterial infections. Edema and low hemoglobin concentration were also associated with unfavorable outcomes. The main limitation identified was the absence of validation procedures for the few prognostic models developed so far.

Citation: Belo VS, Struchiner CJ, Barbosa DS, Nascimento BWL, Horta MAP, et al. (2014) Risk Factors for Adverse Prognosis and Death in American Visceral Leishmaniasis: A Meta-analysis. PLoS Negl Trop Dis 8(7): e2982. doi:10.1371/journal.pntd.0002982

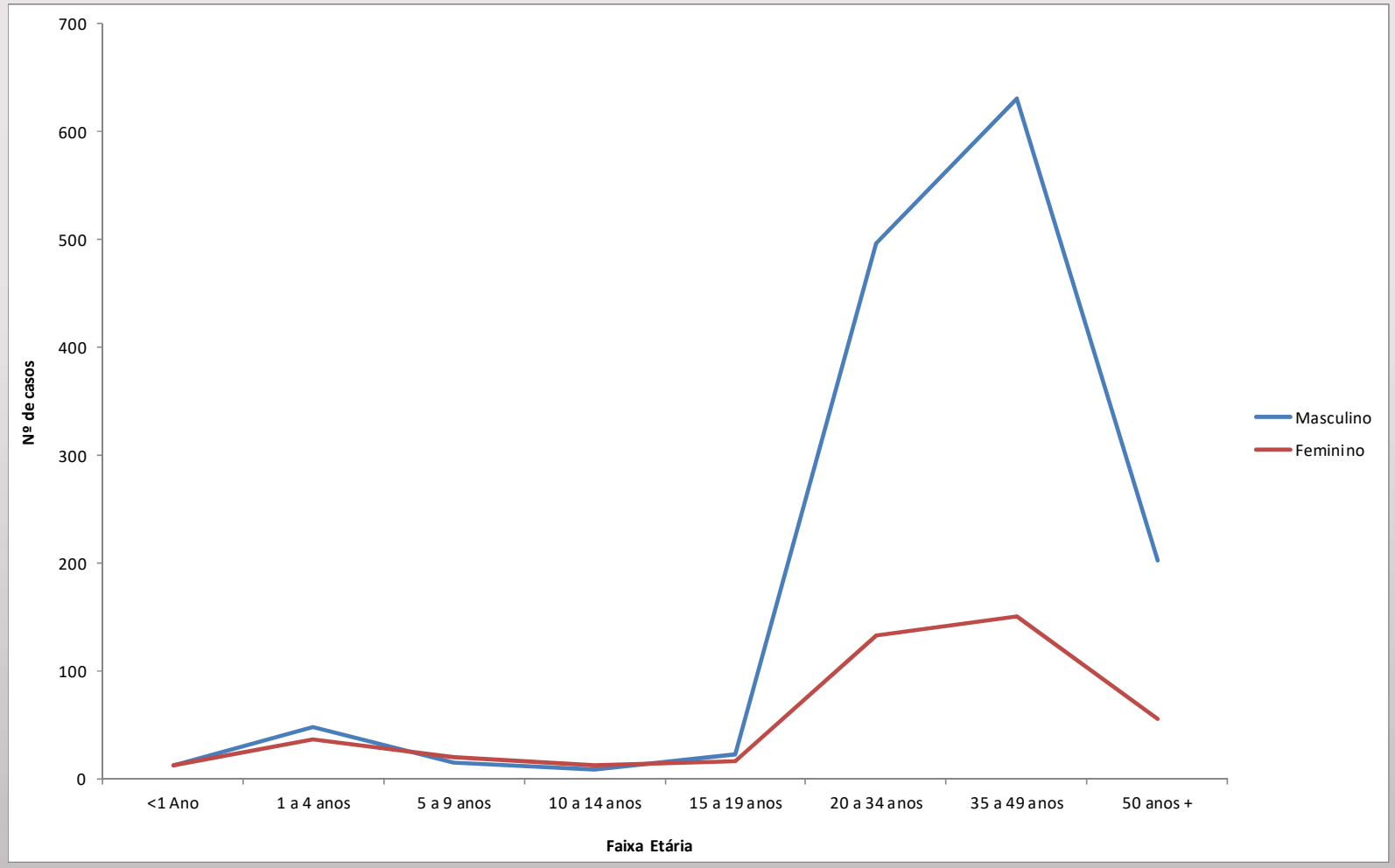
LV em Imunossuprimidos

Casos e percentual de coinfecção LV e HIV, Brasil, 2001 a 2015



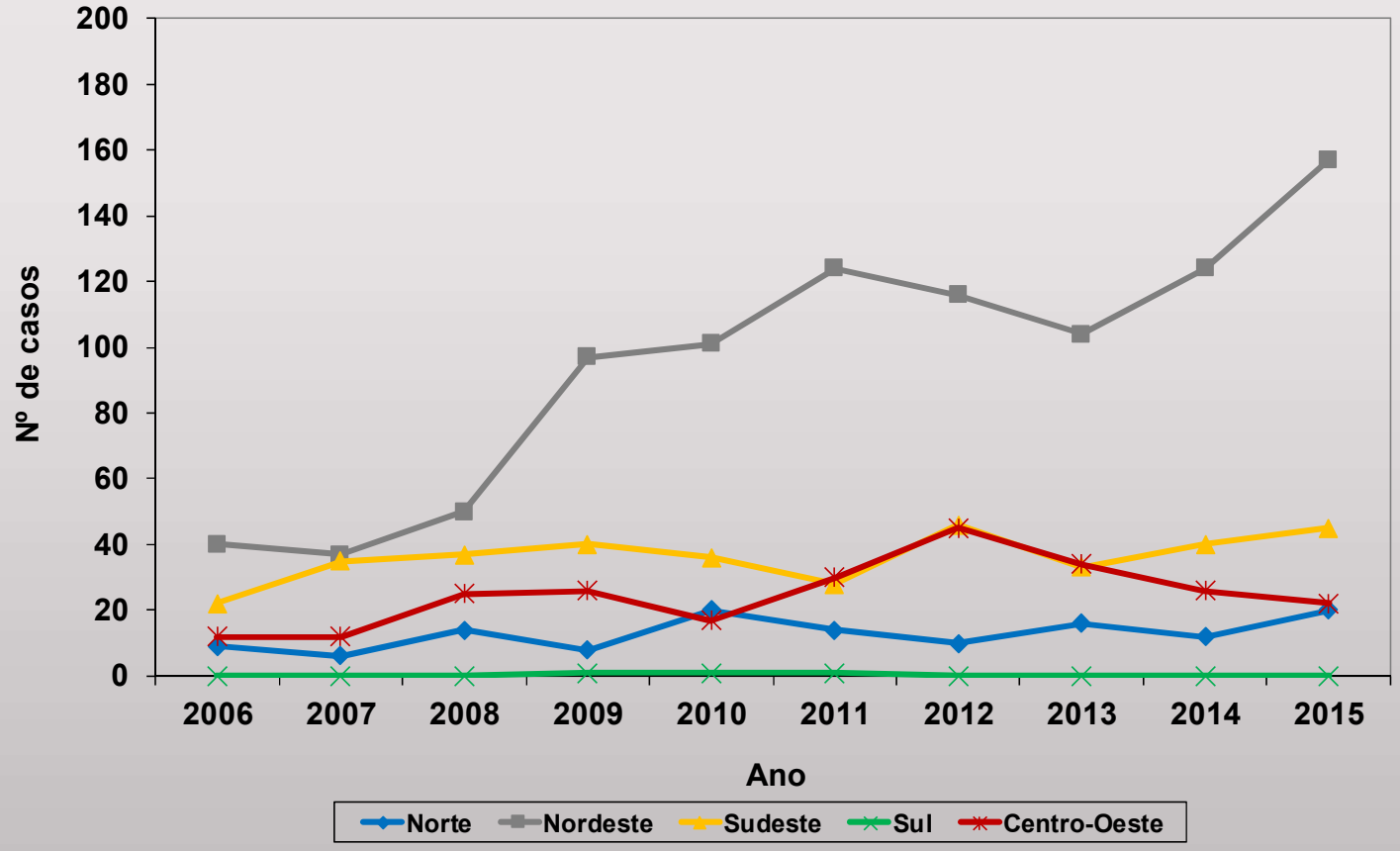
Fonte: SVS/MS.

Casos de coinfecção LV/HIV segundo sexo e faixa etária, Brasil, 2006 a 2015



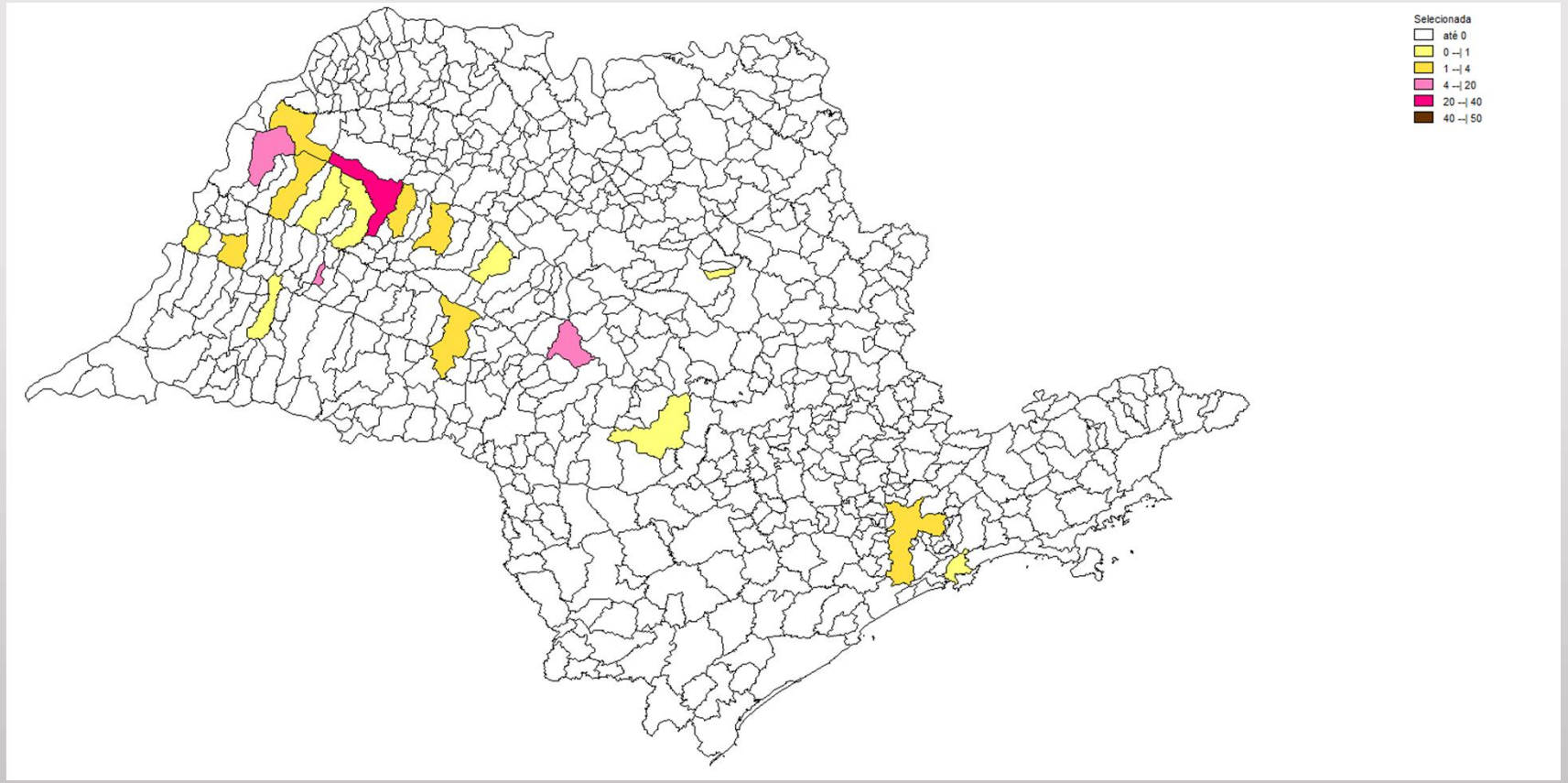
Fonte: SVS/MS.

Número de casos de coinfecção LV/HIV por Região, Brasil, 2006 a 2015



Fonte: SVS/MS.

Coinfecção LV-HIV São Paulo



Letalidade e Falha Terapêutica LV-HIV

Ano	LV confirmad	Total de Óbtios	Letalidade total (%)	LV/HIV	Letaldade LV/HIV (%)	Total de Falha	Total Falha (%)	HIV Falha	HIV Falha (%)
1999	17	5	29,41	3	0	0	0,00	0	0,00
2000	15	0	0,00	1	0	0	0,00	0	0,00
2001	57	3	5,26	3	0	0	0,00	0	0,00
2002	115	13	11,30	8	25,00	0	0,00	0	0,00
2003	156	23	14,74	10	10,00	1	0,64	1	10,00
2004	131	13	9,92	13	30,77	1	0,76	1	7,69
2005	155	16	10,32	12	25,00	2	1,29	2	16,67
2006	250	10	4,00	13	15,38	3	1,20	3	23,08
2007	248	22	8,87	30	6,67	7	2,82	3	10,00
2008	300	24	8,00	35	20,00	15	5,00	7	20,00
2009	184	15	8,15	25	20,00	14	7,61	4	16,00
2010	86	4	4,65	15	20,00	8	9,30	2	13,33
TOTAL	**1714**	**148**	**8,63**	**168**	**17,26**	**51**	**2,98**	**23**	**13,69**

Fonte: CVE/SES/SP

High levels of T lymphocyte activation in *Leishmania*-HIV-1 co-infected individuals despite low HIV viral load

Joanna R Santos-Oliveira[1], Carmem BW Giacoia-Gripp[2], Priscilla Alexandrino de Oliveira[3], Valdir S Amato[4], Jose Ângelo L Lindoso[5], Hiro Goto[5], Manoel P Oliveira-Neto[6], Marise S Mattos[6], Beatriz Grinsztejn[6], Mariza G Morgado[2], Alda M Da-Cruz[1*]

BMC Infectious Diseases 2010, **10**:358

Table 1 Clinical and laboratorial characteristics of HIV-1 co-infected leishmaniasis patients and control groups

Parameters	AVL/HIV-1 patients (n = 9)	ATL/HIV-1 patients (n = 8)	HIV-1 infected* (n = 16)	Healthy subjects (n = 8)
Age, years, (median)	38 (35-50)[a]	44 (38-54)[b]	39 (33-49)[c]	26 (25-30)[abc]
Male sex, n, (%)	9 (100)[cd]	8 (100)[ef]	15 (94)[f]	4 (50)[def]
CD4+T Cell count, cells/mm^3	62 (52-127)[g]	404 (294-597)[h]	380 (223-450)[i]	1,106 (957-1,300)[ghi]
Current AIDS diagnosis, Number of cases (%)	9 (100)	6 (75)	8 (50)	——
Time of clinical remission of leishmaniasis, months	8 (6-12)	11 (7.5-14)	——	——
Patients with undetectable viremia, (%)	5 (55.6)	4 (50)	9 (56.2)	——
Viral load levels of patients with detectable viremia, copies/mL	142,240 (24,025-279,321)	6,200 (2,012-78,176)	12,010 (2,000-136,625)	——

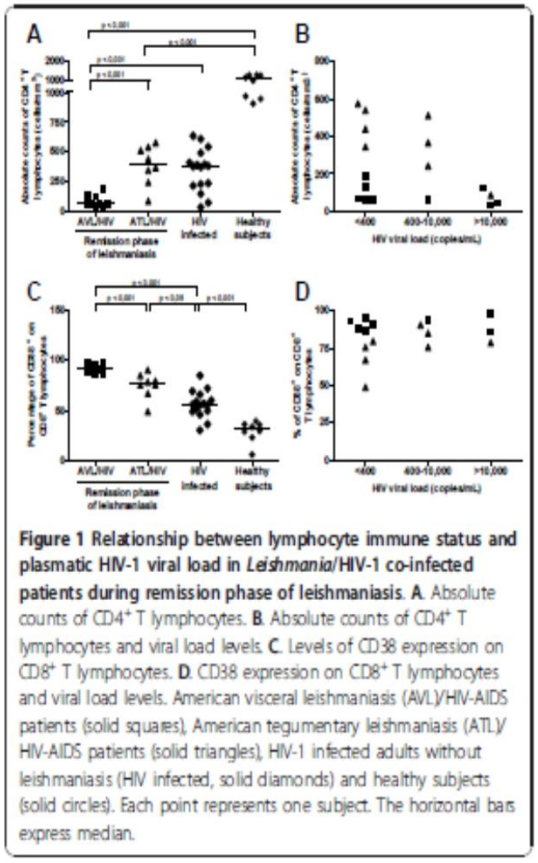


Figure 1 Relationship between lymphocyte immune status and plasmatic HIV-1 viral load in *Leishmania*/HIV-1 co-infected patients during remission phase of leishmaniasis. **A**. Absolute counts of CD4$^+$ T lymphocytes. **B**. Absolute counts of CD4$^+$ T lymphocytes and viral load levels. **C**. Levels of CD38 expression on CD8$^+$ T lymphocytes. **D**. CD38 expression on CD8$^+$ T lymphocytes and viral load levels. American visceral leishmaniasis (AVL)/HIV-AIDS patients (solid squares), American tegumentary leishmaniasis (ATL)/HIV-AIDS patients (solid triangles), HIV-1 infected adults without leishmaniasis (HIV infected, solid diamonds) and healthy subjects (solid circles). Each point represents one subject. The horizontal bars express median.

Table 3 Multivariate linear regression analysis to evaluate the association between T cell activation (CD38 + on CD8+ T lymphocytes) and independent variables in leishmaniasis and HIV-1 co-infected patients

Independent variables	Dependent variable: Percentage of CD38$^+$ on CD8$^+$ T lymphocytes		
	Coef[1]	SE[2]	*P*
Leishmania infection (presence or absence)	24.88	4.63	0.000011
CD4$^+$ T cell count, cells/mm^3	-0.02	0.013	0.13
Viral load levels (detectable or undetectable)	4.12	4.85	0.39

1 Coef - Correlation coefficient, 2 SE - Standard error

Obs. HIV-1 infected patients were also included in this analysis.

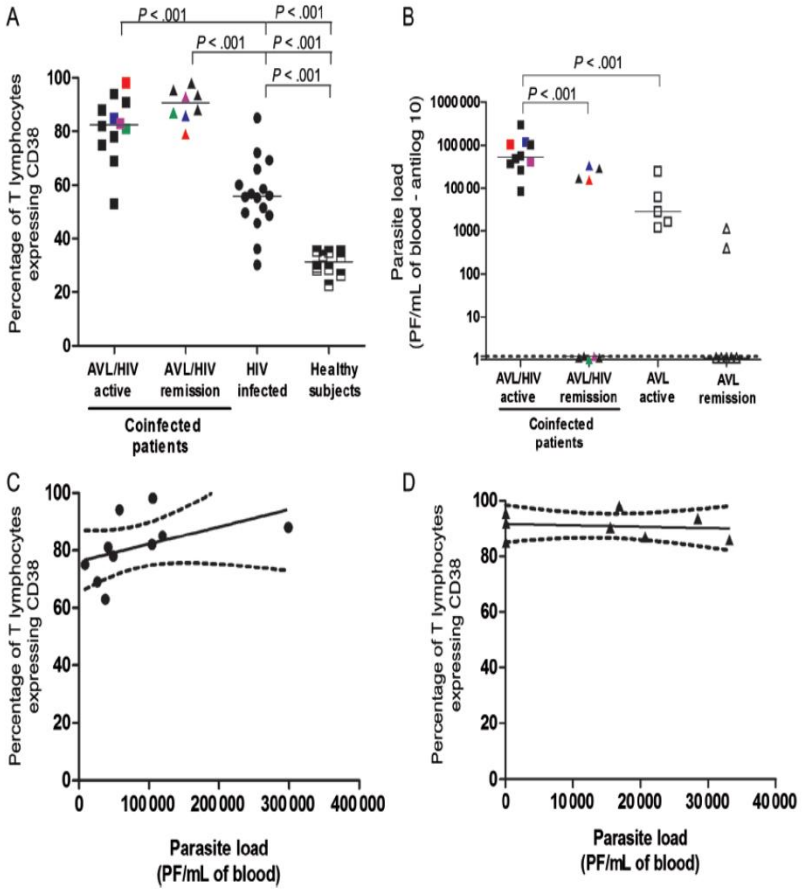
Table 2 CD4+ T cell counts and viral load levels of HIV-AIDS associated leishmaniasis patients (visceral or tegumentary) and HIV-1 infected control group

Patient's Number	CD4$^+$ T cells counts(cells/mm^3)	Viral load levels (copies/mL)
VL/HIV-AIDS		
1	78	< 400
2	59	5,810
3	33	316,402
4	129	< 400
5	61	< 400
6	45	242,240
7	187	< 400
8	124	42,240
9	68	< 400
TL/HIV-AIDS		
1	367	1,700
2	440	< 400
3	512	2,324
4	86	146,351
5	541	< 400
6	345	< 400
7	576	< 400
8	242	10,000
HIV-1 infected		
1	146	136,625
2	543	< 400
3	215	< 400
4	34	12,010
5	230	253,761
6	609	< 400
7	391	< 400
8	491	< 400
9	377	< 400
10	73	1,750
11	371	10,000
12	236	< 400
13	635	< 400
14	382	2,000
15	394	55,239
16	410	< 400

Microbial Translocation Induces an Intense Proinflammatory Response in Patients With Visceral Leishmaniasis and HIV Type 1 Coinfection

Joanna R. Santos-Oliveira,[1] Eduardo G. Regis,[2] Carmem B. W. Giacoia-Gripp,[3] Joanna G. Valverde,[6] Priscilla Alexandrino-de-Oliveira,[7] Jose Ângelo L. Lindoso,[8] Hiro Goto,[8] Manoel P. Oliveira-Neto,[4] Jorge O. Guerra,[9] Beatriz Grinsztejn,[4] Selma B. Jerônimo,[6] Mariza G. Morgado,[3] and Alda M. Da-Cruz[1,5]

The Journal of Infectious Diseases 2013;208:57–66



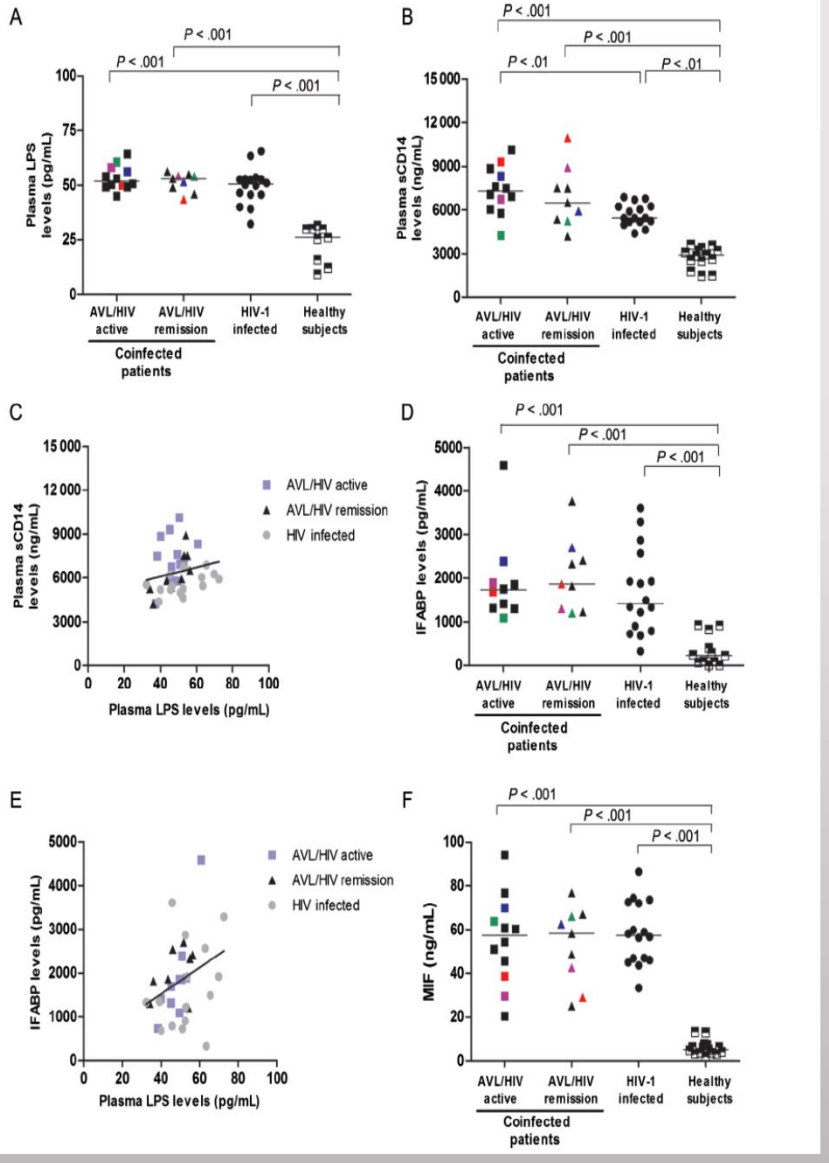


Table 1. Multivariate Analysis of Factors Associated With Cell Activation, Evaluated on the Basis of the Percentage of CD38-Positive Cells Among CD8$^+$ T Lymphocytes, Among Patients Coinfected With *Leishmania (Leishmania) infantum* and Human Immunodeficiency Virus Type 1 (HIV) and Those With HIV Infection Only

	Percentage of CD38$^+$ Cells Among CD8$^+$ T lymphocytes		
Variable	Correlation Coefficient[a]	Standard Error	*P*
CD4$^+$ T-cell count (cells/mm^3)	−0.021	0.014	.875
Viral load (copies/mL)	0.049	0.001	.624
Leishmaniasis (presence or absence)	0.817	5.478	.0001
LPS level (pg/mL)	0.373	0213	.001
sCD14 level (pg/mL)	0.061	0.002	.609
IFABP level (pg/mL)	0.153	0.002	.097
MIF level (ng/mL)	0.124	0.118	.218

Table 3. Multivariate Analysis of the Association Between Proinflammatory Cytokine Levels and Viral Load, Lipopolysaccharide (LPS) Level, Soluble CD14 (sCD14) Level, and *Leishmania* Infection Among Patients Coinfected With *Leishmania (Leishmania) infantum* and Human Immunodeficiency Virus Type 1 (HIV) and Those With HIV Infection Only

Variable	LPS Level, *P*	Viral Load, *P*	sCD14 Level, *P*	*Leishmania* Infection, *P*
TNF level	.296	.709	.980	.003
IL-1β level	.685	.766	.979	.122
IL-6 level	.018	.849	.527	.005
IL-8 level	.008	.968	.019	.001
IL-17 level	.939	.856	.246	.001
MIP-1β level	.968	.563	.011	.001
MIF level	.141	.399	.877	.969

Abbreviations: IL-1β, interleukin 1β; IL-6, interleukin 6; IL-8, interleukin 8; IL-17, interleukin 17; LPS, lipopolysaccharide; MIF, macrophage migration inhibitory factor; MIP-1β, macrophage inflammatory protein 1β; TNF, tumor necrosis factor.

Table 2. Plasma Proinflammatory Cytokine Levels in the Study Population

Cytokine	Active AVL/HIV (n = 5)	Remission AVL/HIV (n = 7)	HIV Infected	Active AVL (n = 5)	Remission AVL (n = 7)	Healthy Subjects (n = 8)	P^a	P^b	P^c	P^d
IFN-γ	2795 (1344–7104)	2411 (1415–6157)	150 (56–332)	1143 (445–4446)	783 (367–3482)	19 (5.3–145)	.0001	.0001	.126	.05
TNF	490 (284–1503)	374 (302–1207)	165 (86–200)	143.5 (37.7–555)	100 (57.3–588.5)	2 (1.5–8.5)	.0001	.001	.05	.07
IL-6	536 (61–6128)	947 (276–9068)	81 (45–110)	416 (211–557)	49 (30–115)	1 (0.3–2.5)	.0001	.006	.47	.04
IL-8	2447 (1050–10 844)	3244 (2439–17 999)	170 (130–220)	8000 (1887–13 578)	4325 (427–8988)	2.5 (1.5–3.0)	.01	.006	.536	.445
IL-1β	16 (3.5–209)	112.5 (17.1–351)	15 (10–20)	9.7 (4–226)	7.5 (2–138)	0.5 (0.4–0.62)	.01	.0001	.958	.05
IL-17	231 (118–417)	256 (161–500)	65.2 (46–90)	288 (102–398)	193.5 (131–626.6)	2 (2–16)	.0008	.0006	.874	.837
MIP-1β	2157 (430–3928)	546 (441–923)	243 (165–318)	730.3 (418–3363)	571.5 (426–1111)	14.3 (0.1–50.2)	.008	.008	.924	.571

Microbial Translocation Induces an Intense Proinflammatory Response in Patients With Visceral Leishmaniasis and HIV Type 1 Coinfection

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The Journal of Infectious Diseases 2013;208:57–66

Conclusions. LPS levels along with the immune consequences of *Leishmania* infection were associated with elevated cellular activation in coinfected patients. As a consequence, secondary chemoprophylaxis for leishmaniasis or even the use of antiinflammatory drugs or antibiotics may be considered for improving the prognosis of AVL/HIV.

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PLoS NEGLECTED TROPICAL DISEASES

Predictors of Visceral Leishmaniasis Relapse in HIV-Infected Patients: A Systematic Review

Gláucia F. Cota[1,3]*, Marcos R. de Sousa[2], Ana Rabello[1]

1 Post-Graduate Program in Health Sciences, René Rachou Institute, Fundação Oswaldo Cruz, Belo Horizonte, Minas Gerais, Brazil, 2 Post-Graduate Program in Adult Health Sciences, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, 3 Eduardo de Menezes Hospital, Fundação Hospitalar do Estado de Minas Gerais-FHEMIG, Belo Horizonte, Minas Gerais, Brazil

Recidiva de LV persiste alta mesmo com uso de HAART

A profilaxia secundária confere proteção parcial (67% x 31%)

São fatores relacionados com recidiva:

- CD4+ inferior a 100 cels/mL ao diagnóstico de LV;
- recuperação insuficiente de CD4+ após o tratamento;
- episódios prévios de recidiva

Leishmaniasis among organ transplant recipients

Antinory et al. Lancet Infect. Dis, 2008

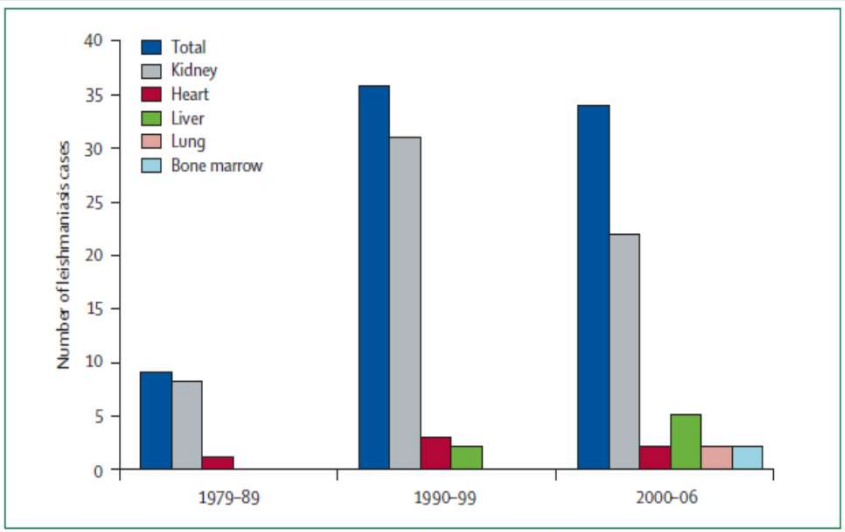


Figure 1: Cases of leishmaniasis among transplant recipients per year of report (1979–2006)

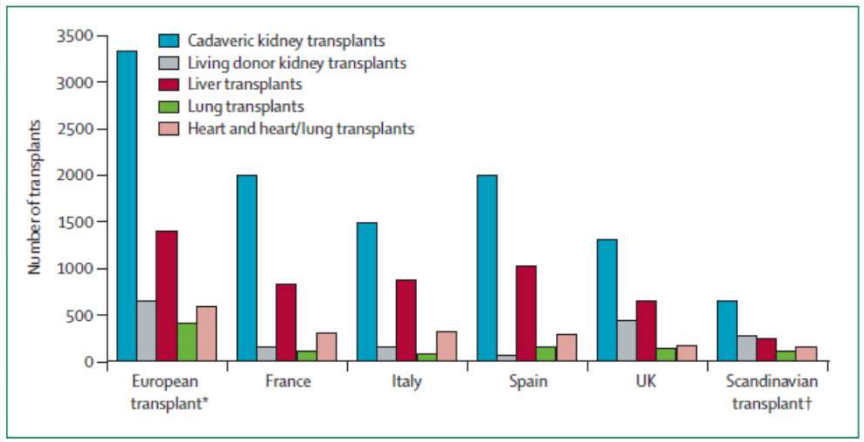


Figure 3: Transplant activity in Europe, 2003
*European transplant includes Germany, Austria, Belgium, Luxembourg, the Netherlands, and Slovenia.
†Scandinavian transplant includes Denmark, Norway, Finland, and Sweden.

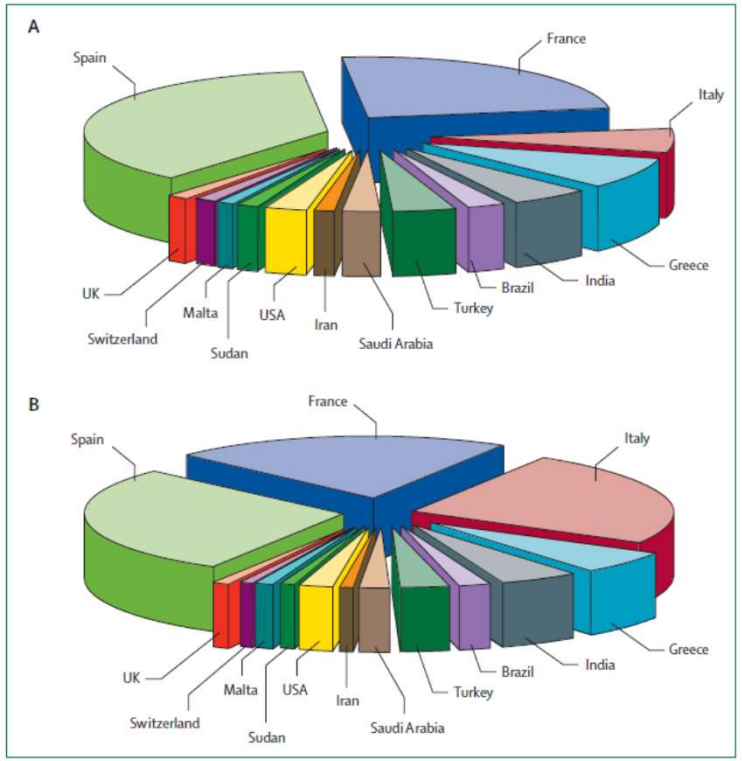


Figure 2: Countries reporting cases of leishmaniasis among transplant recipients according to single case reports (A) and cumulative cases reported (B)

	Transplant recipients	HIV-positive*	HIV-negative†	Total
Fever	59/63 (94%)	267/330 (81%)	177/179 (99%)	503/572 (88%)
Hepatomegaly	23/55 (42%)	254/330 (77%)	154/179 (86%)	431/564 (76%)
Splenomegaly	43/57 (75%)	244/330 (74%)	176/179 (98%)	463/566 (82%)
Weight loss	13/36 (36%)	28/90 (31%)	..	41/126 (33%)
Lymphadenopathy	..	12/240 (5%)	10/121 (8%)	22/361 (6%)
Anaemia (haemoglobin <12 g/dL)	51/59 (86%)	260/294 (88%)	134/158 (85%)	445/511 (87%)
Leucopenia (white blood cells <4000 per µL)	55/59 (93%)	266/294 (90%)	79/158 (50%)	400/511 (78%)
Thrombocytopenia (<150 000 platelets per µL)	50/59 (85%)	231/294 (79%)	126/158 (80%)	407/511 (80%)
Serology (IFAT ≥1/40)	45/49 (92%)	113/237 (48%)	126/135 (93%)	284/421 (67%)
Bone marrow microscopy	59/60 (98%)	282/348 (81%)	128/158 (81%)	469/566 (83%)
Bone marrow culture	23/28 (82%)	105/151 (70%)	39/53 (74%)	167/232 (72%)

..=not reported. IFAT=indirect fluorescent antibody test. *Cumulative analysis of references 10, 72, 78, and 80. †Cumulative analysis of references 10, 72, 79, and 81. Values show number of patients with clinical feature/total patients tested (%).

Table: Comparative clinical and biological features of visceral leishmaniasis among transplant recipients, HIV-positive patients, and immunocompetent HIV-negative patients

Risk factors, clinical features and outcomes of visceral leishmaniasis in solid-organ transplant recipients: a retrospective multicenter case–control study

TABLE 1. Frequency of VL in solid-organ transplant recipients at ten Spanish and two Brazilian hospitals

	Total		Spain		Brazil		
Transplant	Cases per total transplants	% (95% CI)	Cases per total transplants	% (95% CI)	Cases per total transplants	% (95% CI)	RR (95% CI)[a], p
Kidney	25/12 895	0.2% (0.2–0.3)	15/11 819	0.1% (0.1–0.2)	10/1076	0.9% (0.5–1.6)	7.4 (3.1–17.4), <0.001
Liver	4/8681	0.05% (0.01–0.1)	1/7360	0.01% (0.0–0.1)	3/1321	0.2% (0.1–0.6)	16.1 (1.57–99.9), 0.01
Heart	6/2669	0.2% (0.1–0.5)	5/2535	0.2% (0.1–0.4)	1/134	0.7 (0.04–3.6)	0.3 (0.03–6.0), 0.27
Lung	1/894	0.1% (0.00–0.5)	1/877	0.1% (0.0–0.6)	0/17	—	—
All	36/25 139	0.1% (0.1–0.2)	22/22 591	0.1% (0.1–0.2)	14/2548	0.5% (0.3–0.9)	5.7 (2.7–11.6), <0.001

VL, visceral leishmaniasis; RR, relative risk; CI, confidence interval.
[a]Comparison of frequencies in Spain and Brazil.

TABLE 2. Univariate analysis of risk factors for VL in SOT recipients

Variable	Patients (n = 36), n (%)	Control subjects (n = 72), n (%)	OR (95% CI)	p
Male sex	27 (75.0)	54 (75.0)	1.0 (0.4–2.5)	1.00
Age, years, median (range)	46 (14–76)	45 (10–76)	0.8 (0.4–1.9)	0.50
Diabetes mellitus	7 (19.4)	18 (25.0)	1.4 (0.5–3.7)	0.52
CMV disease within preceding 6 months	5 (13.9)	5 (6.9)	0.5 (0.1–1.7)	0.30
CMV replication within preceding 6 months	7 (19.4)	6 (8.3)	0.4 (0.1–1.2)	0.12
Receipt of lymphocyte-depleting antibody within preceding 12 months	5 (13.9)	7 (9.7)	0.7 (0.2–2.3)	0.53
Use of cyclosporin vs. tacrolimus	31 (86.1)	65 (90.3)	1.5 (0.4–5.1)	0.53
Use of mycophenolate	21 (58.3)	42 (58.3)	1.0 (0.4–2.2)	1.00
Receipt of high-dose steroids within preceding 6 months[a]	15 (41.7)	16 (22.2)	2.5 (1.1–5.9)	0.03

VL, visceral leishmaniasis; SOT, solid-organ transplant; OR, odds ratio; CI, confidence interval; CMV, cytomegalovirus.
[a]High-dose prednisone was defined as >20 mg of prednisone for >1 month or >2 pulses of 1 g intravenous methylprednisolone.

Clemente et al. Clin Microbiol Infect 2015; 21: 89–95

TABLE 3. Independent risk factors for VL in SOT recipients as defined by multivariate logistic regression

Predictor	Wald's χ^2	p	OR	95% CI
Constant	0.032	0.857	1.07	NA
Receipt of high-dose steroids within preceding 6 months	4.313	0.038	2.50	1.05–5.94

For logistic regression analysis, we considered variables with p <0.20 (i.e., receipt of high-dose steroids or CMV replication) or possible contributing factors to the occurrence of VL according to the literature (e.g., eosinophils, albumin, kidney transplantation). The use of high-dose steroids within the preceding 6 months was identified as the only risk factor for LV and increased the risk of developing the disease by 2.5-fold.
VL, visceral leishmaniasis; SOT, solid-organ transplant; OR, odds ratio; CI, confidence interval; NA, not applicable.

TABLE 4. Clinical and laboratory characteristics of 36 SOT recipients with VL

Variable	Patients, no. (%)
Male sex	27 (75.0)
Age, median years (range)	46 (14–76)
Time from transplant to diagnosis, median months (range)	9 (1–150)
Follow-up, median months (range)	51 (2–237)
Previous symptomatic VL infection	0
Positive HIV serology	0
Amphotericin use	0
Main signs and symptoms	
Temperature >38°C	31 (86.1)
Visceromegaly	29 (80.6)
Pancytopenia	17 (47.2)
Coexisting infections	13 (36.1)
Bacterial	8 (22.2)
CMV	5 (13.9)
Tuberculosis	1 (2.8)
Influenza A H1N1	1 (2.8)
Severe disease	
Intensive care unit admission	11 (30.6)
Shock at presentation	3 (8.3)
Laboratory abnormalities at presentation	
Albumin, g/dL	3.1 (1.6–4.4)
Serum creatinine, mg/dL	3.9 (0.5–11)
Haemoglobin, g/dL	11.2 (7.5–15.0)
Platelet count, cells/μL	99 900 (18 500–300 000)
Leukocyte count, cells/μL	3320 (1000–14 000)
Neutrophils, cells/μL	2160 (170–7840)
Eosinophils, cells/μL	181 (0–1120)

Note: Data are presented as no. (%) of patients, unless otherwise indicated. CMV, cytomegalovirus; SOT, Solid Organ Transplant; VL Visceral Leishmaniasis.

TABLE 5. Diagnostic methods in transplant patients with VL

Method	Total	Positive, *n* (%)
Microscopy		
Bone marrow	36	29 (80.6)
Blood	4	3 (75.0)
PCR[a]		
Bone marrow	4	3 (75.0)
Blood	3	2 (66.7)
Culture		
Bone marrow	20	11 (56.0)
Blood	3	1 (33.3)
Serology[b]	29	22 (75.9)

VL, visceral leishmaniasis; PCR, polymerase chain reaction.
[a]A variety of PCR-based methods were used according to the protocol of each institution.
[b]Includes different methods: indirect immunofluorescence, enzyme immunoassay, DAT rK39 and urinary antigen.

TABLE 6. Treatment and outcomes of 36 SOT recipients with VL

Drug chosen as first treatment	(*n* = 36)	
Amphotericin B deoxycholate	4	(11.1)
Liposomal amphotericin B	22	(61.1)
Pentavalent antimonials	9	(25.0)
Miltefosine	1	(2.8)
All treatment regimens [a]	(*n* = 36)	
Amphotericin B	30	(83.3)
Pentavalent antimonials	9	(25.0)
Others	2	(5.5)
Days of treatment, median (range)	10	(3 – 34)
Cure within the first month of treatment [b]	33/35	(94.2)
Secondary prophylaxis after cure (drug option)	12/35	
Amphotericin B	9	(25.7)
Others	3	(8.6)
Scheme of secondary prophylaxis	(*n* = 35)	
Daily to every other week	9	(25.7)
Monthly	3	(8.6)
Disease after cure (recurrence) *	(*n* = 35)	
With prophylaxis	1/12	(8.3)
Without prophylaxis	8/23	(34.8)
Number of episodes/patient	(*n* = 9)	
1	4	(44.4)
2	2	(22.2)
3	2	(22.2)
4	1	(11.1)
Time from the end of treatment to relapse	(*n* = 9)	
≤6 months	4	(44.4)
6-12 months	3	(33.3)
>12 months	2	(22.2)
Relapse treatment	(*n* = 9)	
Liposomal amphotericin B	7	(77.7)
Pentavalent antimonials	1	(11.1)
Miltefosine	1	(11.1)
Crude mortality at 30 days	1/36	(2.8)

Note: Data are presented as n. (%) of patients or median (range); SOT, Solid Organ Transplant; VL, Visceral Leishmaniasis; CMV, cytomegalovirus; [a] treatment option included first, sequential or combined treatment; [b] number of patients who survived more than 1 month after treatment (*n*=35); * p value = 0.19

Outras Imunodeficiencias

- Tumor de Wilms
  - Recidiva
  - Profilaxia secundaria
- Síndrome de Griscelli
  - Recidiva
  - Profilaxia secundaria
- Sindrome Hiper IgM
  - Recidiva
  - Profilaxia secundaria

Diagnóstico da LV

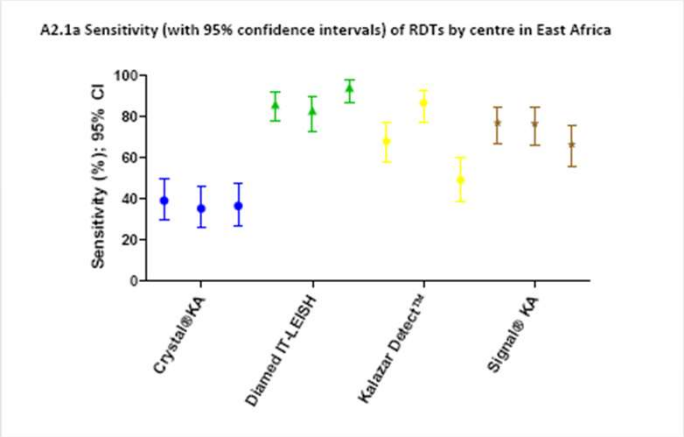
Diagnóstico Parasitológico

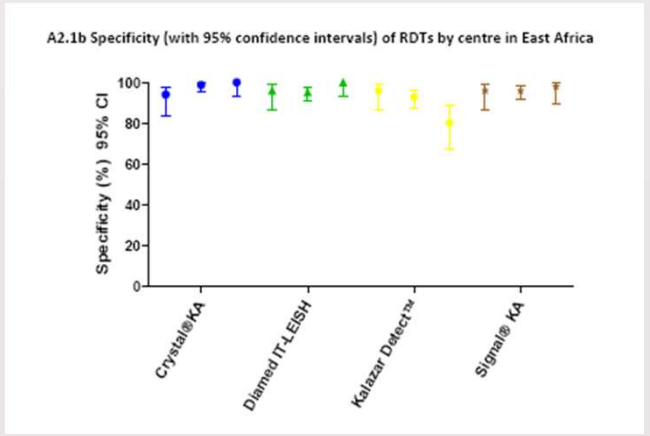
- Parasitológicos
  - Pesquisa direta: Amastigotas
    - Aspirado medula osea
  - Cultura: Promastigotas
    - Aspirado medula osea
  - Inoculação em animais
    - Hamster

Diagnóstico Imunológico

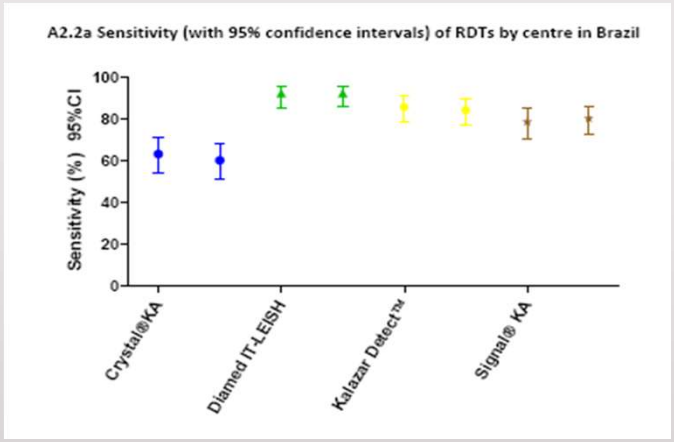
- Detecção de anticorpos
  - Imunofluorescencia
  - ELISA
  - Imunocromatográfico
    - rK39

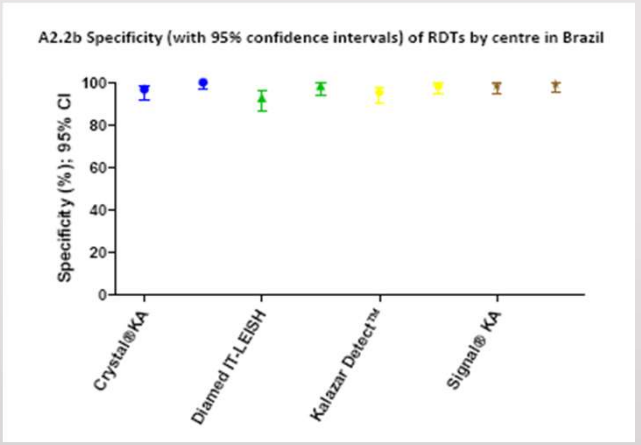
Africa



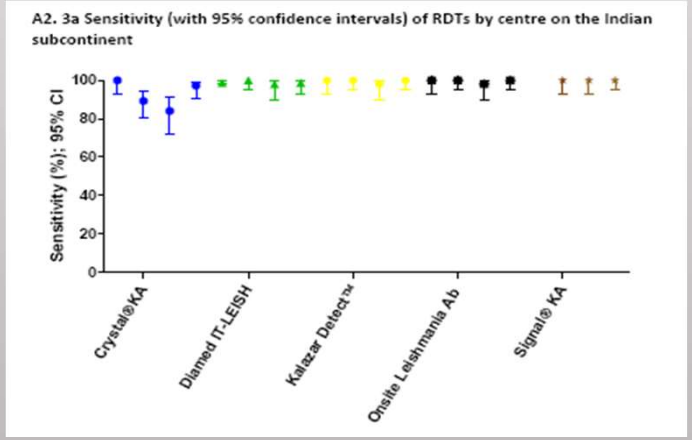


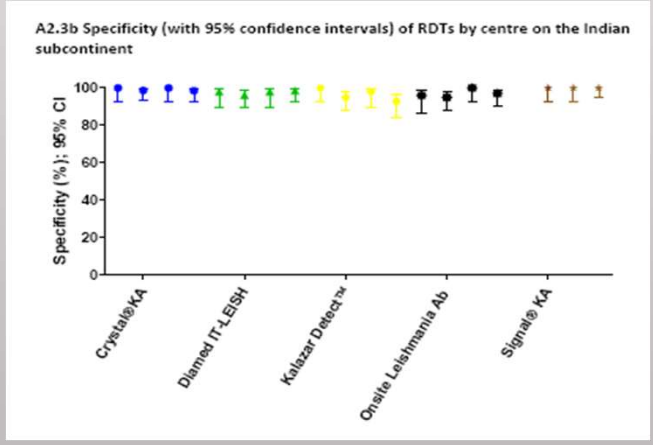
Brasil





India





Teste rápido: LV

	Sample Size			DAT Titer, Cases (%)			Average Age of Patients (y)		HIV Status[a] (%)		
										Known	
	Cases	HEC	Non-VL Disease Condition Controls	Low (≤100)	Medium (1:200–1:6400)	High (>1:6400)	Case	Controls	Unknown	Positive	Negative
East Africa	250	210	40	0.4	8.8	90.8	14	20	47.2	0	52.8
Brazil	237–250	206–209	42–45	0.0	11.6	88.4	19	27	98.6	0	1.4
ISC	250	210	39	0.0	3.2	96.8	24	31	50.8	0.5	48.7

Abbreviations: DAT, direct agglutination test; HEC, healthy endemic control; HIV, human immunodeficiency virus; ISC, Indian subcontinent; VL, visceral leishmaniasis.

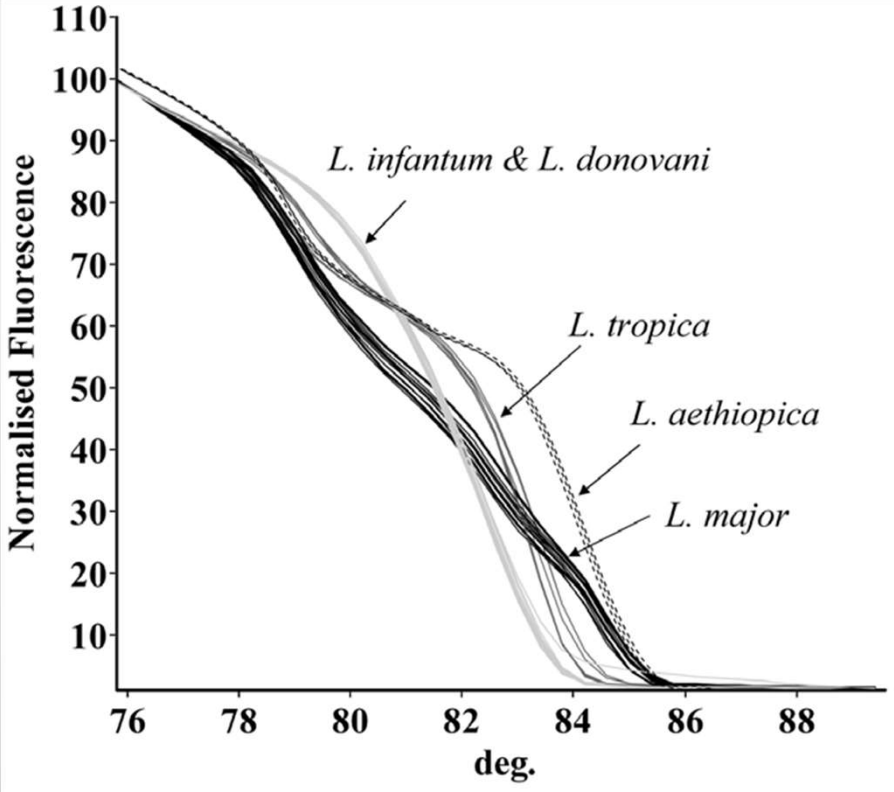
[a] Includes cases and controls combined.

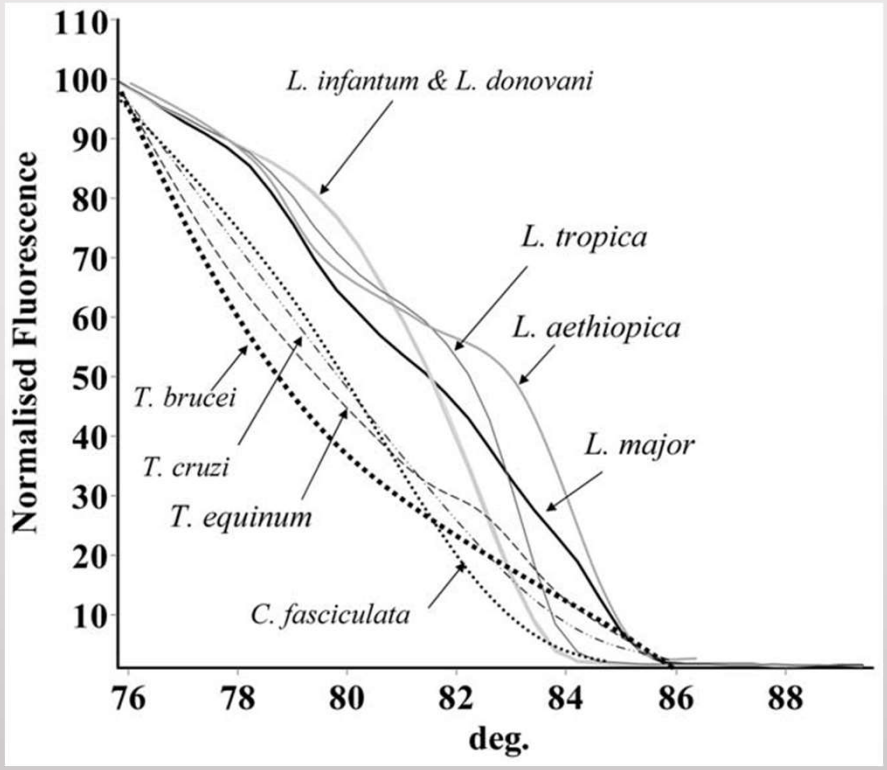
		East Africa		Brazil		Indian Subcontinent	
Product	Manufacturer	Sensitivity (95% CI) (n = 250)	Specificity (95% CI) (n = 250)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI) (n = 250)	Specificity (95% CI) (n = 249)
CrystalKA	Span Diagnostics	36.8% (31.1%–42.9%)	98.0% (95.4%–99.1%)	61.5% (55.2%–67.4%)[a]	98.4% (95.9%–99.4%)[b]	92.8% (88.9%–95.4%)	99.2% (97.1%–99.8%)
DiaMed-IT LEISH	Bio-Rad Laboratories	87.2% (82.5%–90.8%)	96.4% (93.3%–98.1%)	92.0% (87.8%–94.8%)[c]	95.6% (92.2%–97.5%)[d]	98.8% (96.5%–99.6%)	97.6% (94.8%–98.9%)
Kalazar Detect	InBios International,	67.6% (61.6%–73.1%)	90.8% (86.6%–93.8%)	84.7% (79.7%–88.7%)[e]	96.8% (93.9%–98.4%)[f]	99.6% (97.8%–99.9%)	96.0% (92.8%–97.8%)
Signal–KA	Span Diagnostics	73.2% (67.4%–78.3%)	96.4% (93.3%–98.1%)	79.2% (73.7%–83.8%)[g]	98.8% (96.6%–99.6%)[h]	100% (97.9%–100%)[i]	100% (97.8%–100%)[j]
OnSite Leishmania Ab Rapid	CTK Biotech	NA	NA	NA	NA	99.6% (97.8%–99.9%)	96.8% (93.8%–98.4%)

Biologia Molecular

- PCR
  - Gênero específico:
    - kDNA, gp63, tubulina, SSU rDNA, ITR
  - Espécie
    - Hsp 70, G6PD, Manose Isomerase,
    - PCR-RFLP
  - Real-time PCR

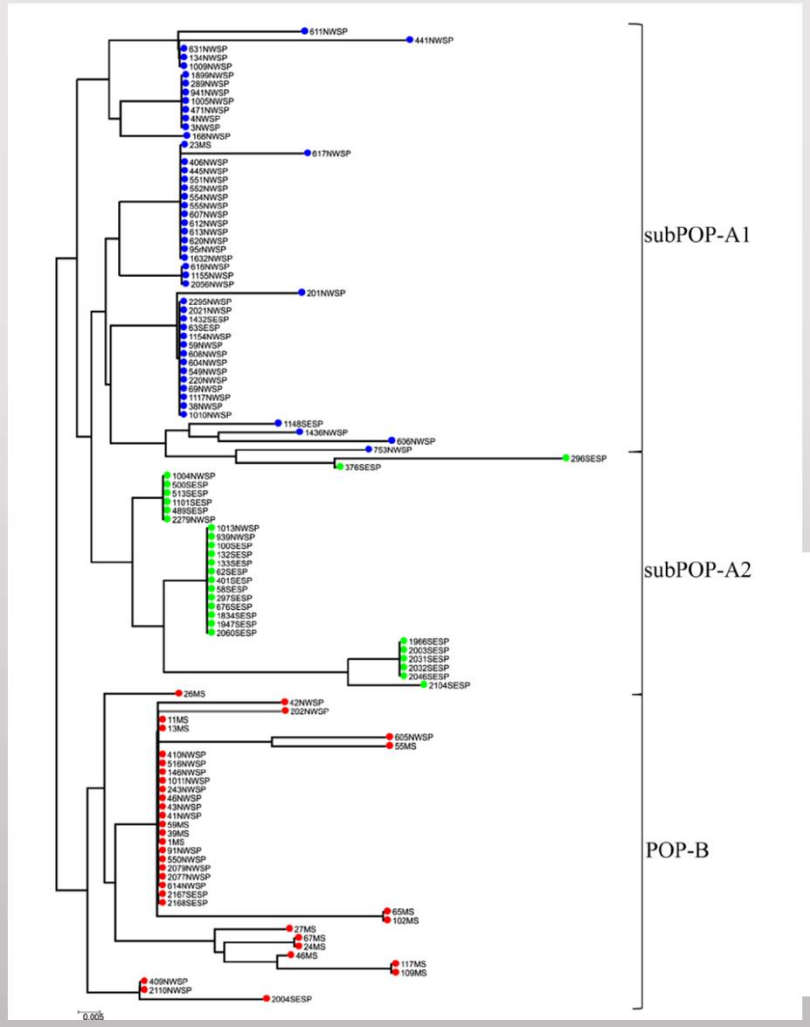
HRM: ITS-1

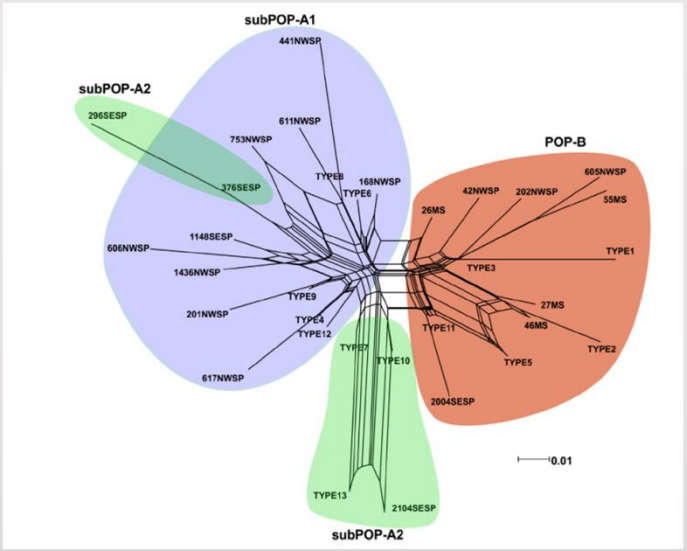


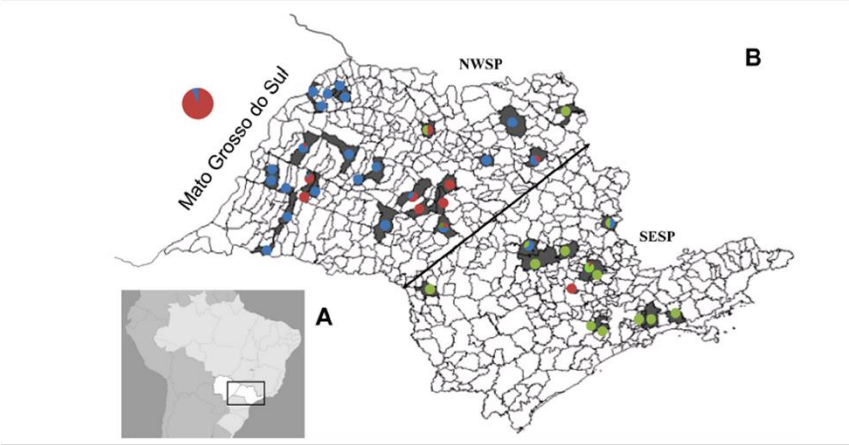


Talmi-Frank et al, PNTD, 2010

Distribuição de *L.infantum* (São Paulo)



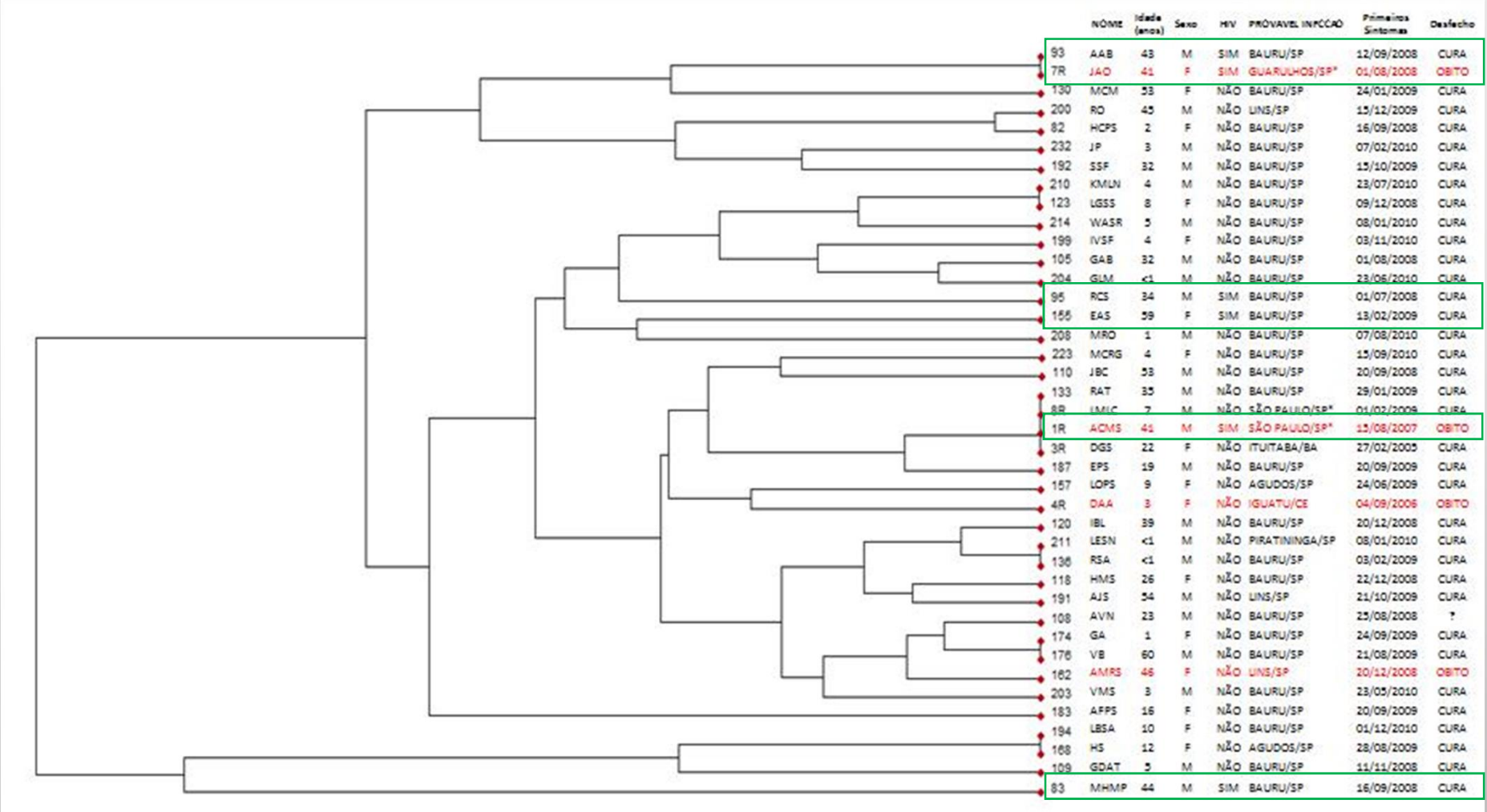




G. Motoie et al./Infection, Genetics and Evolution 18 (2013) 48–59

➢ *Avaliação molecular de amostras de L. (L.) infantum*

Árvore fenética (UPGMA) construída com os dados de RFLP do kDNA, mostrando a distribuição de 40 isolados de *Leishmania infantum* e tabela correspondente



	NOME	Idade (anos)	Sexo	HIV	PROVAVEL INFECCAO	Primeiros Sintomas	Desfecho
93	AAB	43	M	SIM	BAURU/SP	12/09/2008	CURA
7R	JAO	41	F	SIM	GUARULHOS/SP*	01/08/2008	OBITO
130	MCM	53	F	NÃO	BAURU/SP	24/01/2009	CURA
200	RO	45	M	NÃO	LINS/SP	15/12/2009	CURA
82	HCPS	2	F	NÃO	BAURU/SP	16/09/2008	CURA
232	JP	3	M	NÃO	BAURU/SP	07/02/2010	CURA
192	SSF	32	M	NÃO	BAURU/SP	15/10/2009	CURA
210	KMLN	4	M	NÃO	BAURU/SP	23/07/2010	CURA
123	LGSS	8	F	NÃO	BAURU/SP	09/12/2008	CURA
214	WASR	5	M	NÃO	BAURU/SP	08/01/2010	CURA
199	IVSF	4	F	NÃO	BAURU/SP	03/11/2010	CURA
105	GAB	32	M	NÃO	BAURU/SP	01/08/2008	CURA
204	GLM	<1	M	NÃO	BAURU/SP	23/06/2010	CURA
95	RCS	34	M	SIM	BAURU/SP	01/07/2008	CURA
155	EAS	59	F	SIM	BAURU/SP	13/02/2009	CURA
208	MRO	1	M	NÃO	BAURU/SP	07/08/2010	CURA
223	MCRG	4	F	NÃO	BAURU/SP	15/09/2010	CURA
110	JBC	53	M	NÃO	BAURU/SP	20/09/2008	CURA
133	RAT	35	M	NÃO	BAURU/SP	29/01/2009	CURA
6R	LMLC	7	M	NÃO	SÃO PAULO/SP*	01/02/2009	CURA
1R	ACMS	41	M	SIM	SÃO PAULO/SP*	15/08/2007	OBITO
3R	DGS	22	F	NÃO	ITUITABA/BA	27/02/2005	CURA
187	EPS	19	M	NÃO	BAURU/SP	20/09/2009	CURA
157	LOPS	9	F	NÃO	AGUDOS/SP	24/06/2009	CURA
4R	DAA	3	F	NÃO	IGUATU/CE	04/09/2006	OBITO
120	IBL	39	M	NÃO	BAURU/SP	20/12/2008	CURA
211	LESN	<1	M	NÃO	PIRATININGA/SP	08/01/2010	CURA
136	RSA	<1	M	NÃO	BAURU/SP	03/02/2009	CURA
118	HMS	26	F	NÃO	BAURU/SP	22/12/2008	CURA
191	AJS	54	M	NÃO	LINS/SP	21/10/2009	CURA
108	AVN	23	M	NÃO	BAURU/SP	25/08/2008	?
174	GA	1	F	NÃO	BAURU/SP	24/09/2009	CURA
176	VB	60	M	NÃO	BAURU/SP	21/08/2009	CURA
162	AMRS	46	F	NÃO	LINS/SP	20/12/2008	OBITO
203	VMS	3	M	NÃO	BAURU/SP	23/05/2010	CURA
183	AFPS	16	F	NÃO	BAURU/SP	20/09/2009	CURA
194	LBSA	10	F	NÃO	BAURU/SP	01/12/2010	CURA
168	HS	12	F	NÃO	AGUDOS/SP	28/08/2009	CURA
109	GDAT	5	M	NÃO	BAURU/SP	11/11/2008	CURA
83	MHMP	44	M	SIM	BAURU/SP	16/09/2008	CURA

Tratamento da LV

Tratamento da Leishmaniose Visceral

- **Antimonial pentavalente:**
  - **N-metil glucamina: Glucantime**
  - **Estibogluconato de sódio: Pentostan**
- **Anfotericina B**
  - Desoxicolato: ???
  - Lipossomal
- **Miltefosine**
  - **Kalazar Indiano**

REVISÃO SISTEMÁTICA: TRATAMENTO DA LV HUMANA NA AMÉRICA LATINA

Country	Type of study	Number of subjects	Mean patient age (years)	Treatment interventions	Dose and route	Follow-up period	Outcomes (%)	Ref.
Brazil	Open-label	10	20.0	Amphotericin B cholesterol dispersion	2.0mg/kg/d for 10 d. I.V.	6–12 months	Cure 10/10 (100)	[90]
Brazil	Open-label	10	19.0	Amphotericin B cholesterol dispersion	2.0mg/kg/d for 7 d. I.V.	6–12 months	Cure 10/10 (100)	[90]
Brazil	Open-label	10	16.5	Amphotericin B cholesterol dispersion	2.0mg/kg/d for 5 d. I.V.	12 months	Cure 9/10 (90)	[91]
							Relapse 1/10 (10)	
Brazil	Open-label Phase II	13	7.6	Liposomal amphotericin B	14mg/kg (total) . I.V.	6 months	Cure 8/13 (61)	[86]
							Failure 1/13 (8)	
							Relapse 4/13 (31)	
Brazil	Open-label Phase II	4	7.5	Liposomal amphotericin B	10mg/kg (total) I.V.	6 months	Cure 4/4 (100)	[86]
Brazil	Open-label Phase II	15	10.1	Liposomal amphotericin B	20mg/kg (total) I.V.	6 months	Cure 13/15 (87)	[86]
							Relapse 2/15 (13)	
Brazil	Open-label, dose-escalating trial	4	19.0	WR6026 (sitamaquine)	1.0mg/kg/d for 28 d. Oral.	12 months	Cure 0/4 (0)	[89]
Brazil	Open-label, dose-escalating trial	6	32.8	WR6026 (sitamaquine)	1.5mg/kg/d for 28 d. Oral	12 months	Cure 1/6 (17)	[89]
Brazil	Open-label, dose-escalating trial	6	23.8	WR6026 (sitamaquine)	2.0mg/kg/d for 28 d. Oral.	12 months	Cure 4/6 (67)	[89]
Brazil	Open-label, dose-escalating trial	5	23.8	WR6026 (sitamaquine)	2.5mg/kg/d for 28 d. Oral	12 months	Cure 1/5 (20)	[89]
Brazil	Open-label, dose-escalating trial	1	22.0	WR6026 (sitamaquine)	3.25mg/kg/d for 28 d. Oral	12 months	Cure 0/1 (0)	[89]

Romero and Boelaert, PLOS , 2010

Table 3. Potential regimens of LAMB that have been developed for use against VL*.

Regimen	Cost (USD) [70]	Efficacy (phase of trial done)	Comments
LAMB i.v. 10 mg/kg single dose	126	95% (P3)	South Asia only, poor efficacy in East Africa
LAMB 20 mg/kg over 4 doses	252	98% (P4)	South Asia only and possibly Europe and Latin America, poor efficacy in East Africa
LAMB 5 mg/kg + MF 100 mg/kg/day for 8 days	88 – 109	97.5% (P3)	South Asia only; teratogenicity of MF may hinder uptake
LAMB 5 mg/kg + PM 15 mg/kg/day for 11 days	79	97.5% (P3)	South Asia only; use of daily PM injections may hinder uptake
LAMB 30 mg/kg over 6 – 10 doses	378	90% (observational field data only)	East Africa only; no clinical trial data available at this dose

*Based on data from the WHO expert committee report 2010.

LAMB: Liposomal amphotericin B (all trials here have used AmBisome™); MF: Miltefosine; PM: Paromomycin.

M. Balasegaram et al. *Expert Opin. Emerging Drugs* (2012) **17**(4)

Efficacy and safety of available treatments for visceral leishmaniasis in Brazil: A multicenter, randomized, open label trial

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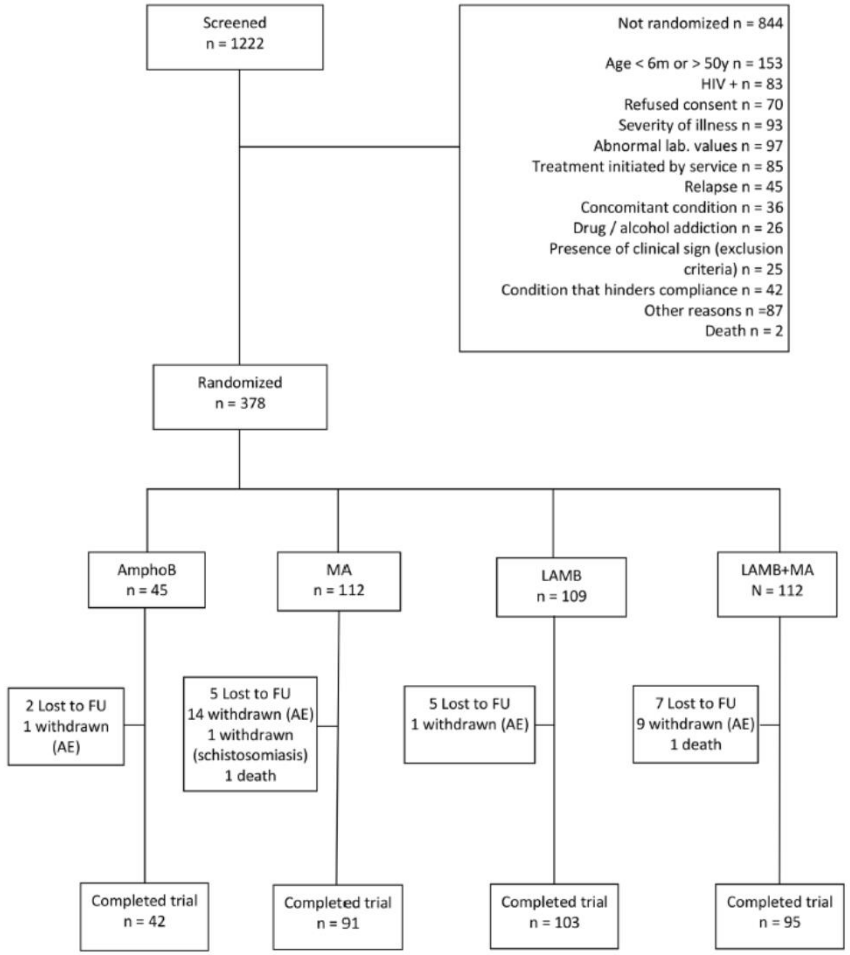

Fig 1. CONSORT patient flowchart. Flow diagram of the progress through the phases of the trial. AmphoB = amphotericin B deoxycholate; MA = meglumine antimoniate; LAMB = Liposomal amphotericin B.

Table 1. Baseline demographic, clinical and laboratory characteristics of 332 participants effectively randomized to the three remaining arms of the trial.

Characteristics	MA n = 111	LAMB n = 109	LAMB + MA n = 112
Demographic			
Age (median, years)	4.77	4.36	3.36
Percentile 25 and 75	(2.05–10.37)	(2.13–10.27)	(1.84–9.19)
Interval	(0.61 to 47.61)	(0.56 to 48.64)	(0.49 to 48.83)
Male			
% (n)	58.6 (65/111)	54.1 (59/109)	52.7 (59/112)
Time of exposure in endemic area (median, years)	4.42 (n = 110)	3.96 (n = 108)	3.17 (n = 111)
Percentile 25 and 75	(1.83–9.94)	(1.88–8.92)	(1.75–8.00)
Interval	(0.25 to 42.92)	(0.42 to 48.67)	(0.50 to 44.08)
Time of illness evolution (median, months)	1.0	1.0 (n = 108)	0.80
Percentile 25 and 75	(0.5–2.0)	(0.5–2.0)	(0.5–2.0)
Interval	(0.16 to 30.0)	(0.23 to 13.0)	(0.16 to 12.00)
Physical exam			
Weight (median, kg)	16.7	15.2	15.0
Percentile 25 and 75	(12.0–28.5)	(11.6–29.4)	(10.8–30.6)
Interval	(2.0 to 84.7)	(6.5 to 76.0)	(5.8 to 79.0)
Splenomegaly			
% (n)	98.2 (109/111)	100 (109/109)	100 (112/112)
Spleen size below the left costal margin (median, cm)	6.5 (n = 109)	7.0 (n = 108)	7.0 (n = 107)
Percentile 25 and 75	(5.0–10.0)	(5.0–10.0)	(5.0–9.0)
Interval	(0.0 to 25.0)	(1.0 to 18.0)	(2.0 to 23.0)
Hepatomegaly			
% (n)	99.1 (110/111)	94.5 (103/109)	97.3 (109/112)
Liver size below the right costal margin (median, cm)	4.0	4.0 (n = 108)	4.0 (n = 109)
Percentile 25 and 75	(3.0–6.0)	(3.0–6.0)	(3.0–6.0)
Interval	(0.0 to 16.0)	(0.0 to 11.0)	(0.0 to 11.0)
Bleeding			
% (n)	2.7 (3/111)	2.8 (3/109)	0.9 (1/112)
Edema			
% (n)	9.9 (11/111)	6.4 (7/109)	7.1 (8/112)
VL diagnosis tests			
rK39 rapid test positivity			
% (n)	92.8 (103/111)	94.5 (103/109)	93.7 (104/111)
Positive direct examination for parasite in bone marrow smear			
% (n)	64.9 (61/94)	66.7 (60/90)	54.5 (54/99)
Positive culture of bone marrow aspirate			
% (n)	48.9 (45/92)	44.4 (40/90)	48.4 (45/93)
Bacterial cultures			
Positive blood culture			
% (n)	6.5 (7/108)	1.9 (2/107)	10.4 (11/106)
Positive urine culture			
% (n)	5.1 (5/98)	5.5 (5/91)	9.8 (9/92)
Complete Blood Count			
Leukocytes count/uL	2970	2880	2870
Percentile 25 and 75	(2000–4030)	(1990–4500)	(1880–3982)
Interval	(760 to 11300)	(880 to 12660)	(1000 to 9860)

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Table 2. Treatment efficacy at six months follow-up as per ITT approach.

Treatment	% of participants cured (n/total)	% of participants not cured (n/total)	Difference in cure rate—% (95% CI)	p-value (χ^2)
MA (Comparator)	77.5 (86/111)	22.5 (25/111)		
LAMB	87.2 (95/109)	12.8 (14/109)	9.7 (-0.28 to 19.68)	0.060[a]
LAMB + MA	83.9 (94/112)	16.1 (18/112)	6.4 (-3.93 to 16.73)	0.222[b]
Total	82.8 (275/332)	17.2 (57/332)		

Table 3. Treatment efficacy at six months follow-up as PP approach.

Treatment	% of participants cured (n/total)	% of participants not cured (n/total)	Difference in cure rate—% (95% CI)	p-value (χ^2)
MA (Comparator)	94.5 (86/91)	5.5 (5/91)		
LAMB	92.2 (95/103)	7.8 (8/103)	-2.3 (-9.23 to 4.60)	0.528[a]
LAMB+MA	98.9 (94/95)	1.1 (1/95)	4.4 (-0.73 to 9.53)	0.112[b]
Total	95.1 (275/289)	4.9 (14/289)		

Table 4. Early withdrawal rate due to the occurrence of AE/SAE during treatment as per ITT.

Treatment	Early withdrawal rate due to occurrence of AE/SAE—% (n/total)	Difference in early withdrawal rate—% (95% CI)	p-value (χ^2)
MA (Comparator)	13.5 (15/111)		
LAMB	0.92 (1/109)	-12.6 (-19.18 to -5.97)	<0.001[a]
LAMB+MA	8.9 (10/112)	-4.6 (-12,86 to 3,66)	0.278[b]
Total	7.8 (26/332)		

Contraindicações dos medicamentos utilizados no tratamento específico da leishmaniose visceral

- **Antimonato de meglumina**

- insuficiência renal;
- insuficiência hepática;
- insuficiência cardíaca;
- uso concomitante de medicamentos que alteram o intervalo QTc (>450 ms);
- gravidez;
- hipersensibilidade aos componentes da formulação.

- **Anfotericina B lipossomal**

- hipersensibilidade aos componentes da formulação**.**

- **Anfotericina B desoxicolato**

- insuficiência renal;
- hipersensibilidade aos componentes da formulação.

Tratamento específico

- Indicações de uso da anfotericina B lipossomal:

Indicações	Grau de recomendação
idade menor que 1 ano	D
idade maior que 50 anos	D
escore de gravidade: clínico > 4 ou clínico-laboratorial > 6	D
insuficiência renal	A
insuficiência hepática	D
insuficiência cardíaca	D
intervalo QT corrigido maior que 450 ms	D
uso concomitante de medicamentos que alteram o intervalo QT	D
hipersensibilidade ao antimonial pentavalente ou a outros medicamentos utilizados para o tratamento da LV	D
infecção pelo HIV	D
comorbidades que comprometem a imunidade	D
uso de medicação imunossupressora	D
falha terapêutica ao antimonial pentavalente ou a outros medicamentos utilizados para o tratamento da LV	D
gestantes	D

Recomendações da Anfotericina B lipossomal

- 1- Recomendação do CDC:
  - Imunocompetentes a dose de 3 mg/kg/dia, com dose total de 21 mg / kg.
  - Para pacientes imunossuprimidos: 4 mg/kg/d com dose total de até 40 mg/kg.
- 2- Orientação da OPAS para tratamento de pacientes com LV:
  - Dose de 3-5 mg/kg/d de anfotericina b lipossomal por 3 a 6 dias até completar 20 mg/kg de dose total.
  - Coinfectados com HIV:
    - dose recomendada é de 3-5 mg/kg/d, com dose total entre 20-40 mg/kg.
- 3- Recomendação do Ministério da Saúde
  - 3 mg/kg/dia, durante sete dias
  - 4 mg/kg/dia, durante cinco dias.
    - Taxa de recidiva:
      - 6,22%
      - Segura e eficaz para o tratamento da LV.

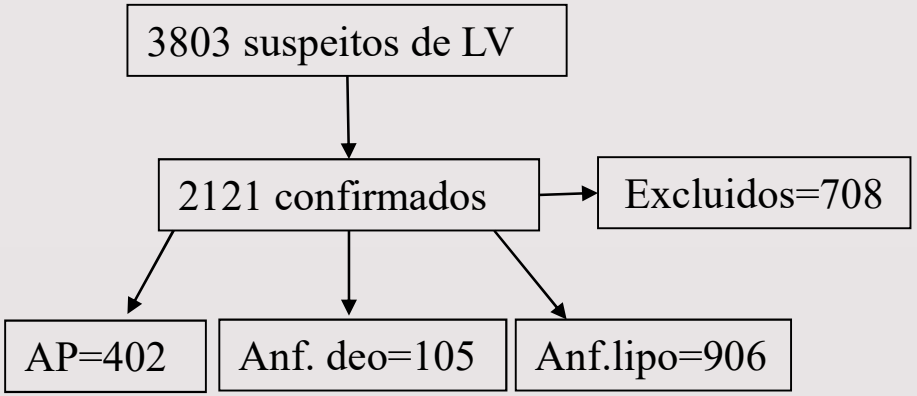
NOTA TÉCNICA

- Centro de Vigilância Epidemiológica, revoga a indicação de dose a ser aplicada no tratamento com a anfotericina B lipossomal contida no Manual de Vigilância e Controle da Leishmaniose Visceral Americana do Estado de São Paulo (edição 2006, item A.1, páginas 38/39). A dose de recomendação passa a ser de 3 mg/kg/dia por sete dias ou 4 mg/Kg/ dia durante cinco dias de anfotericina B lipossomal para o tratamento de pacientes com leishmaniose visceral, considerando a baixa taxa de recidiva e seguindo as recomendações vigentes do Ministério da Saúde e de órgãos nacionais e internacionais de saúde pública.

Tratamento LV no Estado de São Paulo

- Anfotericina b lipossomal
  - 4 mg/kg/dia por 5 días (total de 20 mg/kg)
  - 3 mg/kg/dia por 7 días (total de 21 mg/Kg)
- Antimonial pentavalente
  - 20 mg/kg/dia por 28 dias

Avaliação da resposta terapêutica da LV no estado de São Paulo: 2007 a 2015

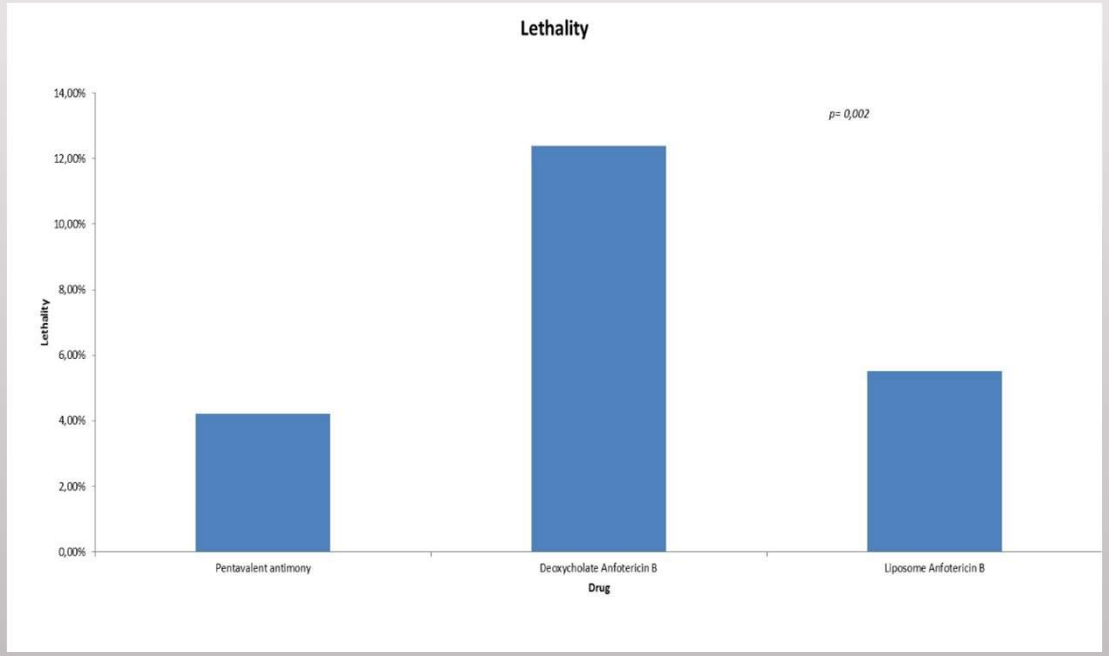


Adultos sexo masculino:
20 a 59 anos de idade

Letalidade geral=7,8%

- AP=4,23%
- **Anf deo=12,38%**
- Anf lipo=5,52%

> 60 anos



Prognostic factors for death from visceral leishmaniasis in patients treated with liposomal amphotericin B in an endemic state in Brazil

Bruna Dias Tourinho[a,b,c], Frederico Figueiredo Amâncio[d], Marcela Lencine Ferraz[b] and Mariângela Carneiro[a,c,*]

Table 4. Prognostic factors for death due to visceral leishmaniasis in patients treated with liposomal amphotericin B (LAmB) in the state of Minas Gerais, Brazil, 2008–2012

Variable	Odds ratio (CI 95%)	Odds ratio adjusted (CI 95%)	p
Age between 35 and 49 years	2.6 (1.4–4.8)	2.7 (1.3–5.4)	0.005
Age over 50 years	3.1 (1.8–5.2)	2.6 (1.3–4.9)	0.004
Jaundice	3.4 (2.2–5.2)	2.2 (1.2–3.7)	0.006
Kidney disease	2.4 (1.5–3.6)	2.8 (1.6–4.9)	0.000
Infection	2.4 (1.6–3.7)	2.4 (1.5–4.1)	0.001
Edema	2.8 (1.8–4.4)	2.0 (1.1–3.4)	0.012
Platelets <50 000/mm^3	4.0 (2.6–6.2)	3.6 (2.1–6.0)	0.000
Aspartate aminotransferase >100U/L	2.2 (1.4–3.4)	2.2 (1.3–3.8)	0.005
Assistance in non-specialized institutions	2.2 (1.3–3.6)	1.9 (1.0–3.5)	0.046

R2: 0.2302
Log likelihood: –196.40118
ROC curve area: 0.8151

Trans R Soc Trop Med Hyg 2017; **111**: 163–171

Escore clínico-laboratorial de gravidade para pacientes com LV

Tabela 3 - Modelos de prognóstico construídos pela adição de variáveis clínicas ou de variáveis clínicas e laboratoriais, ponderadas pela força da associação estatística para a morte em pacientes com menos de 2 anos de idade com diagnóstico de leishmaniose visceral – Teresina, 2005-2008

Variável	Peso da variável no modelo clínico	Peso da variável no modelo clínico e laboratorial
Idade		
< 12 meses	1	1
> 12 meses	0	0
Sangramento		
1-2 sítios	1	1
3-4 sítios	2	2
5-6 sítios	4	4
Edema	1	2
Icterícia	1	-
Dispneia	1	1
[1]AST ou ALT acima de 100 UK/L	-	3
Pontuação máxima	08	11

Nota: [1]AST – aspartato aminotransferase; ALT – alanina aminotransferase.

Tabela 2 - Modelos de prognóstico construídos pela adição de variáveis clínicas ou de variáveis clínicas e laboratoriais, ponderadas pela força da associação estatística para a morte em pacientes com mais de 2 anos de idade diagnosticados com leishmaniose visceral – Teresina, 2005-2008

Variável	Peso da variável no modelo clínico	Peso da variável no modelo clínico e laboratorial
Idade		
2-20 anos	-	-
20-40 anos	1	1
>40 anos	2	2
Sangramento		
1-2 sítios	1	1
3-4 sítios	2	2
5-6 sítios	3	3
Aids	2	3
Edema	1	1
Icterícia	1	1
Dispneia	1	1
Infecção bacteriana	1	1
Leucócitos abaixo de 1.500/mm³	-	2
Plaquetas abaixo de 50.000/mm³	-	3
[1]Insuficiência renal	-	3
Pontuação máxima	11	20

Nota: [1]Taxa de filtração glomerular abaixo de 60 mL/min/m2 ou creatinina sérica acima dos níveis superiores para a idade.

Fonte: Manual “leishmaniose visceral: recomendações clínicas para redução da letalidade”

Tratamento Suporte

- Antibioticoterapia
  - Quadro infeccioso definido (A)
    - Pneumonia, Impetigo, Celulite, Otite, ITU
  - Sepse (quadro presumido) (A)
  - Neutropênico febril (D)
  - Crianças < 2 meses sem sinais de localização (D)
    - CCIH local ou
    - Ceftriaxone e oxacilina

Tratamento de Suporte

- Suporte hemoterápico
  - Concentrado de Hemáceas
    - Hb < 7,0 g/dL ou HT < 21% (D)
  - Concentrado de plaquetas
    - < 10.000 plaquetas com sangramento (D)
  - Plasma fresco
    - Sangramento e instabilidade hemodinâmica (D)

Tratamento de Suporte

- Fator estimulador de colônias de granulócitos
  - Neutropênicos graves (D)
- Vitamina K (D)
  - Icterícia e sangramento
  - AP < 70%
- Suporte Nutricional (D)
  - Preferência via enteral

Lv em imunodeprimidos

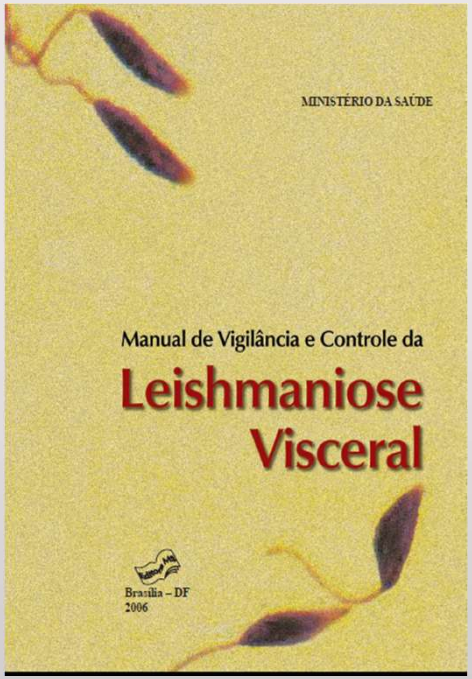
- Tratamento
  - Efetividade:
    - Imunocompetentes: 93-97%
    - HIV+: 55-66%
    - Transplantados: 84%
  - Anfotericina B lipossomal (3mg/Kg/d)
  - Antimonial – alta toxicidade!
- Profilaxia secundária:
  - Não necessária????
  - Diminuir dose do imunossupressor???

Acta Trop, 2004; Ann Rheum Dis, 2012;
Lancet Infect Dis, 2008; Clin Microbiol Infect, 2014

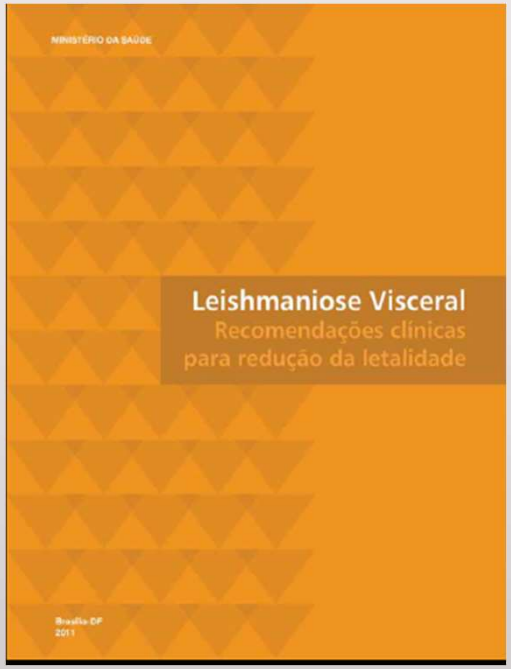
Problemas atuais

- Desabastecimento de kits para diagnóstico
- Espalhamento da LV
- Coinfecção com HIV
- Transplantados
- Recidiva
- Toxicidade das drogas
- Educação em Saúde

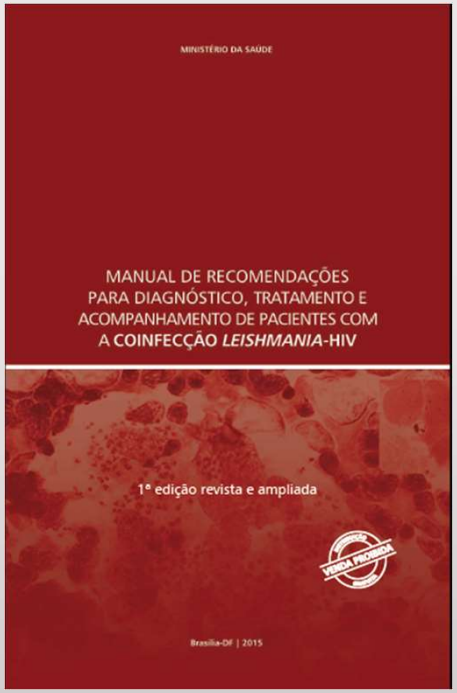
Manuais e Guias atuais



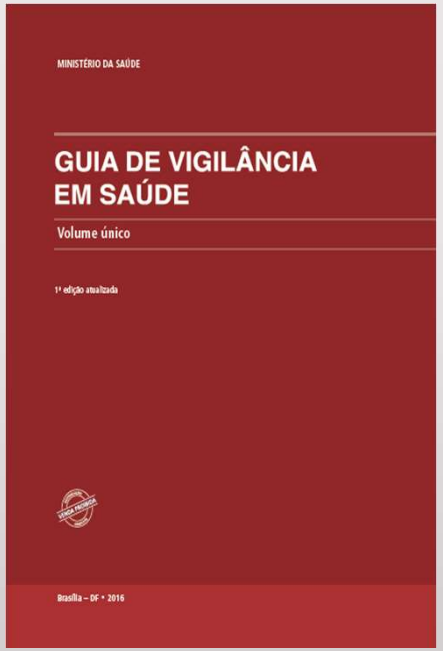
2003



2011



2015



2015

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