TREATMENT

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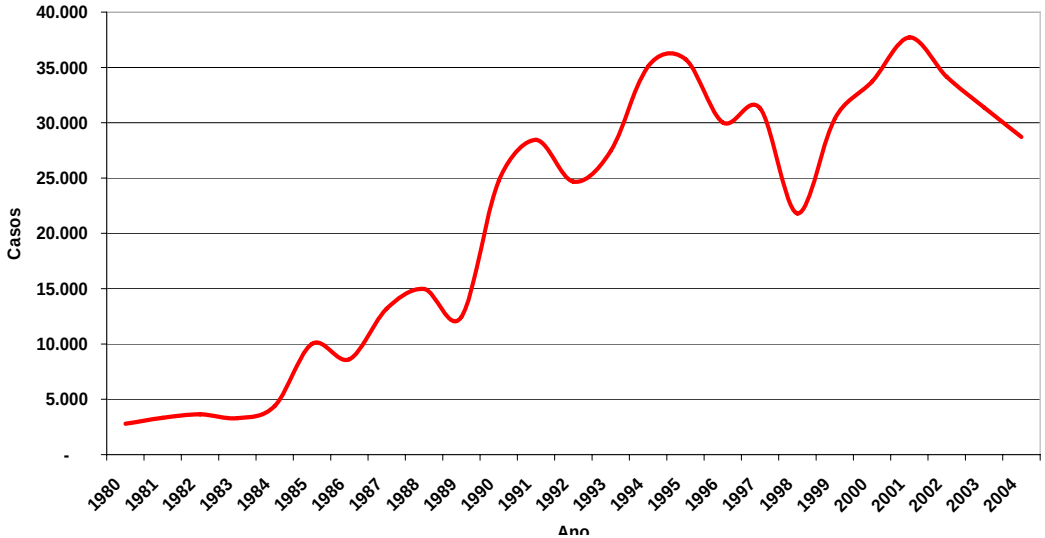
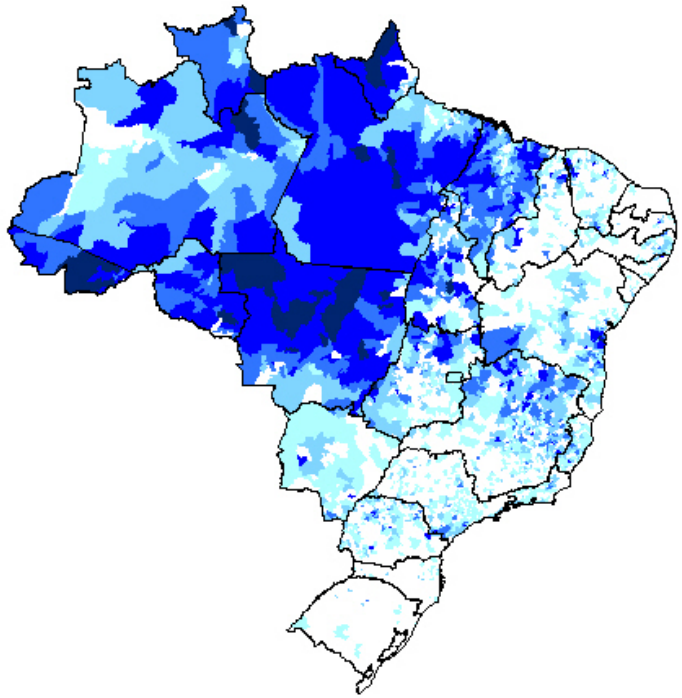
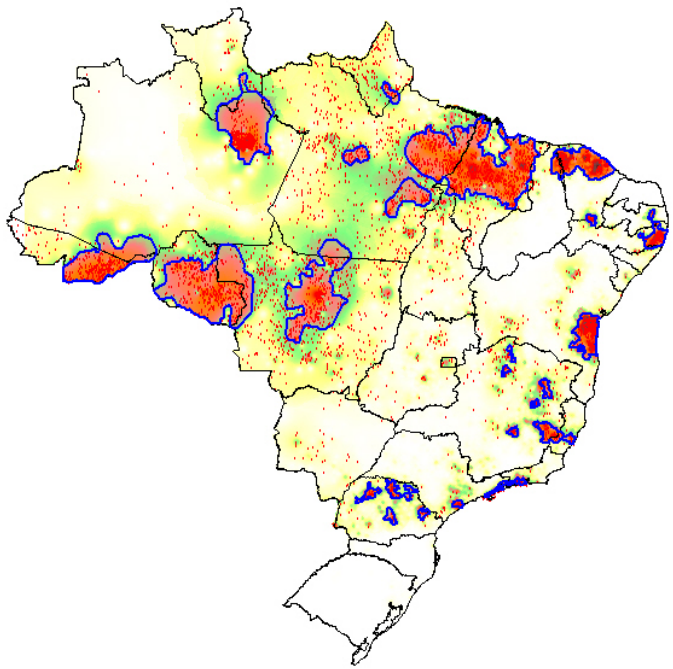
The numbers and distribution of cutaneous and mucosal disease in Brazil





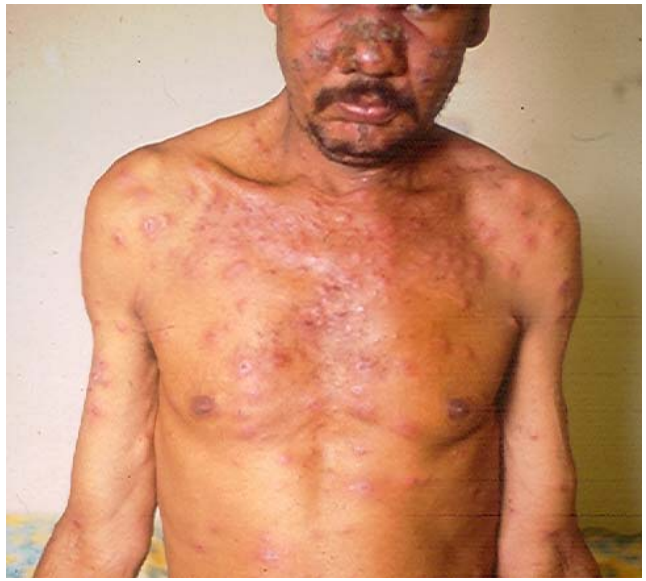


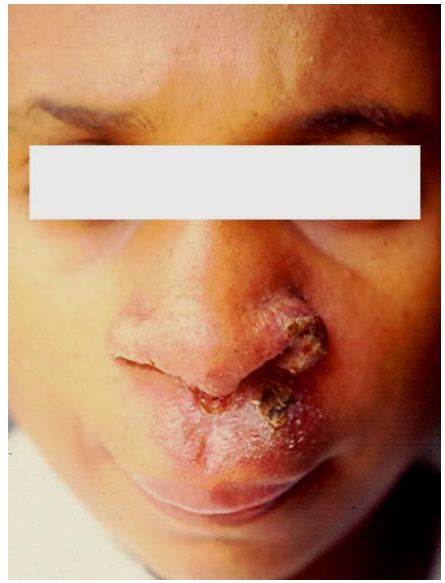
Annual incidence/100,000 - 2005

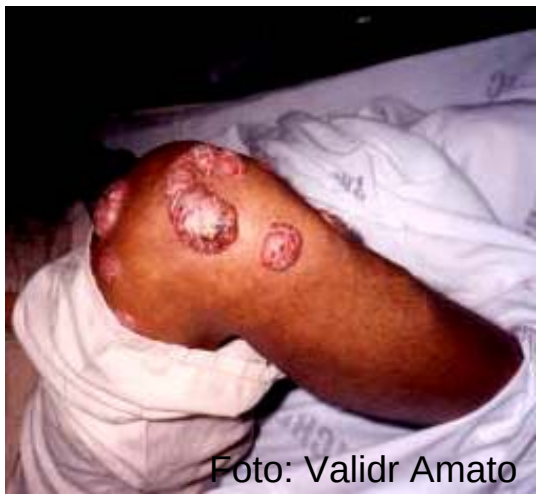
0 a	10	(690)
10 a	40	(759)
40 a	100	(429)
100 a	400	(327)
400 a	1.550	(54)

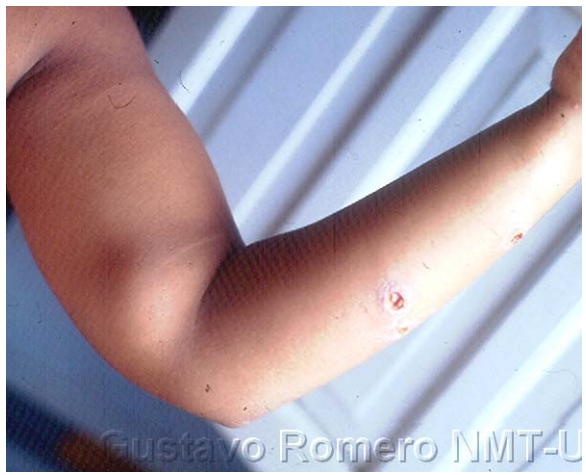
Main *Leishmania* spp. in the Americas

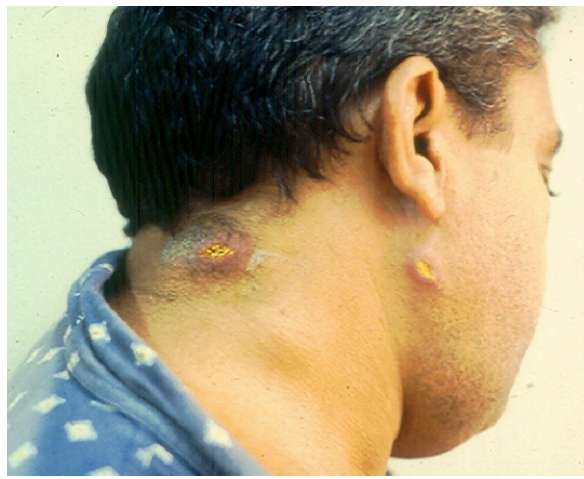
- *L. (V.) braziliensis*
- *L. (V.) guyanensis*
- *L. (V.) panamensis*
- *L. (L.) mexicana*
- *L. (L.) amazonensis*
- *L. (L.) chagasi*

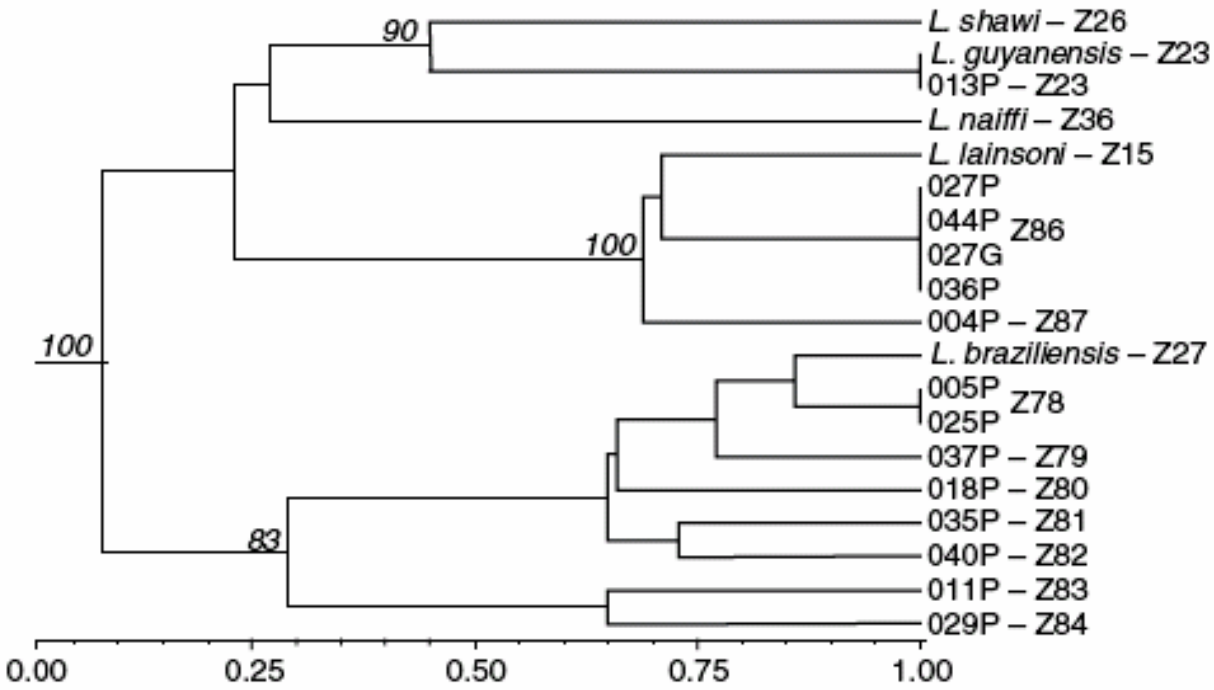












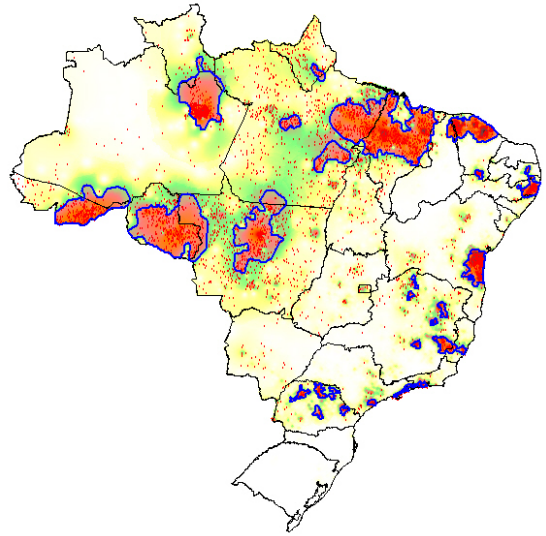


Figure 3 Dendogram obtained through the UPGMA algorithm and Jaccard's similarity coefficient.

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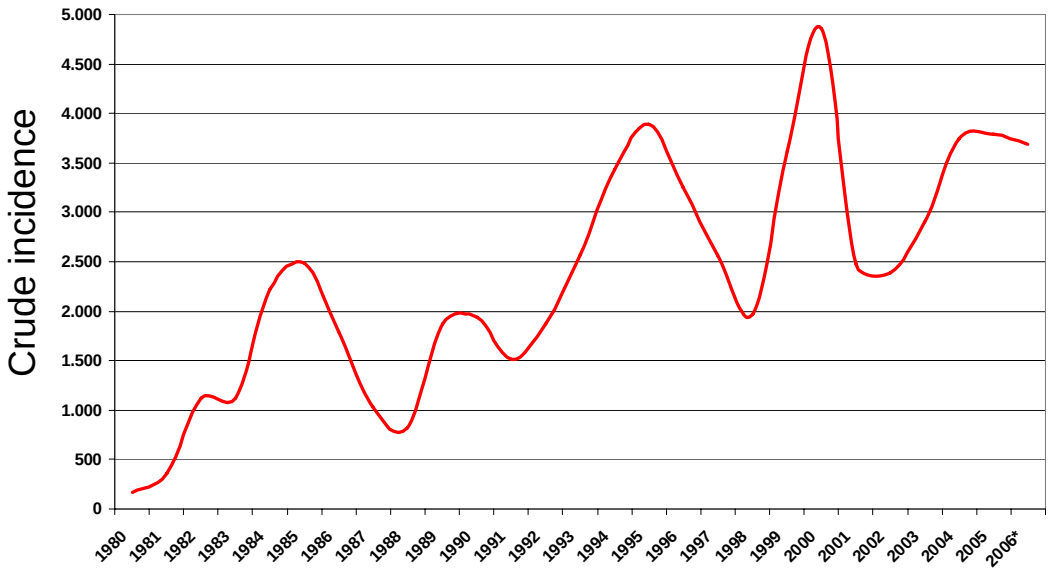
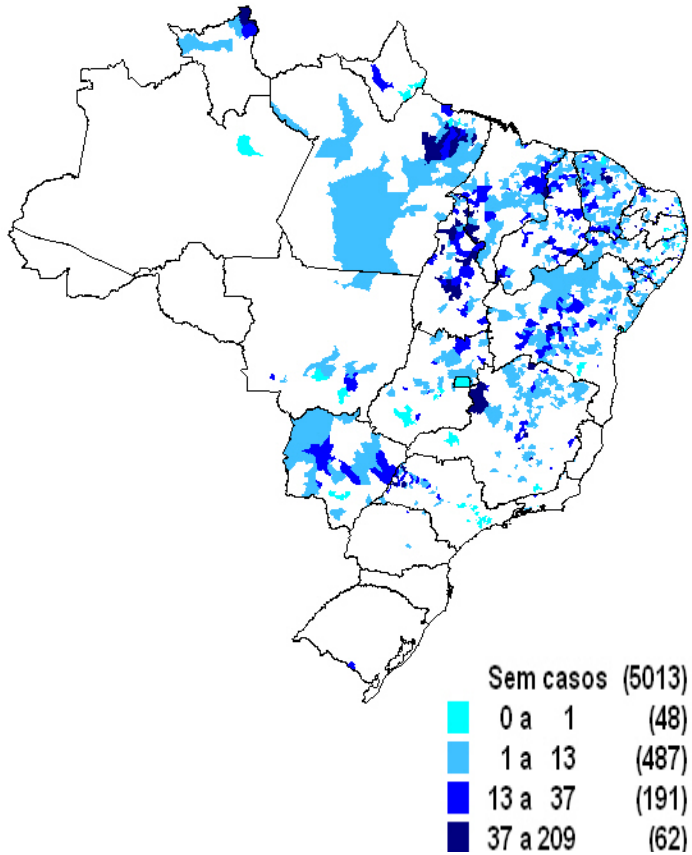
Species diversity causing human cutaneous leishmaniasis in Rio Branco, state of Acre, Brazil

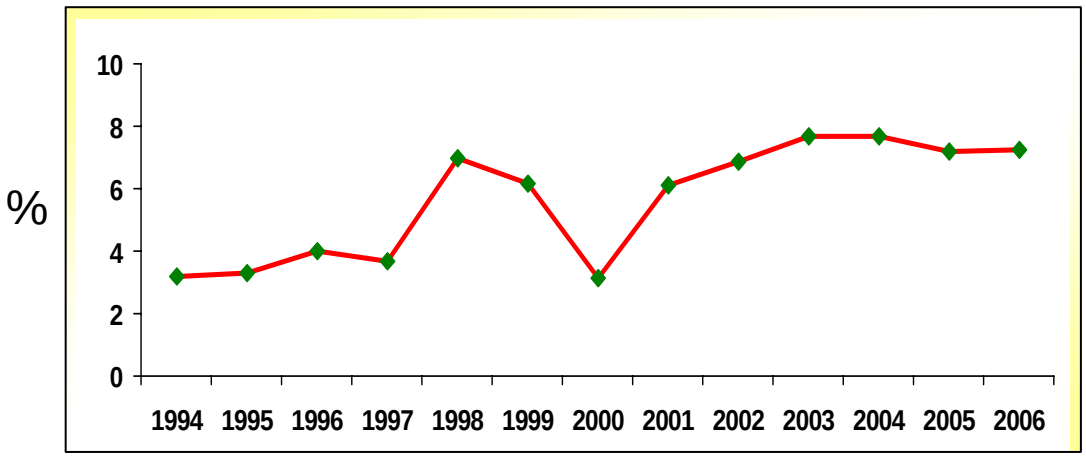
Anna Christina Tojal da Silva[1], Elisa Cupolillo[2], Ângela Cristina Volpini[2], Roque Almeida[3] and Gustavo Adolfo Sierra Romero[1]

The numbers and distribution of visceral disease in Brazil



Annual incidence/100,000 - 2006





Fatality rate – Visceral leishmaniasis - Brazil, 1994-2006

Drugs

- Antimonials
- Amphotericin B
- Pentamidine
- Ketoconazol
- Aminosidine
- Miltefosine
- Azithromycin
- Immunomodulators
  - GM-CSF
  - Pentoxifylline
  - Imiquimod

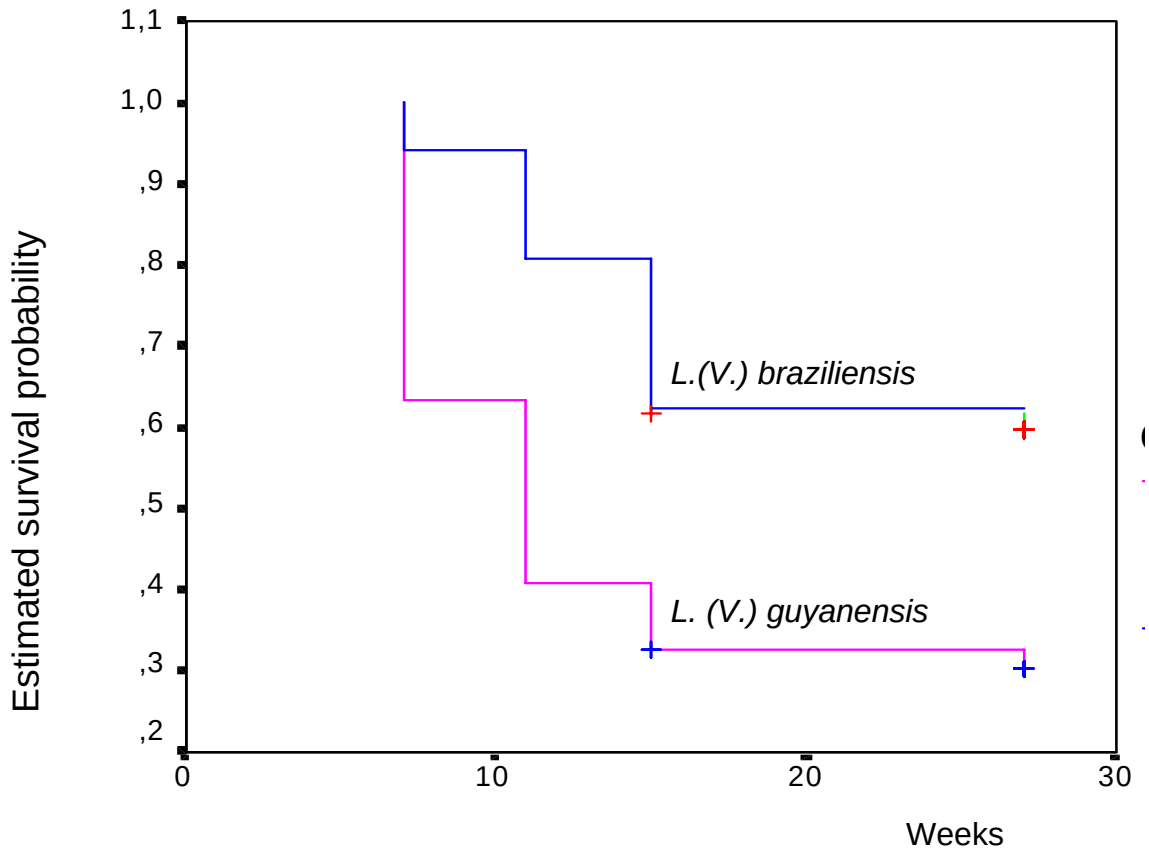
- Is it necessary to validate the efficacy of drugs which were developed in other regions?

Sympatric circulation and therapeutic outcome

- *L. braziliensis*
  - 24/25 (96%) cure rate with sodium stibogluconate
  - 7/23 (30%) cure rate with ketoconazol
- *L. mexicana*
  - 4/7 (57%) cure rate with sodium stibogluconate
  - 8/9 (89%) cure rate with ketoconazol

Navin and cols., J Infect Dis 165:528-534;1992

Comparison of *L. (V.) braziliensis* and *L. (V.) guyanensis* in Brazil



Romero and cols., Am J Trop Med Hyg 65:456 – 465; 2001.

Miltefosine in Colombia, Guatemala and Bolivia

- 28 day treatment and 6 month follow-up (*per protocol*)
  - Colombia (CL)
    - 40/44 (91%) cure rate with miltefosine
    - 9/24 (38%) cure rate with placebo
  - Guatemala (CL)
    - 20/38 (53%) cure rate with miltefosine
    - 4/19 (21%) cure rate with placebo

      - **Soto and cols**., Trans Roy Soc Trop Med Hyg 100:s34-s40; 2006

- 28 day treatment and 12 month follow-up (*per protocol*)
  - Bolivia (ML)
    - 30/36(83%) cure rate for mild disease
    - 21/36(58%) cure rate for severe disease

      - **Soto and cols**., Clin Infect Dis 44:350356; 2007

Are available antimonials equivalent?

- Comparison of Chinese (not generic) SS versus MA in Brazil – equivalent efficacy; higher toxicity of SS
    - Saldanha and cols., Rev Soc Bras Med Trop 32: 383-387; 1999
- Comparison of generic SS and Pentostam in Sudan – equivalent in efficacy and toxicity
    - Veeken and cols., TM&IH 5:311-317;2000
- Comparison of generic SS versus Pentostam in Kenya – equivalent efficacy and toxicity
    - Moore and cols., WHO Bull 79: 388-393; 2001
- Comparison of generic SS versus Pentostam in Ethiopian patients – equivalent efficacy and toxicity
    - Ritmeijer and cols., Trans R Soc Trop Med Hyg 95:668-672;2001

Antimonial quality and toxicity

- Batch variability
  - Osmolarity
  - Sb concentration
  - Trivalent species
- Contamination with heavy metals

TABLE III

Physico-chemical characteristics of two lots of meglumine antimoniate used for treatment of patients with cutaneous leishmaniasis in Brazil [a]

Characteristic	Lot A [b]	Lot B [c]
PH	4.5 (0.05) [4.48-4.56]	6.7 (0.05) [6.78-6.83]
Osmolarity (mosm/l)	708.9 (5.86) [704.7-713.1]	959.3 (22.44) [952.5-965.7]
Total antimony ($Sb^{III} + Sb^{V}$) (mg/ml)	103.9 (1.4)	88.1 (1.2)
Trivalent antimony (mg/ml)	3.45 (0.31)	1.82 (0.25)
Heavy metals		
Lead (mg/l)	52.71 (1.29)	< 0.20
Arsenic (mg/l)	35.79 (1.54)	< 0.90
Cadmium (mg/l)	0.132 (0.014)	< 0.04

a: numbers in parenthesis correspond to SD. Numbers in brackets correspond to 95% CI; *b*: meglumine antimoniate, lot 011/00 A (Eurofarma Laboratórios, Ltda., São Paulo, Brazil); *c*: meglumine antimoniate, lot 0595L061 (Rhodia Farma, Ltda., São Paulo, Brazil)

Romero and cols., Mem Inst Oswaldo Cruz 98:145-149; 2003

Is there an ideal antimonial dose and treatment duration?

Recommendations in Brazil

- CL
  - 15 (10-20) mg/kg/d for 20 days IV or IM
- ML
  - 20 mg/kg/d for 30 days IV or IM
- VL
  - 20 mg/kg/d for 20 to 30 days IV

Some experience with *L. (V.) braziliensis* CL in Corte de Pedra, Bahia, Brazil

Sb dose (mg/kg/dia)	Duration (days)	Follow-up (month)	# of patients cure/observed	Cure rate (%)	95% CI	Reference
20	20	3	17/ 21	81,0	58,1 – 94,6	(MERCHAN-HAMANN, 1989)
10	20	3	17/ 23	73,9	51,6 – 89,8	(MERCHAN-HAMANN, 1989)
20	10	3	6 / 17	35,3	14,2 – 61,7	(MERCHAN-HAMANN, 1989)
10	10	3	6 / 16	37,5	15,2 – 64,6	(MERCHAN-HAMANN, 1989)
10	20	5	14 / 23	60,9	38,5 – 80,3	(SÁNCHEZ, 1995)
20	20	3	36/ 58	62,1	48,4 – 74,5	(SALDANHA, 1997)
20	20	6	31/ 52	59,6	45,1 – 73,0	(ROMERO et al., 2001)
20	20	12	12/ 22	54,5	32,2 – 75,6	(MACHADO et al., 2002)

Pentamidine: would it be the first choice for *L. guyanensis* / *L. panamensis* infection?

- Colombia
- Suriname
- Brazil
- French Guyana

The role of aminosidine/paromomycin

- Non-inferiority trial compared with amphotericin B in India
  - Equivalent
    - Sundar and cols., N Engl J Med 356:2571-2581;2007
- Associated with SS (17 days) in Sudan
    - Melaku and cols., Am J Trop Med Hyg 77:89-94;2007
- Not-effective in ML in Peru compared to MA
  - 100% failure rate
    - Llanos-Cuentas and cols., Am J Trop Med Hyg 76:1128-1131;2007
- Topical treatment in association with parenteral drugs

Recommendations for conventional amphotericin B and liposomal amphotericin B in Brazil

- Amphotericin B deoxycholate – first choice for VL and ML in HIV co-infected patients and severe VL cases
- Liposomal amphotericin B
  - Renal failure
  - One kidney
  - Renal transplantation
  - Systemic diseases with nephropathy
    - Lupus, diabetes, etc
  - Cardiac failure (functional classes III and IV)
  - Severe toxicity associated with conventional amphotericin B

Immune modulation role?

- Topical GM-CSF plus parenteral MA in 5 CL refractory patients in Brazil. 100 % good response.
  - **Almeida and cols**., Am J Trop Med Hyg 73:79-81;2005
- Pentoxifylline plus MA in 10 ML refractory patients in Brazil
  - **Lessa e cols**., 2001 Am J Trop Med Hyg 65:87-89
- Pentoxifylline plus MA (11 patients) versus MA (12 patients) for 30 days in ML treatment-naive patients in Brazil
  - Higher cure rate and faster healing
    - **Machado and cols**., Clin Infect Dis 44:788-793;2007
- Pentoxifylline plus MA (32 patients) versus MA (31 patients) in CL in Iran
  - 81.3% cured
  - 51.6% cured
    - **Sadeguian and cols**. Int J Dermatol 45:819-821;2006

Leishvacin in Brazil

Combined

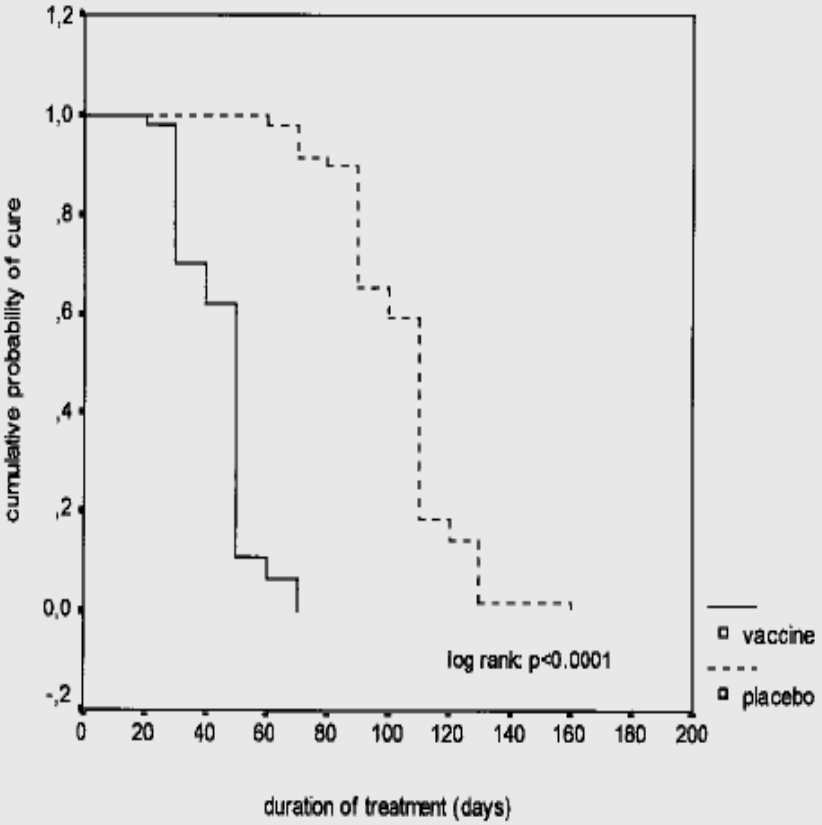


Figure 1 Kaplan–Meier plot of the probability of cure according to therapeutic regimen

Machado-Pinto and cols., Int J Dermatol 2002; 41:73-78

Is topical treatment safe for CL caused by *L. (V.) braziliensis?*

- *L. (V.) braziliensis* persistence in spite of treatment is well documented
- ML is associated with multiple risk factors
- Mucosal leishmaniasis is a rare event
- There is no unquestionable evidence supporting that parenteral treatment of CL would decrease the risk of ML

Imiquimod

- Imiquimod. plus MA standard therapy, open-label trial in 12 patients with previous failure with antimonial in Peru. Six month follow-up
  - 90% cure
    - Arévalo and cols., Clin Infect Dis 2001;33:1847-1851

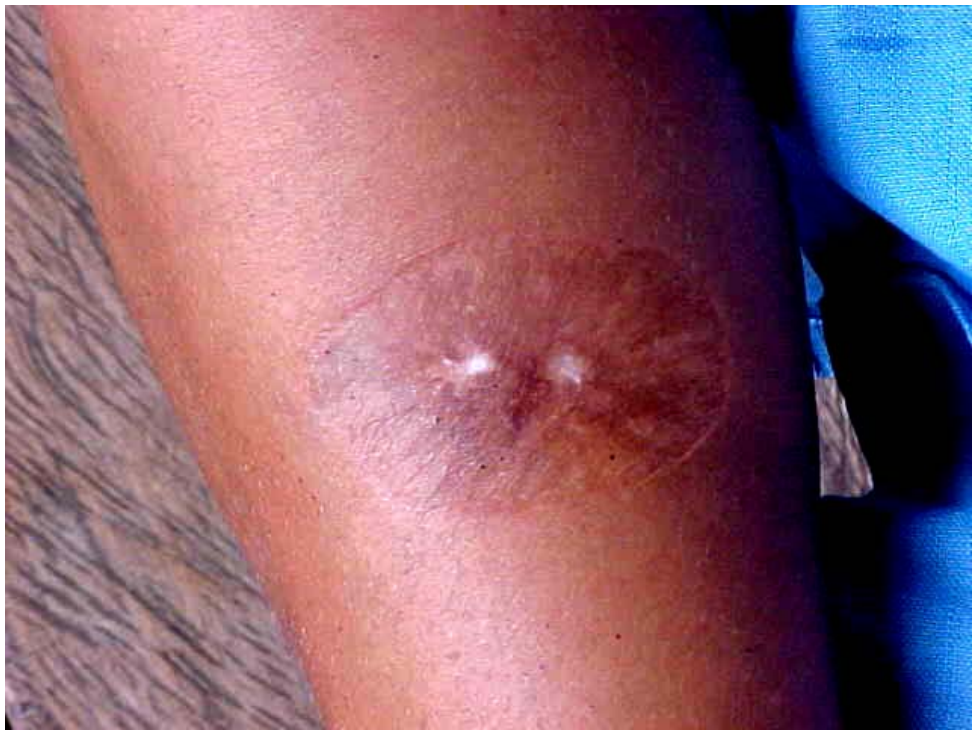
- Imiquimod (7 patients) versus combination with MA (7 patients) versus MA (7 patients) in Peru. Open-label trial in naïve treatment patients
  - 100% failure alone
  - 100% cure for the combination
  - 57% cure for control group
    - Arévalo and cols., Clin Infect Dis 2007;44:1549-1554

- Imiquimod plus MA (59 patients) versus placebo plus MA (60 patients) in Iran. Endpoint evaluated 4 weeks after treatment)
  - 44.1 versus 48.3 cure, respectively.
    - Firooz and cols., Arch Dermatol 2006;142:1575-1579

How should we deal with the resistant cases? and the HIV co-infected patients?

- Combination therapy
- Prolonged therapy
- Higher doses
- Secondary prophylaxis

Do we need another cure criteria?



Trials in Brazil

- Low-dose versus standard dose of MA for CL
- Azithromycin (plus topical paromomycin) versus MA for CL
- Miltefosine versus MA for CL
- Amphotericin B versus MA for VL in children
- Miltefosine versus MA for VL
- amphotericin B, Liposomal amphotericin B and SS versus MA for VL
- SS and pentamidine versus MA for *L. guyanensis* CL