Os Grande Endemias : Leishmaniases

18.10.2018
14: 00h

The Leishmaniases in Brazil: Ecology & Control

Ministério da Saúde

BRASIL UM PAÍS DE TODOS GOVERNO FEDERAL

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

FAPESP

A disease cannot be controlled without knowledge of its method of transmission

Once known the challenge is to find the sites in the life cycle that lower the basic reproductive value (R_0) of the pathogen

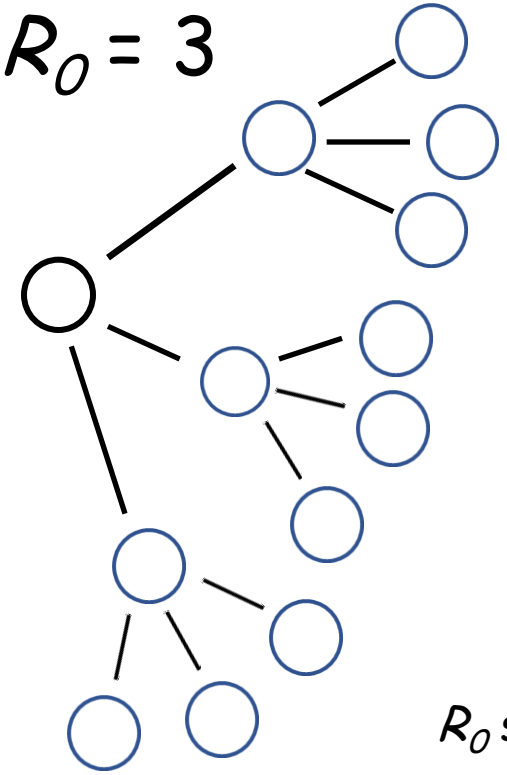
Prevenir a expansão de uma doença é.....

$$R_0$$

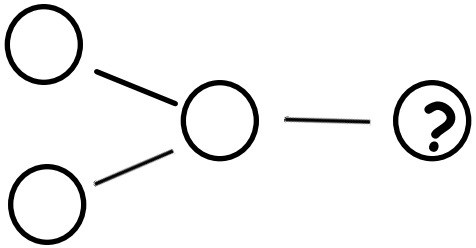
$$\Downarrow$$

Número de reprodução básica (R_0)

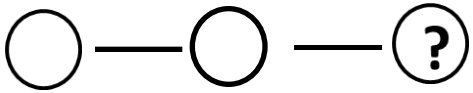
$R_0 = 3$



$R_0 = 0{,}5$



$R_0 = 1$



Erradicação mais viável com R_0 baixo

R_0 sarampo = 15; variola;= 5; malaria = 80; CVL = 1,09 -~11

Mutliple host concept $R_0=1$

Depending on host (S_1 & S_2) critical densities (N_1 & N_2) one can replace the other if it falls below the threshold

John Snow
The Principal is Simple
Cholera in Soho
London

1854

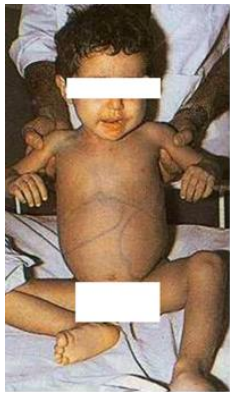
Find and treat the source

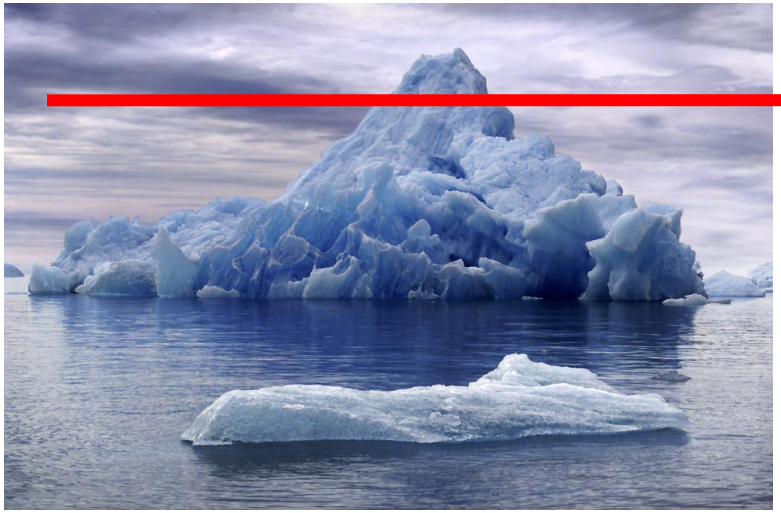
Can this be done for American Visceral and Cutaneous leishmaniasis?

The American Leishmaniases are Zoonoses

Man - tip of the iceberg
Not a reservoir host

15 *Leishmania* species recorded in man

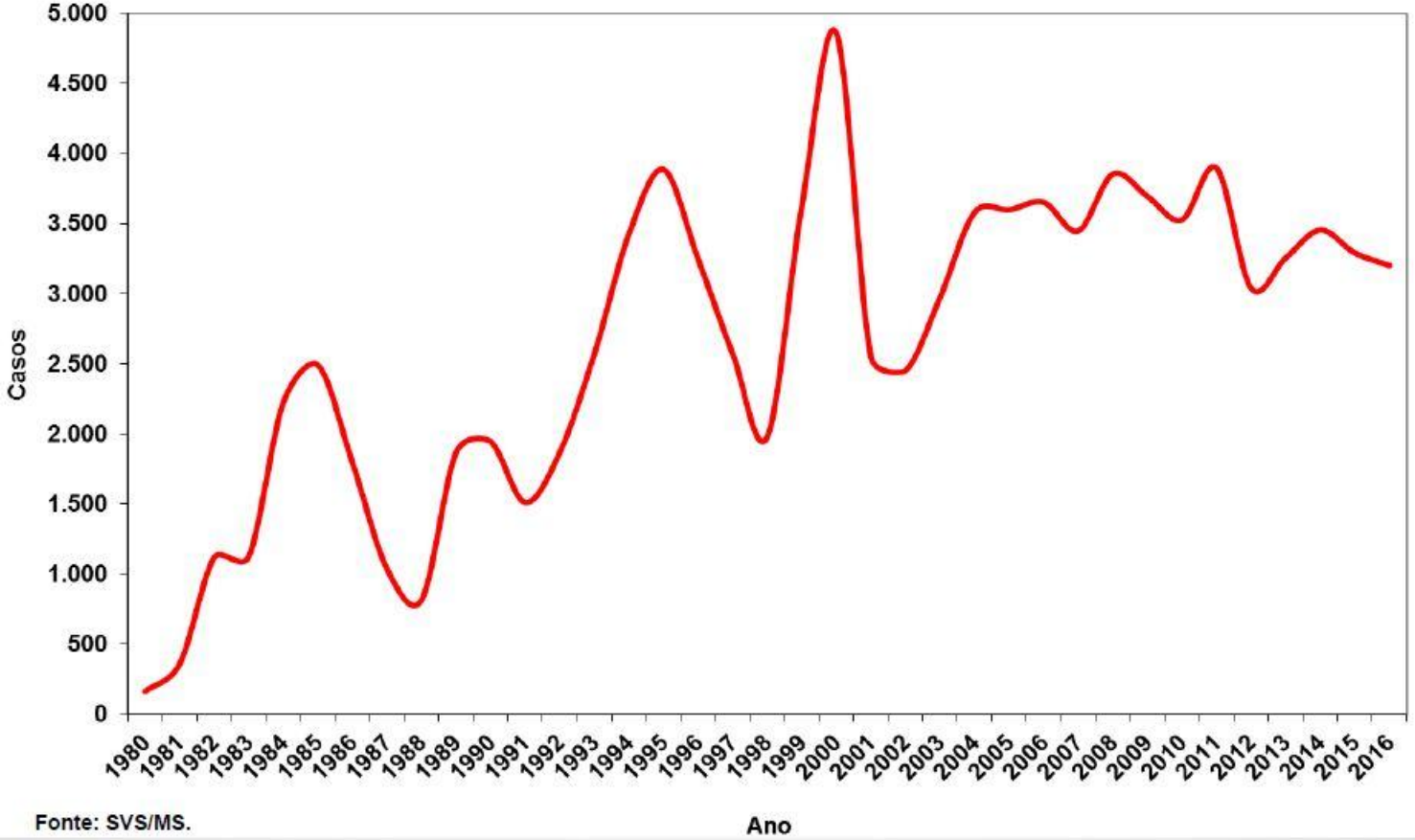




There are 20 named neotropical *Leishmania* species

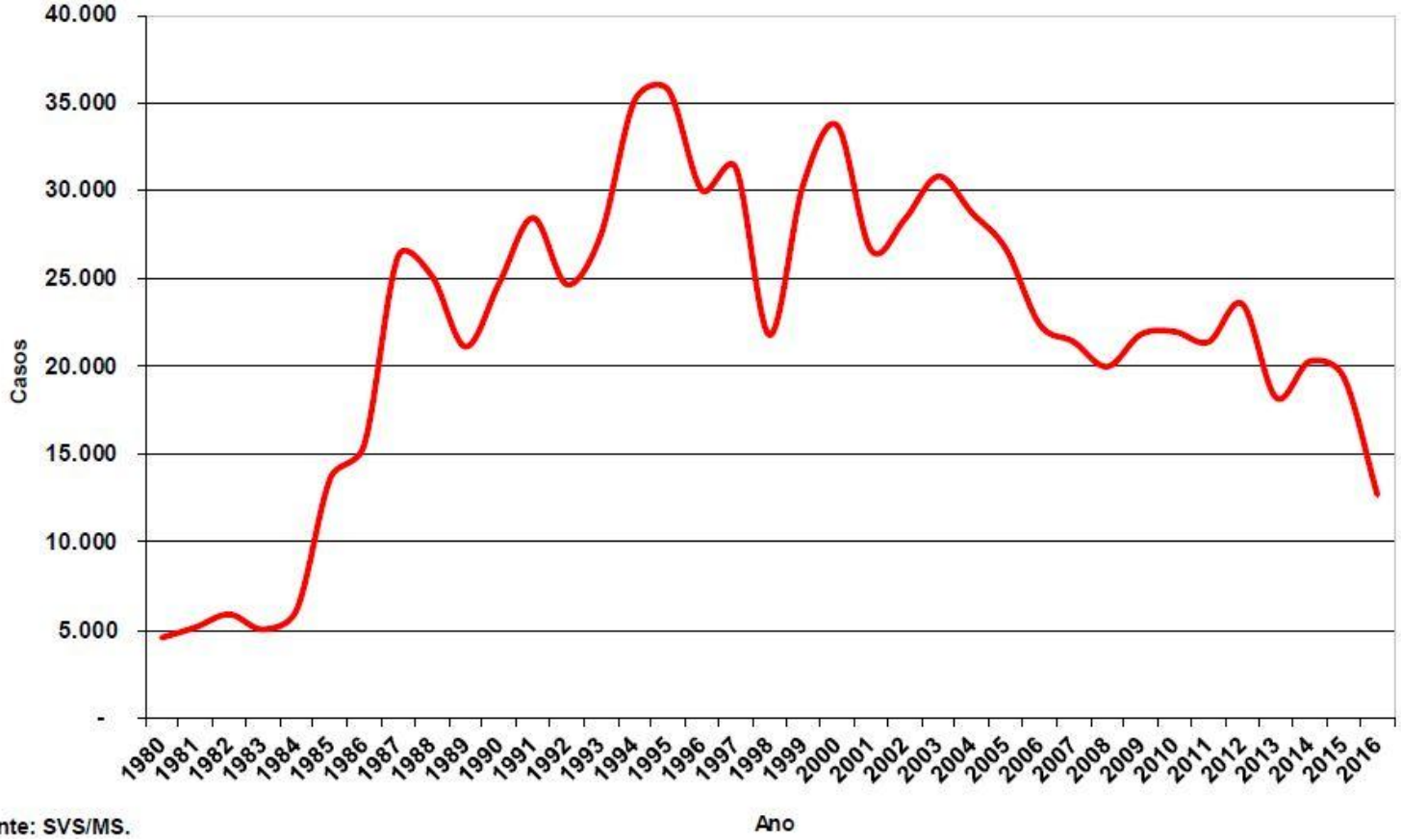
Jeffrey Shaw
ICB, USP

Casos de leishmaniose visceral no Brasil, 1980 a 2016



Fonte: SVS/MS.

Casos de leishmaniose tegumentar no Brasil, 1980 a 2016



Fonte: SVS/MS.

Clinical case

Sub clinical
Visceral
Leishmaniasis

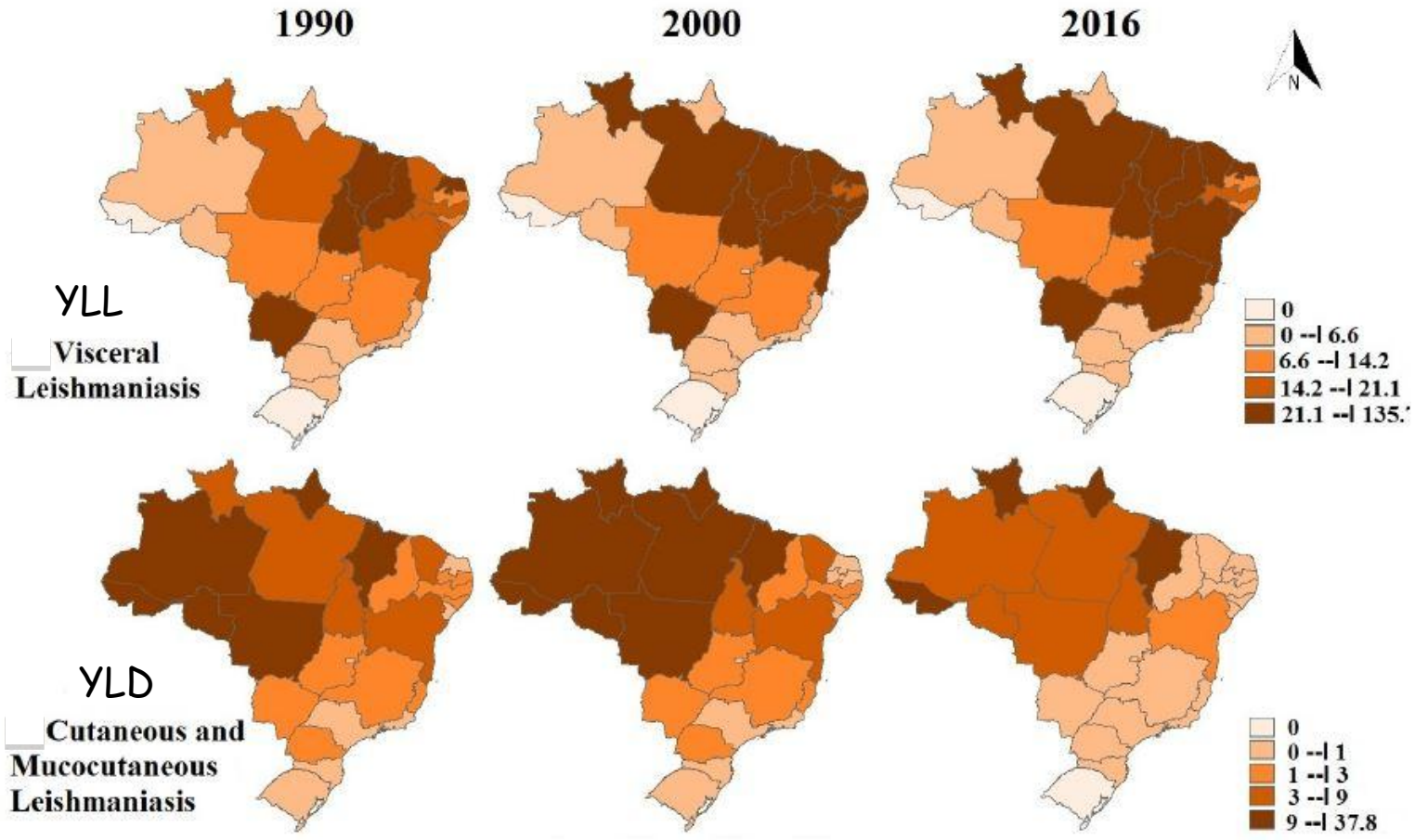
Sub Clinical
Cutaneous
Leishmaniasis

Levels of personnel impact

Years of **L**ife **L**ost (**YLL**)

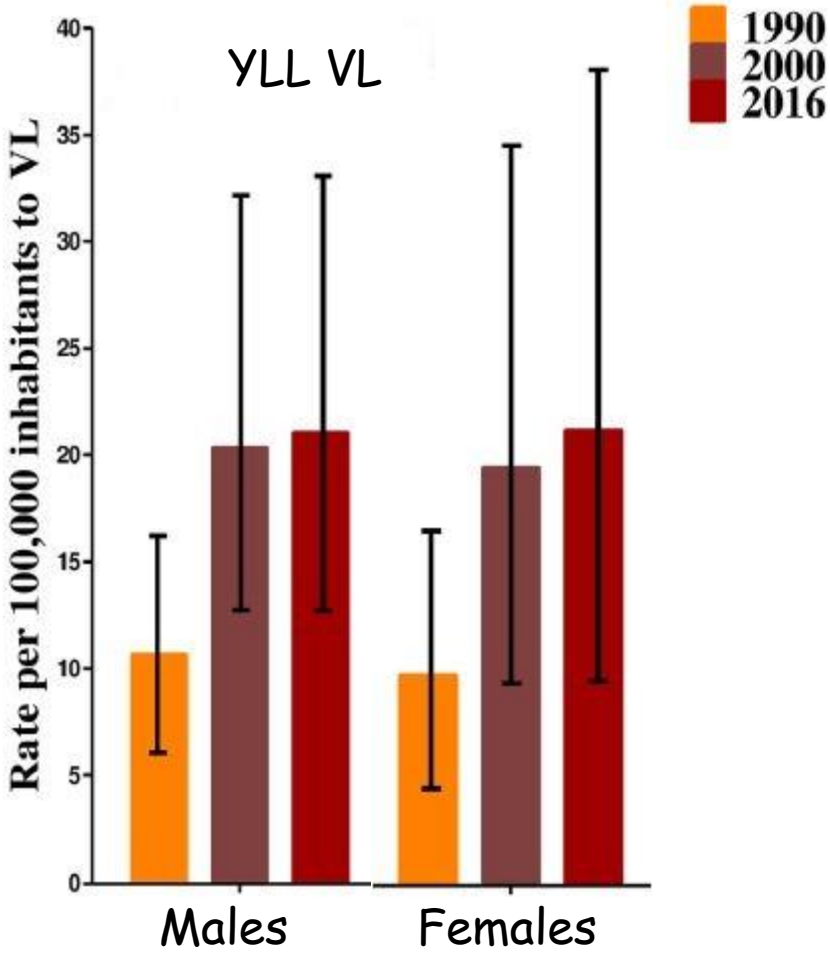
Years of **L**ived **D**isability (**YLD**)

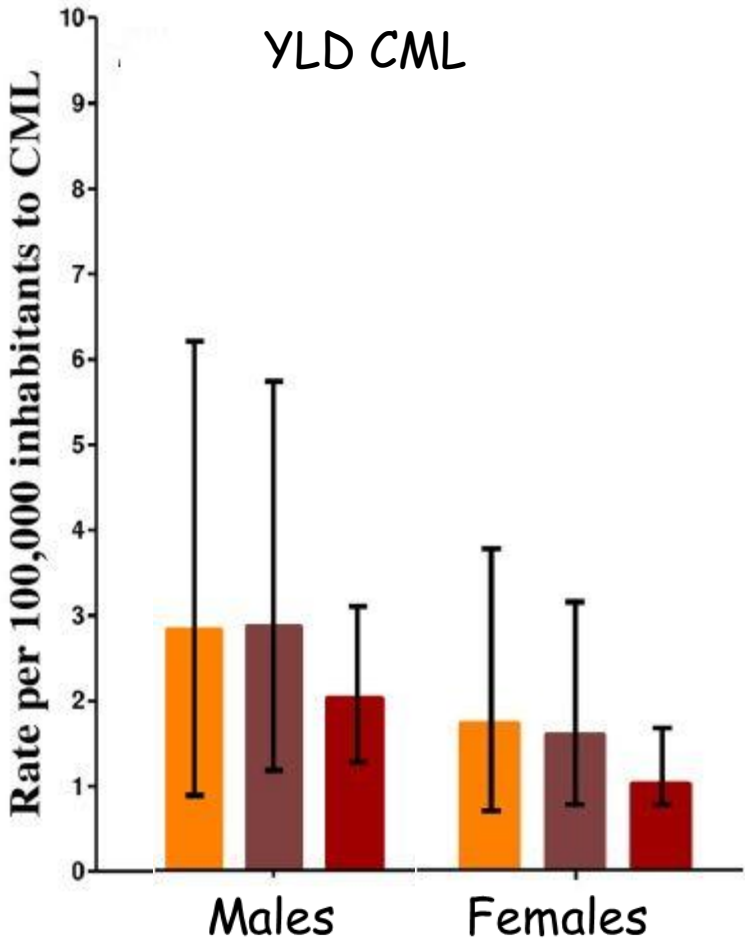
Years of **L**ife **L**ost (YLL) and **Y**ears of **L**ived **D**isability (YLD) *



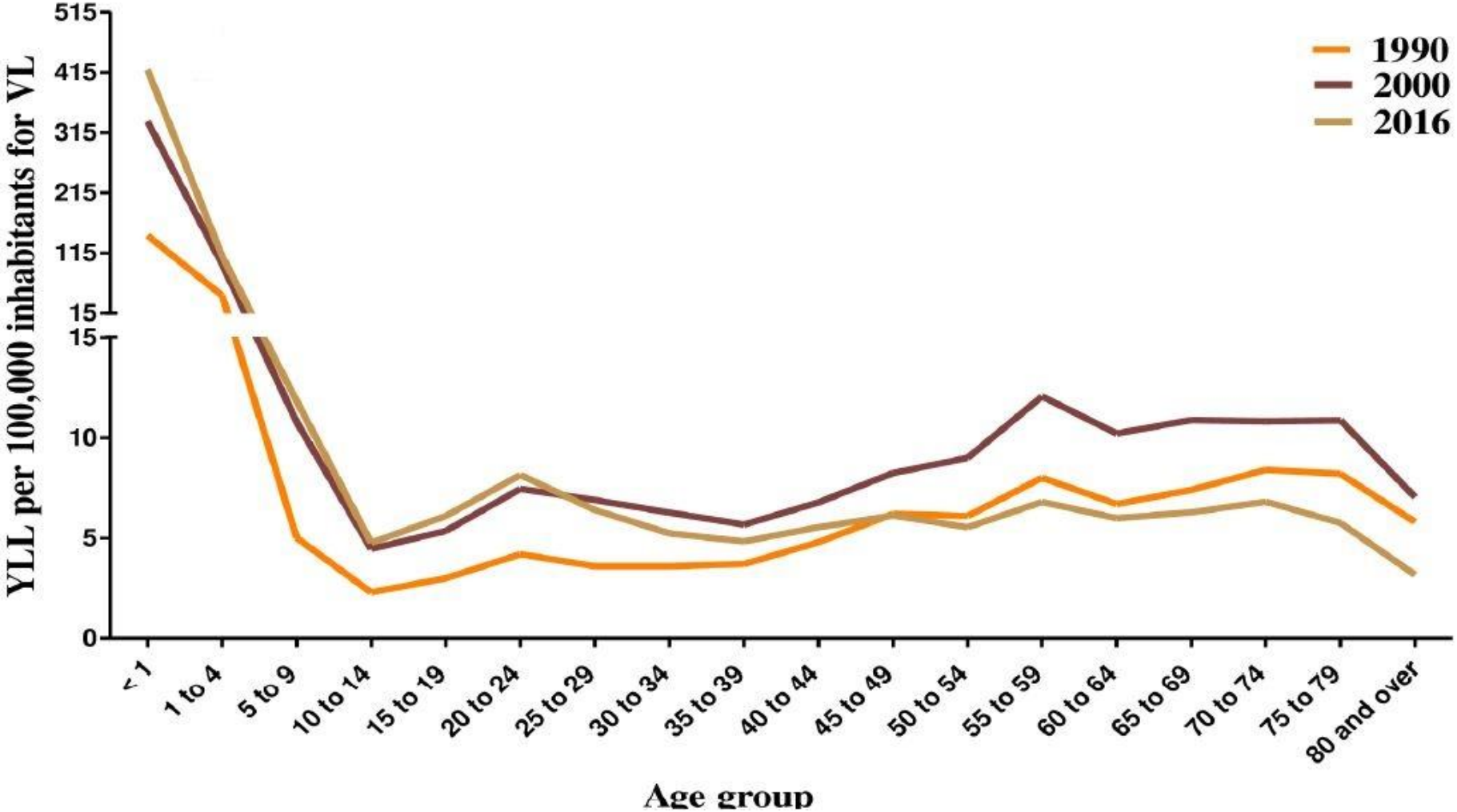
* Bezerra et al 2018

Age-standardized rates of **Y**ears of **L**ife **L**ost (YLL) and Years **L**ived with Disability (**YLD**) per 100,000 inhabitants



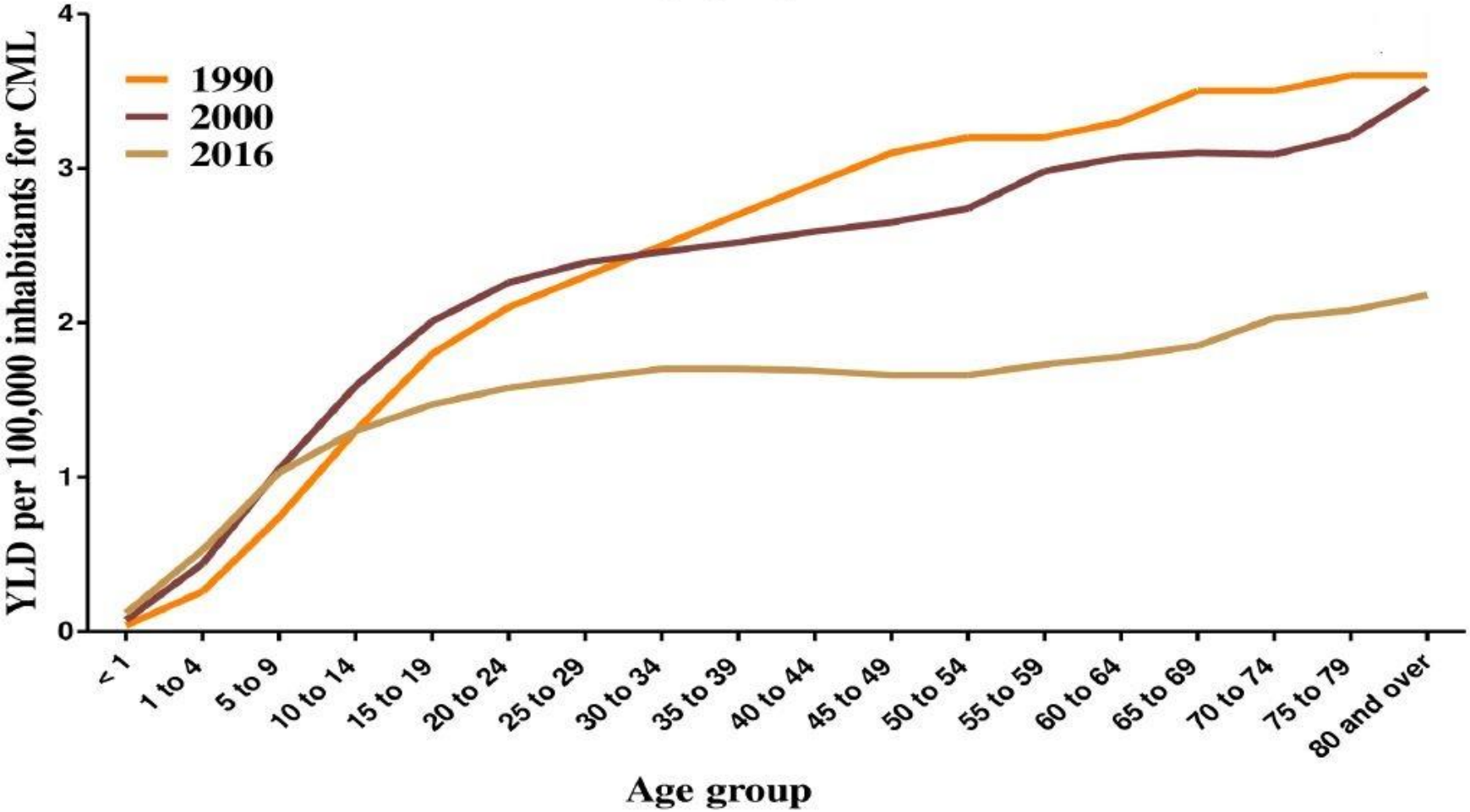


Age standardized rates for **Y**ears of **L**ife **L**ost (**YLL**) per 100,000 inhabitants for visceral leishmaniasis *



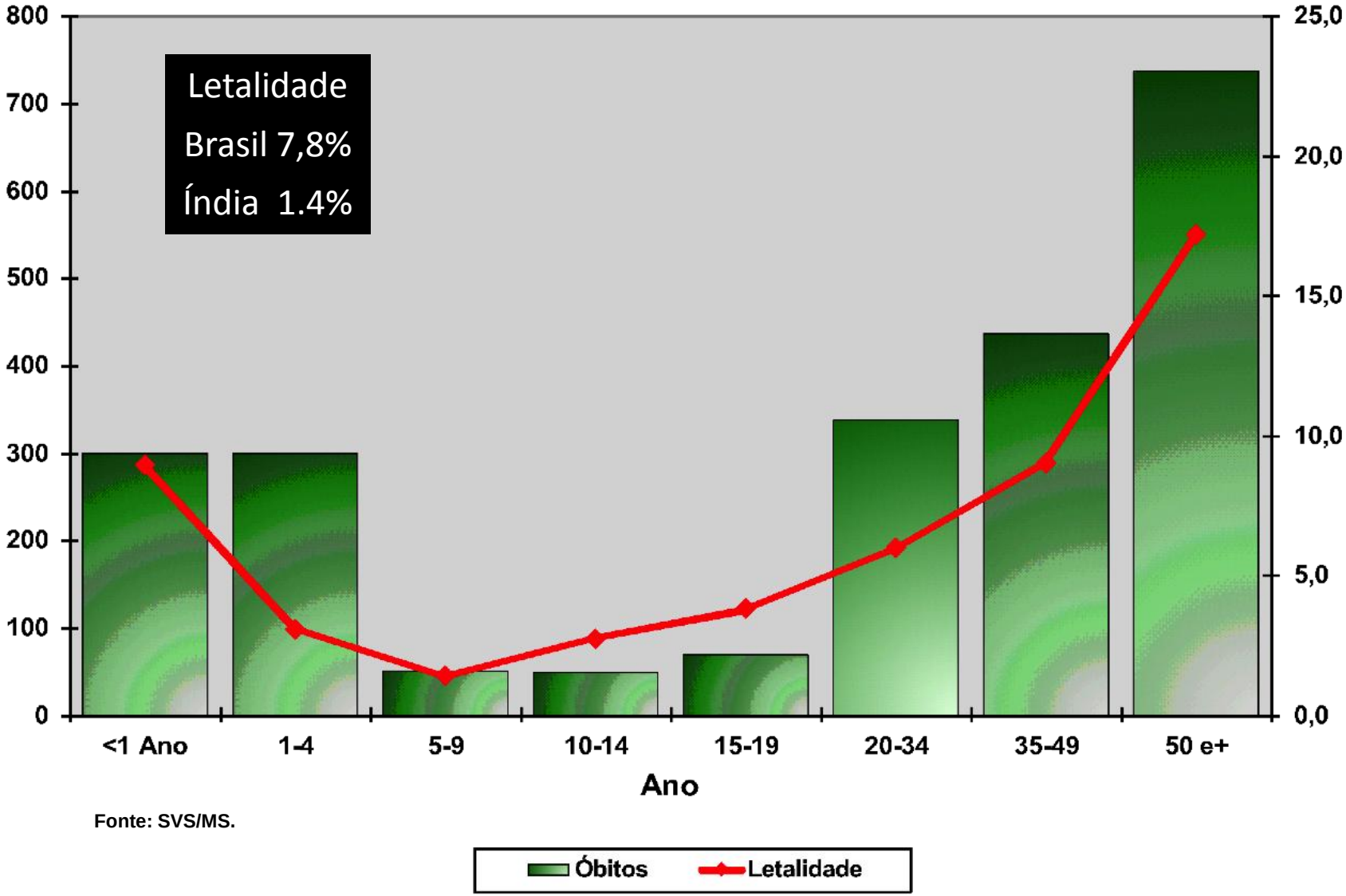
* Bezerra et al 2018

Age standardized rates for **Y**ears of **L**ived **D**isability (**YLD**) 100,000 inhabitants for for cutaneous leishmaniasis*



* Bezerra et al 2018

Óbitos e letalidade por faixa etária, Brasil, 2006 a 2015



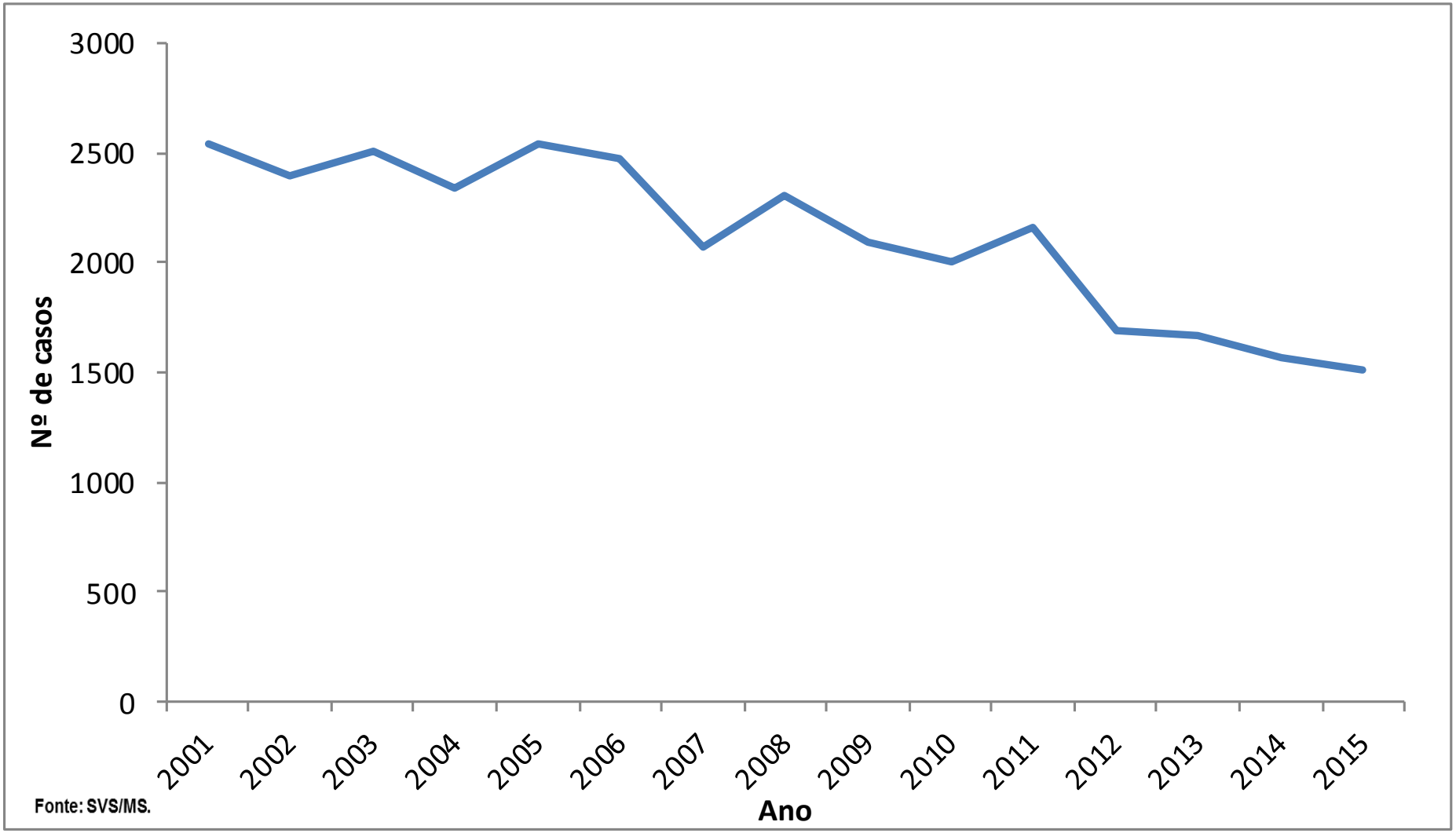
Fonte: SVS/MS.

Epidemiological changes of visceral leishmaniasis in Brazil

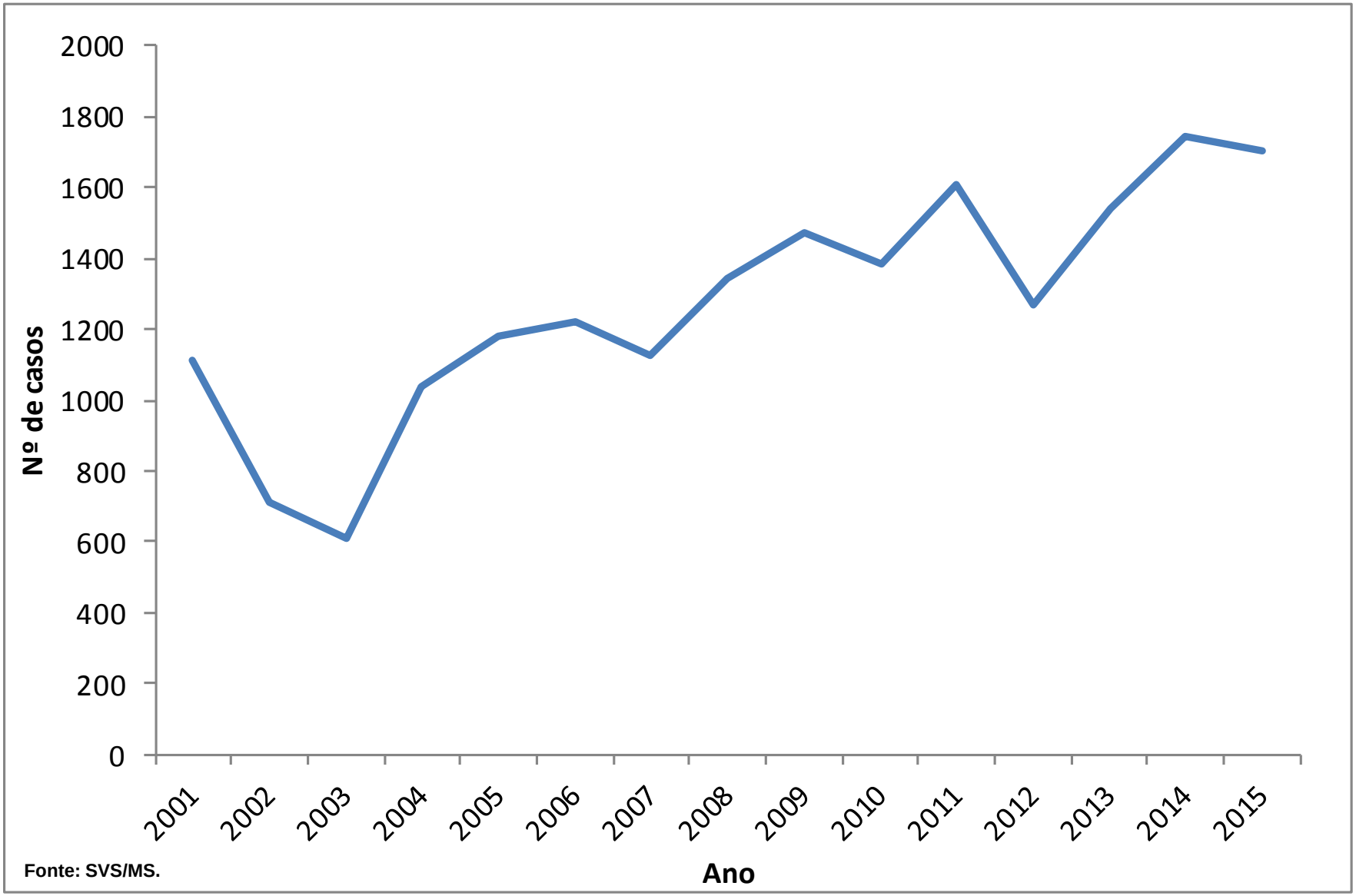
Brazilian Visceral leishmaniasis

Historically endemic in rural areas
but now
Endemic in urban areas

Casos de LV nos municípios **inicialmente** classificados como de **transmissão intensa ou moderada**, Brasil, 2001 a 2015



Casos de LV nos municípios **inicialmente** classificados como de **transmissão esporádica ou sem transmissão**, Brasil, 2001 a 2015



	Native population of endemic region	Immigrants (Tourists. Professionals, Settlers)
Skin test	High % +ve	Small % +ve
Disease	Rare	Common

Two scenarios to explain the expansion of VL where transmission was low or absent

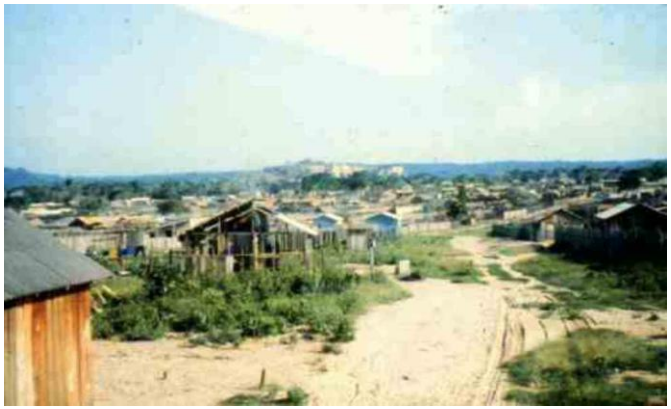
The expansion of traditional vector populations

The participation of new vector species

But an infected reservoir must be present!

The urbanization of *Lutzomyia longipalpis*

More than 15 major Brazilian cities are now facing VL control problems



Santarem, PA

Campo Grande, MTS

Brasilia, DF

Belo Horizonte, MG

In São Paulo State

Between 1990 and 1999

No autochthonous VL cases reported

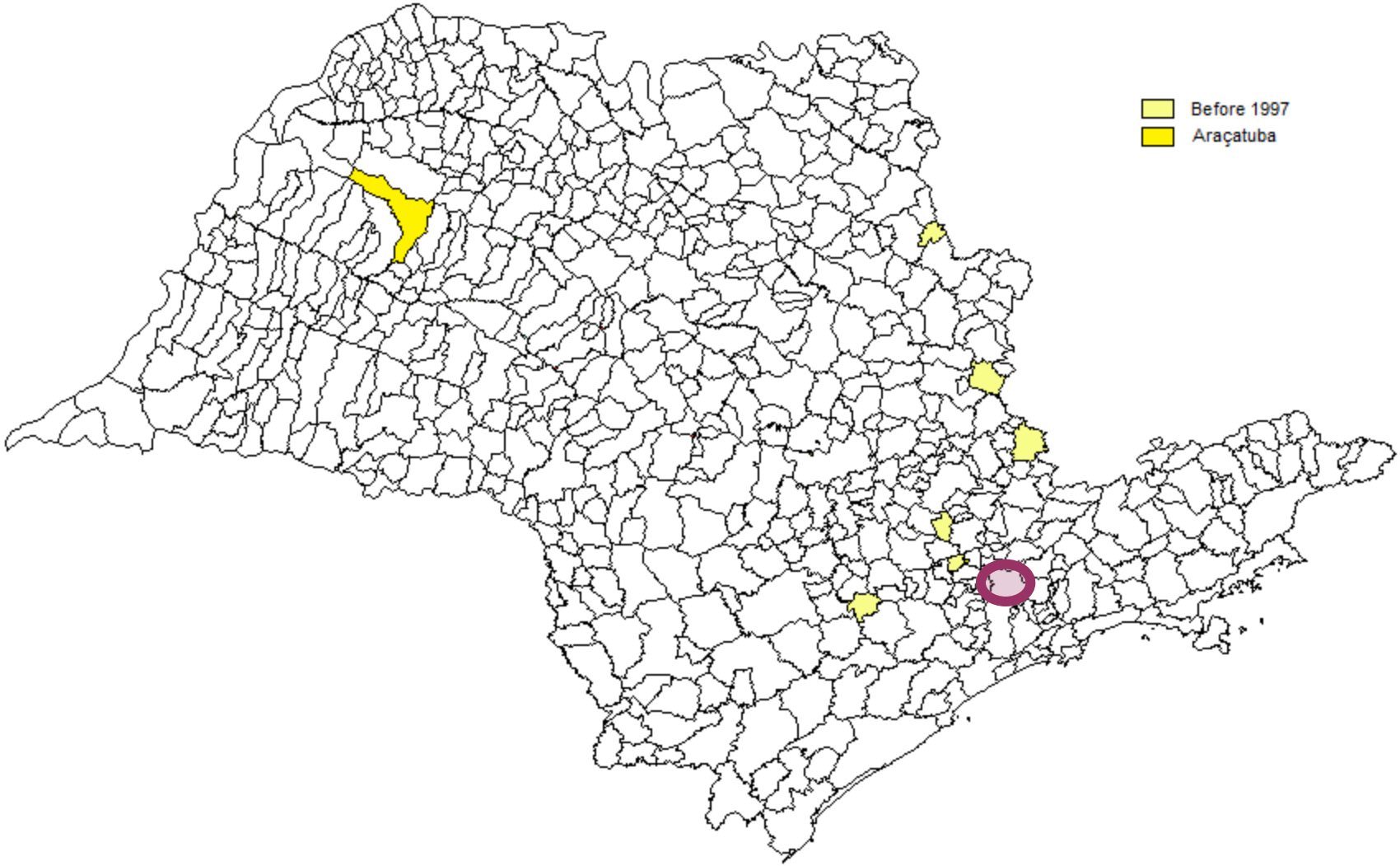
Between 2000 and 2012

2,146 cases with 169 deaths (7.9%)

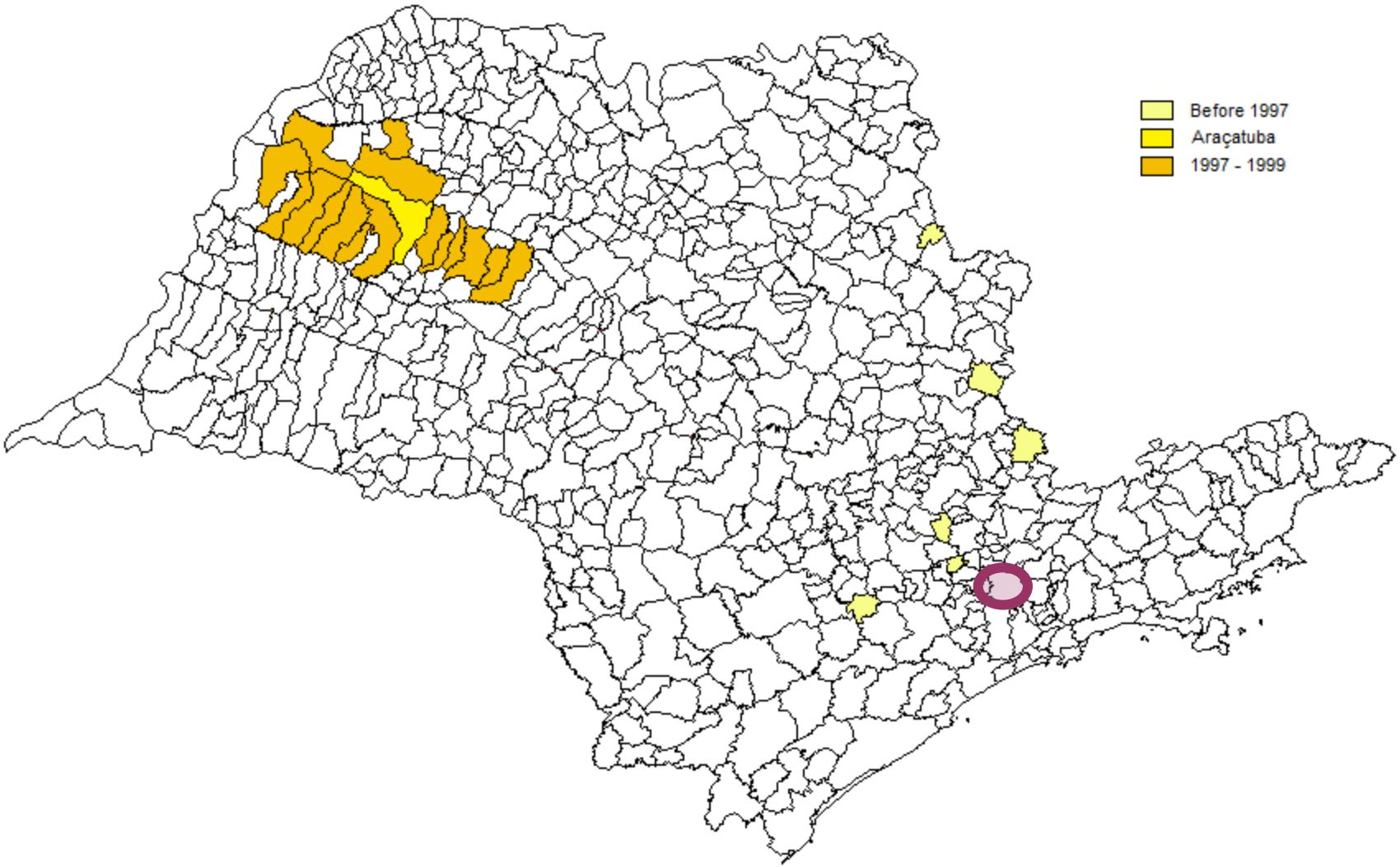
Up until 2015 a total of 2,620 VL cases were reported in São Paulo State

Lu. longipalpis in São Paulo before 1997

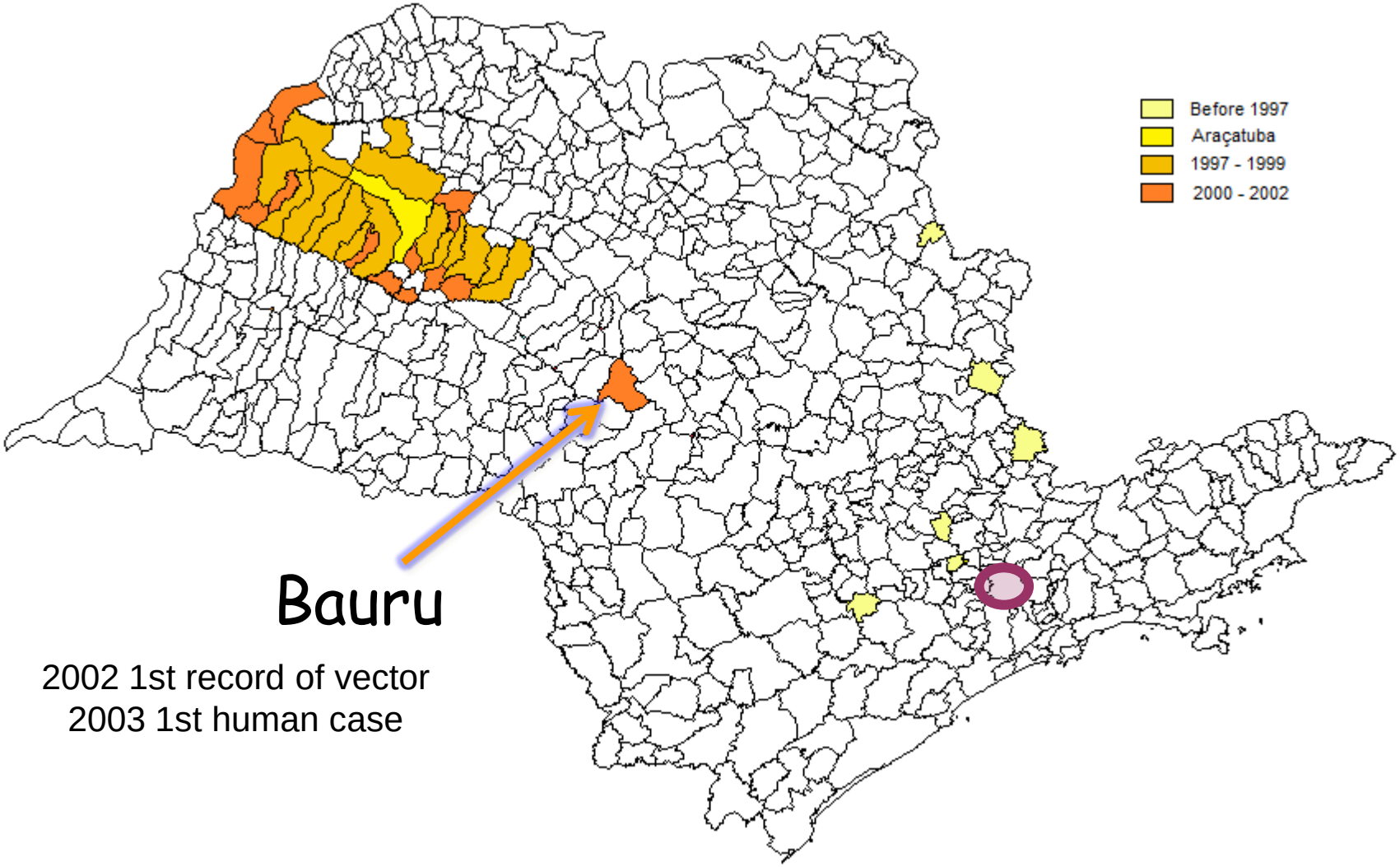
Lu. longipalpis found in Araçatuba 1997



2 years later 1999

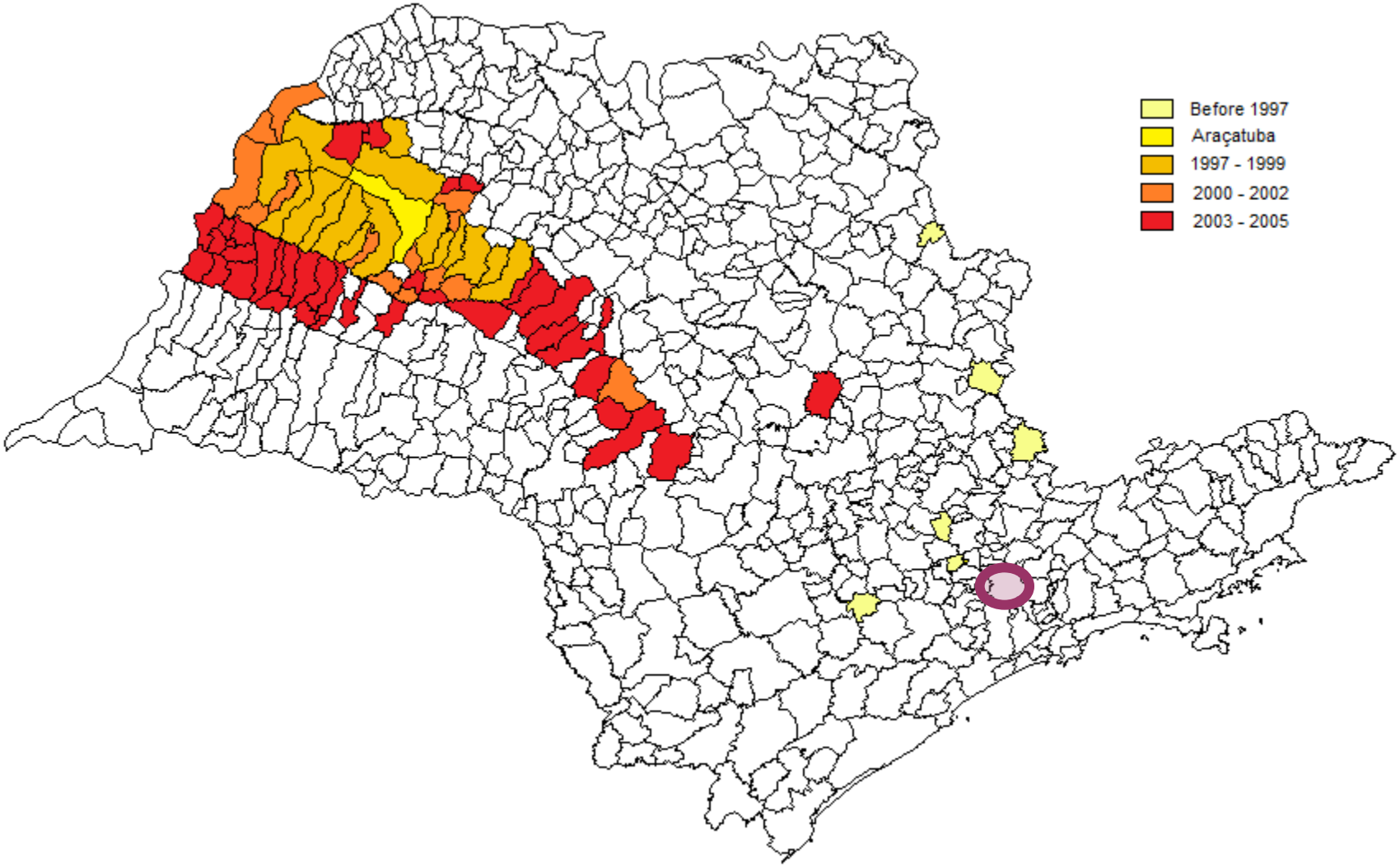


5 yrs later 2002

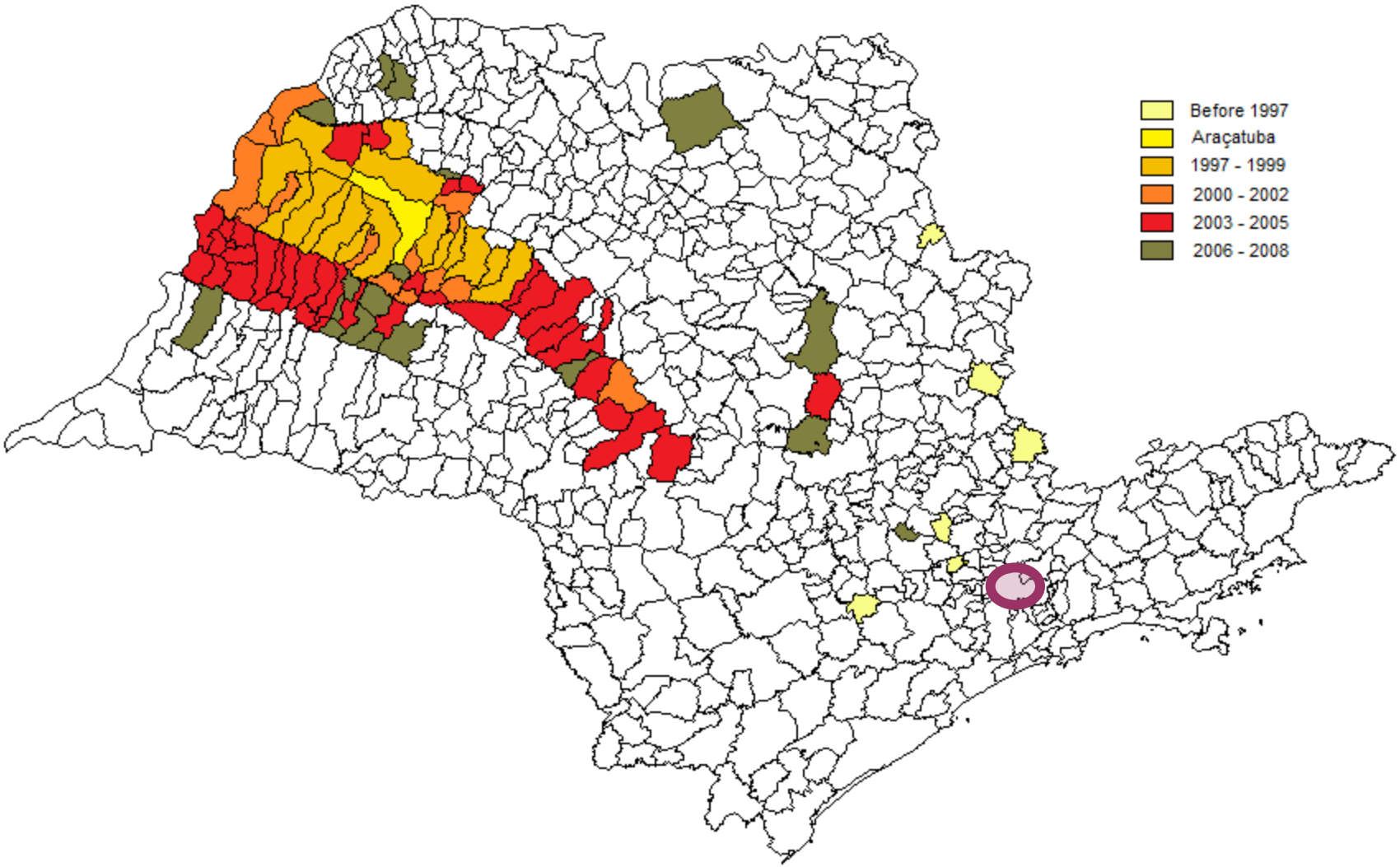


2002 1st record of vector
2003 1st human case

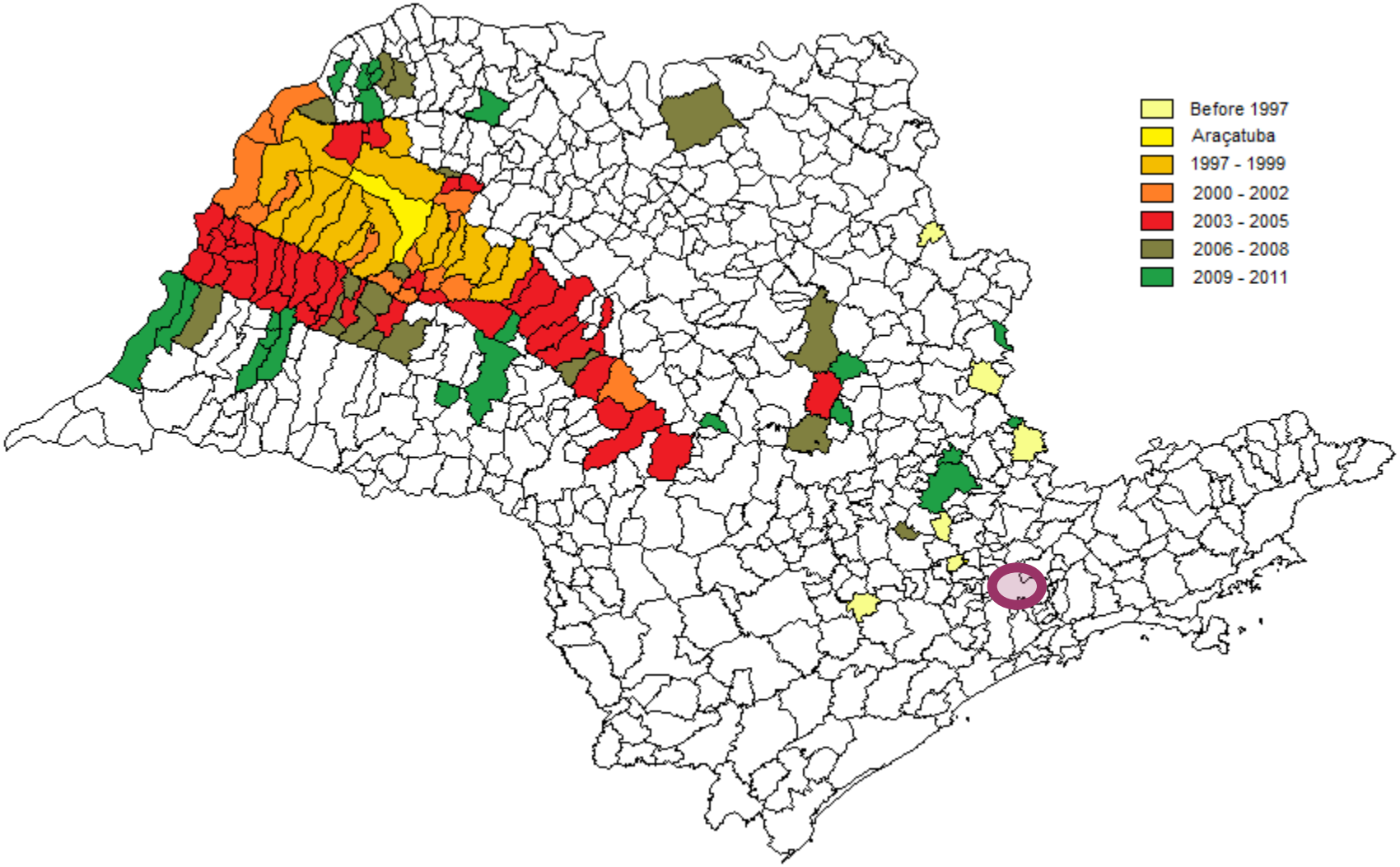
8 yrs later - 2005



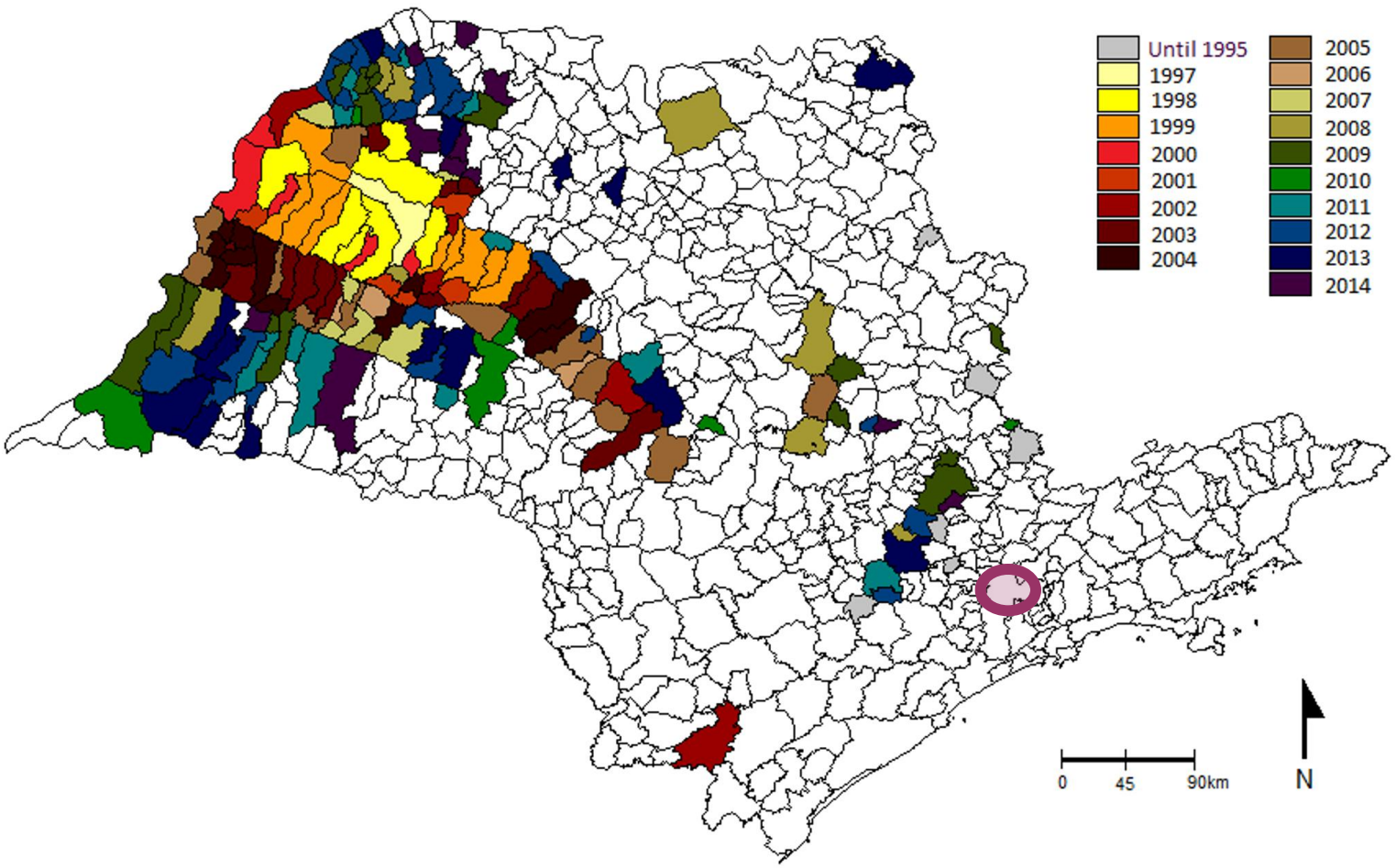
11 yrs later - 2008



14 yrs later - 2011

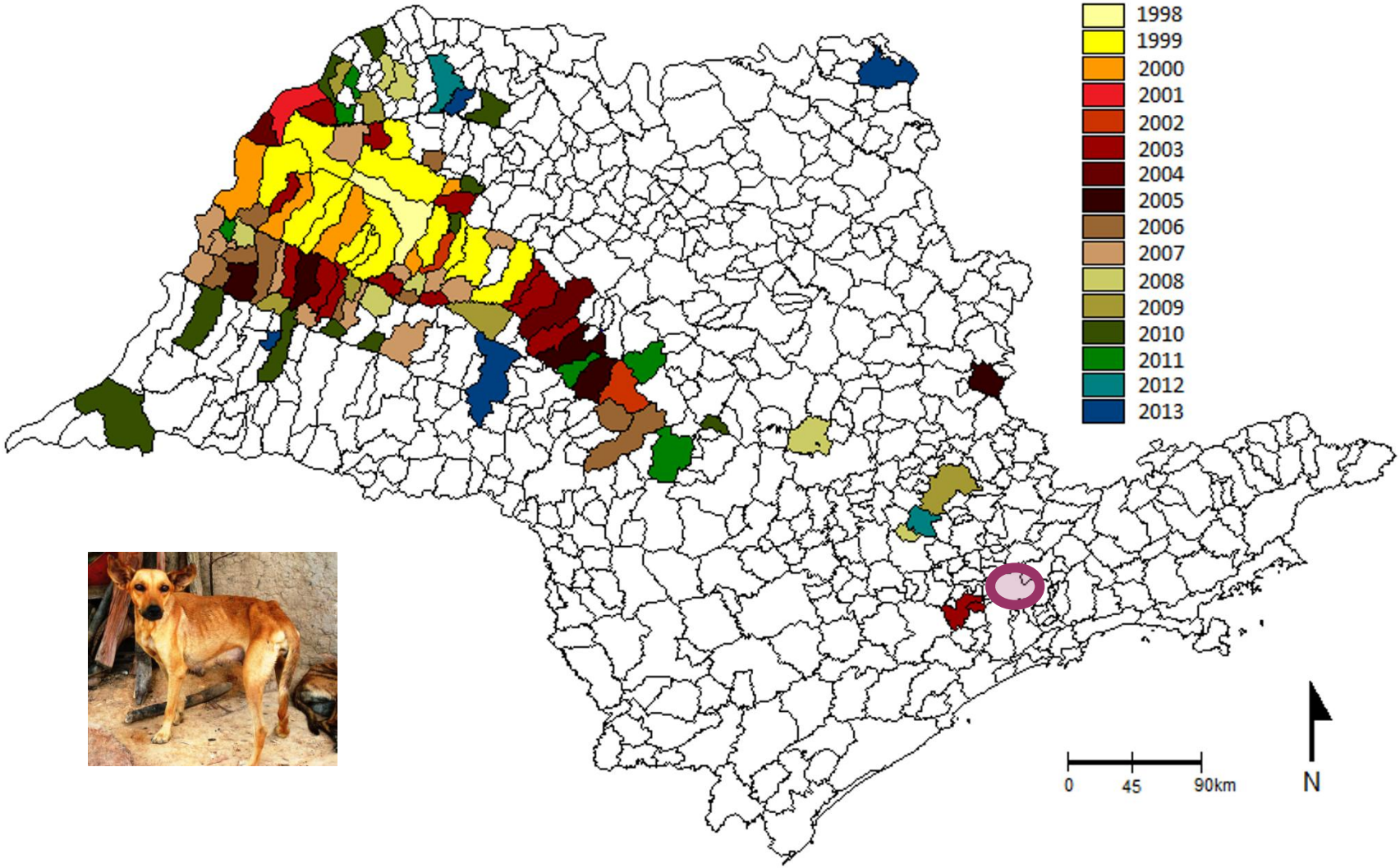


17 yrs later - 2014

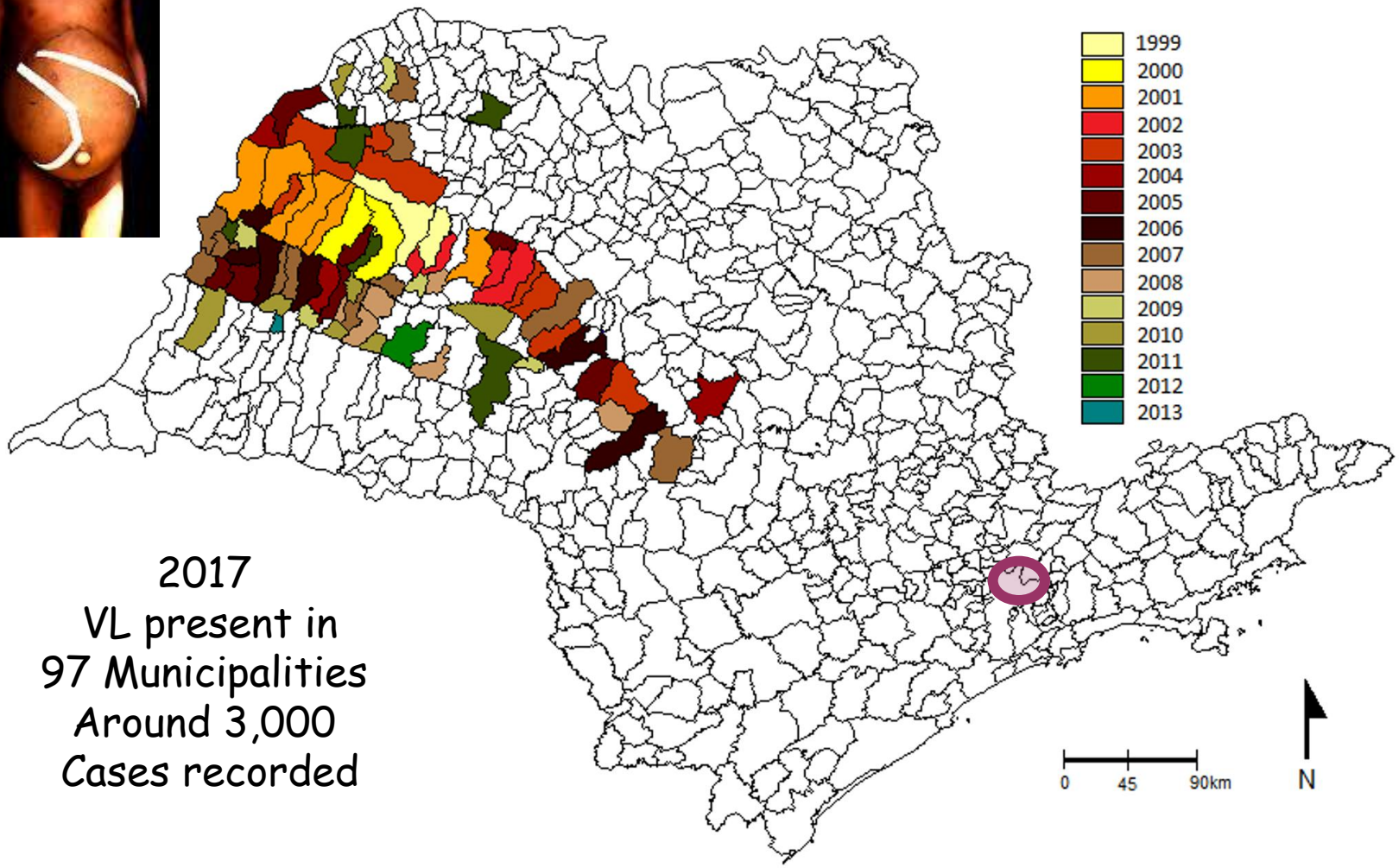


Casanova et al 2015

The spread of canine VL in SP

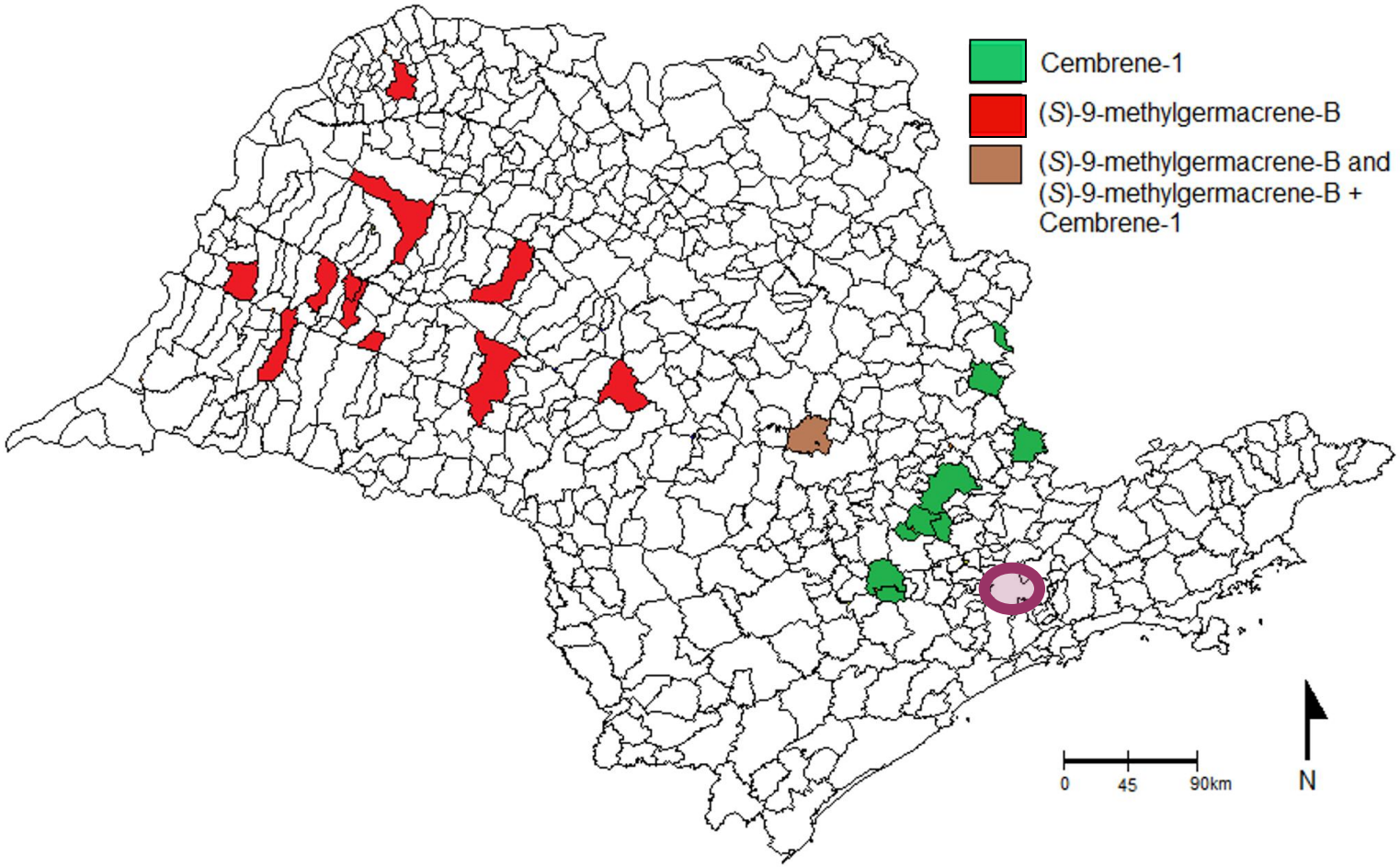


The spread of human VL in SP



2017
VL present in
97 Municipalities
Around 3,000
Cases recorded

Is one *Lu.longipalpis* genotype more capable of expansion than another and is it a more efficient vector?



Casanova et al 2015

Changing Vectors

Permissive

Non-permissive

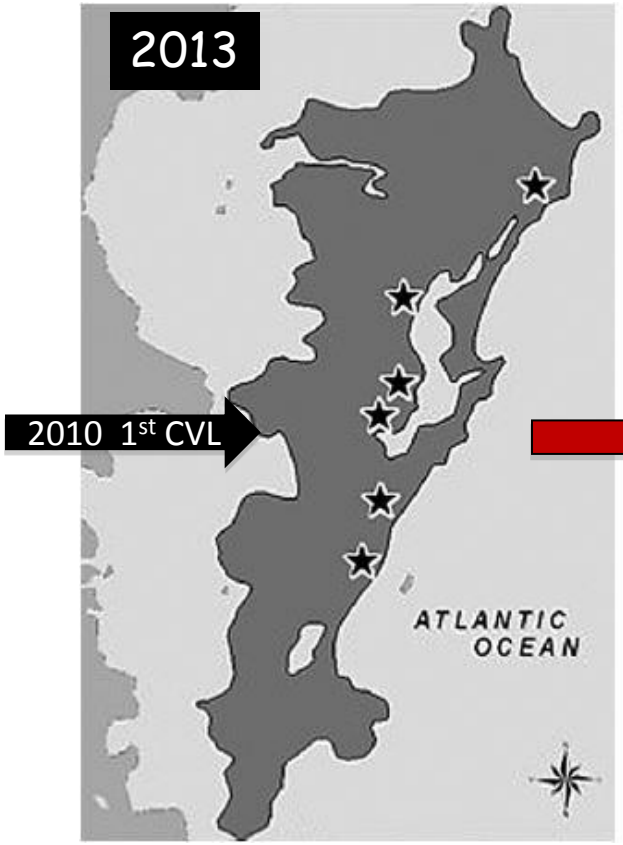
Lutzomyia longipalpis
Lutzomyia almerioi *
Migonemyia migonei *
Nyssomyia neivai *
Pintomyia evansi (CO)

* +ve PCR for *L. infantum*

Is *Lu. longipalpis* the only VL vector in Brazil?

New evidence suggests that it is not!

VL Florianopolis, SC



2017
2 human cases

So far *Lutzomyia longipalpis* has not be found
Association with forest
Most probable vector(s) * *Pintomyia fischeri & Nyssomyia neivai*

* +ve PCRs Personnel communication Mario Steindel

VL Guarujá, SP *

2017
2 fatal human cases

So far *Lutzomyia longipalpis* has not be found
Association with forest
Most probable vector *Nyssomyia intermedia* *

* Cassanova personel communicatior

VL Porto Alegre, RS

2016
CVL recorded

2017
PCR +ve sand flies

2017
3 VL cases
(1 fatal)

So far *Lutzomyia longipalpis* has not be found
Association with forest
Most probable* vector(s)
Pintomyia fischeri, Migonemyia migonei, Lutzomyia gaminarai *

* +ve PCR JD Andrade-Filho personnel communication

Frontiers of Control

Reservoir

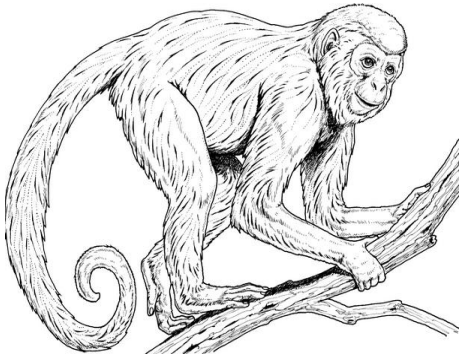
Vector

(Leishmania's Achilles' heel)
(Calcanhar de Aquiles)

Man

Treat

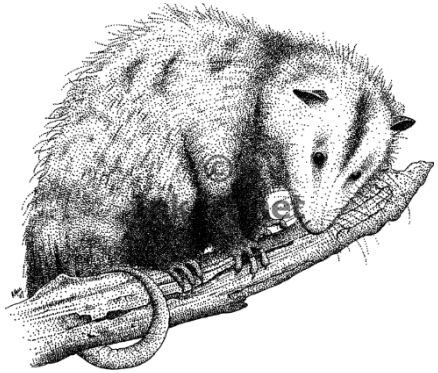
Why is leishmaniases control so difficult?

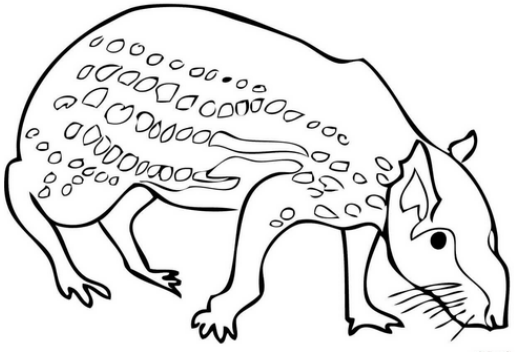


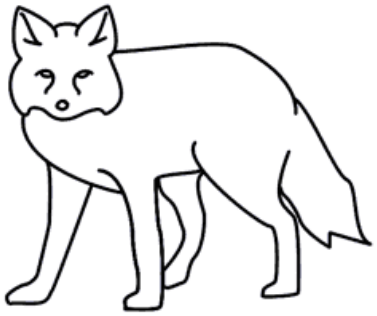
Reservoirs

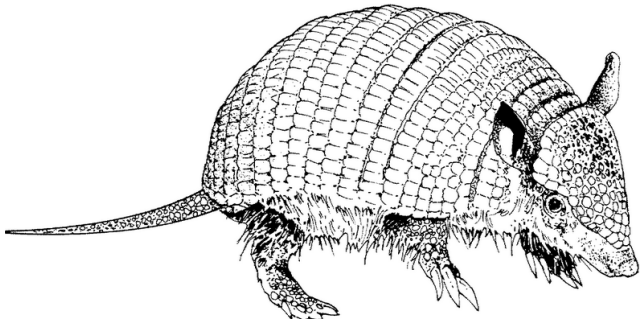
Cutaneous leishmaniasis

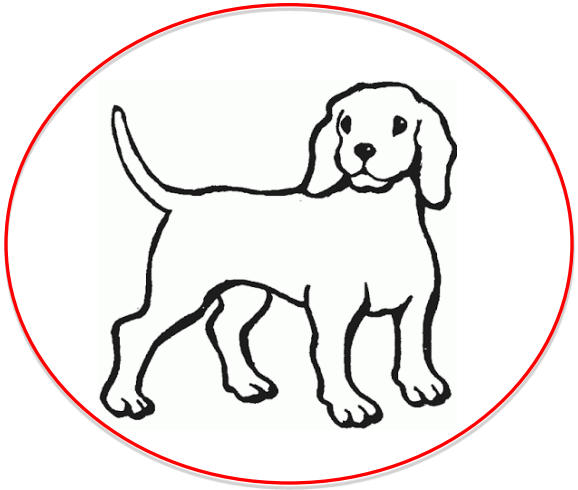
Environmental Management



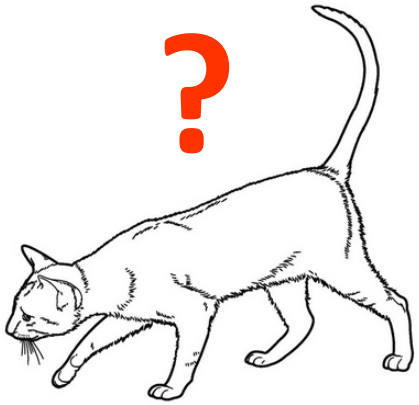






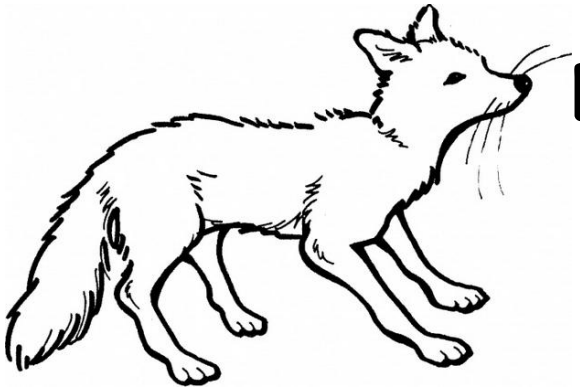


Reservoirs

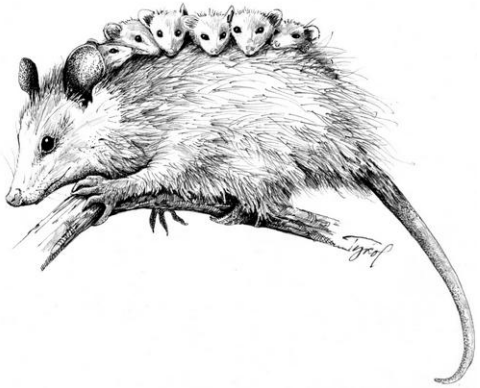


Visceral Leishmaniasis

Feasible to Control of canine infection



But by what method?



An intervention can be evaluated with mathematical models

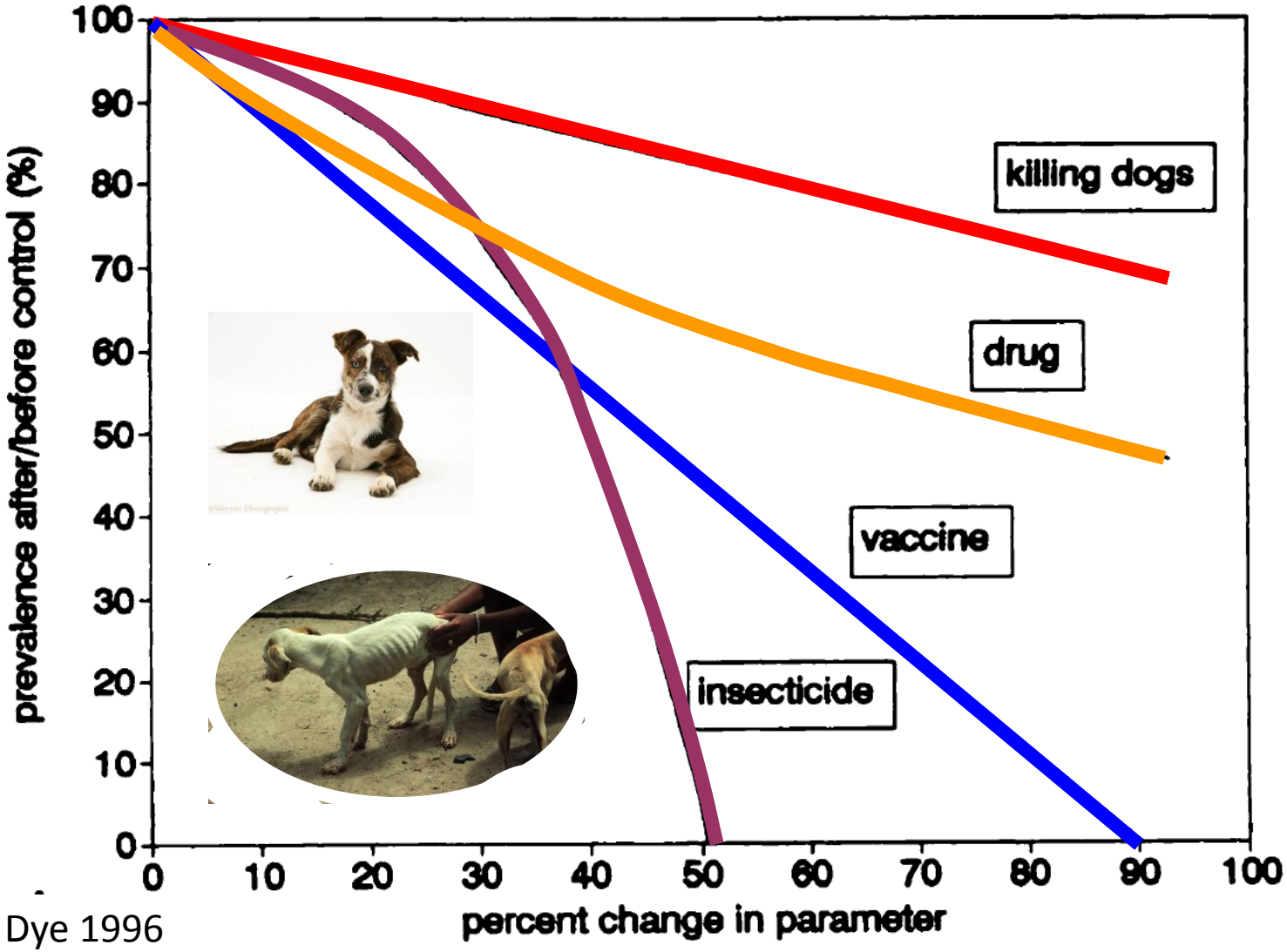
Results vary according to the equations & indices

One model* for CVL used 27 indices

10 Human , 10 Dog & 3 Sand fly índices
with 4 Dog variables

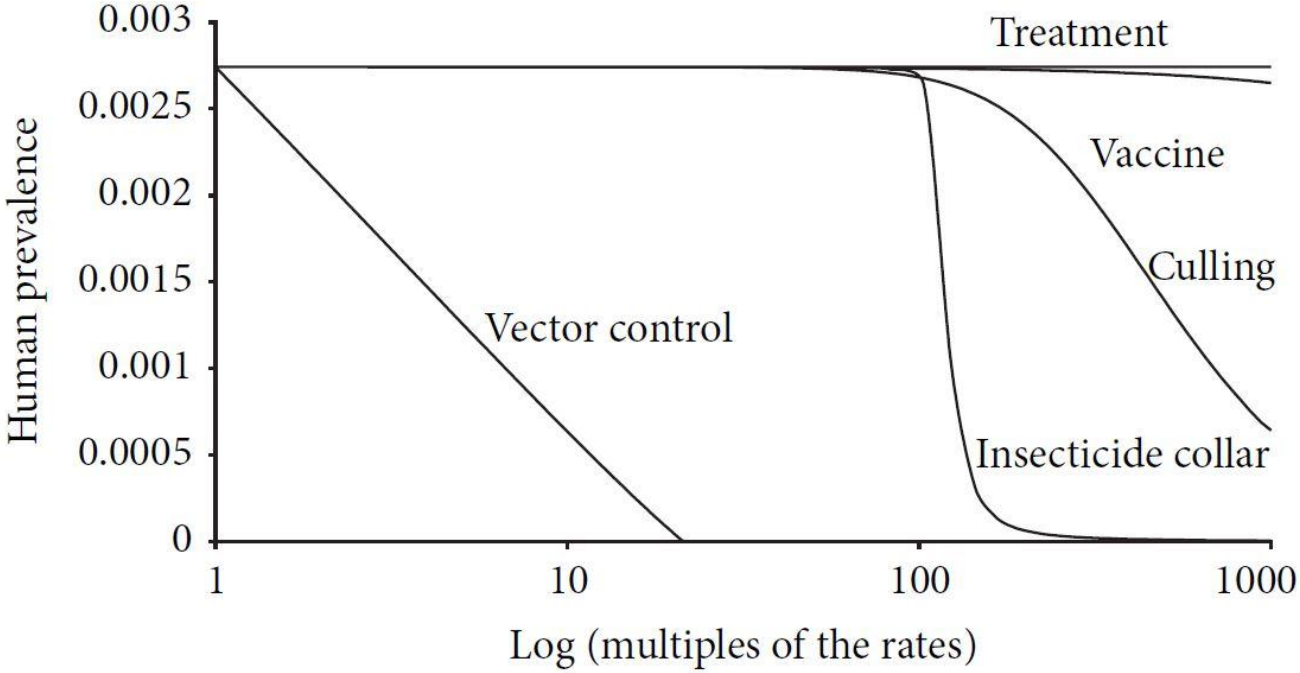
* Ribas et al 2013

The impact of different control methods on canine visceral leishmaniasis



after Dye 1996

Efficacy of CVL control methods*

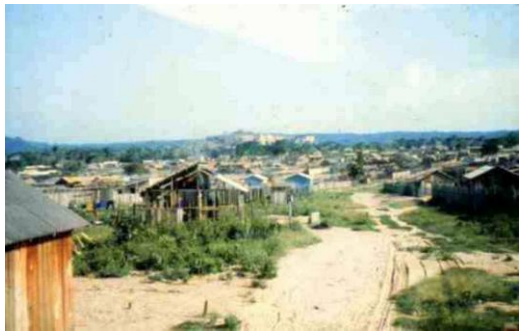


10 Human , 10 Dog & 3 Sand fly índices
4 Dog variables (Treatment, Culling, Vaccination rates and Insecticide collars)

* Ribas et al 2013 Sci Wld Jr

Unexpected effects of Dog Culling

Santarém – Alencar – 1962 – 3 cases – 11 dogs

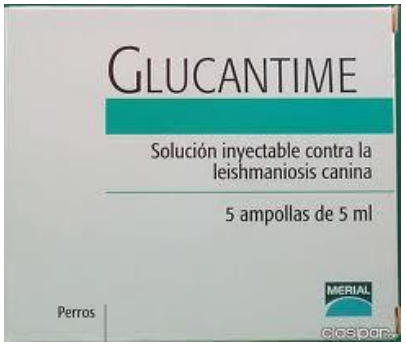


VL Epidemic began in 1982
In 6 months of 1984 51 cases found *

CanVL was exported to the northern banks of the Amazon River

1985
CanVL
endemic

Lainson et al 1985



Should we treat dogs?

Meglumine antimoniate

Danger - Resistance

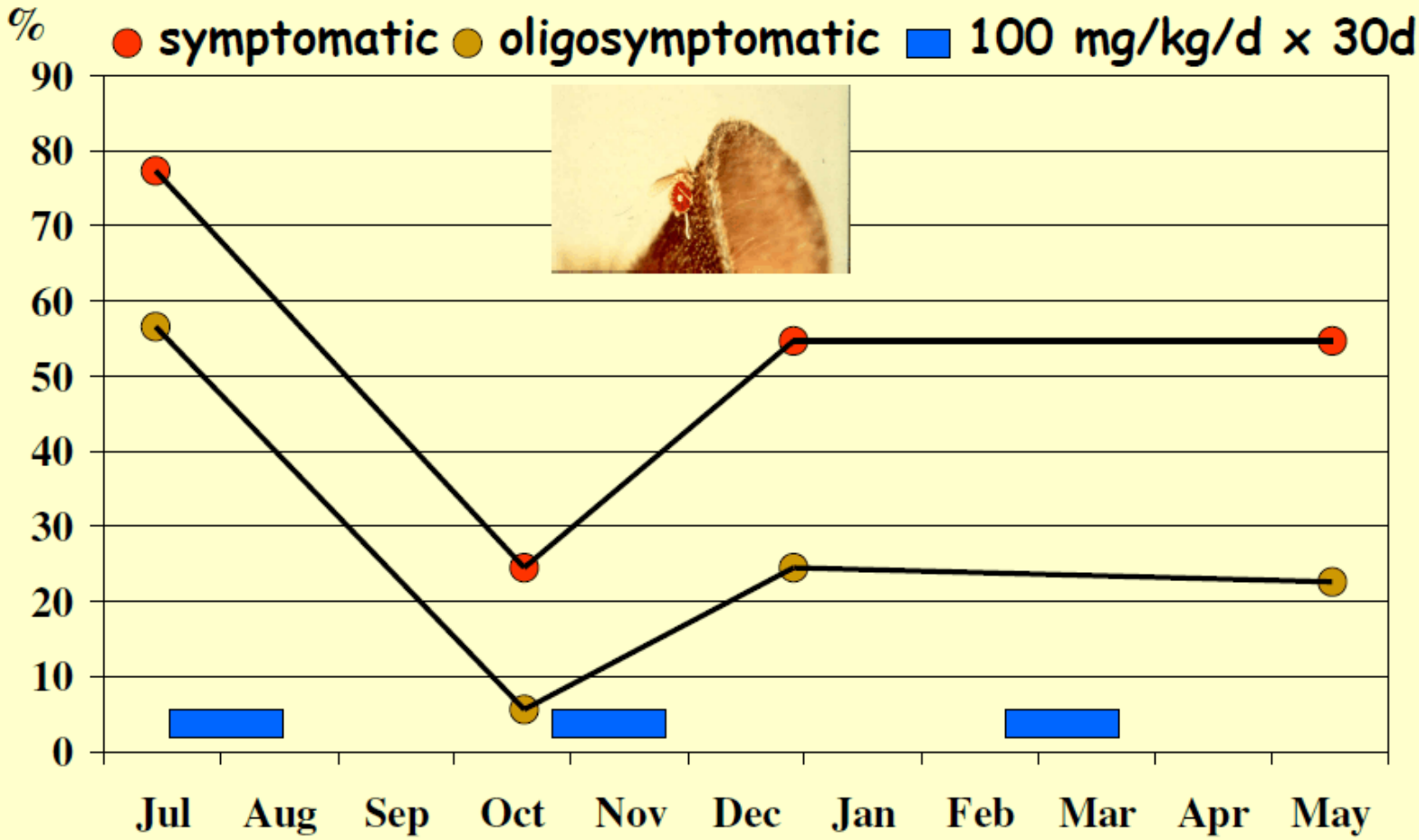
In Europe this is not considered important as patients are treated with **Liposomal amphotericin B** (Ambisome®)

R$ 2,300 90ml
1 ml/10 kg oral
28 days

Milteforan™ (Miltefosine)

Allopurinol

Infection rates in *Phlebotomus perniciosus* fed on dogs under meglumine antimoniate treatment (Gradoni et al 1987)



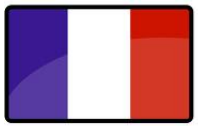
Available Vaccines for canine visceral leishmaniasis

LEISHMUNE® (FML)

LEISH-TEC®

CANILEISH®

(LiESP/QA-21)



The levels of protection in the field are presently controversial

CANILEISH® (LiESP/QA-21)

Experimental results in Beagles

A significant reduction in the number of animals that developed acute infections

Reduction but not elimination of infectiousness to sand flies

Vectors

Many different species

Strategies will depend on knowing the habits of the different species

Based on a vector's biology
Avoid contact

Rarely used
It can be very efficient

Control of leisure habits

Construction Company - Amapá State, Brazil

High incidence of cutaneous leishmaniasis in work force

Common factor – most cases in hunters
Solution – prohibit hunting and entering forest at night
Result – drastic reduction of cases

Limitations – only possible in controlled communities but local communities can be notified of the danger via **educational programs** and a advised to avoid forest

Time of year

Serra dos Carajás, Pará State Endemic for *L .(V.) braziliensis*

The vector *Psychodopygus wellcomei* hibernates in the dry season

Seasonal transmission - No cases in dry season

Jeffrey Shaw
ICB, USP

Environmental management

Potentially one of the most important control methods

Why?

Community based - long term sustainability. Less dependant on the availability of governmental funds (NGOs)

Requirements: knowledge of vector ecology and education of population in endemic area

Effectiveness: Shown to reduce the density of visceral and cutaneous leishmansis vectors

Danger of inadequate sustainability of vector control

Vector population reduced

↓

Transmission rate lowered

↓

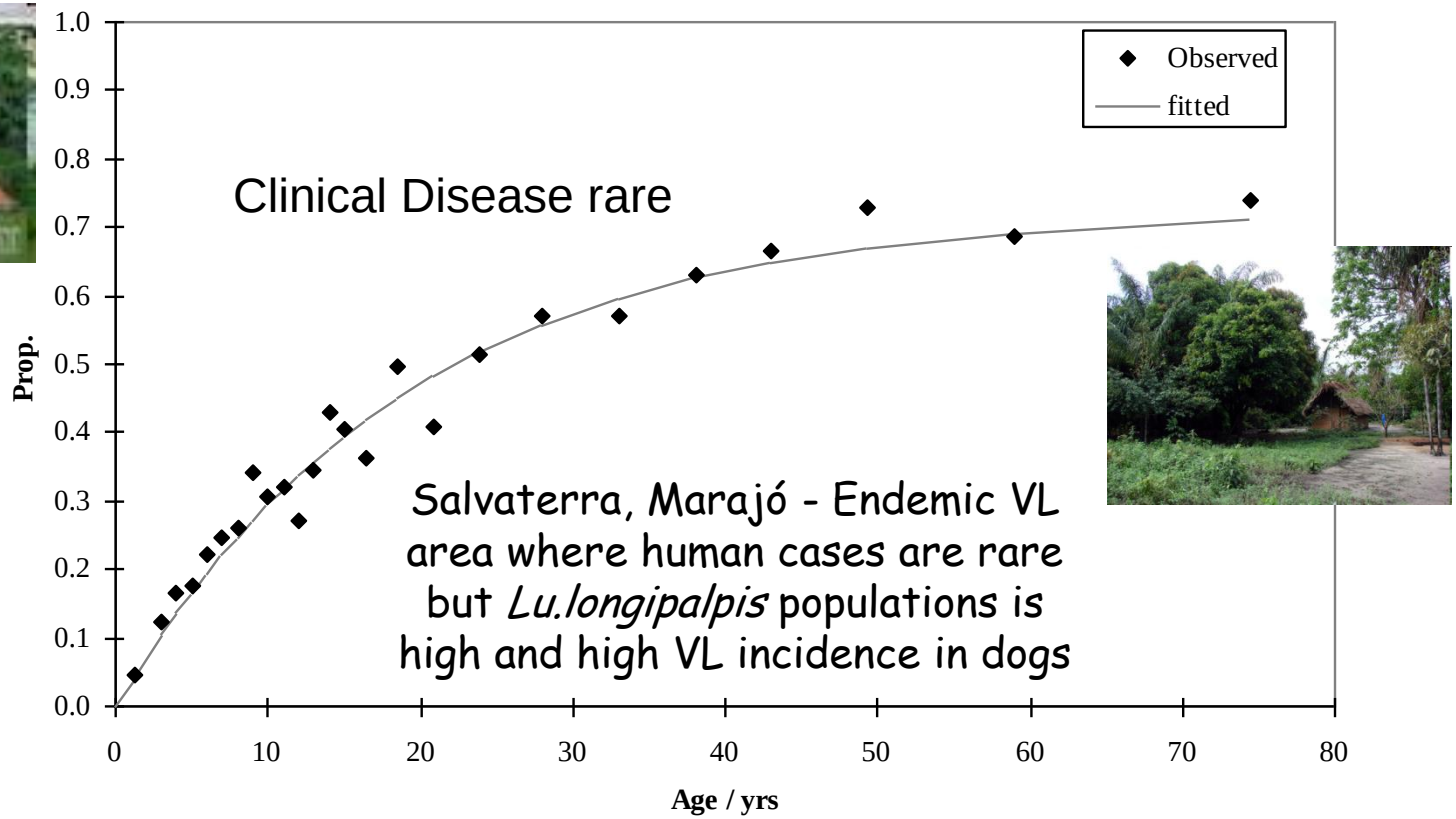
Host population's acquired immune status altered

Control interrupted or stopped

Return of increased transmission levels can potentially lead to an epidemic

An Ethical consideration

If you reduce the sand fly population could you be reducing protection against clinical disease?

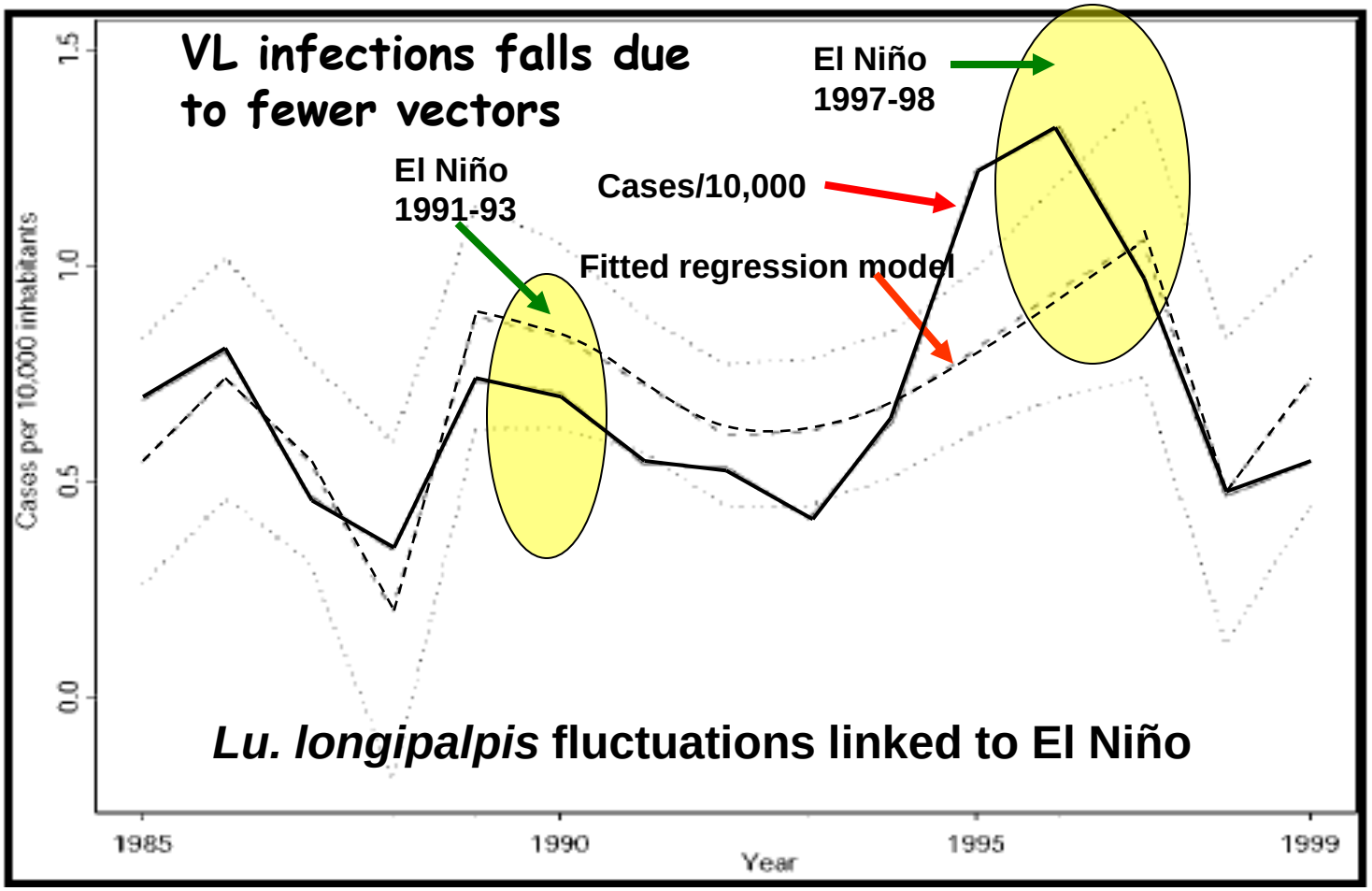


+ve Skin tests are evidence of recovery from infection [1] and are associated with sand fly saliva antibodies [2]

[1] Skin test +ve/age Courtenay et al unpublished observations; [2] Barral et al 2000

El Niño & La Nina 3 -7 years

Lasts for 6-18 months



Source Franke et al 2002

Canine visceral leishmaniasis

Reduce or eliminate contact with the vector *Lu. longipalpis*

Inseticide impregnated collars

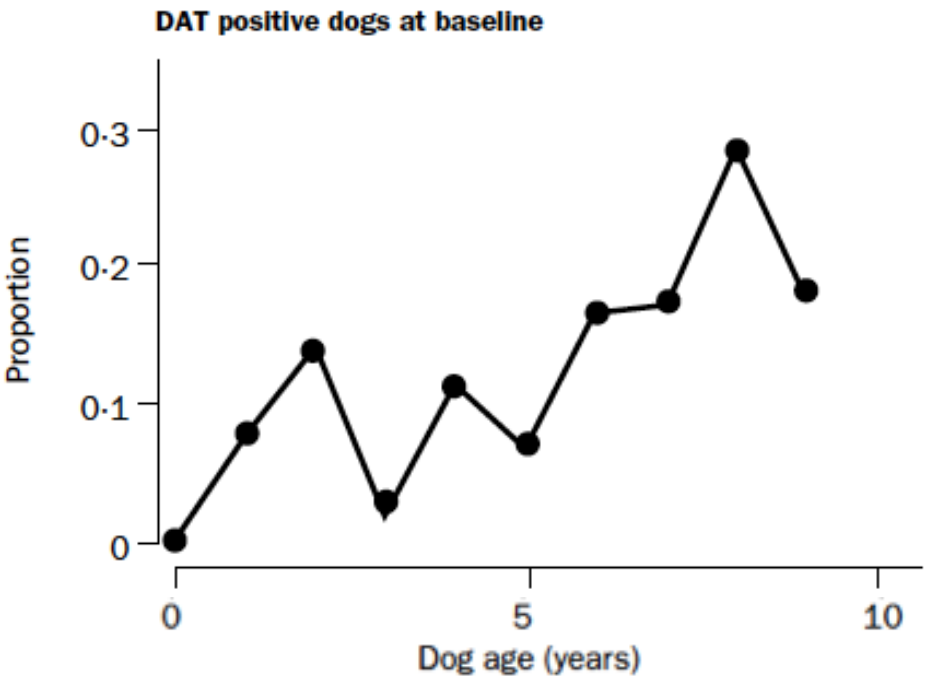
Difficulties: Loss of collar

What is the minimum coverage that will cut transmission levels efficiently to dogs and man?

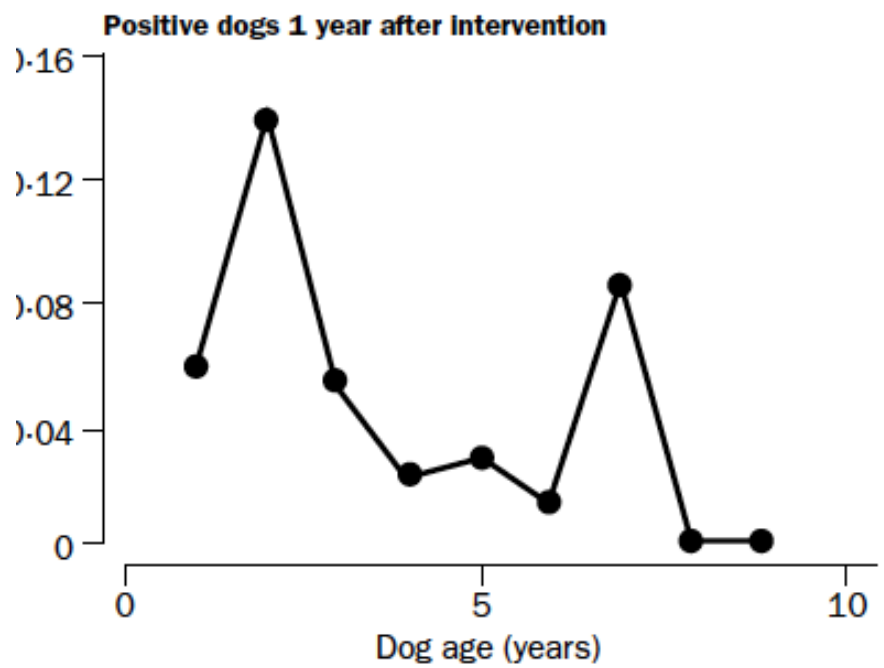
Deltamethrin dipping/baths

Improve formulation

Proportion of dogs with positive direct agglutination VL tests *



Before use of collars



After use of collars for 1 year

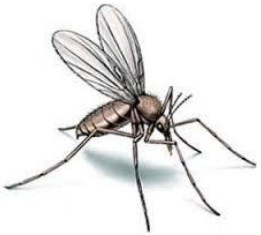
* Gavgani et a., 2002

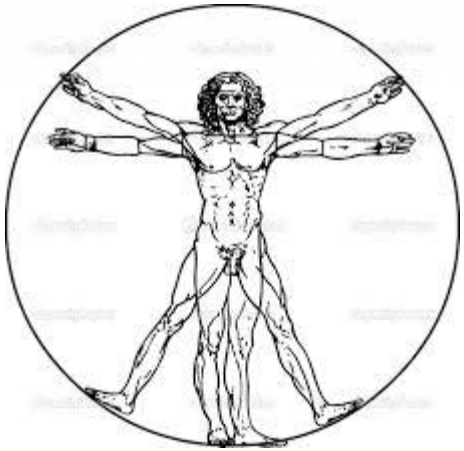
Application of residual insecticide in the domestic environment

Models have shown that ineffective control may provoke changes in vector feeding preferences

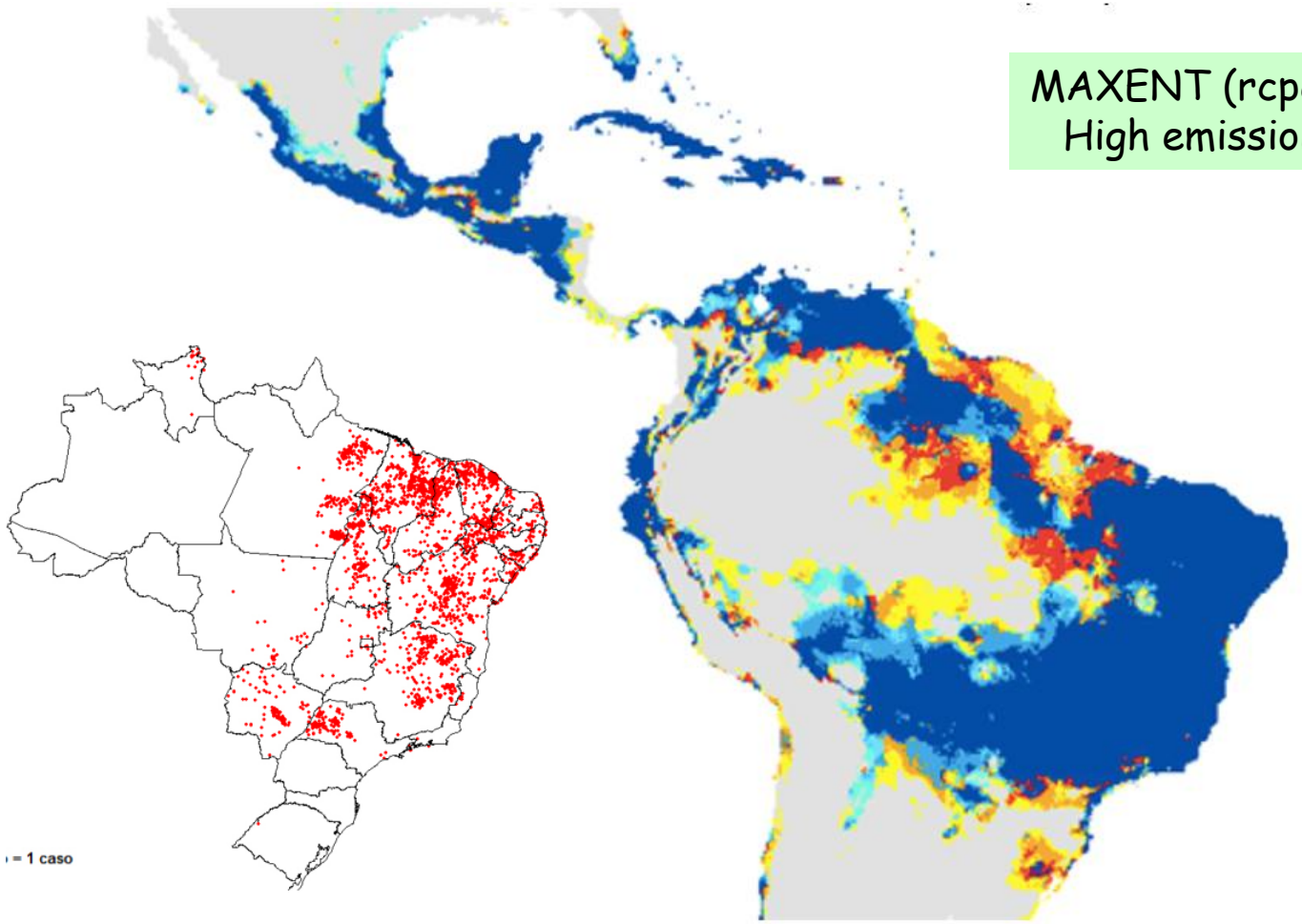
Such as

Dog → Man



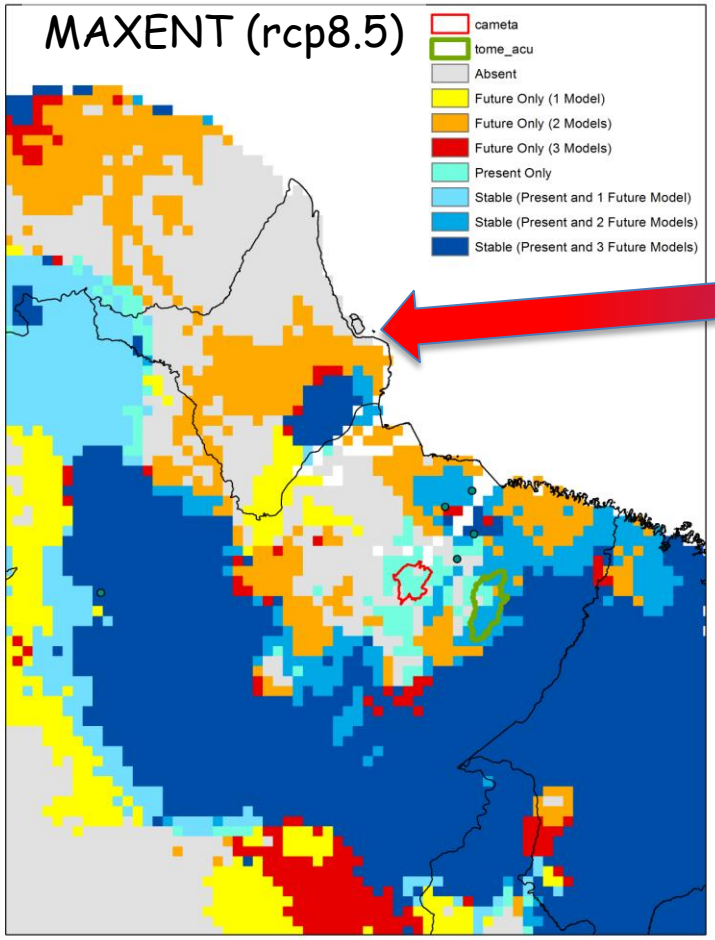


An early warning system - Predicting the distribution of vector ecological niches – *Lutzomyia longipalpis* *



* Peterson et al 2017

An early warning system
Predicting the distribution of vector ecological niches – *Lu.longipalpis* *



Predicted but first record only in 2013

* Peterson et al 2017

Sand Fly Biology

Visceral leishmaniasis chemotherapy

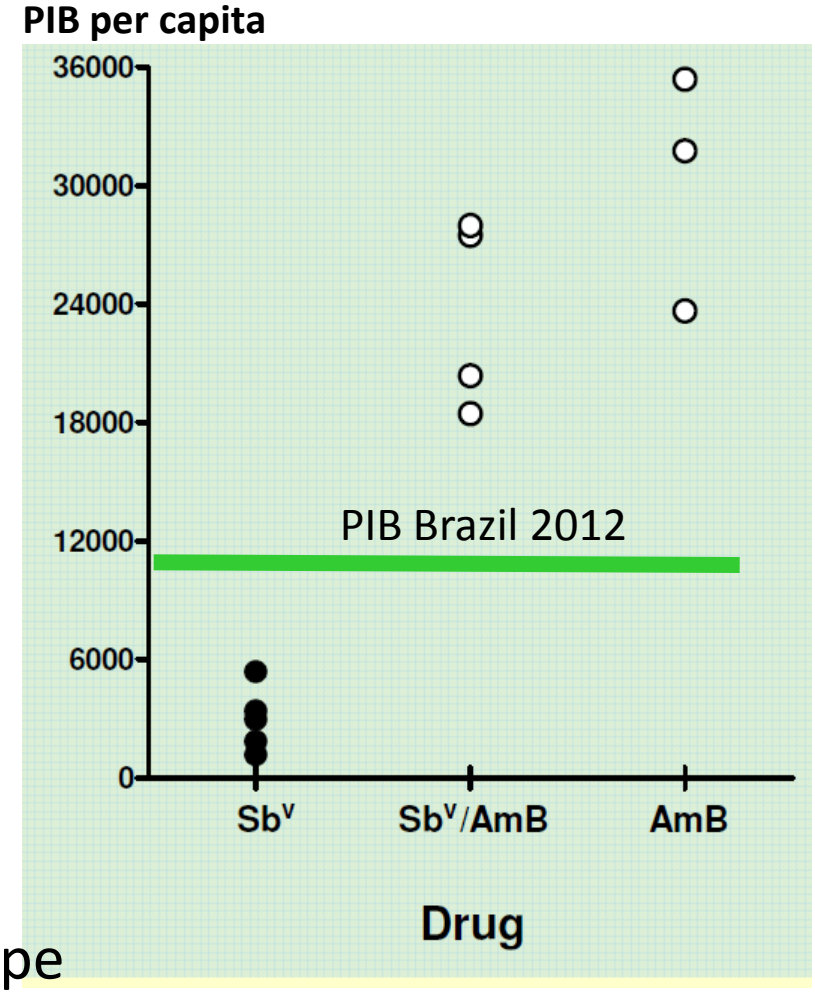
New Drugs – Expensive

1. **Liposomal amphotericin B** (Ambisome®)
   VL

2. **Paromomycin**
   VL oral India
   Only available if purchased in large quantities

Global changes in the treatment regime of human visceral leishmaniasis

Clear relationship to the national PIB*



● Africa e Asia

○ Southern Europe

*Gradoni et al, TM&IH 2008

Leishmaniasis – Diagnosis
The Corner Stone of Control

The methods used for man and reservoirs, such as dogs, are basically the same

Accurate diagnosis is crucial for successful control

An Excellent Example of Test Evaluation

MAJOR ARTICLE

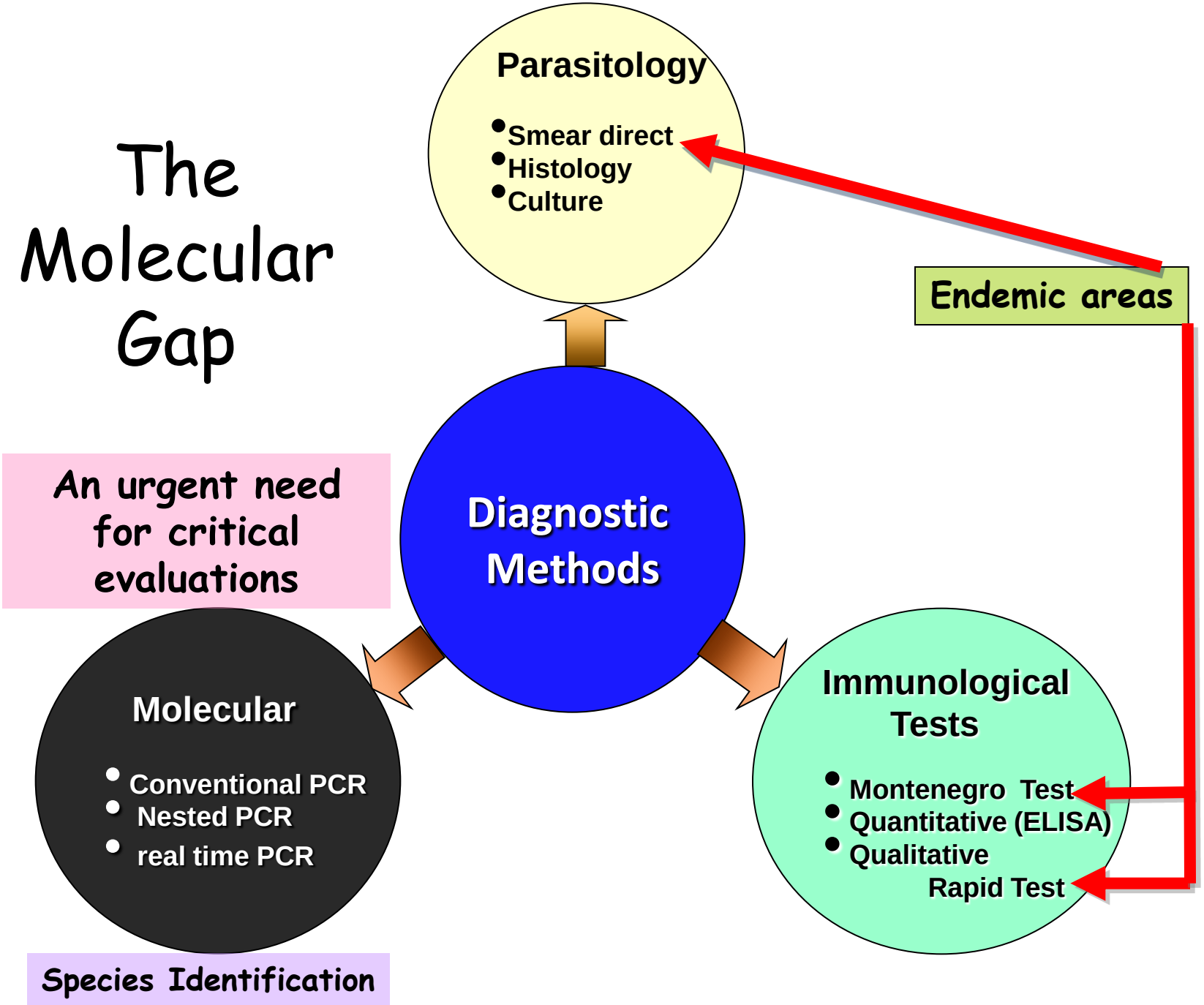
Clinical infectious diseases

A Global Comparative Evaluation of Commercial Immunochromatographic Rapid Diagnostic Tests for Visceral Leishmaniasis

Jane Cunningham,[1,a] Epco Hasker,[2,a] Pradeep Das,[3] Sayda El Safi,[4] Hiro Goto,[5] Dinesh Mondal,[6] Margaret Mbuchi,[7] Maowia Mukhtar,[8] Ana Rabello,[9] Suman Rijal,[10] Shyam Sundar,[11] Monique Wasunna,[7] Emily Adams,[12] Joris Menten,[2] Rosanna Peeling,[13] and Marleen Boelaert[2] for the WHO/TDR Visceral Leishmaniasis Laboratory Network[b]

In Brazil the sensitivity of 5 kits varied from 61,5% to 92,0% but the specificity of all was high

The Molecular Gap



Education & Community Participation

The life cycle

How to avoid being bitten

Boost individual responsibility

FOR

Your house and pets

Conclusions

Ethical problems if long term financial support is not available

The leishmaniases will continue to be a serious public health problem in Brazil

They will

Never **be**