

Challenges in Developing a New Treatment for Chagas Disease

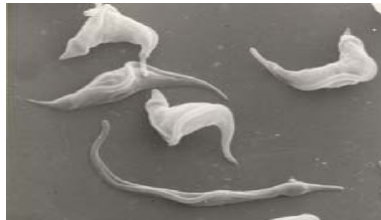
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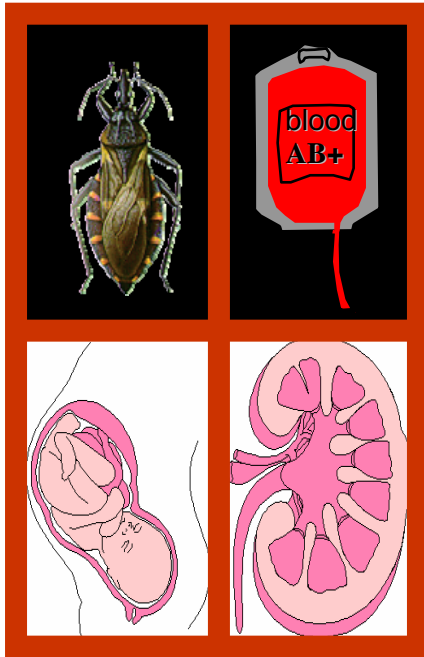


Carlos Chagas



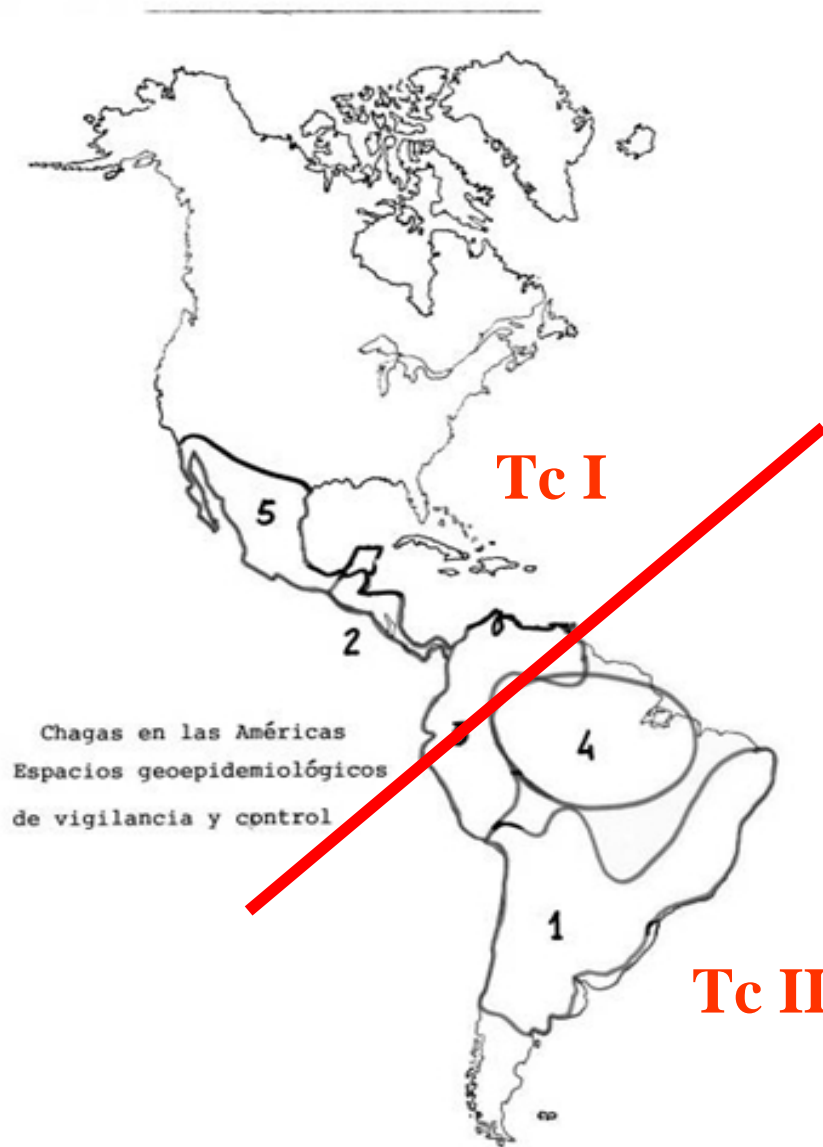
Salvador Mazza





T. Cruzi Transmission

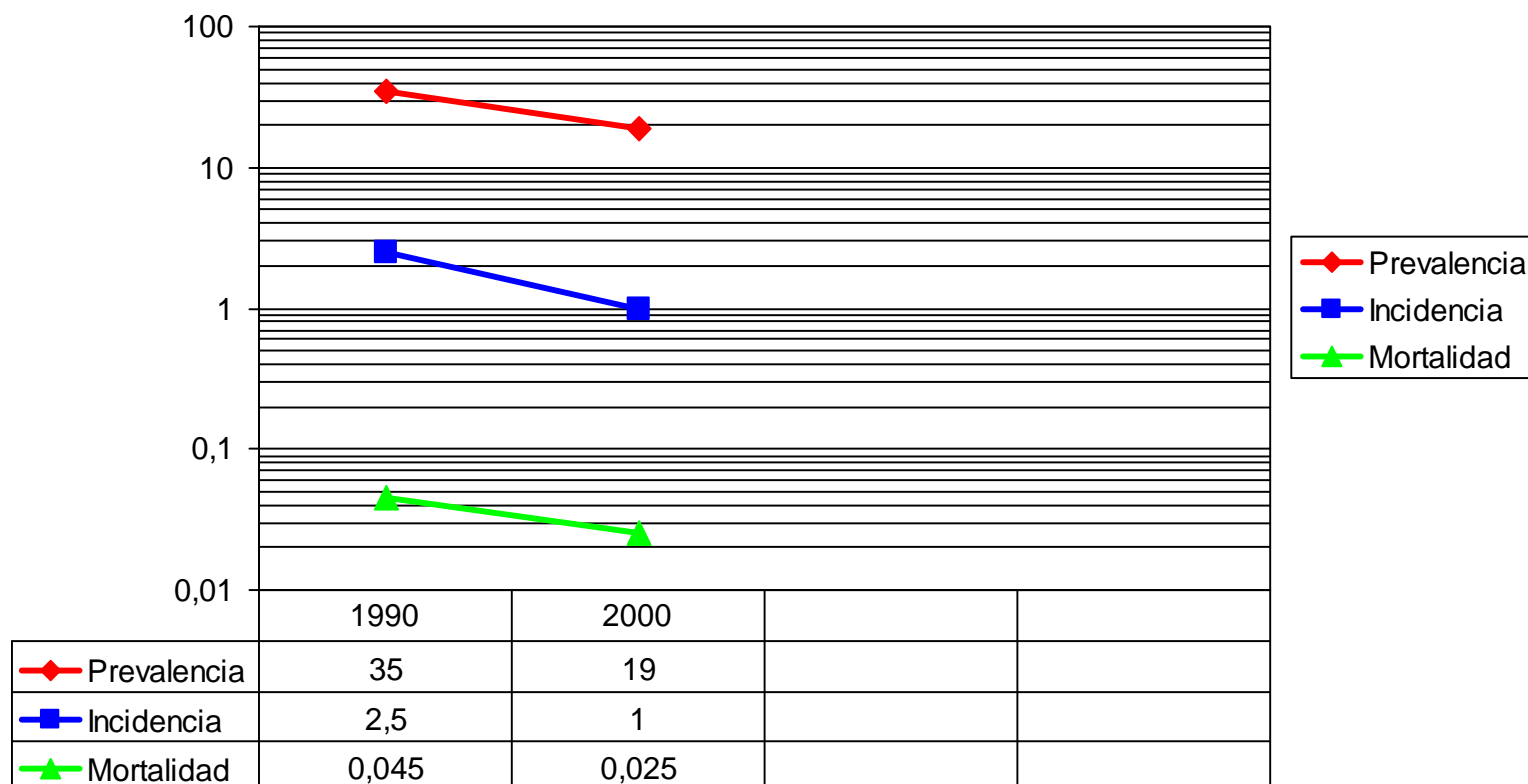
	w/o Control	w/ Control
Vector-borne transmission	>80%	10%
Blood transfusion	16%	<0.01
Congenital	2%	>80%
Other mechanisms: <i>(i.e. oral, organ transplant, laboratory accident)</i>	<1%	<1%



Initiatives for interrupting vectorial and transfusional transmission of *Trypanosoma cruzi*

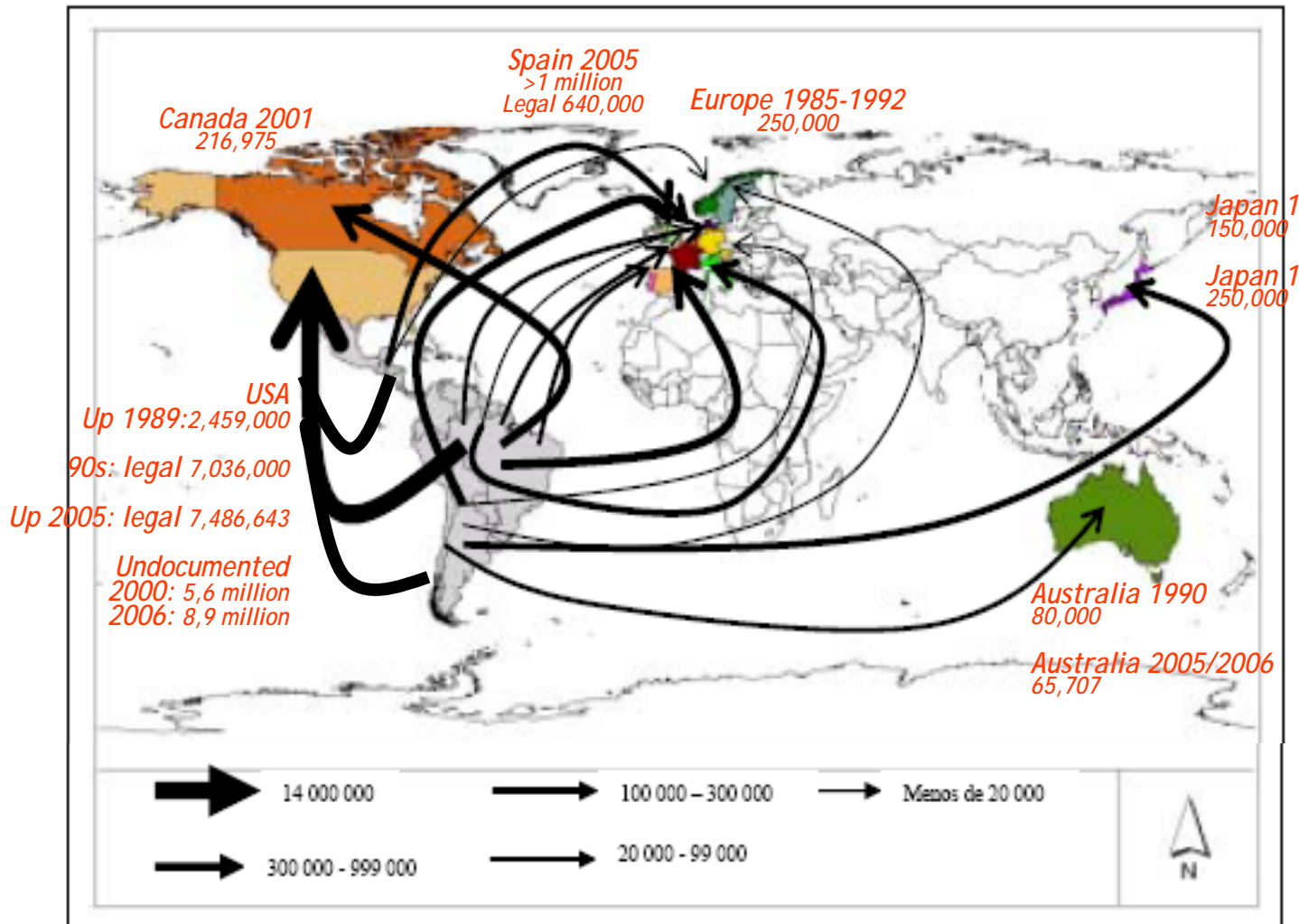
Trend of epidemiological indexes of Chagas' disease in Latin America, 1990-2000

Rates x 1000 inhabitants



Source: Moncayo, A. The Burden of Disease: Chapter 13, Chagas disease, World Health Organization, World Bank, Harvard University Eds. Boston 2003

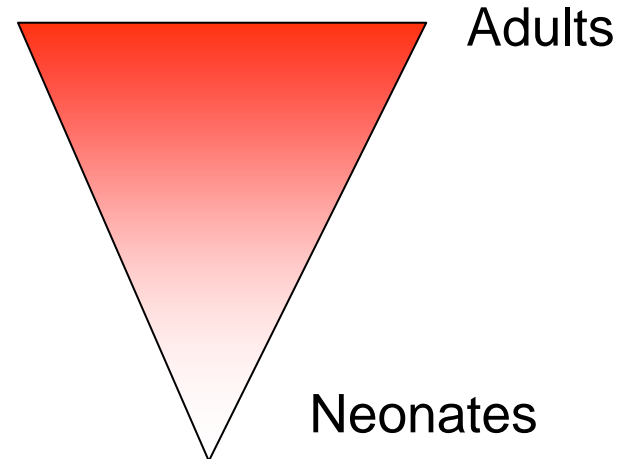
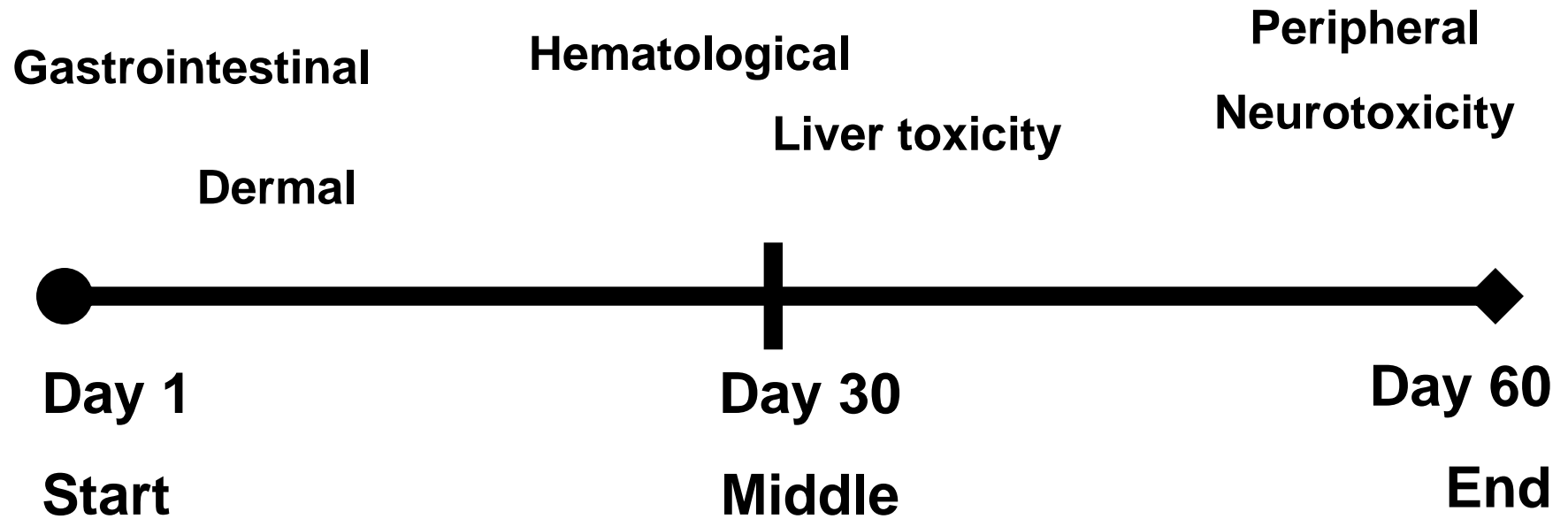
Migration Flows from Latin America Chagas' disease



Current Recommendations for Specific Treatment against *T. cruzi* Infection

- All patients in the acute phase
- Children and young patients in the chronic phase
- Laboratory or surgical accidents
- Organ transplant recipients or donors
- Chronic phase, indeterminate or incipient cardiac form in adults may be considered for treatment, although with limited evidence

Side Effects: Timeline

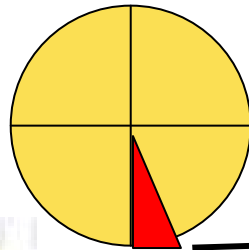


Tolerability Monitoring

- Weekly contact with the patient
- Laboratory testing

Treatment of children: there are no adequate formulations for pediatric use

Product sheet with problem



1/16 doses each 12 hs ???

New approaches

Solution: UNR Argentina

Suspension: LAFEPE Brazil

Adapted tablet size: DNDi/LAFEPE Brazil

Some concerns with tablet fragmentation

- Improper dosages
- Drug may not disperse uniformly when grinded and suspended in liquids
- Potential impact on:
 - Pharmacokinetics
 - Safety
 - Efficacy

Different parameters to take into account for a new formulation or new presentation

- Ease of administration (preparation and dosing)
- Accuracy of dose administered
- Flexibility of dose
- Stability of the preparation
- Acceptability/suitability of the preparation
- Excipients acceptability
- Manufacturing and financial implications

Some alternatives

Liquid formulations

- Syrup
- Reconstitutable dry suspensions

Solid formulations

- Immediate release tablets
- Effervescent, soluble or dispersible tablets
- Chewable tablets
- Orodispersible dosage forms
- Multiparticulate preparations

Registered drugs with anti-*T. cruzi* activity

- Posaconazole (antifungal)
- Bisphosphonates (osteoporosis)
- Miltefosine (antineoplastic, antiprotozoal)
- Clomipramine (tricyclic antidepressant)
- Liposomal amphotericin (antifungal, antiprotozoal)

Evaluation of Combination Treatment

Objectives

- Different types of combination treatments depending on the main objectives of the treatment:
- Improvement of efficacy
- Delay of development of resistance to the individual components of the combination
 - With low levels of resistance, low prevalence and deficiencies in laboratory testing: impact of resistance to antiparasitic agents is insidious.
 - Unless clinical drug trials are conducted, resistance and its impact often go unrecognized
- Improvement of safety profile
- Reduction of dose and duration of treatment regimens
 - Side effects of Bz and Nftx are both dose and time-dependent

Evaluation of Combination Treatment

Pragmatic decision for short term evaluation:

Combination of registered compounds
(Benznidazole/Nifurtimox) with drugs with
demonstrated activity in Chagas' disease

Animal studies - Combination studies

Combination candidates

Benznidazole +

Nifurtimox +

Itraconazole

Ravuconazole

Posoconazole

TAK 187

Miltefosine

Evaluation of library of existing compounds

Priorities:

- Determine IC50s for hits from existing libraries
- Toxicology/pharmacology review of hits
- Proceed to *in vivo* models as monotherapy if justified
- Prioritize partner drugs from existing libraries and current Chagas therapy
- Assay for additive/synergistic effects in vivo
- Review of hits as scaffolds for lead optimization

How to assess a treatment during chronic phase?

- Immunological tests
 - Serological tests - Commercially Available
 - Need long follow up to demonstrate efficacy
 - Serological tests - Not commercially available, tested as useful
 - Need shorter time of follow up, but > 3 years
 - Need validation
 - Specific cellular response (under research)
- Parasitological tests
 - Direct tests (low sensitivity)
 - Xenodiagnosis (only in centers of reference, low sensitivity)
 - Hemoculture (available, low sensitivity)
 - PCR (higher sensitivity, currently under standardization, new techniques quantitative PCR with rapid developments)

Need for clinical research

Etiological treatment

- To develop and assess new formulation or presentation of old drugs
- To assess new application of drugs for other indications
- To develop novel drugs
- To develop new tools to assess efficacy of current and new treatments in short time
 - To validate and standardize PCR test

Needs for clinical research

Other issues

- To develop new tools to diagnose congenital *T. cruzi* infection at the time of delivery
- To find and assess markers of evolution of disease
- To gather evidence for selection of interventions in case management

They are waiting for...



the researcher to research,

the politician to decide,

and the health worker to do

Thank you !!

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