

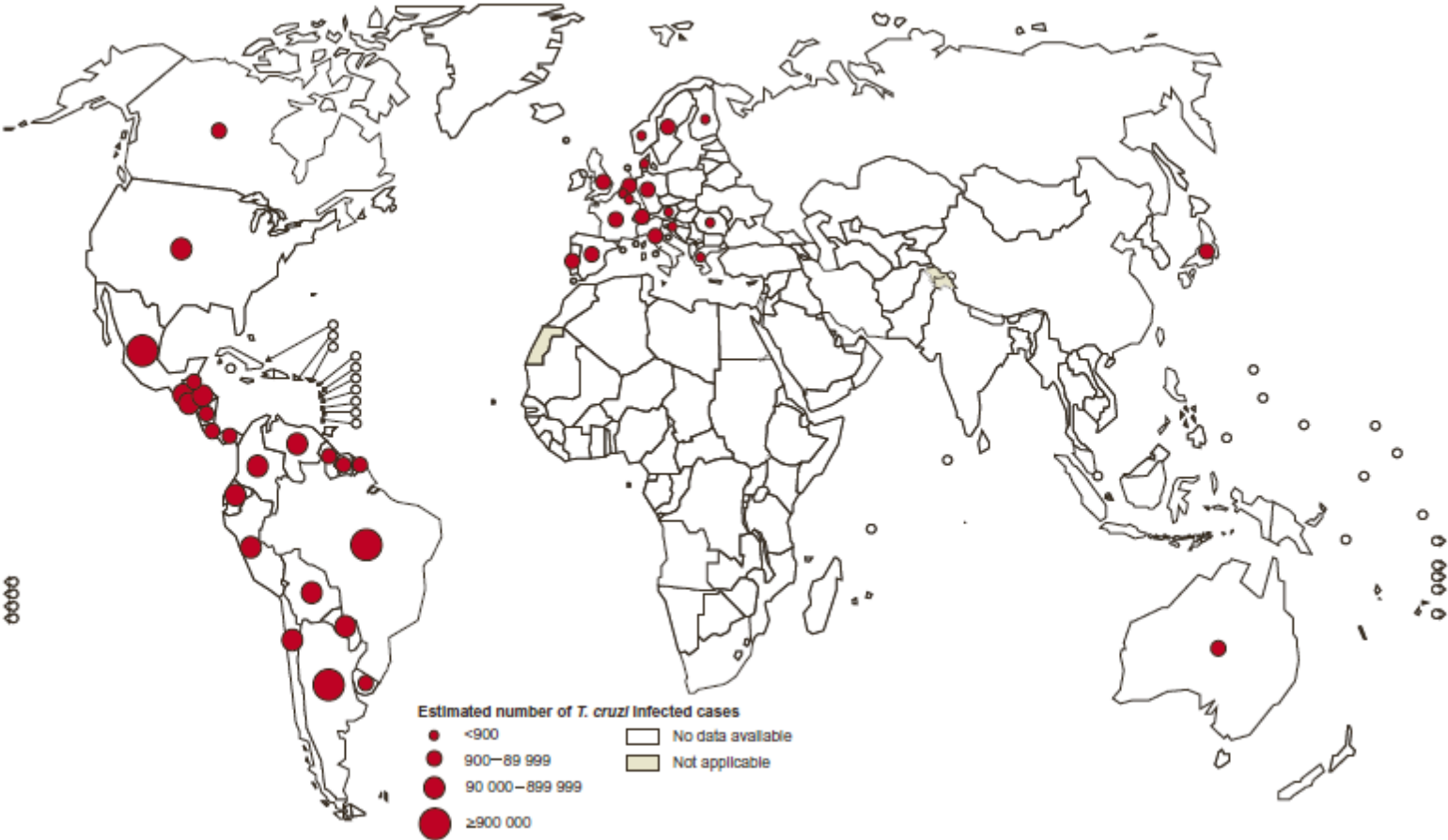
Frontiers in Science on Neglected Diseases

Chagas Disease: recent clinical developments

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INP Fatala Chaben-ANLIS, Ministerio de Salud. CONICET
Advisor Board DNDi Latin America

Sao Paulo 13-14, 2014

Global distribution of cases of Chagas disease, based on official estimates, 2006–2010



Source: Sustaining the drive to overcome the global impact of neglected tropical diseases. Second WHO report on neglected tropical diseases; 2013. Chapter Chagas Disease.

Clinical studies in 60-70

CHEMOTHERAPY OF CHAGAS' INFECTION IN MAN • J. A. CERISOLA

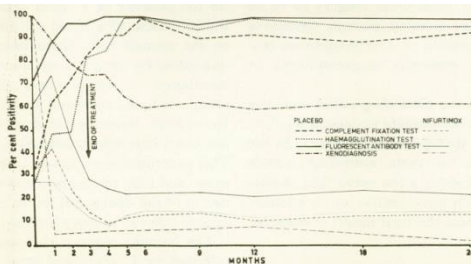


Figure 1. Serological and parasitological evolution in acute Chagas' infection (51 untreated patients and 550 treated with nifurtimox).

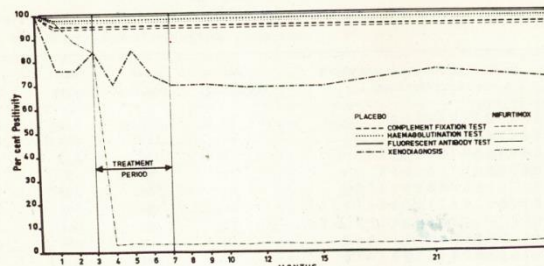


Figure 2. Serological and parasitological evolution in chronic Chagas' infection. (30 untreated patients and 30 treated with nifurtimox).

Evolución clínico-parasitológica y tolerancia a la droga de 33 niños con infección chagásica crónica tratados con Bay 2502 *

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Abstract

Clinical-Parasitological Evolution and Drug's Tolerance in Chronic Chagasic Children Treated with Bay 2502

Bay 2502 was administered to thirty-three children with chronic Chagas' infection. All these children had positive serology and 25% of them had also positive xenodiagnosis. As control, seven similar children received only a placebo.

Table 11. Chronic Chagas' infection. Nifurtimox. Summary of results as per duration and site of treatment.

Site	90-120 days			30-60 days		
	Failures	Cured	%	Failures	Cured	%
Argentina	1	18	94.7	1	9	90.0
Chile	1	8	88.9	1	5	83.3
Pôrto Alegre	0	13	100.0	2	15	88.2
Brasília	5	4	44.4	2	4	66.7
Total	7	43	86.0	6	33	84.6

Between treatments $p > 0.10$ not significant
 Between Argentina, Chile, and Pôrto Alegre $p > 0.10$ not significant
 Between Brasília and the rest $p < 0.005$ very significant



Table 7. Therapeutic results in conclusive cases. Pôrto Alegre (Brazil)

Treatment	Cases not cured	Cases cured	%	Total cases
Long	0	13	100.0	13
Short	2	15	88.2	17
Total	2	27	93.1	29

Table 17. Comparison of treatment results chronic Chagas' disease (Argentina)

Treatment	No. Cases	No. Cured	Percentage Cured
Nifurtimox	29	27	93
Benznidazole	31	29	94

Table 9. Therapeutic results in conclusive cases, Brasília

Treatment	Cases not cured	Cases cured	%	Total cases
Long	5	4	44.4	9
Short	2	4	66.7	6
Total	7	8	53.3	15

Preclinical and Clinical studies in 90

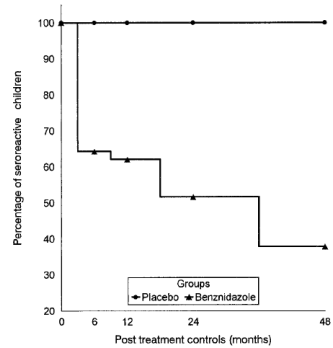
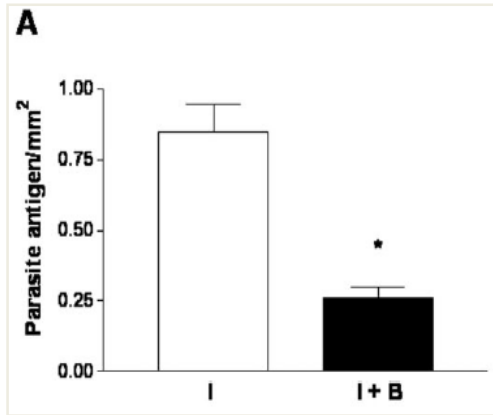


FIGURE 1. Decrease in the percentage of children with reactive serology against *Trypanosoma cruzi* (indeterminate phase of Chagas' disease) by enzyme immunoassay using the F29 protein after treatment with benznidazole or placebo in Salta, Argentina, 1991–1995.

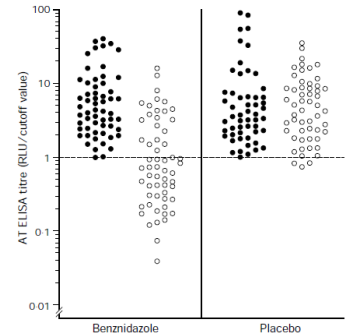


Figure 2: AT ELISA results at trial entry (●) and at end of follow-up (○) for 58 benznidazole-treated and 54 placebo-treated children who completed trial treatment. Broken horizontal line=cut-off; values below this indicate seronegativity.



Figure 2. Kaplan–Meier curves of cumulative percentage of patients who changed clinical group.

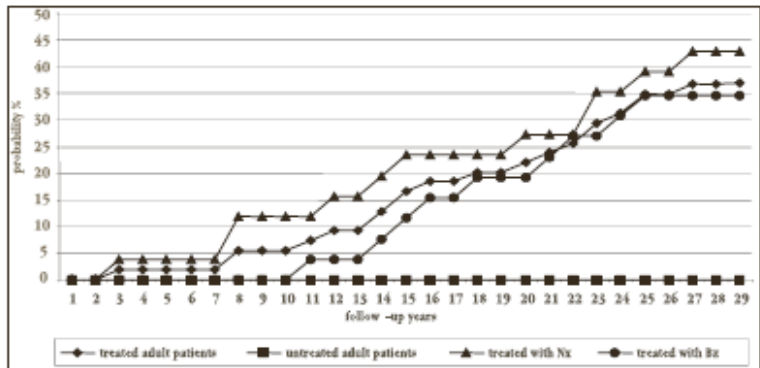
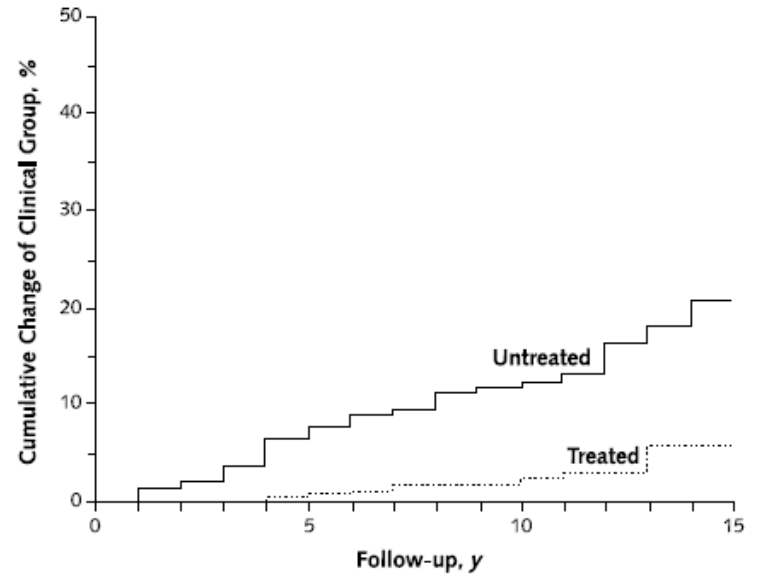


Figure 2 - Probability of negative seroconversion in adult patients with chronic Chagas disease, treated with nifurtimox and/or benznidazole and untreated, over the course of time.

NEW PARADIGM 00

Review Article

Therapy of Chagas Disease: Implications for Levels of Prevention

Antimicrobial Agents and Chemotherapy

Towards a Paradigm Shift in the Treatment of Chronic Chagas Disease

R. Viotti, B. Alarcón de Noya, T. Araujo-Jorge, M. J. Grijalva, F. Guhl, M. C. López, J. M. Ramsey, I. Ribeiro, A. G. Schijman, S. Sosa-Estani, F. Torrico and J. Gascon
Antimicrob. Agents Chemother. 2014, 58(2):635. DOI: 10.1128/AAC.01662-13.
 Published Ahead of Print 18 November 2013.

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NHEPACHA
Red Iberoamericana

Acute Phase

Acute and Chronic Phase

Old Paradigm

New Paradigm

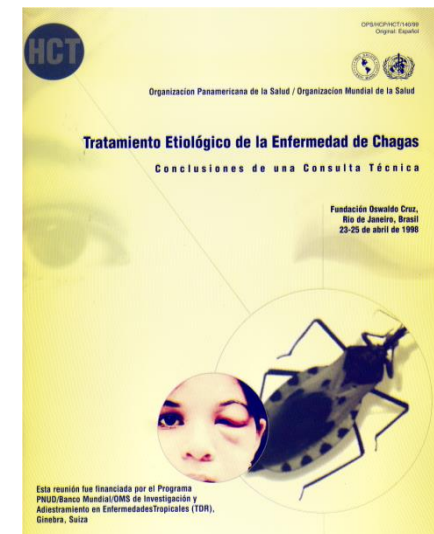
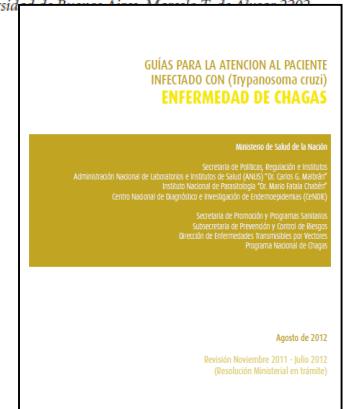
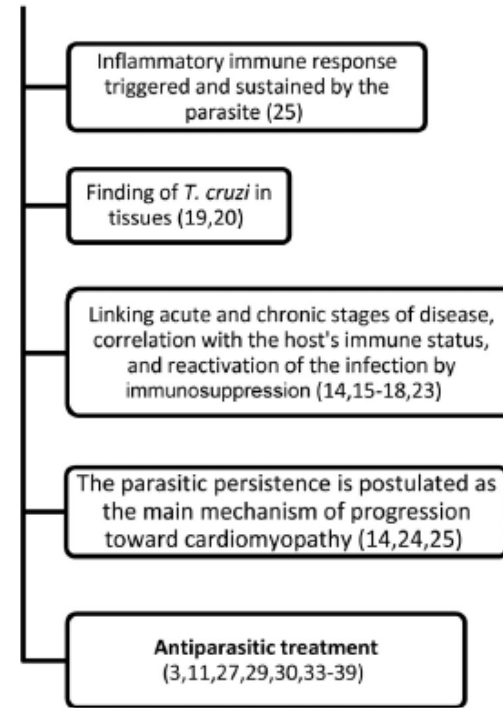
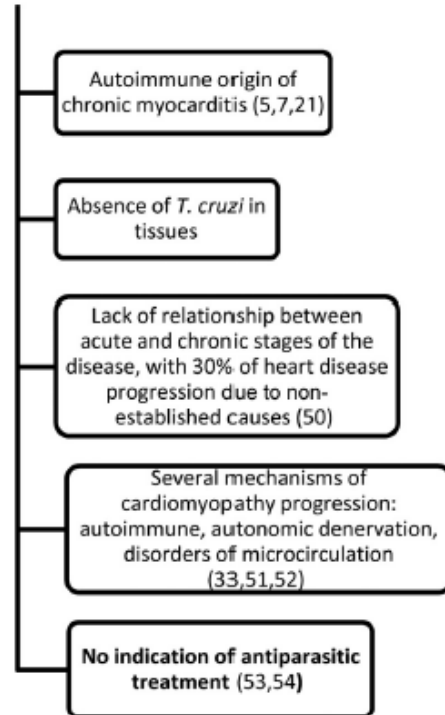


FIG 1 Comparison of concepts belonging to the old and the new paradigms for chronic Chagas disease. Relevant references are given in parentheses.

Diverse strong of recommendation (A-E) and level of evidence (I-III)

Chagas Disease – The TPP

	Acceptable	Ideal
Target population	Chronic	Chronic and Acute (Reactivations)
Strains	TcI, TcII, TcV and TcVI (according to new 2009 classification)	All according to new classification (2009)*
Distribution	All areas	All areas
Adult/children	Adult	All
Clinical efficacy	Non inferior to benznidazole in all endemic regions (parasitological)	Superiority to benznidazole to different phases of disease (acute and chronic) (parasitological)
Safety	Superiority to benznidazole ** 3 CE plus 2 standard LE or ECG during treatment	Superiority to benznidazole or nifurtimox No CE or LE or ECG needed during treatment
Activity against resistant strains	Not necessary	Active against nitrofurantoin- and nitroimidazole-resistant <i>T. cruzi</i> strains
Contraindications	Pregnancy/lactation	None
Precautions	No genotoxicity; No pro-arrhythmic potential	No genotoxicity; No teratogenicity; No negative inotropic effect; ; No pro-arrhythmic potential
Interactions	No clinically significant interaction with anti-hypertensive, anti-arrhythmic and anticoagulants drugs	None
Presentation	Oral	Oral
Stability	3 years, climatic zone IV	5 years, climatic zone IV
Dosing regimen	Comparable to systemic antifungal treatments	Once daily/ 30days

Some strategies looking for new tripanocidal treatment with better (or at least with the same) efficacy, and more safety

- **Old drugs-scheme and new prescriptions**
 - Benznidazole: **BENEFIT, TRAENA, MADRES**
- **Old drugs and new presentation**
 - Pediatric formulation of benznidazole: **PopPK**;
 - Nanoformulation of Benznidazole: **BERENICE**
- **Registered drugs with anti -*T. cruzi* action**
 - Posaconazole: **CHAGASAZOL, STOP CHAGAS**
- **New compounds**
 - Ravuconazole: **E1224**
 - Fexinidazole
 - Others screened by library of compounds
- **Combination**
 - Benznidazole-Posaconazole: **STOP CHAGAS**

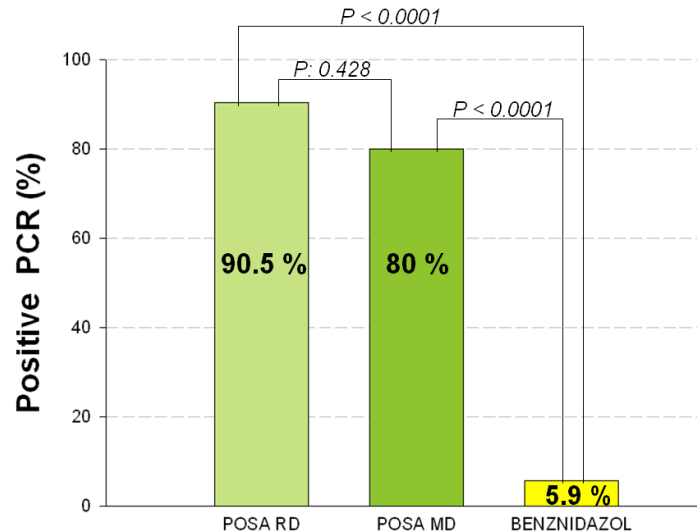
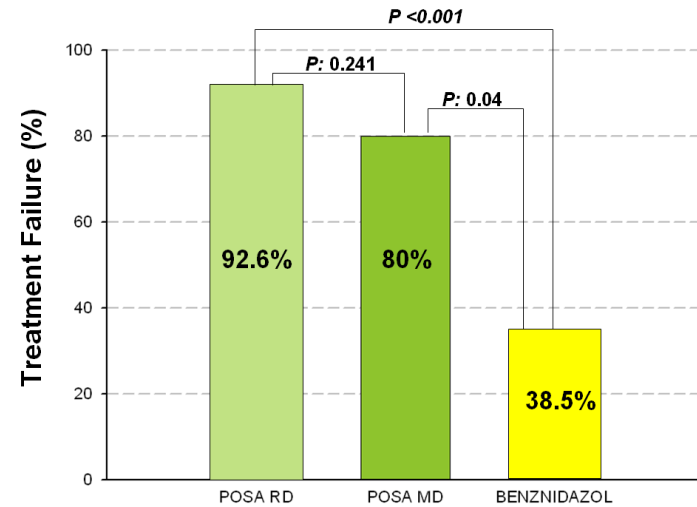
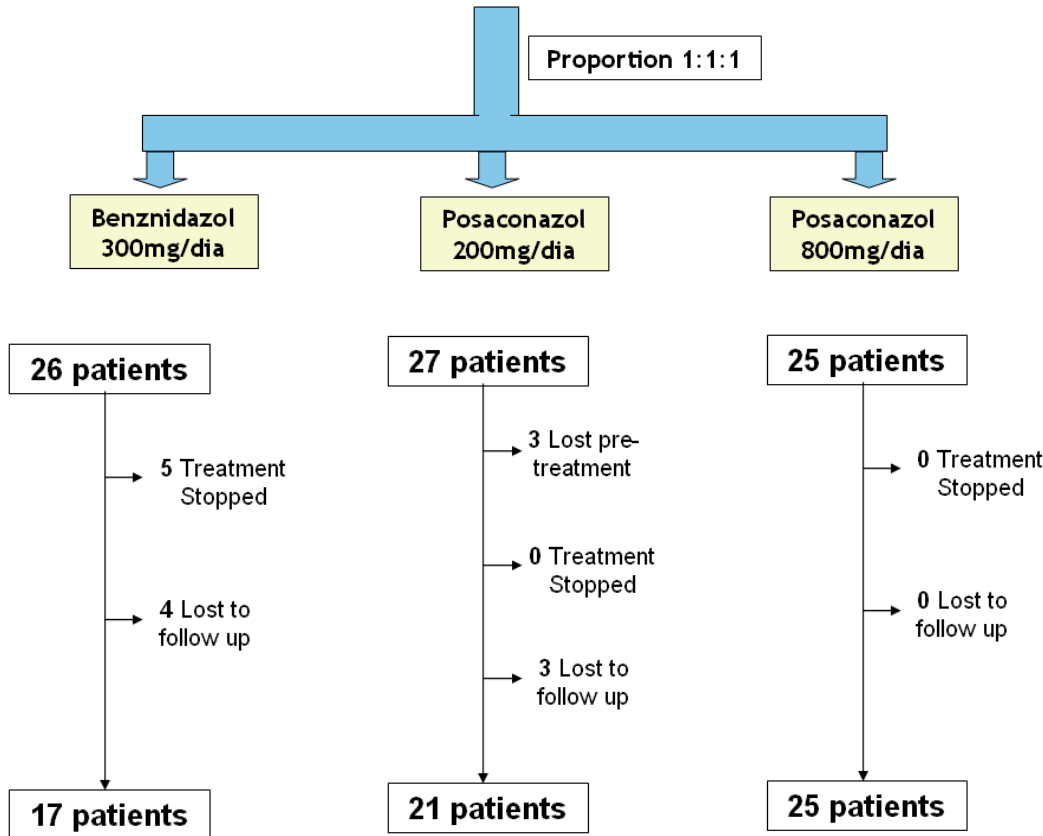
CHAGASAZOL Study: RCT PHASE II

Randomized Trial of Posaconazole and Benznidazole for Chronic Chagas' Disease

Molina I et al N Engl J Med 370;20, 2014

CHAGASAZOL

Proportion 1:1:1



PCR TREATMENT: D0 D7 D14 D28 D45 D60
FOLLOW UP: M4 M6 M8 M12

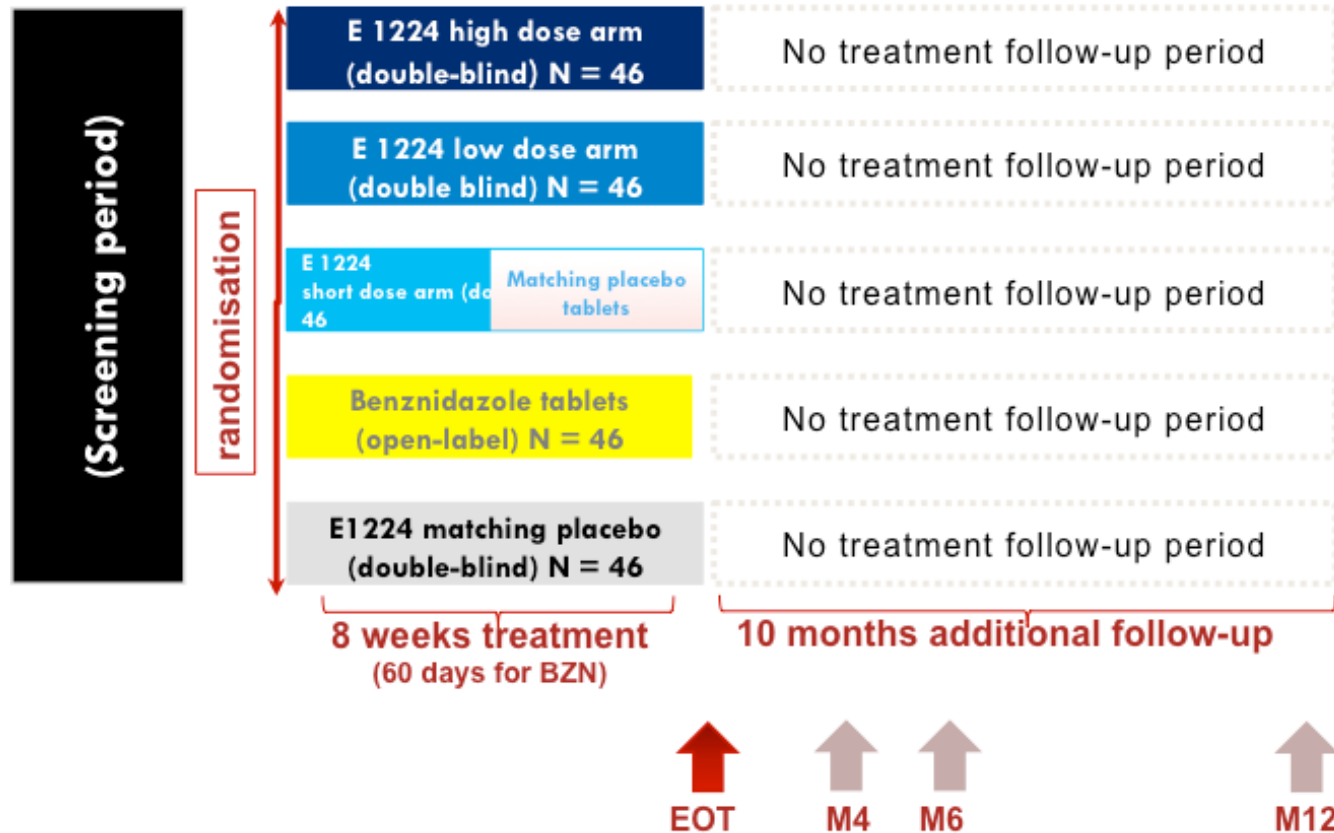
TWICE / 10ML
<40: Positive

E1224 Study: RCT PHASE II

Manuscript in preparation

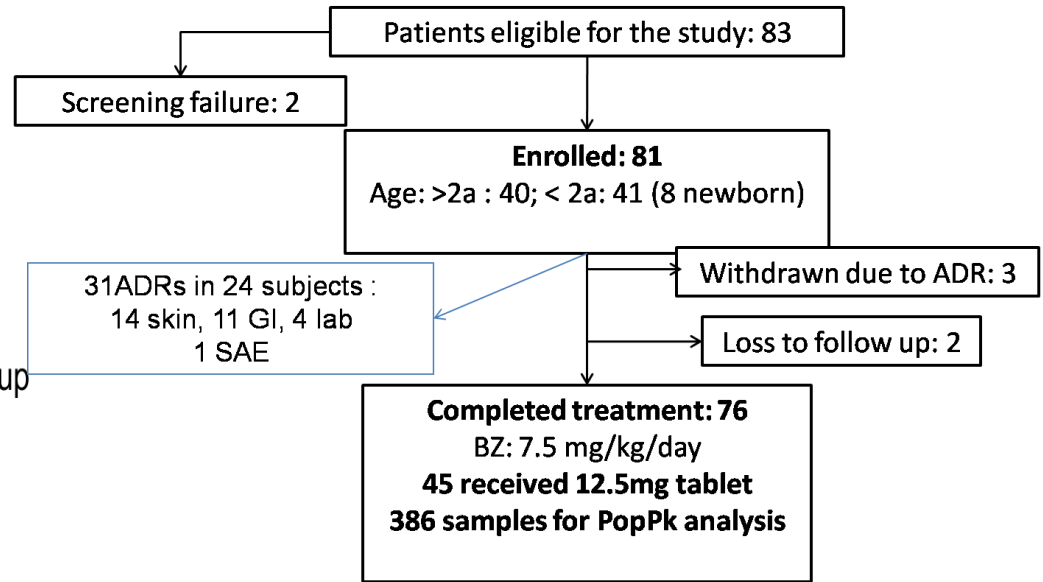
DNDi-CH-E1224-001
NCT01489228

- Efficacy based on serial qualitative and quantitative PCR and other candidate biomarker assessments
- Parasite assessment before and after treatment
- PKPD for both E1224 and BZN

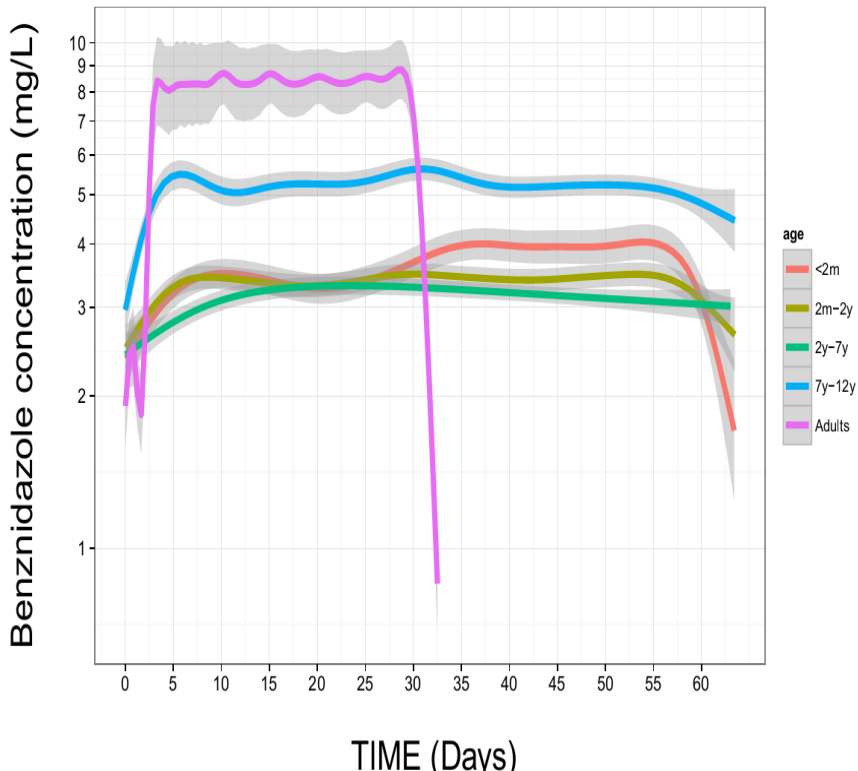


POP PK Project: Prospective population pharmacokinetic cohort study in children

All children had a positive treatment response, with negativization of *T. cruzi* qPCR



BNZ concentrations (polynomial regression) by age group

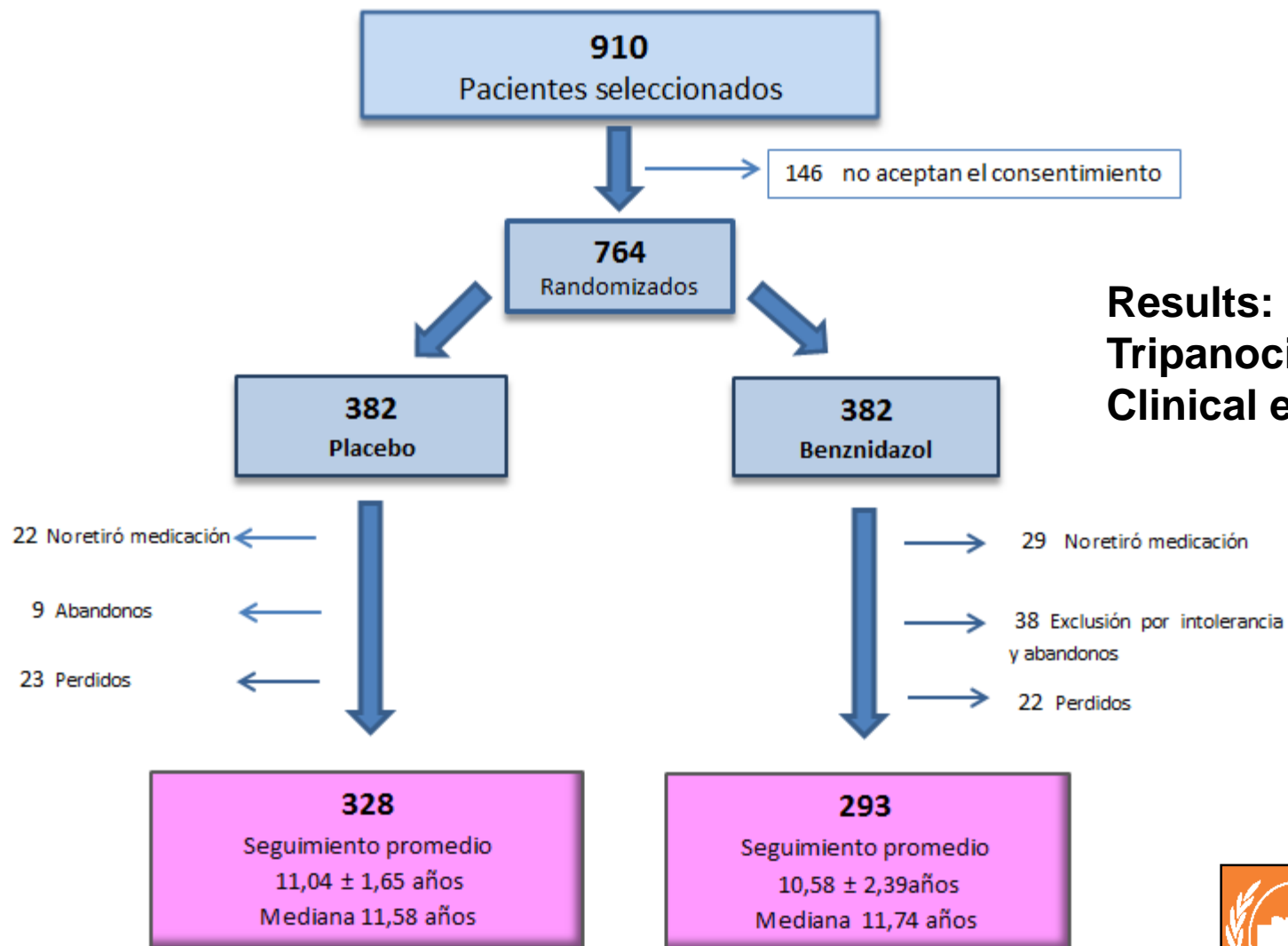


Pediatric network
PEDCHAGAS

TRAENA Study: PHASE III

Manuscript in preparation

Treatment with benznidazole in adult chronic Chagas disease patients



Results:
Tripanocide effect $p < 0.05$
Clinical evolution $p > 0.05$

BENEFIT Project: PHASE III

BENZnidazole Evaluation For Interrupting Trypanosomiasis



October 4, 2011 - Pts recruited = 2,856



Number of centers: 50

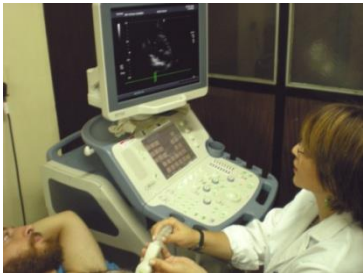
Argentina: 19 (n=559)

Brazil: 25 (n=1360)

Colombia: 4 (n=502)

Bolivia: 1 (n=357)

El Salvador: 1 (78)



2750 patients
Chronic Chagas` heart disease

R

1,375 patients
BENZNIDAZOLE

1,375 patients
PLACEBO

mean follow up: 5.5 years

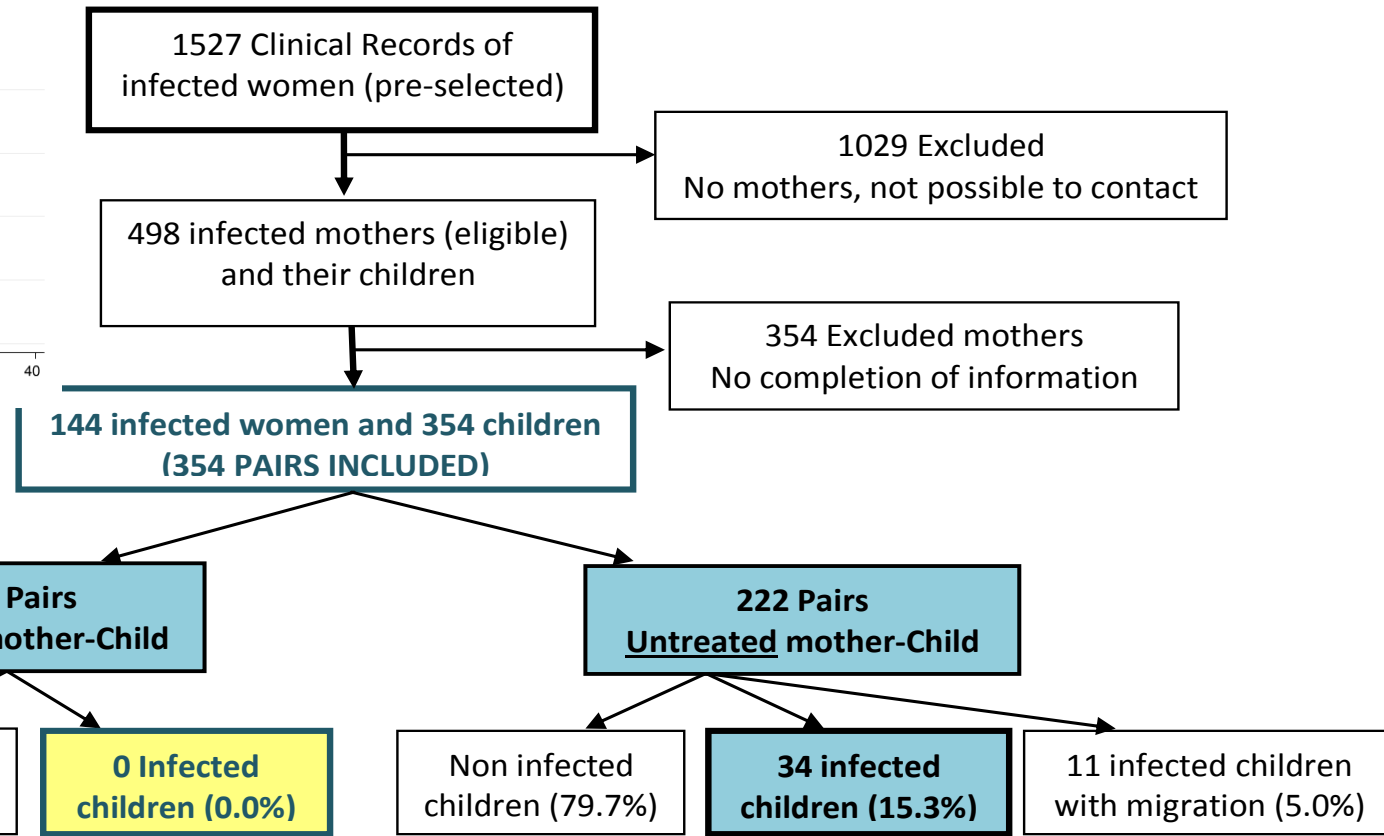
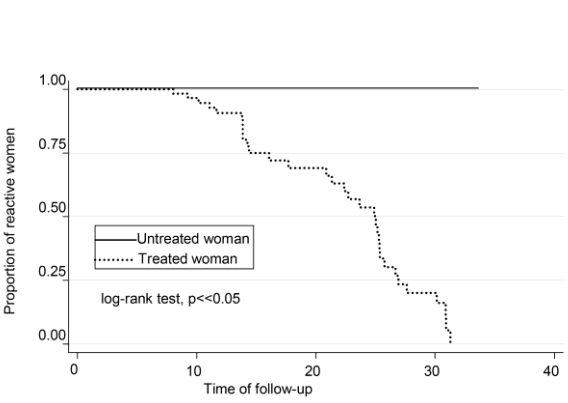
PRIMARY ENDPOINT
Combination of death, cardiac arrest
resuscitation, sustained ventricular tachyarrhythmias, need
for pacemaker or defibrillator implant, thromboembolic
phenomena or hospitalization for CHF, Heart Tx

End of follow up: November 2014; Final Results March 2015

MADRES Study: Observational study

Trypanocide Treatment of Women Infected with *Trypanosoma cruzi* and its Effect on Preventing Congenital Chagas PlosNTD accepted 2014

Objetivo: to asses the efficacy of trypanocidal therapy to prevent congenital Chagas disease

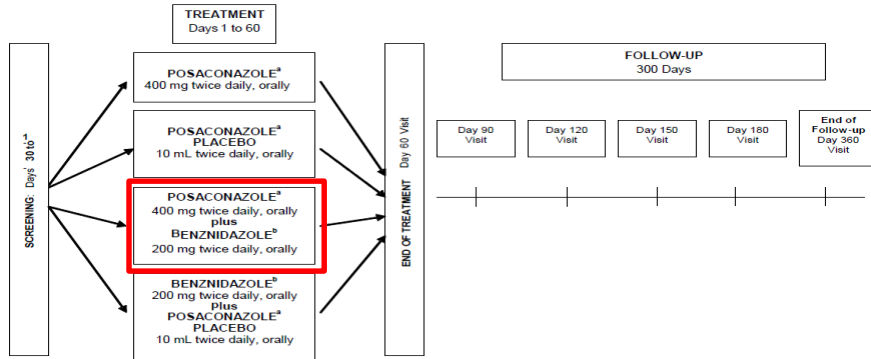


GENERAL CONCLUSION:

The etiological treatment for infection of *T.cruzi* is an **effective strategy for prevention of congenital Chagas (PRIMARY PREVENTION)** and useful tool for deparasitation and prevention of Chagasic cardiopathy **(SECONDARY PREVENTION)**, specially when used at early ages.

PROJECTS ONGOING

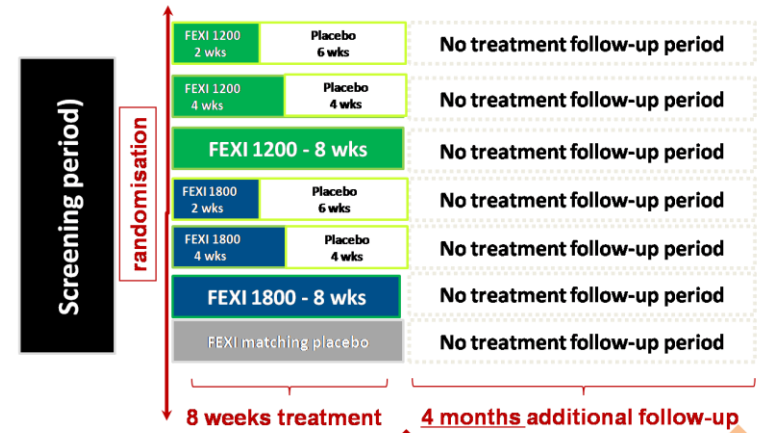
STOP CHAGAS Phase II: Merck



a: Posaconazole will be administered *single* blind.
b: Benznidazole will be administered open label.

Fexnidazole Phase II: DNDi

Proof-of-Concept Dose Ranging Study Evaluation of Dose and duration



20 patients/arm
Stopping rules: fertility and safety
Cardiac and liver safety surveillance

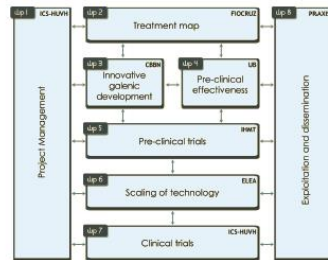
EOT

M4

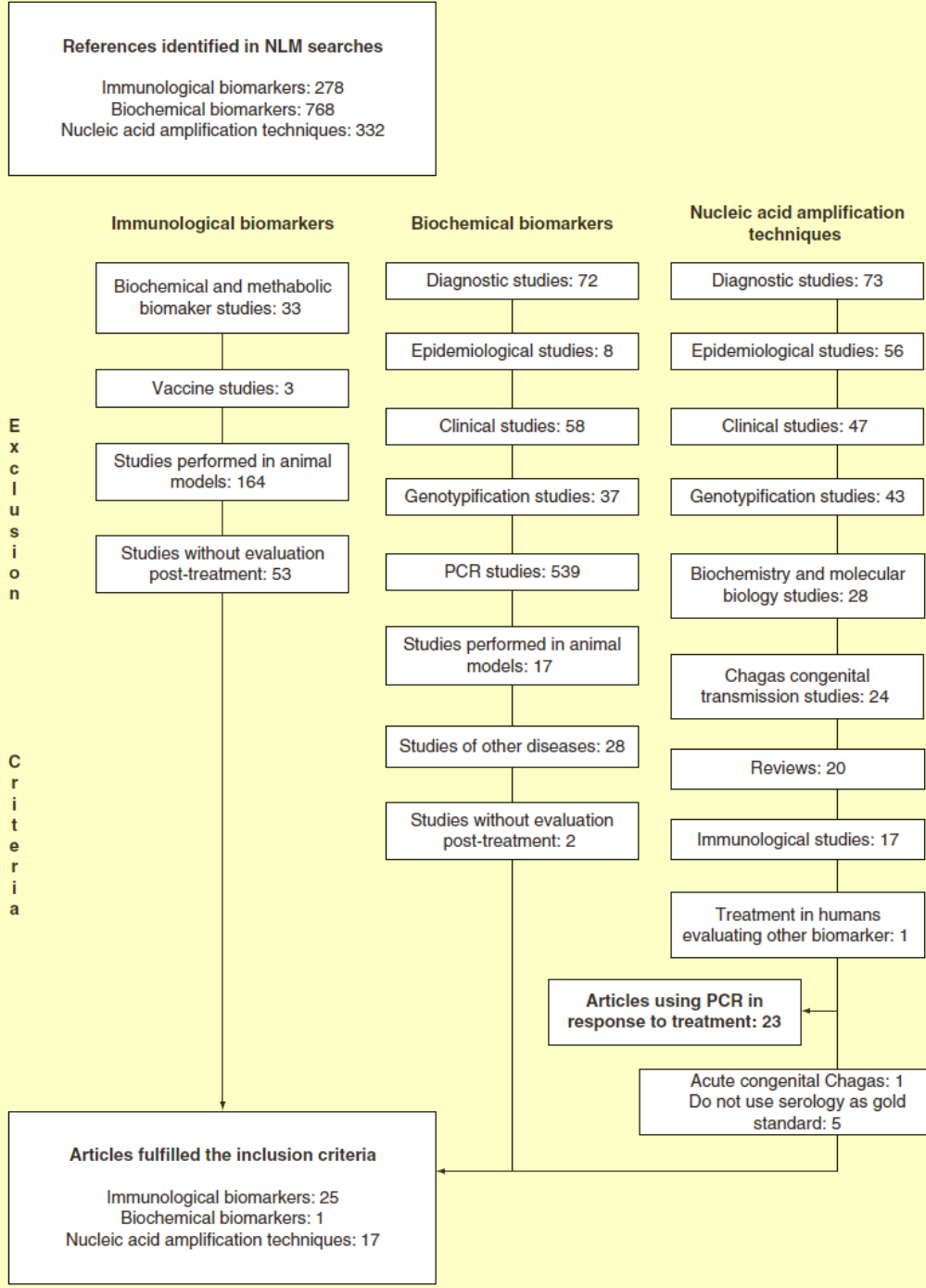
BERENICE Phase I and II WIHP FP7 UC



To ensure its successful completion, BERENICE has been divided into 8 work packages, each dealing with specific tasks.



Maria-Jesús Pinazo*,
M Carmen Thomas,
Jacqueline Bua,
Alina Perrone,
Alejandro-Gabriel Schijman,
Rodolfo-Jorge Viotti,
Janine-M Ramsey,
Isabela Ribeiro,
Sergio Sosa-Estani,
Manuel-Carlos López
and Joaquim Gascon



Articles fulfilled the inclusion criteria

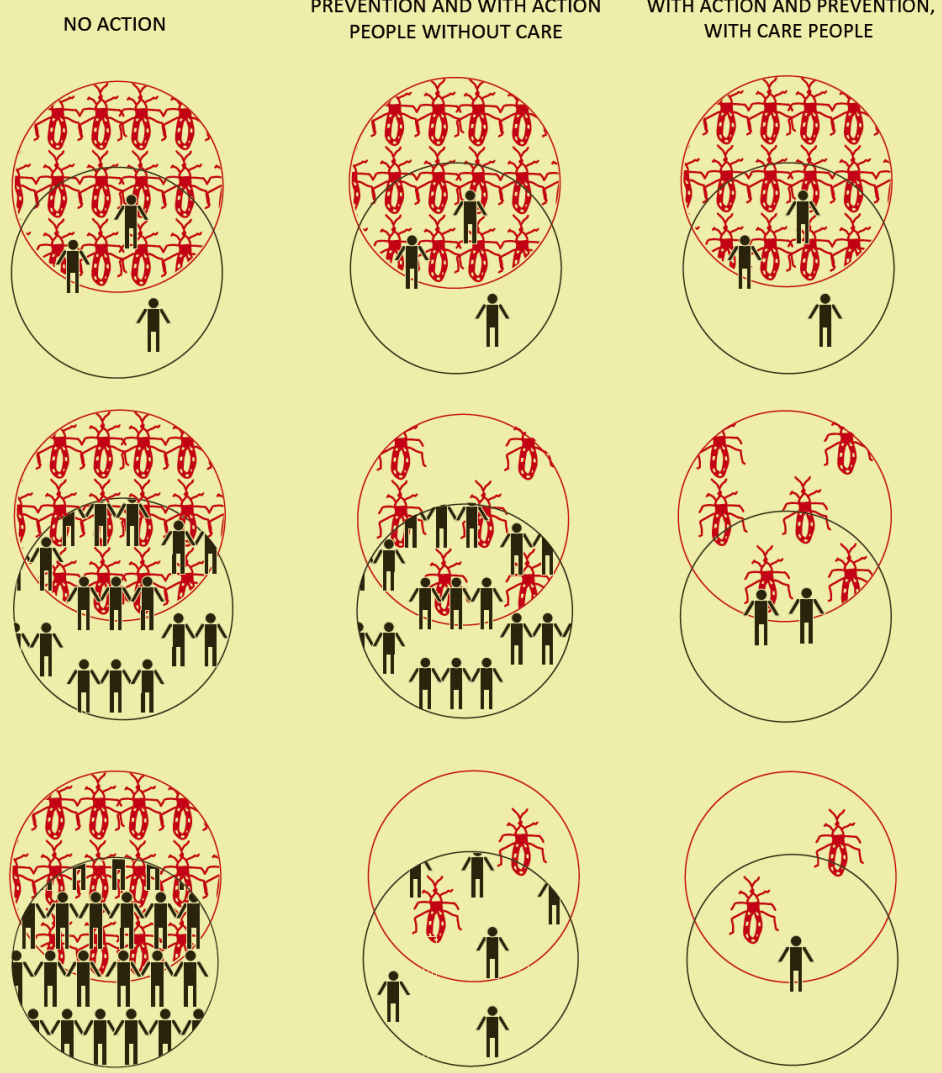
- Immunological biomarkers: 25
- Biochemical biomarkers: 1
- Nucleic acid amplification techniques: 17



Figure 1. Flow of inclusion of studies on biological markers for evaluating.

CONTROL OF CHAGAS DISEASE

COMBINED EFFECT OF PREVENTION AND CARE OF PERSONS



Printed.: Libro "Enfermedad de Chagas. Una síntesis de la experiencia práctica y la investigación médica". Cap 4 Sosa-Estani S. Ed Viotti R y Vigliano C. 2014



THANK YOU MUCHAS GRACIAS
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