

¿Porque el Chagas se puso de moda?

Jaime Altchek MD, PhD

Investigador principal CONICET

Jefe Servicio de Parasitología,

*IMIPP (Instituto multidisciplinario de investigaciones
pediátricas- CONICET)*

*Hospital de Niños Ricardo Gutiérrez,
Buenos Aires, Argentina*

jaltchek@gmail.com



Servicio de Parasitología-Chagas
Hospital de Niños "Ricardo Gutiérrez"
Buenos Aires, Argentina
Centro Colaborador OPS / OMS en
Enfermedad de Chagas Pediátrica (2016)





Falsa sensación de seguridad

seguridad

Table 1 **Estimated demographic and epidemiological parameters of Chagas disease in Latin America by country, 2010**
 Tableau 1 **Estimation des paramètres démographiques et épidémiologiques de la maladie de Chagas en Amérique latine par pays, 2010**

Latin American countries – Pays d'Amérique latine	Population	Estimated no. of people infected by <i>T. cruzi</i> – Estimation du nombre de personnes infectées par <i>T. cruzi</i>	Estimated annual no. of new cases due to vectorial transmission – Estimation du nombre annuel de nouveaux cas dus à la transmission vectorielle	Estimated no. of women aged 15–44 years with <i>T. cruzi</i> infection – Estimation du nombre de femmes âgées de 15 à 44 ans infectées par <i>T. cruzi</i>	Estimated annual no. of cases of <i>T. cruzi</i> infec- tion due to congenital transmission – Estimation du nombre annuel de cas d'infection à <i>T. cruzi</i> dus à la transmission congénitale	Estimated prevalence of <i>T. cruzi</i> infec- tion per 100 habitants – Estimation de la prévalence des infections à <i>T. cruzi</i> pour 100 habitants	Estimated incidence due to vectorial transmis- sion per 100 habitants – Estimation de l'incidence due à la transmission vectorielle pour 100 habitants	Estimated incidence of <i>T. cruzi</i> infec- tion due to congenital transmission per 100 live births – Estimation de l'incidence des infections à <i>T. cruzi</i> dus à la transmission congénitale pour 100 naissances vivantes	Estimated population at risk of <i>T. cruzi</i> infection – Estimation de la population exposée au risque d'infec- tion à <i>T. cruzi</i>	Estimated no. of people with Chagasic cardiopathy – Estimation du nombre de personnes atteintes de cardiopathie chagasicque	Estimated prevalence of <i>T. cruzi</i> infec- tion among blood donors – Estimation de la prévalence de l'infection à <i>T. cruzi</i> chez les donneurs de sang
Argentina – Argentine	41 343 000	1 505 235	1 078	211 102	1 457	3.640	0.0020	0.210	2 242 528	376 309	3.130
Belize	315 000	1 040	10	272	25	0.330	0.0030	0.333	70 252	200	N/A
Bolivia – Bolivie	9 947 000	607 186	8 087	199 351	616	6 104	0.0810	0.235	586 434	121 437	2.320
Brazil – Brésil	190 755 799	1 156 821	46	119 298	571	0.03	0.084 per 100.000 – 0.084 pour 100.000	0.020	25 474 365	231 364	0.180
Chile – Chili	17 095 000	119 660	0	11 771	115	0.699	0	0.046	0	35 898	0.160
Colombia – Colombie	45 805 000	437 960	5 274	116 221	1 046	0.956	0.0110	0.114	4 813 543	131 388	0.410
Costa Rica	4 516 000	7 667	10	1 728	61	0.169	0.0002	0.080	233 333	2 300	0.045
Ecuador – Équateur	14 483 499	199 872	2 042	62 898	696	1.379	0.0140	0.317	4 199 793	40 384	0.190
El Salvador	6 952 000	90 222	972	18 211	234	1.297	0.0130	0.187	1 019 000	18 044	1.610
Guatemala	13 550 000	166 667	1 275	32 759	164	1.230	0.0090	0.035	1 400 000	20 833	1.340

Infeccion vectorial (Signo Romaña)



90% asintomáticos



**Mujer francesa en Paris
procedente de Guyana Francesa.**
Emerg Infect Dis 2008; 14: 644-6.



Urban Chagas disease in children and women in primary care centres in Buenos Aires, Argentina

Guillermo Moscatelli^{1/+}, Ada Berenstein², Ana Tarlovsky³, Susana Siniawski², Miguel Biancardi¹,
Griselda Ballering¹, Samanta Moroni¹, Marta Schwarcz⁴, Susana Hernández⁴,
Facundo García-Bournissen¹, Andrés Espejo Cozzi⁴, Héctor Freilij¹, Jaime Altcheh¹

¹Ricardo Gutiérrez Children's Hospital, Department of Parasitology and Chagas, Buenos Aires, Argentina ²Primary Care Centre, Community Action Centre 15, Buenos Aires, Argentina ³Primary Care Centre, Community Action Centre 11, Buenos Aires, Argentina ⁴Interamerican Open University, Centre of Studies on Human Science and Health, Buenos Aires, Argentina



Vías de infección en áreas bajo control vectorial

- Transplacentario: 3-7% de transmisión en hijos de madres en fase crónica.
- Transfusional: por dador infectado.
- Infrecuente: Oral, Transplantes, accidente laboratorio.

La transmisión transplacentaria es la generadora del mayor número de nuevos casos



Madre reactiva

Niño < 8 meses

Niño > de 8 meses

Parasitemia

Serología

(+)

neg

(+)

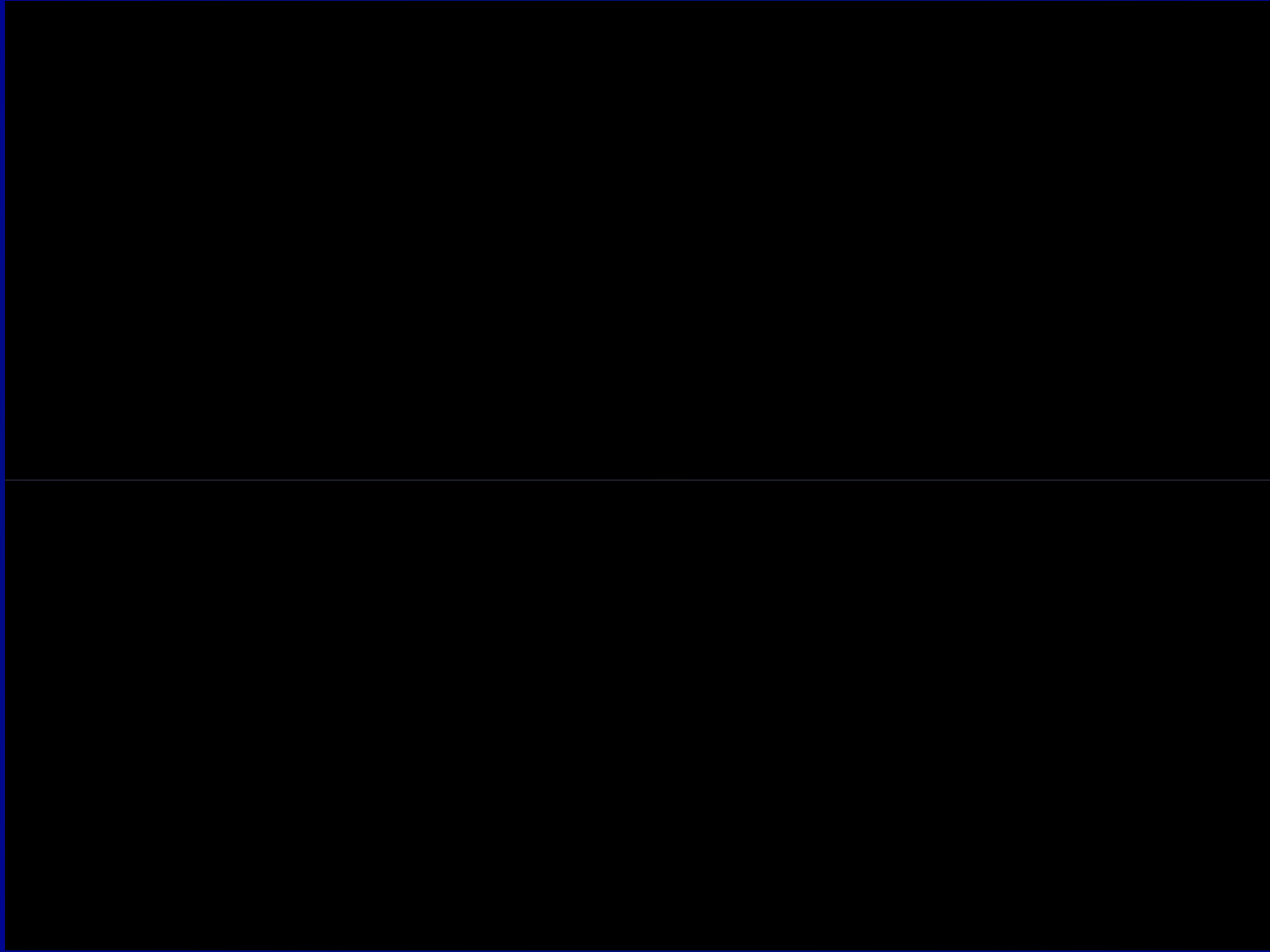
neg

Tratamiento

Freilij H, Altcheh J. 1995, Clin Infect Dis 21;551-5.



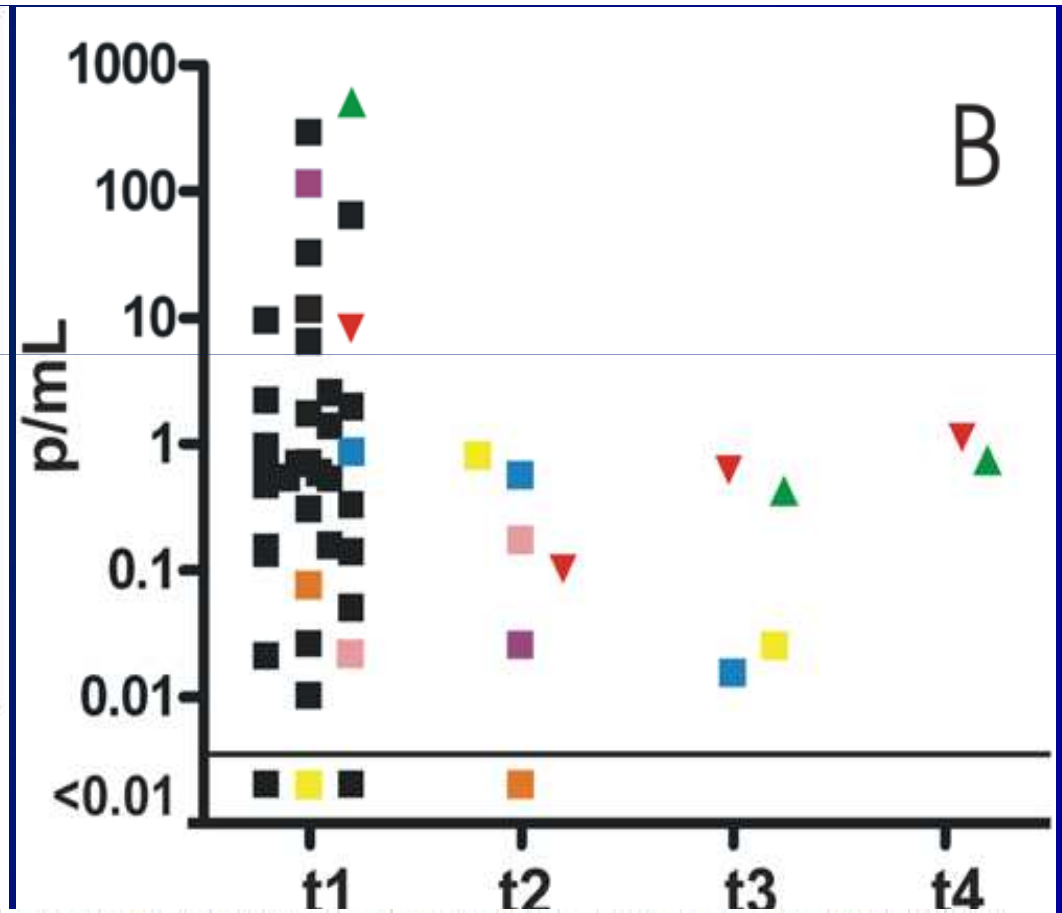
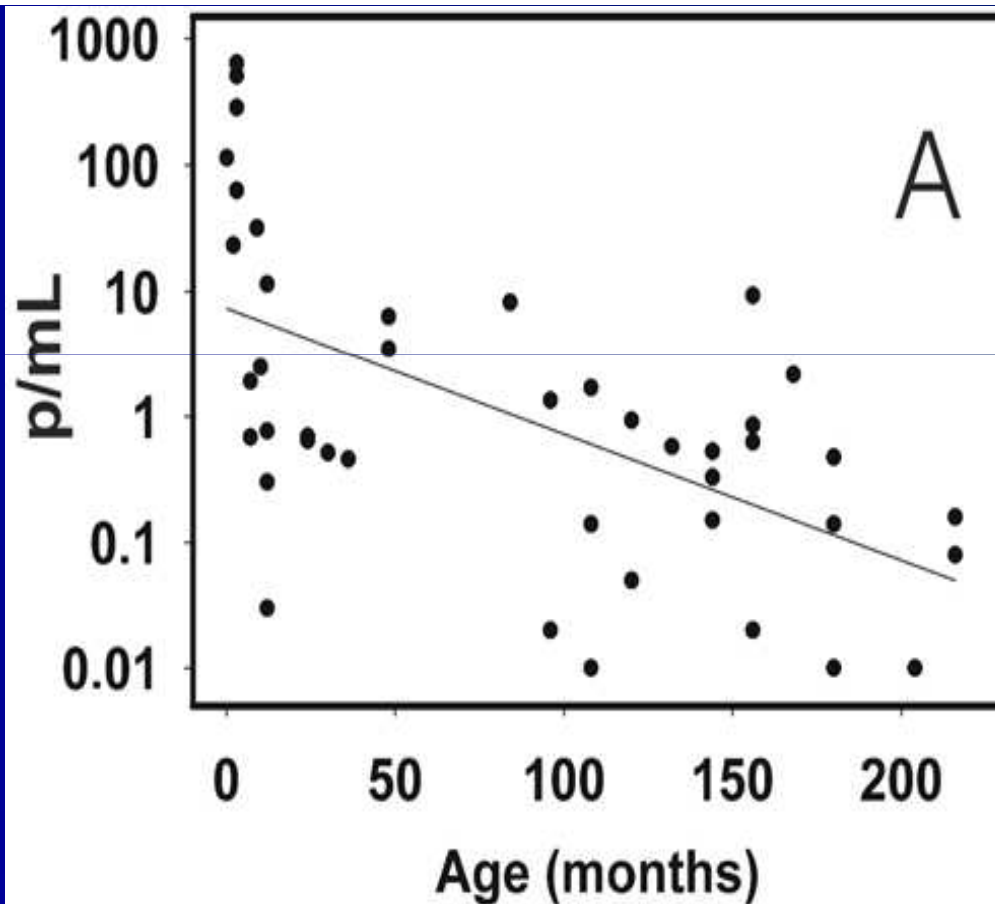




Accurate Real-Time PCR Strategy for Monitoring Bloodstream Parasitic Loads in Chagas Disease Patients

Tomas Duffy¹, Margarita Bisio¹, Jaime Altcheh², Juan Miguel Burgos¹, Mirta Diez³, Mariano Jorge Levin¹, Roberto Rene Favaloro³, Hector Freilij², Alejandro Gabriel Schijman^{1*}

¹Laboratorio de Biología Molecular de la Enfermedad de Chagas, Instituto de Investigaciones en Ingeniería Genética y Biología Molecular (INGEBI-CONICET), Buenos Aires, Argentina, ²Parasitology Unit of the "Ricardo Gutiérrez" Children's Hospital, Buenos Aires, Argentina, ³Transplant Unit of the Instituto de Cardiología y Cirugía Cardiovascular, Fundación "René Favaloro", Buenos Aires, Argentina

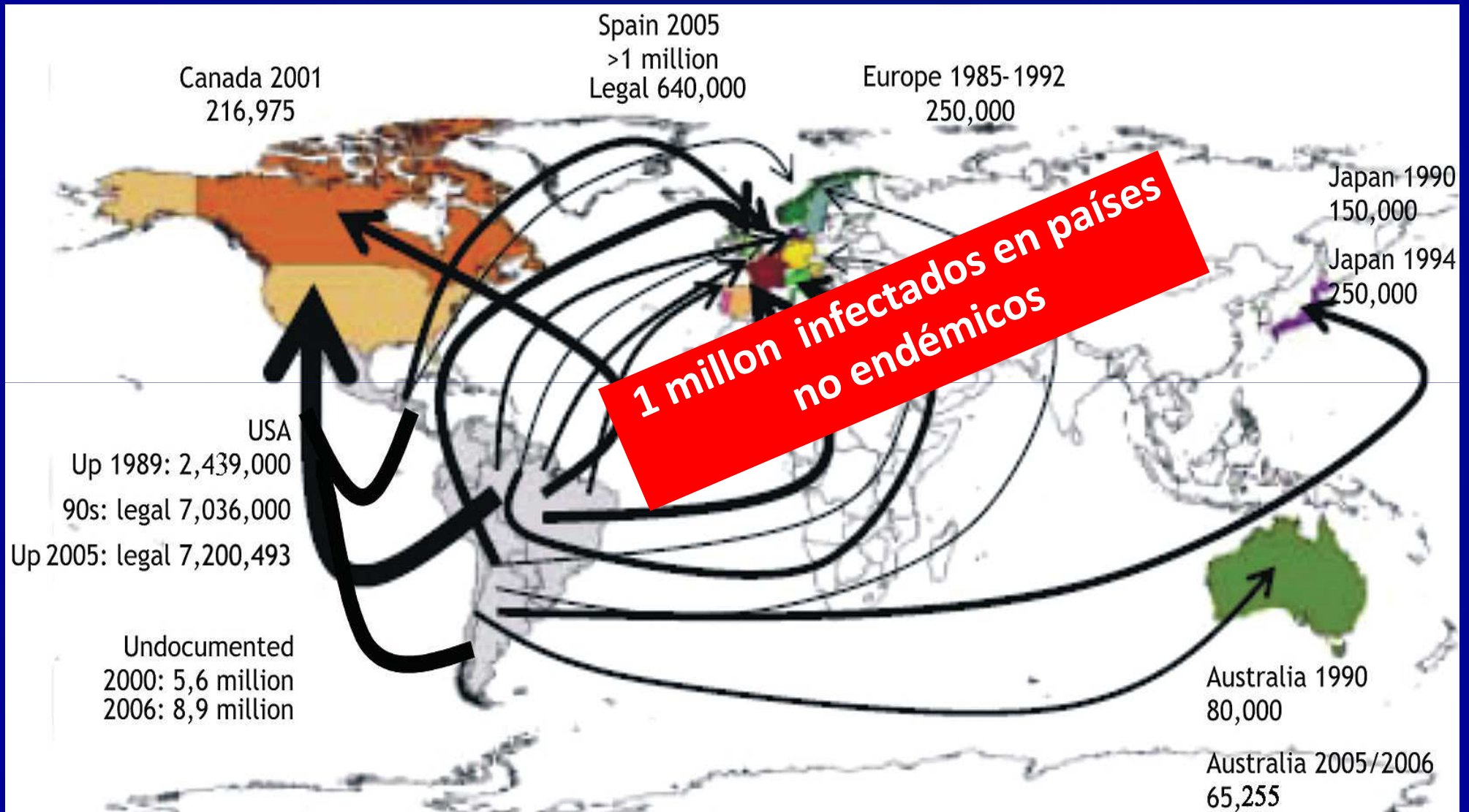


Citation: Duffy T, Bisio M, Altcheh J, Burgos JM, Diez M, et al. (2009) Accurate Real-Time PCR Strategy for Monitoring Bloodstream Parasitic Loads in Chagas Disease Patients. *PLoS Negl Trop Dis* 3(4): e419. doi:10.1371/journal.pntd.0000419



Una madre con enfermedad de Chagas crónica puede transmitir el *T. cruzi* en uno o más embarazos.

Flujo migratorio



1 millón infectados en países no endémicos

Estimated number of Chagas disease cases in North America.



40,000 embarazadas con *T. cruzi*,
con 2,000 casos congénitos

Segun OPS los casos congénitos
producen mas de un cuarto de los nuevos
casos de enfermedad de Chagas

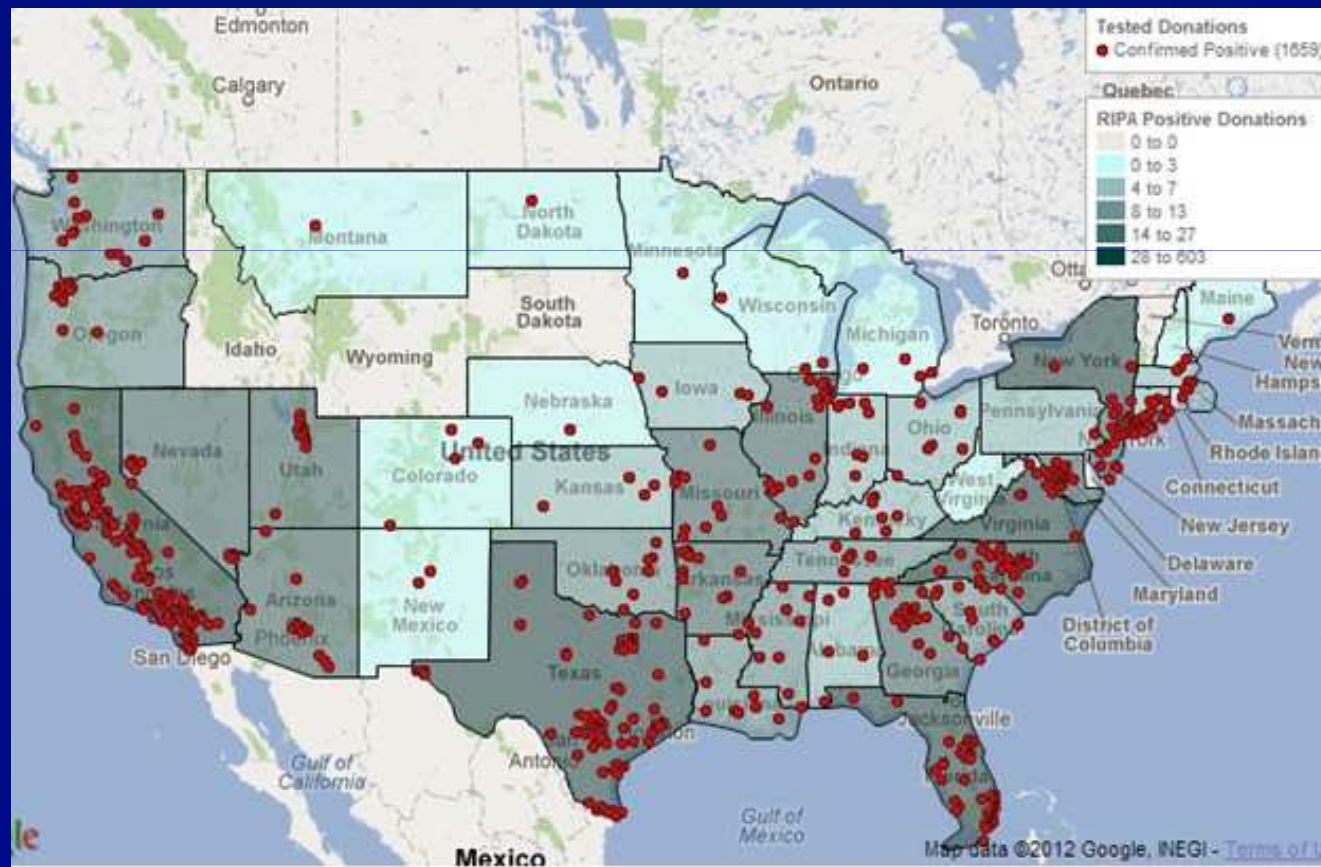
Hotez PJ, Dumonteil E, Betancourt Cravioto M, Bottazzi ME, et al. (2013) An Unfolding Tragedy of Chagas Disease in North America.

PLoS Negl Trop Dis 7(10): e2300. doi:10.1371/journal.pntd.0002300

<http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0002300>

Screening and Treatment of Chagas Disease in Organ Transplant Recipients in the United States, Recommendations from the Chagas in Transplant Working Group

P. V. Chin-Hong; B. S. Schwartz; C. Bern; S. P. Montgomery; S. Kontak; B. Kubak; M. I. Morris; M. Nowicki; C. Wright; M. G. Ison American Journal of Transplantation. 2011;11(4):672-680.



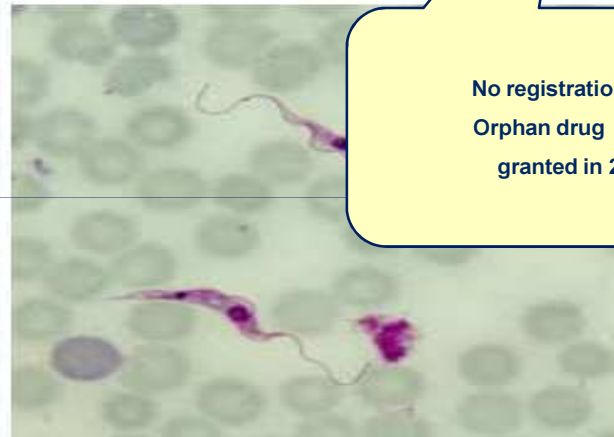


Chagas Disease Public Meeting on Patient-Focused Drug Development



April 28, 2015

Enfermedad de Chagas PDF



No registration fees;
Orphan drug status
granted in 2010

On April 28, 2015, FDA met with patients during one of FDA's Patient-Focused Drug Development meetings to discuss patients' concerns regarding their symptoms and treatment options for Chagas disease. These meetings are important as patients have the opportunity to convey their concerns about current medications and the types of medications they would like to see in the future.

No drugs have yet been shown to meet standards of safety and efficacy for FDA approval for the treatment of Chagas' disease, but several potential treatments are in various stages of clinical investigation. Two investigational drugs are available through the Center for Disease Control and Prevention (CDC), at a doctor's request.

- Benznidazole
- Nifurtimox

[Try our beta test site](#)

IMPORTANT: Listing of a study on this site does not reflect endorsement by the National Institutes of Health. Talk with a trusted healthcare professional before volunteering for a study. [Read more...](#)

[Find Studies](#) | [About Clinical Studies](#) | [Submit Studies](#) | [Resources](#) | [About This Site](#)

Home > Find Studies > Search Results

Text Size

112 studies found for: chagas

[Modify this search](#) | [How to Use Search Results](#)

+ Show Display Options

Only show open studies

Rank	Status	Study
1	Completed Has Results	Abbott ESA Chagas Assay Post-Market Study Condition: Chagas Disease Intervention: Device: Testing Donor Specimens with ESA Chagas
2	Completed	Population Pharmacokinetics of Benznidazole in Children With Chagas Disease Condition: Chagas Disease Intervention: Drug: Benznidazole
3	Completed	Galectin-3 as a Biomarker in Patients With Chagas Disease Condition: Chagas Disease. Intervention:
4	Completed	Assessment of Speckle Tracking Strain Predictive Value for Myocardial Fibrosis in Chagas Disease Condition: Chagas Disease Intervention: Other: No intervention was performed.
5	Completed Has Results	A Study of the Use of Oral Posaconazole (POS) in the Treatment of Asymptomatic Chronic Chagas Disease (P05267) Condition: Chagas Disease Interventions: Drug: Posaconazole; Drug: Placebo for posaconazole; Drug: Benznidazole
6	Completed	MicroRNAs as Biomarkers in Patients With Chagas Disease Condition: Chagas Disease Intervention:
7	Completed	Syndecan-4 as a Biomarker in Patients With Chagas Disease Condition: Chagas Disease Intervention:
8	Completed	Effects of Omega-3 Supplementation on the Cytokine and Lipid Profiles in Patients With Chronic Chagas Cardiomyopathy

[Try our beta test site](#)

IMPORTANT: Listing of a study on this site does not reflect endorsement by the National Institutes of Health. Talk with a trusted healthcare professional before volunteering for a study. Read more...

[Find Studies](#) ▾ | [About Clinical Studies](#) ▾ | [Submit Studies](#) ▾ | [Resources](#) ▾ | [About This Site](#) ▾

[Home](#) > [Find Studies](#) > [Search Results](#)

[Text Size](#) ▾

35 studies found for: chagas children

[Modify this search](#) | [How to Use Search Results](#)


List

By Topic

On Map

Search Details

+ Show Display Options

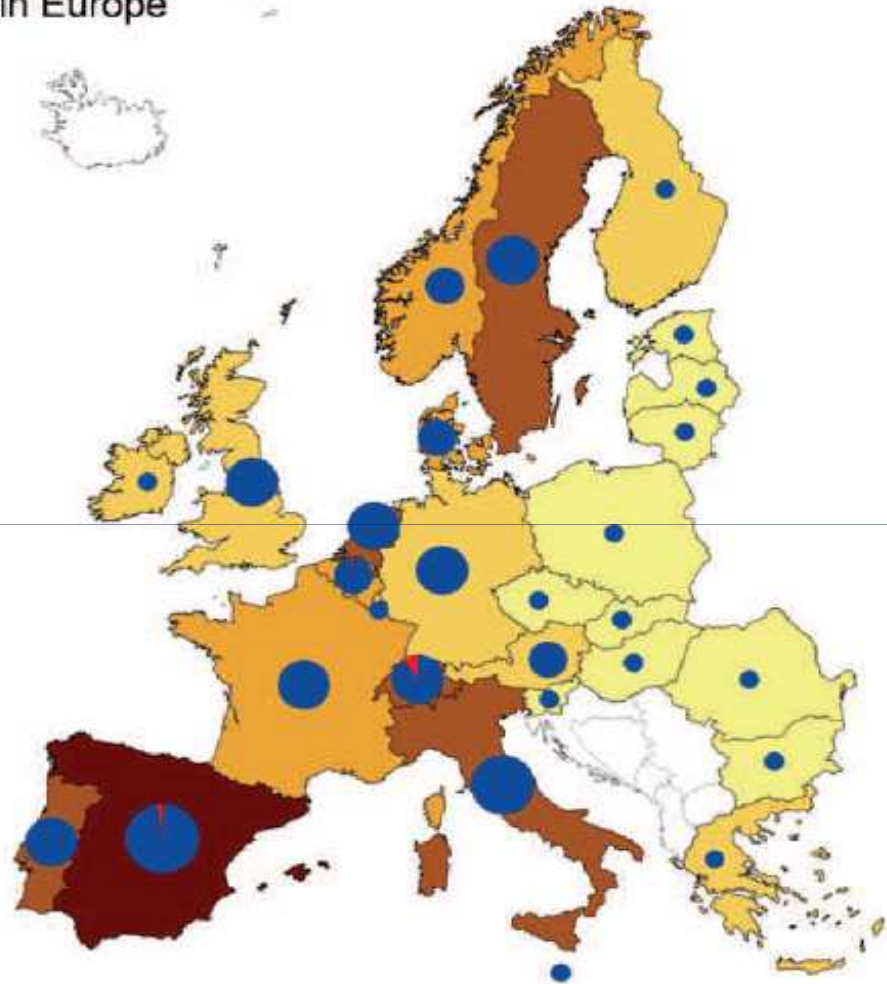
 Download

 Subscribe to RSS

Only show open studies

Rank	Status	Study
1	Completed	Population Pharmacokinetics of Benznidazole in Children With Chagas Disease Condition: Chagas Disease Intervention: Drug: Benznidazole
2	Unknown †	Population Pharmacokinetics Study of Benznidazole in Children With Chagas' Disease Condition: Chagas' Disease Intervention: Drug: Benznidazole 12,5mg or 100mg
3	Recruiting	Prospective Study of a Pediatric Nifurtimox Formulation for Chagas' Disease Condition: Chagas Disease Interventions: Drug: Nifurtimox (BAYA2502); Drug: Nifurtimox (BAYA2502) followed by Placebo
4	Completed	Study of Benznidazole Transfer Into Breastmilk in Lactating Women With Chagas Disease

Chagas in Europe



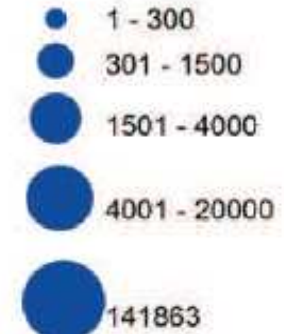
- **100.000 infectados**

- **Mayor prevalencia en España**
- **75,000 casos (approx.60 % mujeres en edad fértil)**
- **94 centros diagnostican CD**
- **2014: approx. 1,800 pts tratados**

Cases per 100,000 inhabitants (in %)



Maxi. estimated cases; In red share of diagnosed patients



Source: "Epidemiology of Chagas' disease in Europe: many calculations, little knowledge": J. Strasen et al. Clin. Res. Cardiol.(2014), 103:1-10

Tratamiento

Benznidazol (Lafepe, Brasil, Abarax[®], ELEA)

Dosis: 5-10 mg/Kg/día en 2 dosis.

Presentación: comprimidos 12.5?, 50 y 100 mg.



Nifurtimox (Lampit[®], Bayer)

Dosis: 10-15 mg/Kg/día en 3 dosis.

Presentación: comprimidos 120 mg. 30 mg ?



Duración: 60 días ?.



Un niño **NO** es un adulto pequeño...

un adulto pequeño,
es un señor bajito



Adverse Events After the Use of Benznidazole in Infants and Children With Chagas Disease



WHAT'S KNOWN ON THIS SUBJECT: Treatment of Chagas disease with benznidazole in adults leads to a high incidence of severe drug reactions. However, benznidazole seems to lead to less frequent (and less severe) ADRs in children, but there are scarce data on the subject.



WHAT THIS STUDY ADDS: We describe a cohort of children with Chagas disease treated with benznidazole. A lower incidence of ADRs was observed in smaller children compared with older children and adults. All ADRs observed were mild, and treatment response was excellent.

**Los niños menores toleran mejor la
medicación**

AUTHORS: Jaime Altcheh, MD,^a Guillermo Moscatelli, MD,^a Samanta Moroni, MD,^a Facundo Garcia-Bournissen, MD,^b and Hector Freilij, MD^a

^a*Servicio de Parasitología y Enfermedad de Chagas, Hospital de Niños R Gutiérrez, Buenos Aires, Argentina; and* ^b*Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada*

KEY WORDS

infant, children, Chagas disease, congenital, benznidazole, adverse events, pediatric pharmacology

ABBREVIATIONS

ADR—adverse drug reaction

CI—confidence interval

IQR—interquartile range

CNS—central nervous system

www.pediatrics.org/cgi/doi/10.1542/peds.2010-1172

doi:10.1542/peds.2010-1172

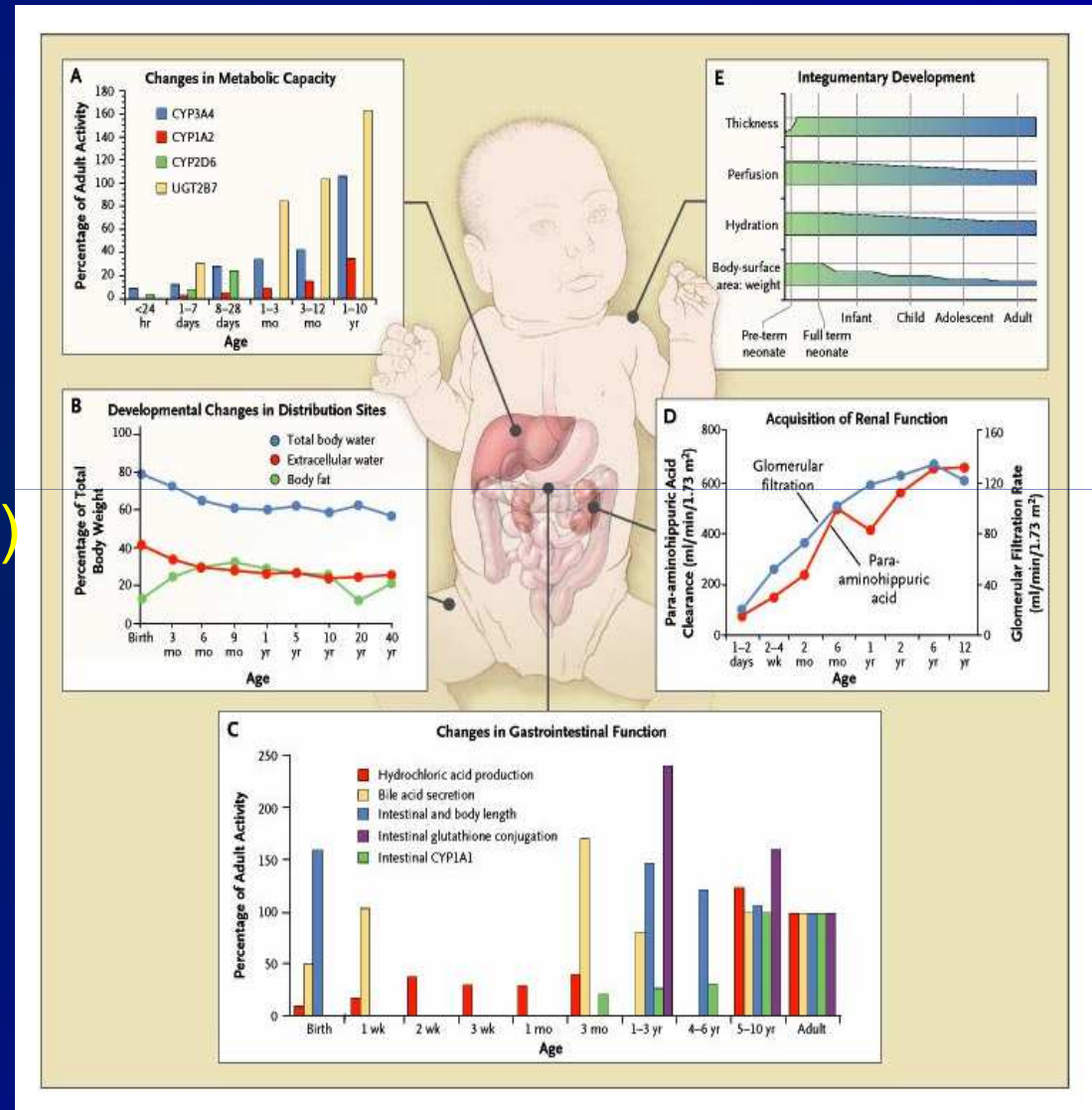
PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Los niños son diferentes

Los niños son diferentes en:

- Absorción
- Distribución
- Función renal (excreción)
- Función hepática (metabolismo)
- Farmacodinamia:
Respuesta terapéutica
Eventos adversos



El problema de las formulaciones



100 mg



$1/8 = 12,5 \text{ mg}$



WARNING:
CHOKING HAZARD - Small Parts
Not for children under 3 years of age

Population Pharmacokinetic Study of Benznidazole in Pediatric Chagas Disease Suggests Efficacy despite Lower Plasma Concentrations than in Adults

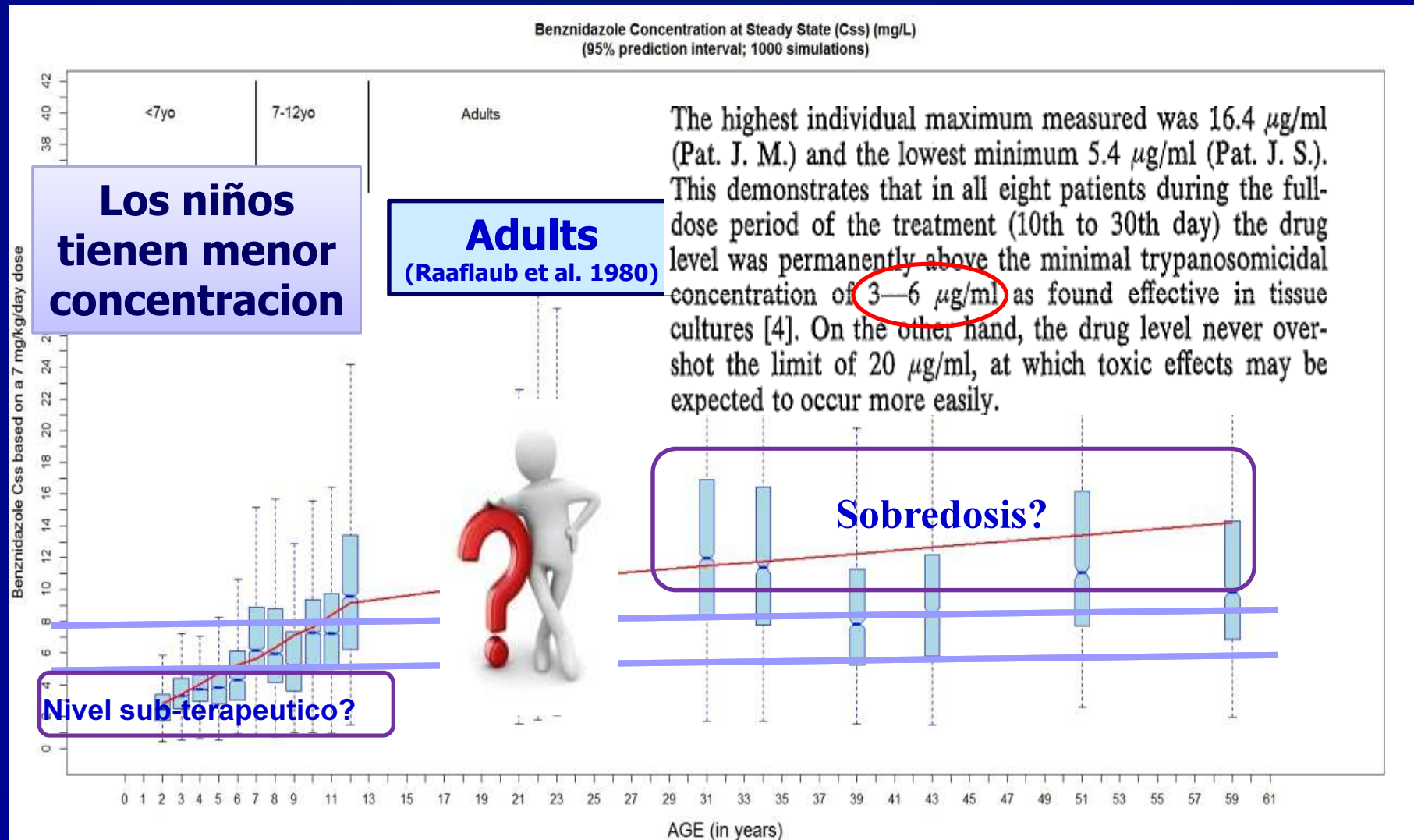
Jaime Altcheh¹, Guillermo Moscatelli¹, Guido Mastrantonio², Samanta Moroni¹, Norberto Giglio¹, Maria Elena Marson², Griselda Ballering¹, Margarita Bisio¹, Gideon Koren³, Facundo García-Bournissen^{1,3*}

¹Servicio de Parasitología y Chagas, Hospital de Niños Ricardo Gutiérrez, Ciudad de Buenos Aires, Argentina, ²Área de Toxicología, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, La Plata, Provincia de Buenos Aires, Argentina, ³Division of Clinical Pharmacology & Toxicology, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

[Clinicaltrials.gov registry # NCT00699387](https://clinicaltrials.gov/ct2/show/study/NCT00699387)



Concentracion en estado estacionario (popPK)



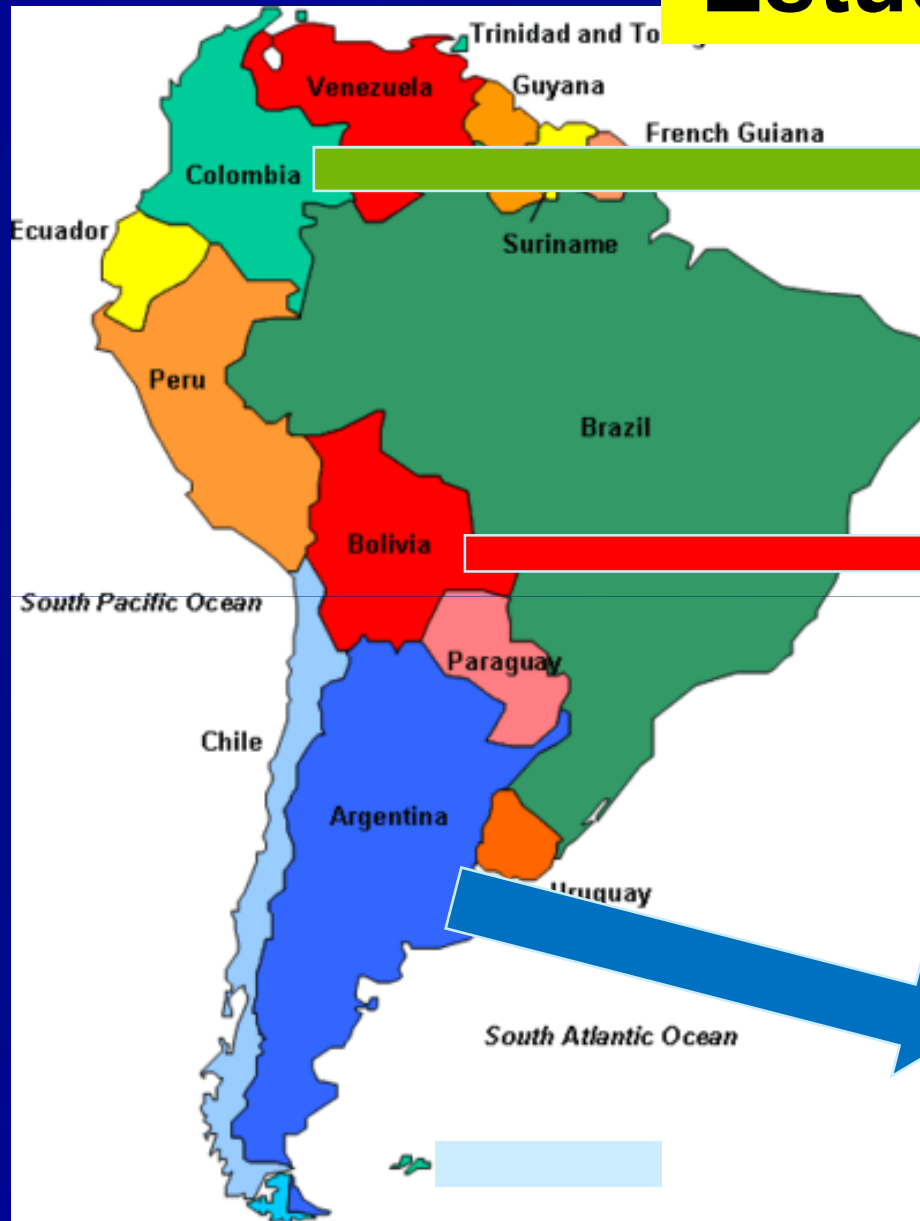
El camino hacia la formulación pediátrica

BAY16027

Estudio prospectivo con control retrospectivo para evaluar la eficacia y la seguridad de una nueva formulación pediátrica de nifurtimox en pacientes de 0 a 17 años con enfermedad de Chagas



Estudio multicéntrico



Colombia
3 centros

Bolivia
3 centros

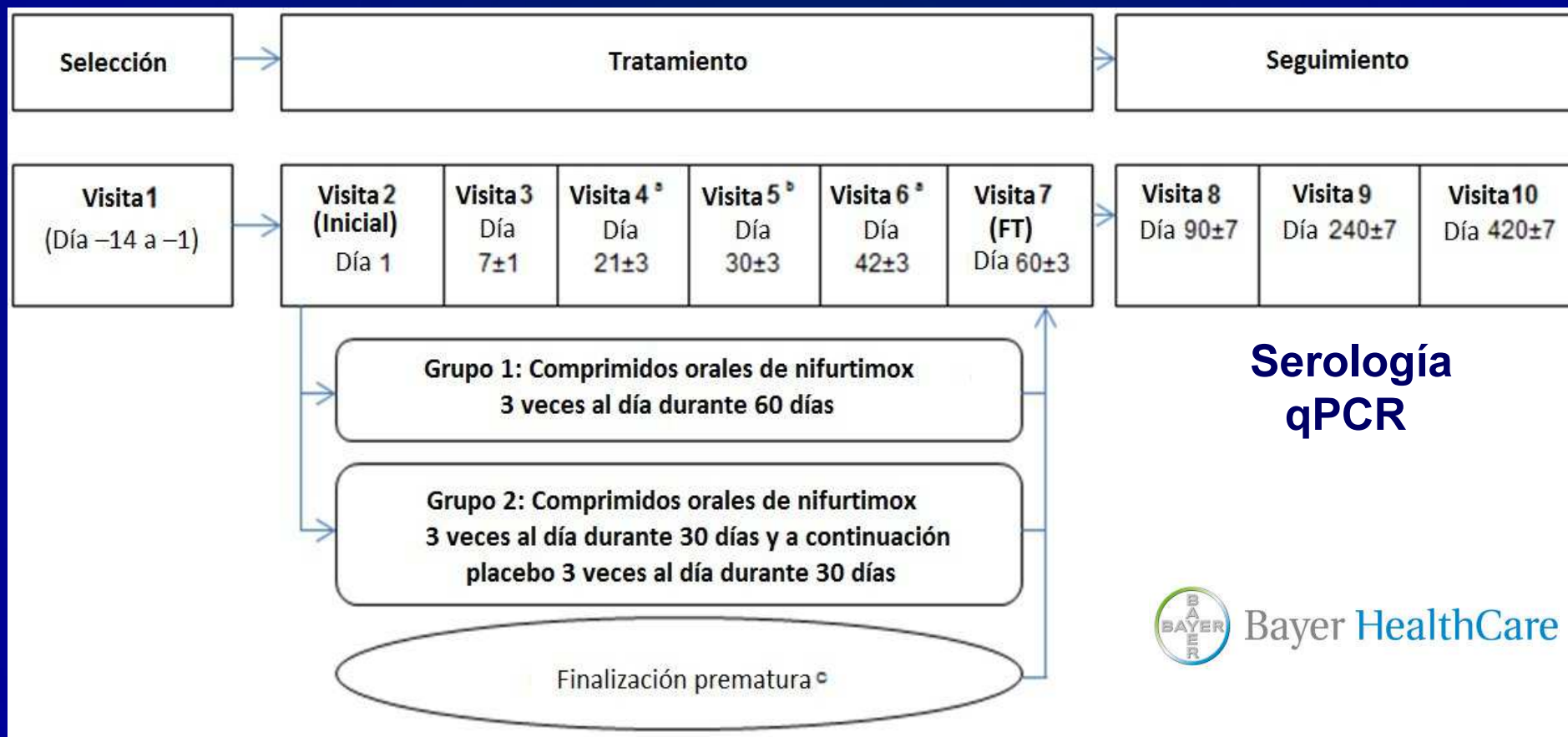
Argentina
18 centros
PEDCHAGAS group

Nifurtimox 120 mg y dispersable de 30 mg

BAY16027

Grupo 1: 60 días de nifurtimox.

Grupo 2: 30 días de nifurtimox, 30 días de placebo.



Formulaciones pediátricas

Plan de desarrollo

Comp de 100 mg BZ, 120 mg NFTX

Tratamiento
60- 90 - 120 días

Escasos datos de eficacia y
seguridad

Farmacocinetica escasa
información en adultos, NO en
niños

Registro en
pocos paises de LatAm

12,5 mg BZ, 30 mg NFTX
dispersables

Tratamientos de 30-60 días

Ensayos clínicos

Ensayos clínicos PK/PD en
niños y adultos

Registro FDA, EMEA

Perspectivas futuras

Lo que planteamos2012

"IT ALWAYS
SEEMS
IMPOSSIBLE
UNTIL
IT'S DONE"

-NELSON MANDELA



- n Nueva formulación BZ pediátrica y estudio de PopPK en menores de 2 años.



- n **PopPK nifurtimox en niños, formulación pediátrica.**



- n Transferencia de nifurtimox y benznidazol a la leche materna



- n Estudios de PopPK de benznidazol en adultos



- n Tiempo: 30 vs 60 días y dosis < en adultos



- n Identificación de los metabolitos de benznidazol, y las enzimas responsables del metabolismo (CYP, etc)



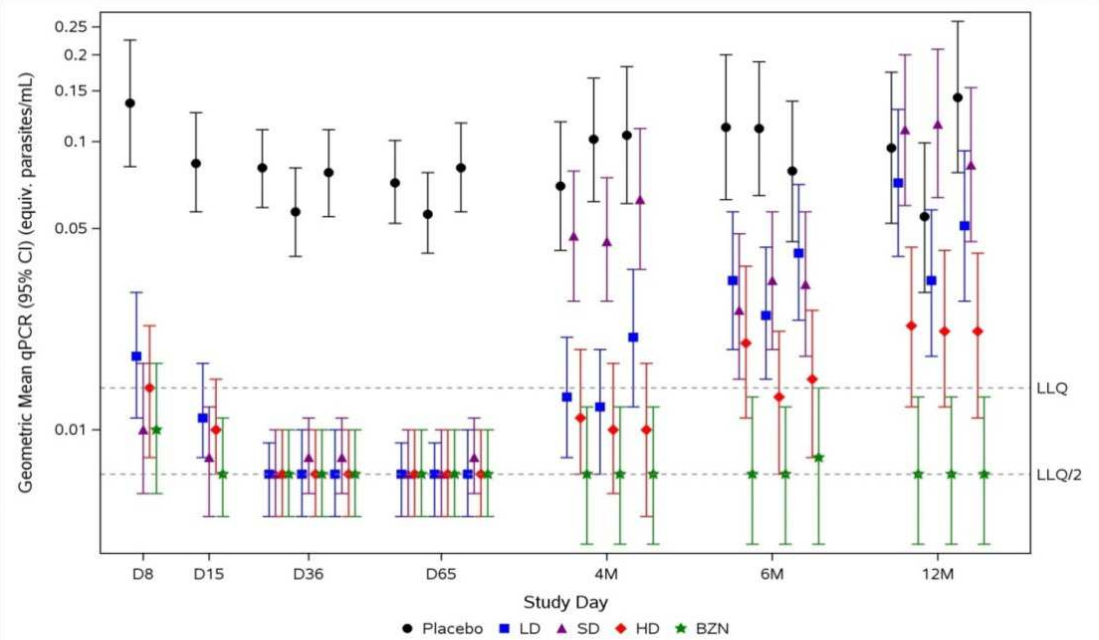
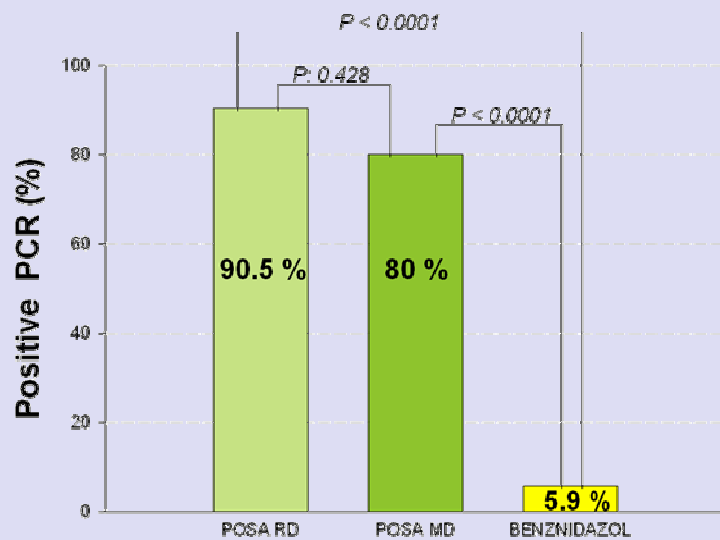
- n Estudios de nuevas drogas para el Chagas.

DNDi

Drugs for Neglected Diseases initiative

CHAGAZASOL (NCT01162967), Posaconazol vs Benznidazol Efectividad a 12 meses

DNDi-CH-E1224-001 (NCT01489228), Ravuconazol, benznidazol y placebo Efectividad a 12 meses



Los azoles no son efectivos para el tratamiento de la enfermedad de Chagas

Prevention of congenital Chagas through treatment of girls and women of childbearing age

Guillermo Moscatelli^{†*}, Samanta Moroni, Facundo García-Bournissen,
Griselda Ballering, Margarita Bisio, Héctor Freilij, Jaime Altchek

Department of Parasitology and Chagas, Ricardo Gutiérrez Children's Hospital, Buenos Aires, Argentina

Serology and mother real-time quantitative polymerase chain reaction (qPCR) results throughout follow-up before treatment and three years after treatment in a children study

Mothers [age at treatment (years)]	Serology (day 0)		qPCR			
	EIA	IHA	IHA	Day 0	3 years	
9	3.5	UN	UN	P	N	
11	16	UN	64	P	N	
11	UN	UN	64	P	N	
12	UN	256	512	P	N	
13	UN	128	UN	P	N	
13	3.5	256	16	P	N	
14	8.1	128	16	N	N	
14	7.4	64	5.1	P	N	
14	3.1	16	2.5	N	N	
16	11.7	1,024	11.3	1,024	P	N
16	12.4	1,024	7.2	64	P	N
16	10.6	128	6.6	64	P	N
16	12	512	10.2	128	P	N
25	11.6	1,024	6.6	256	P	N
34	12.1	2,048	9.5	128	P	N

EIA: enzymatic immunoassay; IHA: indirect haemagglutination assay; N: negative; P: positive; UN: unreactive

8/22 recibieron 30 días de tratamiento

Chagas como una enfermedad pediátrica



Un adulto con enfermedad de Chagas es un niño no tratado



El Chagas se cura





IMIPP (Instituto Multidisciplinario de Investigaciones en Patologías Pediátricas)



Centro Colaborador OPS / OMS en
Enfermedad de Chagas Pediátrica (2016)

