

Dr Jaime Altcheh
Miembro Carrera de
Investigador, Gob BsAs
Jefe del Servicio de
Parasitología



Buenos Aires, Argentina

**Avances en el tratamiento de la
enfermedad de Chagas**

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.



Duración: 30 a 60 días.

1st Technical Meeting

CHAGAS DISEASE CLINICAL RESEARCH

“Relevance and scientific validity of clinical trials
for evaluation of alternative treatment regimens
with Nifurtimox and Benznidazole”

Rio de Janeiro, September 1st, 2009

PLATAFORMA



Acute phases

References	Age (years)	Benznidazol			Nifurtimox		
		n	Dose (mg/kg/d)	Length (days)	n	Dose (mg/kg/d)	Length (days)
Ferreira 1967; 1969	5-10	-	-	-	1	30+20	30+30
					3	25+15	15+75
					1	30+15	5+60
					1	30+15	30+30
Fernandez 1969	1-9	-	-	-	12	30	60
	12-55	-	-	-	12	30	60
Rubio 1969	Congenital <1	-	-	-	4	25+12,5	15+90
Bocca Tourres 1969	?	-	-	-	44	20-30	30
					15	25-30+20	30+30
					18	15-20	60
					65	12-15	90
Lugones 1969; Cerisola 1969; 1970	Children 92%<15	-	-	-	40	15	90
					367	25+15	15+75
Barclay 1978	Children	107	7,5-10	30	-	-	-
	?	32	5	30			
Moya 1985	Congenital <1,5	-	-		40	15	60 = 90
Ferreira 1988	6-13	-	-	-	21	15	90
	2-18	17	5	60	-	-	-
Russomando 1998; 2005	Congenital <1	97	7-10	60	-	-	-
Blanco 2000	Congenital <1	3	5	30	29	10	60

Cancado 2002	<10	6	10-20	40-60	-	-	-
				30-60			
Torrico 2004	Congenital <1	69	7-10	30	-	-	-
Altcheh 2005	Congenital 15d-10y	-	-	-	126	10-15	60
Salas 2007	Congenital <1	31	10	60	-	-	-
IRD 2008- 2009	Congenital <1	59	5	60	-	-	-
		52	7,5	30			

Recent chronic phases (children)

References	Age (years)	Benznidazol			Nifurtimox		
		n	Dose (mg/kg/d)	Length (days)	n	Dose (mg/kg/d)	Length (days)
Cichero 1969	5-12	-	-	-	28	25+15	15+105
	13-14				5	15	120
Bustos 1969	6-19	-	-	-	52	25+15 15	15+105 120
Rubio 1969	2-13	-	-	-	8	25+12,5	15+90
Ferreira 1990	<18	50	5-8	60	50	10-15	60-120
de Andrade 1996	7-12	64	7,5	60	-	-	-
Sosa Estani 1998	6-12	55	5	60	-	-	-
Silveira 2000	7-12	10	5-7	60	2	7-8	60-90
Sosa Estani 2002	1-4	83	5	60	-	-	-
	5-9	91	5	60			
	10-14	59	5	60			
Solari 2001; Schenone 2003	0-10	-	-	-	66	7-10	60
Schijman 2003	3-17	24 {	5-8 -	60 -		- 10-15	60
Streiger 2004	1-6	24	5	30	4	12-15	45-60
	7-14	40			3		

Fase aguda

References	Age (years)	Benznidazol			Nifurtimox			Design*	Follow-up (months) Lost to FU (%)	Efficacy endpoints†	
		n	Dose (mg/ kg/d)	Length (days)	n	Dose (mg/ kg/d)	Length (days)			Serological tests (% neg)	Parasitological tests (% pos)
Ferreira 1967; 1969	5-10	-	-	-	1	30+20	30+30	C nR nB	20m	1/1 (MGR)	0/1 (xeno)
					3	25+15	15+75		-	?	?
					1	30+15	5+60		-	?	?
					1	30+15	30+30		-	?	?
Fernandez 1969	1-55	-	-	-	24	30	60	nC nR nB	24m 50%	(CFT) 42%	(xeno) 50%
Rubio 1969	Congenital <1	-	-	-	4	25+12,5	15+90	nC nR nB	18m 25%	75% (IHA) 100% (CFT)	(xeno) 0%
Bocca Tourres 1969	? ?	-	-	-	44 15 18 65	20-30 25-30+20 15-20 12-15	30 30+30 60 90	C nR B (sero)	12m: ≈40% 61% 7% 5% 45%	3 sero neg + 1 xeno neg: ≈70% 59% 79% 76% 69%	
Lugones 1969; Cerisola 1969; Cerisola 1970	Children 92%<15	-	-	-	43 40 367	NT‡ 15 25+15	- 90 15+75	nC nR nB	24m 46% } 43%	(IHA,IFA,CFT) 0% } 81%	(xeno) 61% neg. Sero: 0% pos. Sero: 44%
Barclay 1978	Children ?	107 32	7,5-10 5	30 30	-	-	-	nC nR nB	18m } 30%	87% (CFT) 91% (IFA)	12% (xeno) 14% (Strout)
Moya 1985	Congenital <1,5	-	-	-	40	15	60=90	C nR nB	6y 0%	(IHA,IFA,CFT) 92%	(xeno) 2%

Fase aguda

References	Age (years)	Benznidazol			Nifurtimox			Design*	Follow-up (months) Lost to FU (%)	Efficacy endpoints†	
		n	Dose (mg/kg/d)	Length (days)	n	Dose (mg/ kg/d)	Length (days)			Serological tests (% neg)	Parasitological tests (% pos)
Ferreira 1988	6-13	-	-	-	-	-	-	nC	-	{(IHA, IFA, CFT)}	{xeno}
	2-18	-	-	-	21	15	90	nR	15y: 28%	100%	0%
Russomando 1998	Congenital	6	7-10	60	-	-	-	nB	9y: 41%	100%	0%
	<2	-	-	-	-	-	-	-	-	{100%}	{0%}
Blanco 2000	Congenital	3	5	30	-	-	-	C	24m	{(EIA,IHA,IFA)}	{(MH)}
	<1	-	-	-	29	10	60	nR	} 0%	} 94%	} 0%
Cancado 2002	<10	-	-	-	-	-	-	nB	24m	-	-
	11-60	6	10-20	40-60	-	-	-	nR	13y	{(EIA,IHA,IFA)}	Not used
15	5-10	-	5-10	30-60	-	-	-	nB	} 0%	} 76%	-
	-	-	-	-	-	-	-	-	-	-	-
Schijman 2003	Congenital	16 {	Congenital	5-8	60	-	-	nC	36m	{(EIA,IHA)}	{(MH,PCR)}
	<2	-	<2	-	-	10-15	60	nR	} 0%	} 87%	} 0%
Altcheh 2005	Congenital	-	Congenital	-	126	10-15	60	nC	3y	{(EIA,IFA)}	Not used
	15d-10y	-	15d-10y	-	-	-	-	nR	32%	87%	-
IRD 2008-2009	Congenital	-	-	-	-	-	-	nB	-	-	-
	<1	68	68	NT	-	-	-	C	10m	{(EIA,IC)}	{(MH at 2m)}
	(Control=not infected)	59	59	5	-	-	-	R	0%	100%	0%
	52	52	7,5	-	-	-	-	B	2%	91%	0%
	-	-	-	-	-	-	-	-	4%	90%	0%

References	Age (years)	Benznidazol			Nifurtimox			Design*	Follow-up (months) Lost to FU (%)	Efficacy endpoints†			
		n	Dose (mg/kg/d)	Length (days)	n	Dose (mg/kg/d)	Length (days)			Serological tests (% neg)	Parasitological tests (% pos)		
Cichero 1969	5-12 13-14	-	-	-	7 28 5	P¶ 25+15 15	120 15+105 120	C nR nB	12m } ?	[CFT,IHA,IFA] } ?	[xeno] 3/4		
												0/6	
Bustos 1969	6-19	-	-	-	15 52 {	P 25+15 15	120 15+105 120	C nR nB	3m } ?	[CFT,IHA,IFA] } 0%	Not used		
Rubio 1969	2-13	-	-	-	8	25+12,5	15+90	nC nR nB	24m 37%	5/5 [CFT] 0/5 [IHA]	[xeno] 0/5		
Ferreira 1990	<18	50	5-8	60	-	-	-	C nR	24m 1.0%	[CFT,IHA,IFA] 6%	[xeno] 30%		
de Andrade 1996; 2004								C R B PP a‡	36m 72m	[atEIA] 36m	[atEIA] 72m	[PCR 36m]	
Galvão 2003	7-12	65 64	P 7,5	60 60	-	-	-		17% 9%	29% 17%	26% 64%	64% 40%	
Sosa Estani 1998; 2002	6-12	51 55	P 5	60 60	-	-	-	C R B PP at	48m 14% 20%	[F29EIA] 0% 62%	[EIA,IHA] 4% 11% 108m- 77%	[xeno] 51% 5%	
Silveira 2000	7-12	10 -	5-7 -	60 -	- 2	- 7-8	- 60-90	C nR nB	8 to 20y } 0%	[CFT,IHA,IFA] 10% 0/2	[xeno] 10% 0/2	[PCR] 10% 0/2	
Sosa Estani 2002	1-4 5-9 10-14	83 74 30	5 5 5	30 30 30	-	-	-	nC nR nB	20m / 60m } 0%	20m [EIA,IHA] 60m 49% 33% 0%	92% 69% 54%	Not used	
Solari 2001; Schenone 2003	0-10	-	-	-	66	7-10	60	nC nR nB	36m 15%	[EIA,IHA] 3%	[xeno] 0%	[PCR] 0%	
Schijman 2003	3-17	24 {	5-8 -	60 -		- 10-15	- 60	C nR nB	36m } 0%	[EIA,IHA] } 12%	[PCR] } 12%		
2004	1-14	24 64	NT 5	- 30	- -	- 7	- 12-15	- 45-60	C§ nR nB	42% } 31%	0% 62% 86%	5-6y:64% 7-8y:58% 9-14:43%	} 0%
Flores Chavez 2006	5-10	35	8	69	-	-	-	nC nR nB	12m	[EIA] 6%	[xeno] 0%	[PCR] 14%	
Duffy 2009	18d-18y	38	5-8	60	-	-	-	nC nR nB	18m Q-PCR at 30d & 60d	Not used	[Q-PCR] 30d: 13% 60d: 5%	[PCR] 5%	

Antibody drop in newborns congenitally infected by *Trypanosoma cruzi* treated with benznidazole

Jean-Philippe Chippaux^{1,2}, Alejandra N. Salas Clavijo¹, Jose A. Santalla², Jorge R. Postigo¹, Dominique Schneider³ and Laurent Brutus³

¹ IRD UR010, Team "Mother's and Child's health in tropical environment", Institut de Recherche pour le Développement, La Paz, Bolivia

² Laboratory of Parasitology, Instituto Nacional de Laboratorios de Salud, Ministry of Health and Sport, La Paz, Bolivia

³ IRD UR010, Team "Mother's and Child's health in tropical environment", Institut de Recherche pour le Développement, Paris, France

Dos grupos de tratamiento: 5 mg/kg/día en 2 dosis por 60 días; o 7.5 mg/kg/día en 1 dosis diaria por 30 días.

Seguimiento con parasitemia (MH) al mes - 2 meses y serología convencional a 8-9 meses.

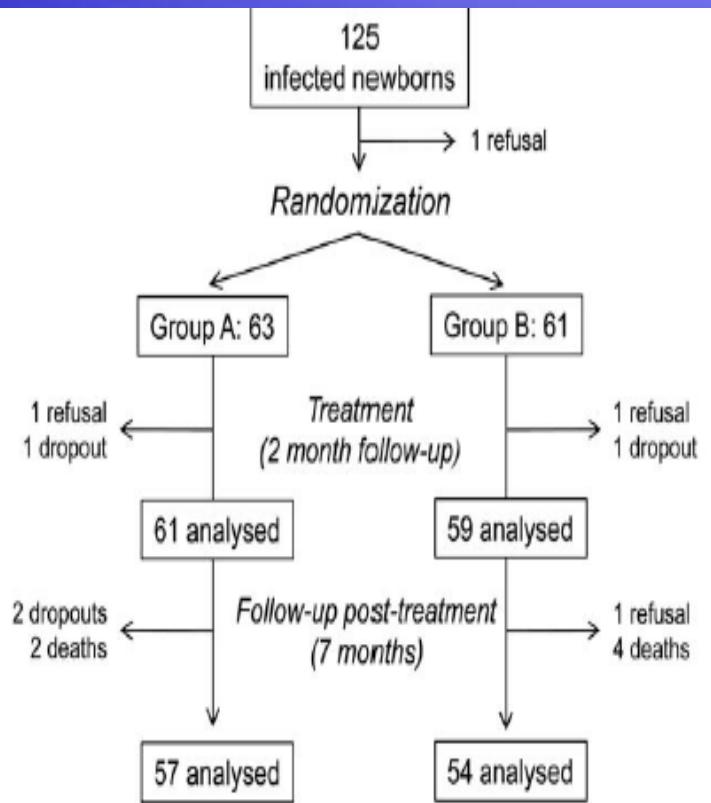
Antibody drop in newborns congenitally infected by *Trypanosoma cruzi* treated with benznidazole

Jean-Philippe Chippaux^{1,2}, Alejandra N. Salas Clavijo¹, Jose A. Santalla², Jorge R. Postigo¹, Dominique Schneider³ and Laurent Brutus³

¹ IRD UR010, Team "Mother's and Child's health in tropical environment", Institut de Recherche pour le Développement, La Paz, Bolivia

² Laboratory of Parasitology, Instituto Nacional de Laboratorios de Salud, Ministry of Health and Sport, La Paz, Bolivia

³ IRD UR010, Team "Mother's and Child's health in tropical environment", Institut de Recherche pour le Développement, Paris, France



Seguimiento

Todas las parasitemias fueron negativas .

Serología fue negativa en 109/110 niños

Puntos a discutir

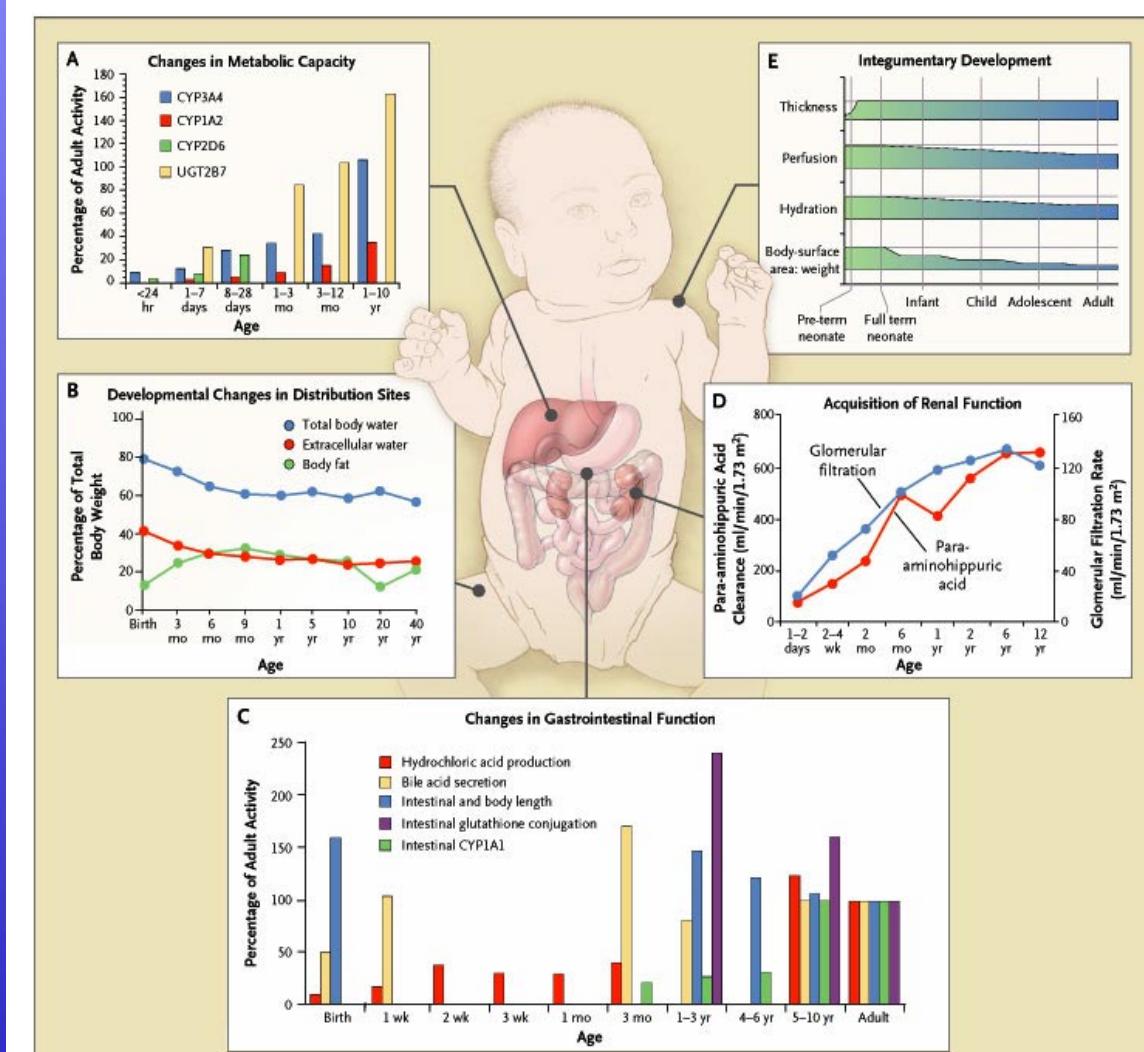
No es claro el tiempo de tratamiento

Los niños son diferentes

Los niños son diferentes en:

- Absorción
- Distribución
- Función renal (excreción)
- Función hepática (metabolismo)

• Farmacodinamia:
Respuesta terapéutica
Eventos adversos



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

^aServicio de Parasitología y Enfermedad de Chagas, Hospital de Niños R Gutierrez, Buenos Aires, Argentina; and ^bDivision 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

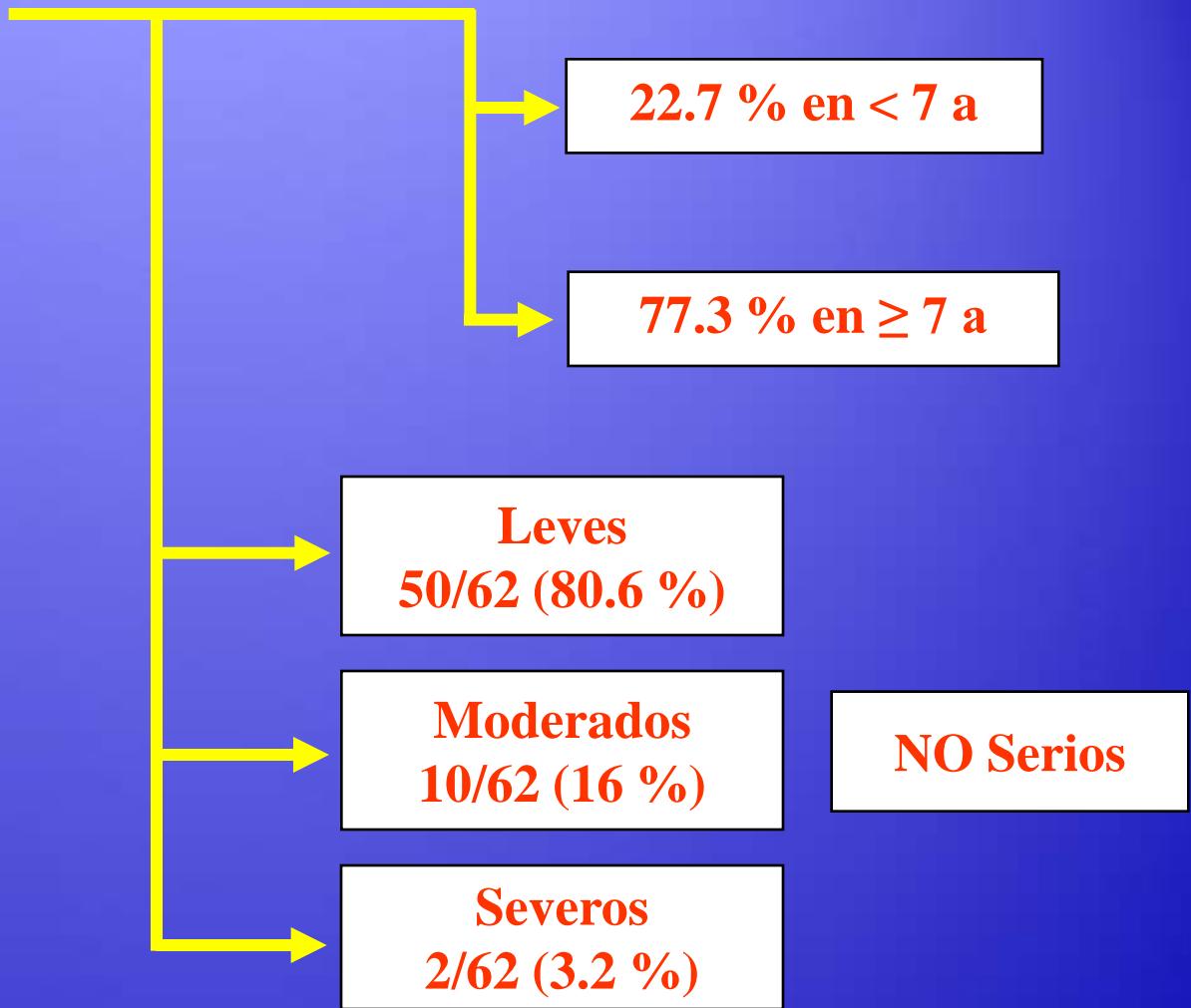
doi:10.1542/peds.2010-1172

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

EVENTOS ADVERSOS (107 pacientes)

- 41% presentaron EA
- 21% en piel
- 9% SNC
- 8.5% GI
- 28% Alt. Bioquímicas
- Edad media 9.9 años
- 73% en los 1^{ros} 10 días



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

Jaime Altcheh, Guillermo Moscatelli, Samanta Moroni, Facundo Garcia-Bournissen and Hector Freilij

Pediatrics published online Dec 20, 2010;
DOI: 10.1542/peds.2010-1172

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Jaime Altcheh¹, Guillermo Moscatelli¹, Guido Mastrandrea², Samanta Moroni¹, Norberto Giglio¹, María Elena Marson², Griselda Ballering¹, Margarita Bisio¹, Gideon Koren³, Facundo García-Bournissen^{1,2*}

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



Estudios comparativos concentración de Bz

Css (7mg/kg/day)	Children	Adults
------------------	----------	--------

≠

Median (mg/L)	4.53	10.96
---------------	------	-------

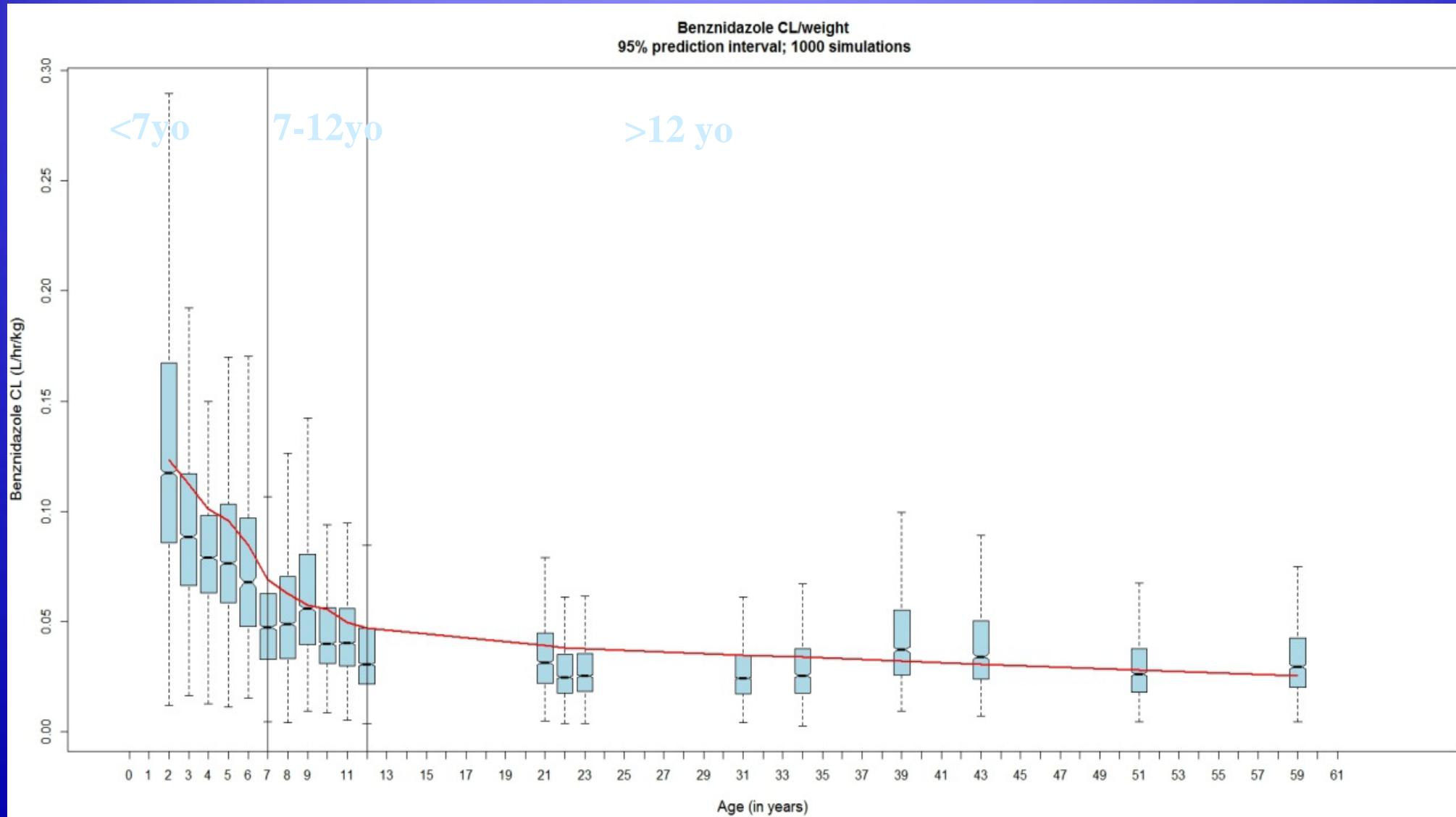
Css (7mg/kg/day)	2-7yo	7-12yo	Adults
------------------	-------	--------	--------

≠ ≠

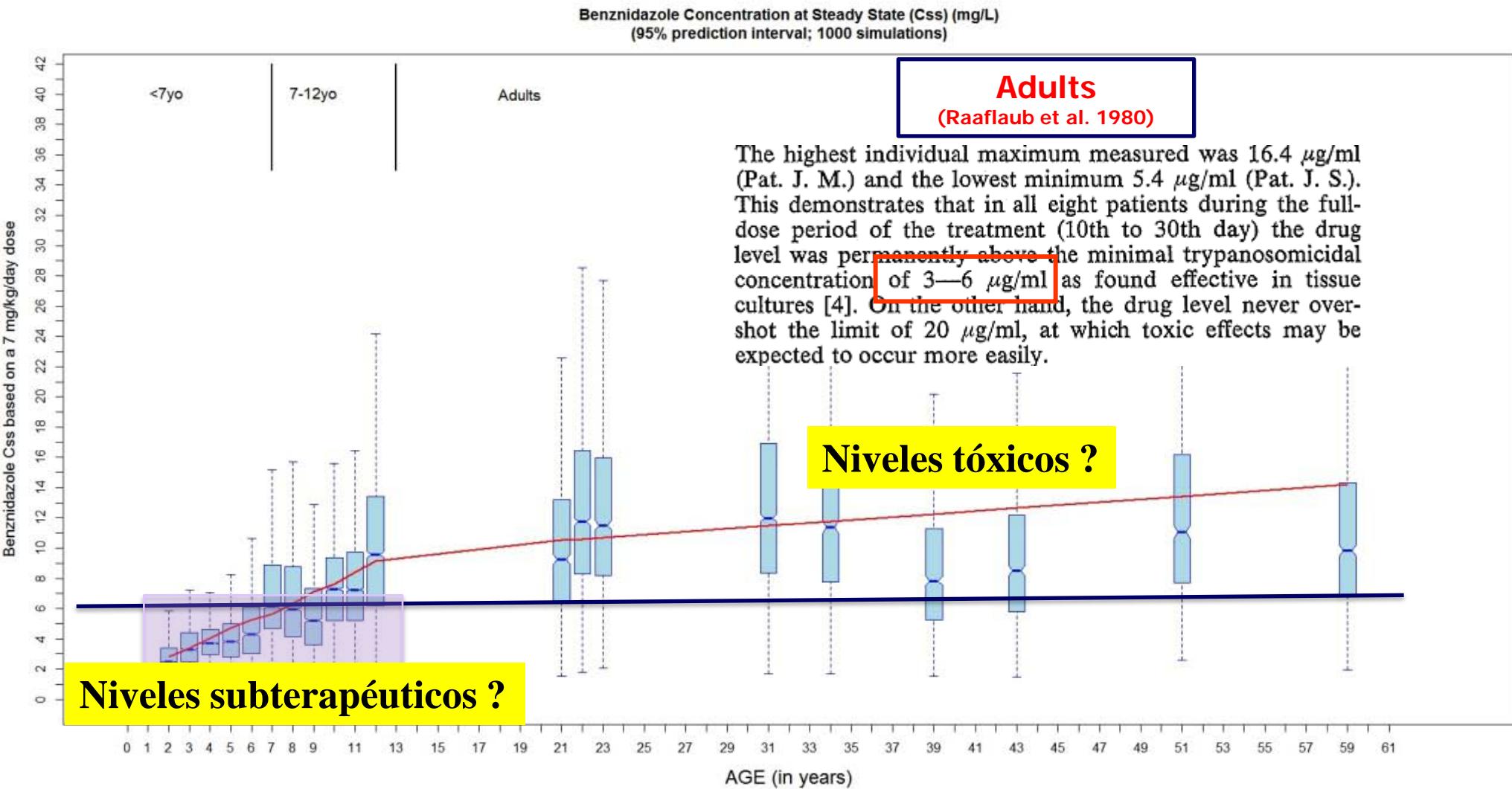
Median (mg/L)	3.18	6.99	10.96
---------------	------	------	-------

95% CI (median)	[2.5 – 3.9]	[5.1 – 8.9]	[7.7 – 15.4]
-----------------	-------------	-------------	--------------

Weight-corrected clearance (popPK)



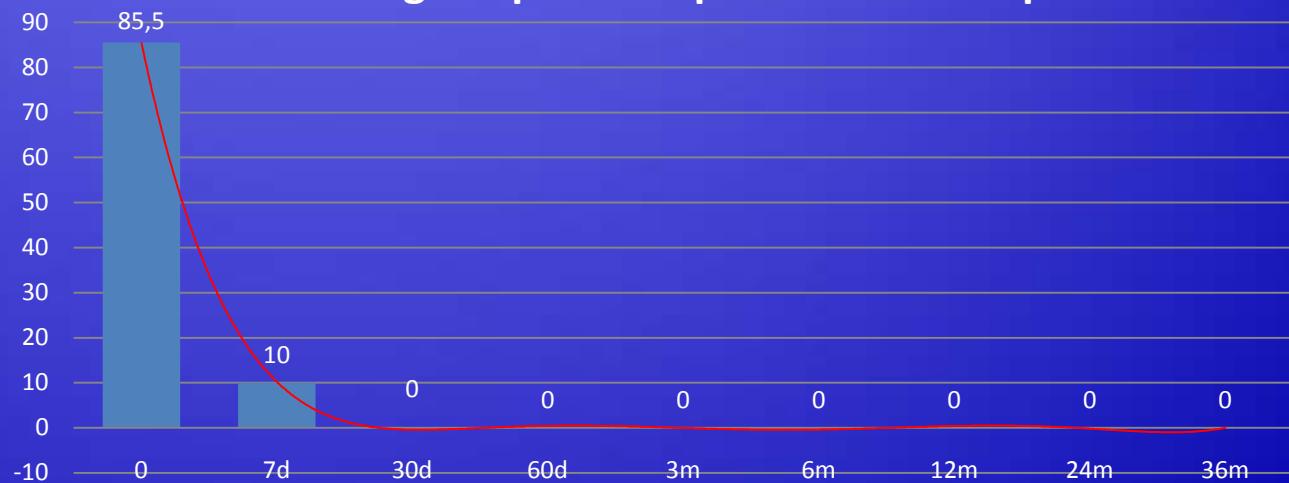
Steady state concentrations (popPK)



qPCR in a cohort of 105 treated children

time	n	+	%	95IC
0	105	90	85,5	77,7-91,1
7d	10	1	10	17-40,2
30d	9	0	0	0-29,9
60d	97	0	0	0-3,8
3m	15	0	0	0-20,3
6m	9	0	0	0-29,9
12m	26	0	0	0-12,8
24m	4	0	0	0-48,9
36m	17	0	0	0-18,4

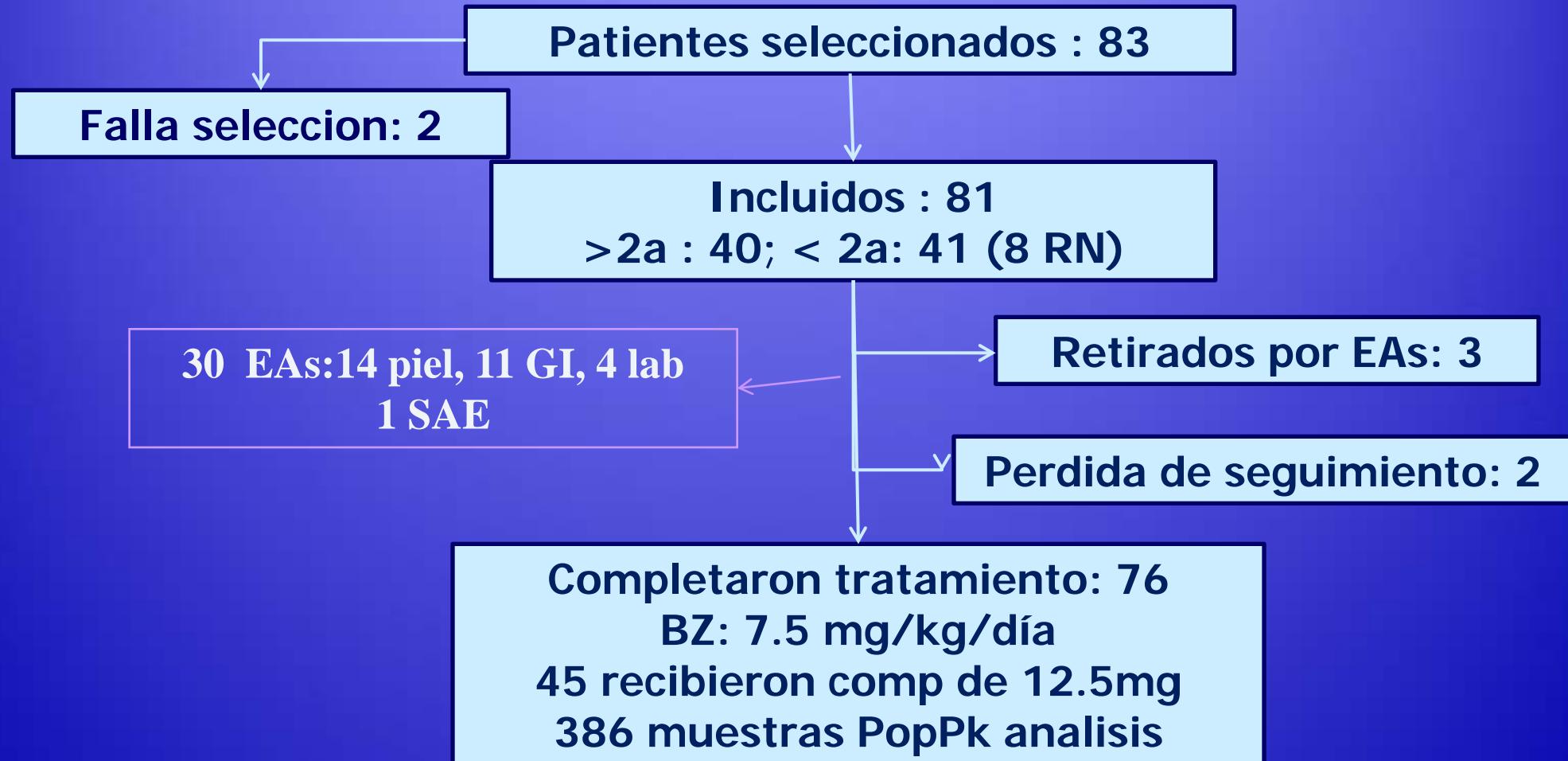
Percentage of positive q PCR at follow-up



Resultados PopPK BZ

- Las concentraciones de benznidazol en niños fueron significativamente menores que las reportadas en adultos tratados con similares dosis/kg de BNZ.
- El tratamiento fue bien tolerado, con pocos eventos adversos y excelente respuesta terapéutica.
- Estas observaciones sugieren que las concentraciones menores en los niños llevan a menor incidencia de eventos adversos, sin afectar la respuesta al tratamiento.

Resultados preliminares



Todos los niños presentaron PCR negativa al final del tratamiento

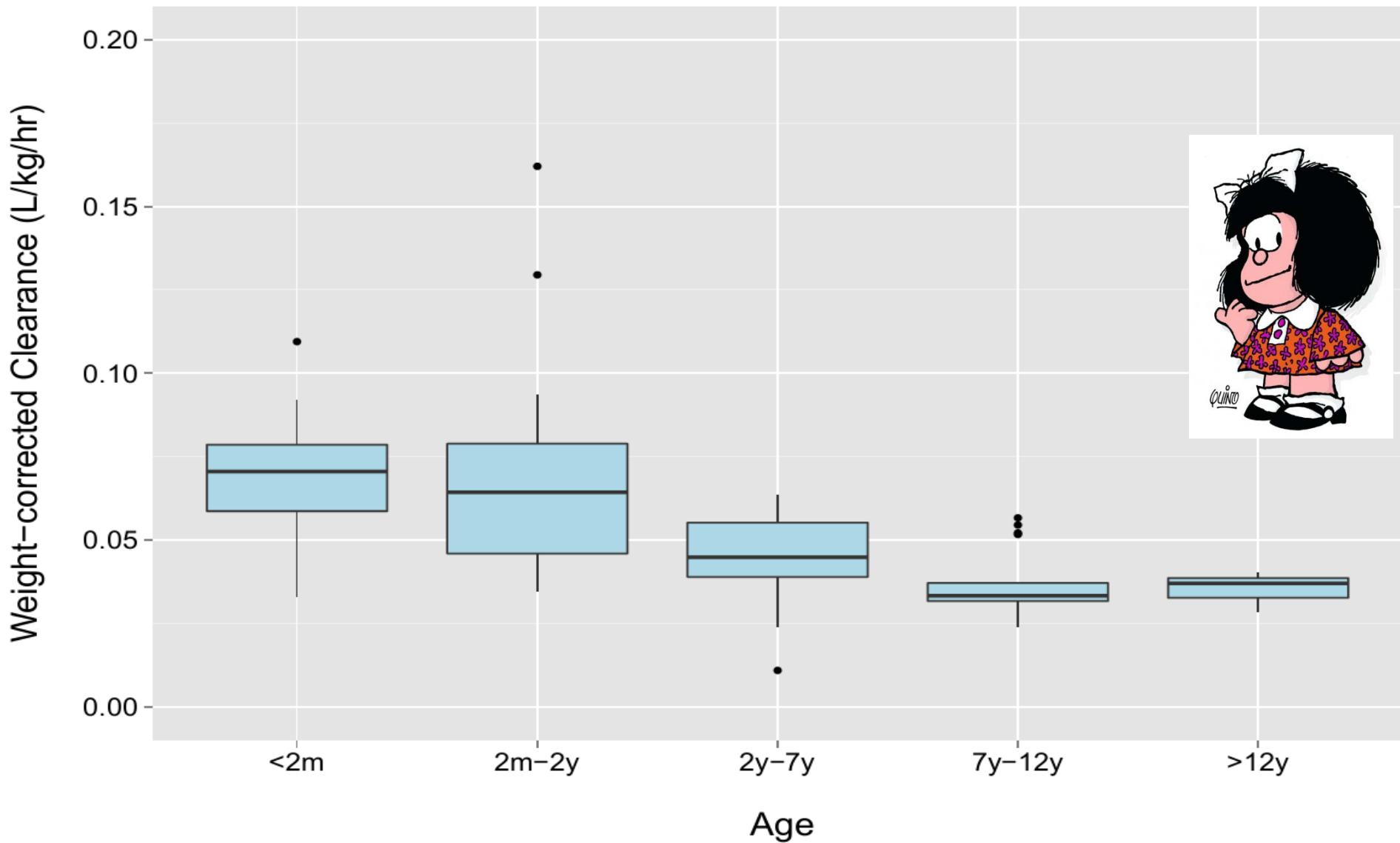
Comparative results (children and adults)

Css (7mg/kg/day)	Children	Adults (Raaflaub, 1980)			
Median (mg/L)	6.6	10.96			
Css (7mg/kg/day)	0-2mo	2-12 mo	1-7 yo	7-12yo	Adults
Median (mg/L)	4.73	6.88	6.61	9.8	10.96

Adult data (re-analyzed) from: Raaflaub J. Arzneimittelforschung. 1980;30(12):2192-4.
Multiple-dose kinetics of the trypanosomicide benznidazole in man.

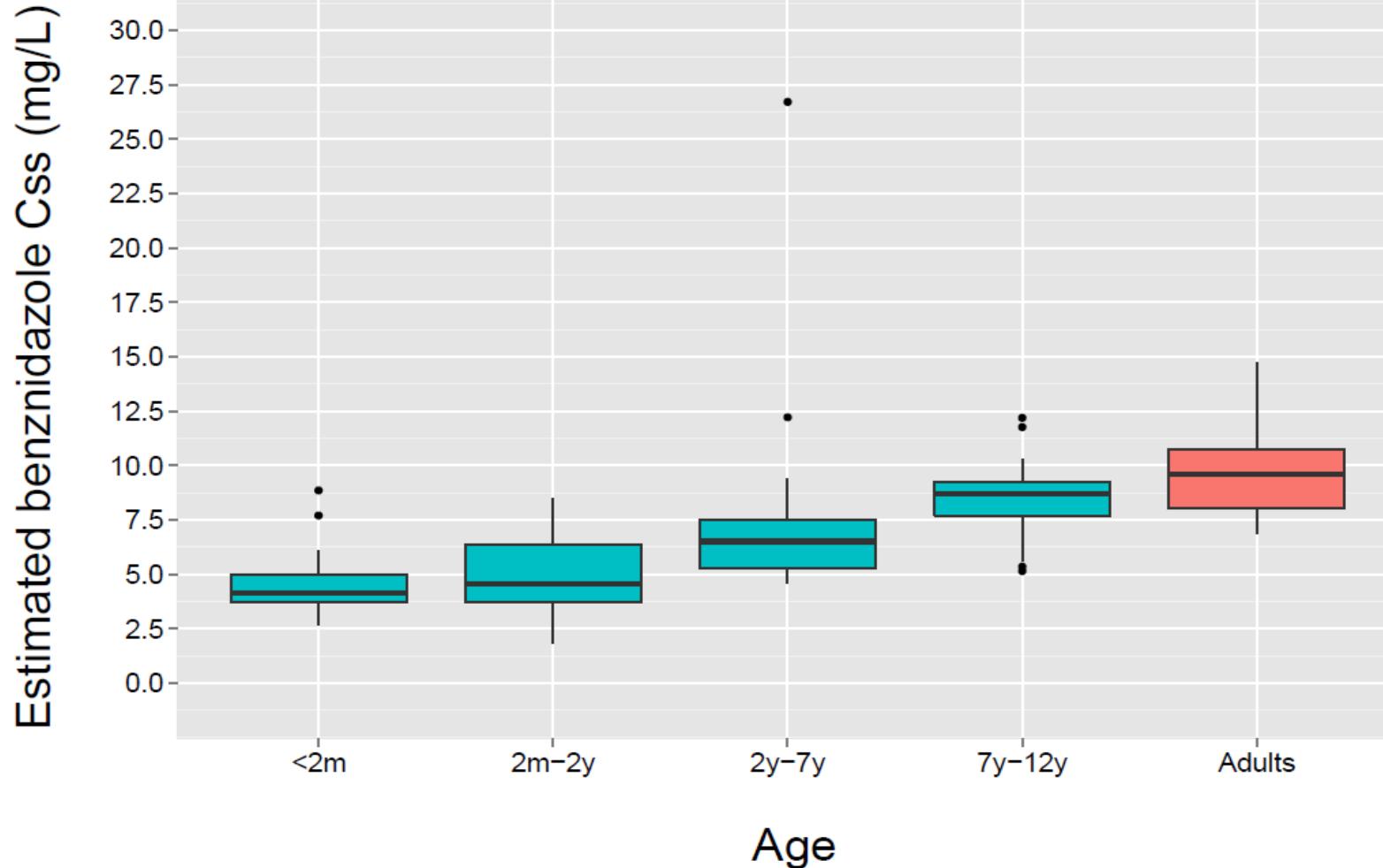
Clearance

Weight-corrected CL by age group – PEDCHAGAS



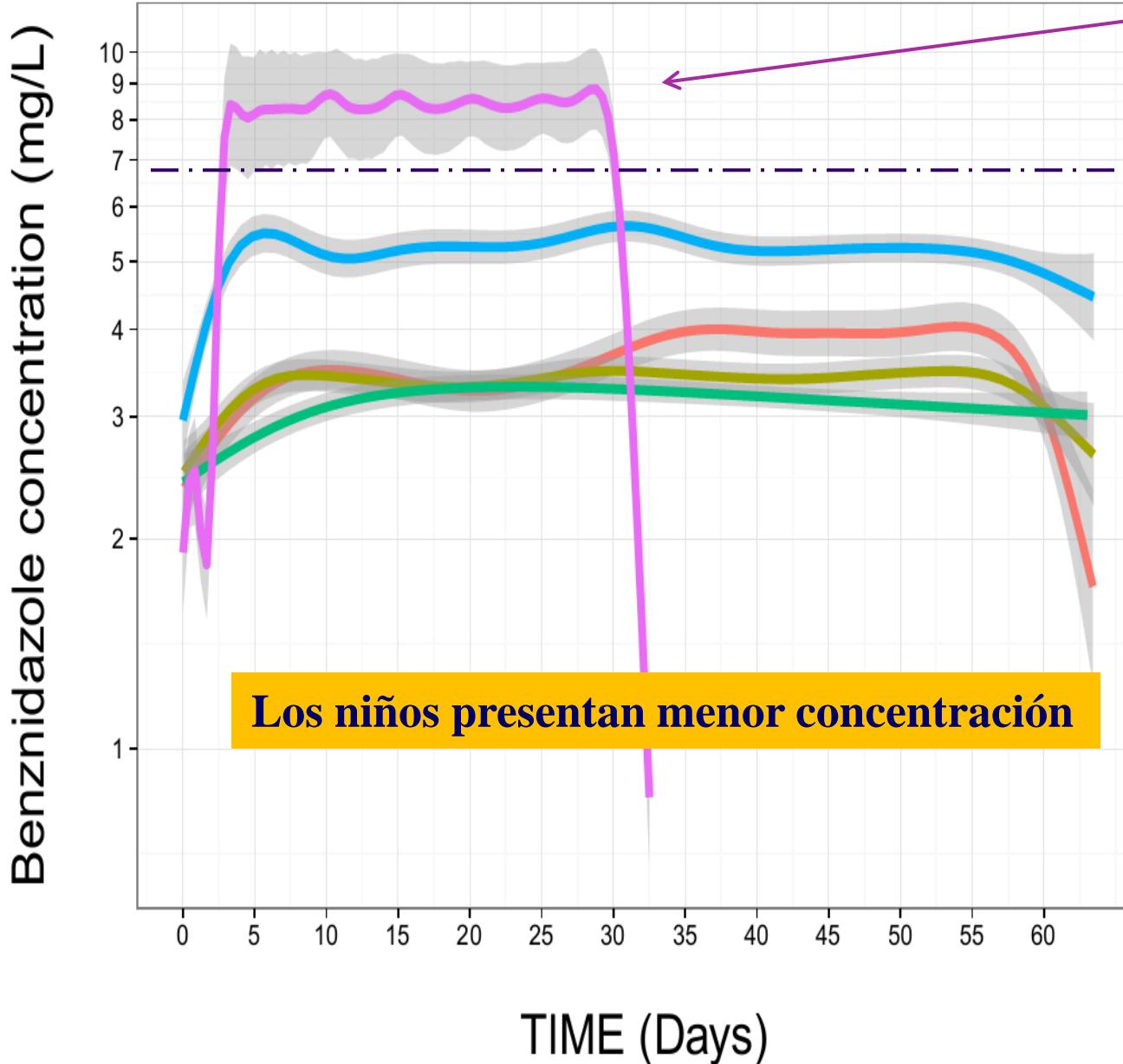
Concentracion

Estimated Css by age group – PEDCHAGAS studies



BNZ concentrations (polynomial regression) by age group

Adultos, Raaflaub 1980



The highest individual maximum measured was 16.4 µg/ml (Pat. J. M.) and the lowest minimum 5.4 µg/ml (Pat. J. S.). This demonstrates that in all eight patients during the full-dose period of the treatment (10th to 30th day) the drug level was permanently above the minimal trypanocidal concentration of 3–6 µg/ml as found effective in tissue cultures [4]. On the other hand, the drug level never overshoot the limit of 20 µg/ml, at which toxic effects may be expected to occur more easily.

age

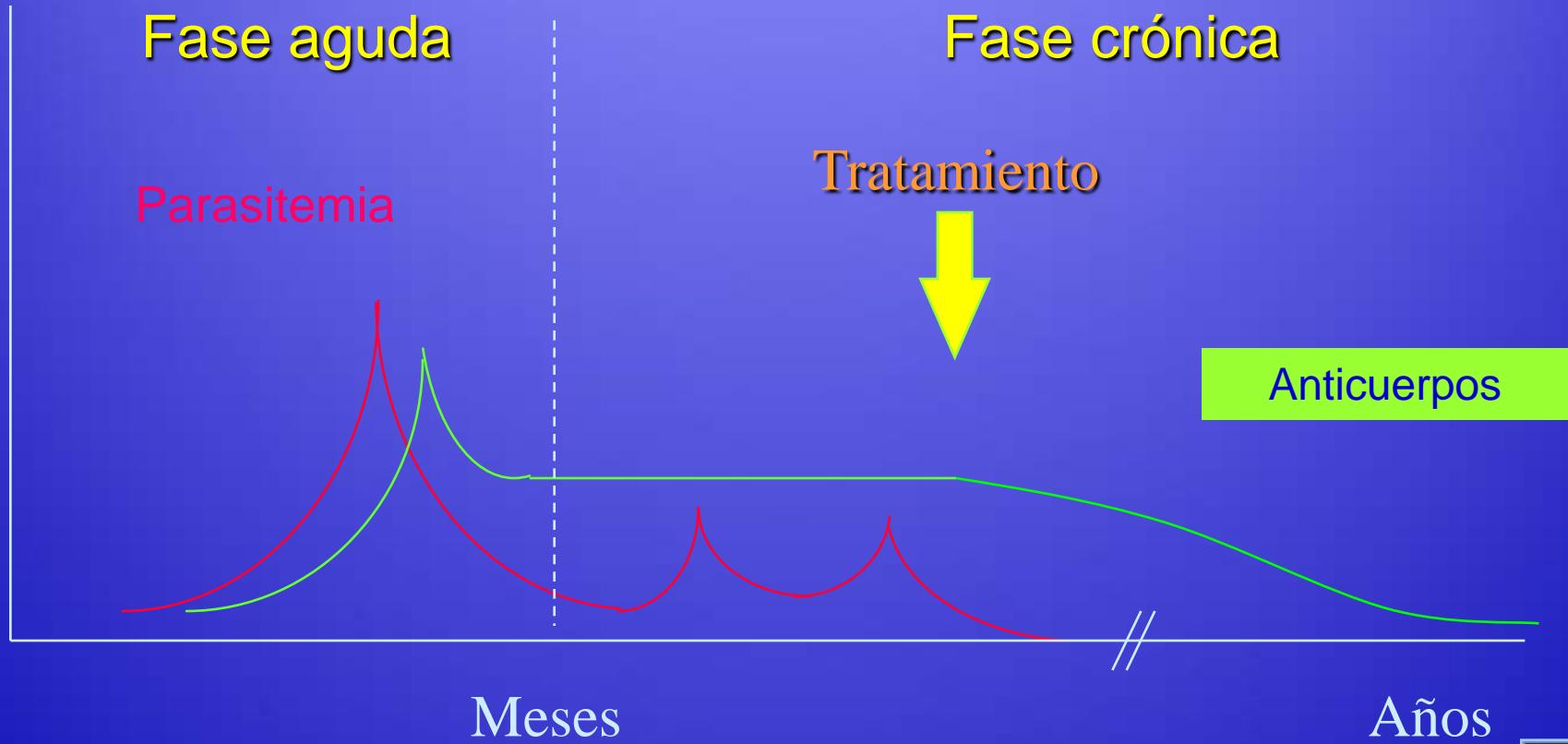
- <2m
- 2m-2y
- 2y-7y
- 7y-12y
- Adults



Puntos a discutir

No es claro el tiempo de tratamiento
¿A que dosis ?

¿Como valoramos la respuesta terapéutica?



Respuesta terapéutica

- n No podemos utilizar puntos finales clínicos dado que la mayoría de los niños cursan la infección en forma asintomática.
- n La negativización de la SC es criterio de curación
- n La mayor limitación es que se requiere largo tiempo de seguimiento (años ó décadas) en sujetos tratados en fase crónica para observar la seronegativización.

¿Hay diferencias regionales ?

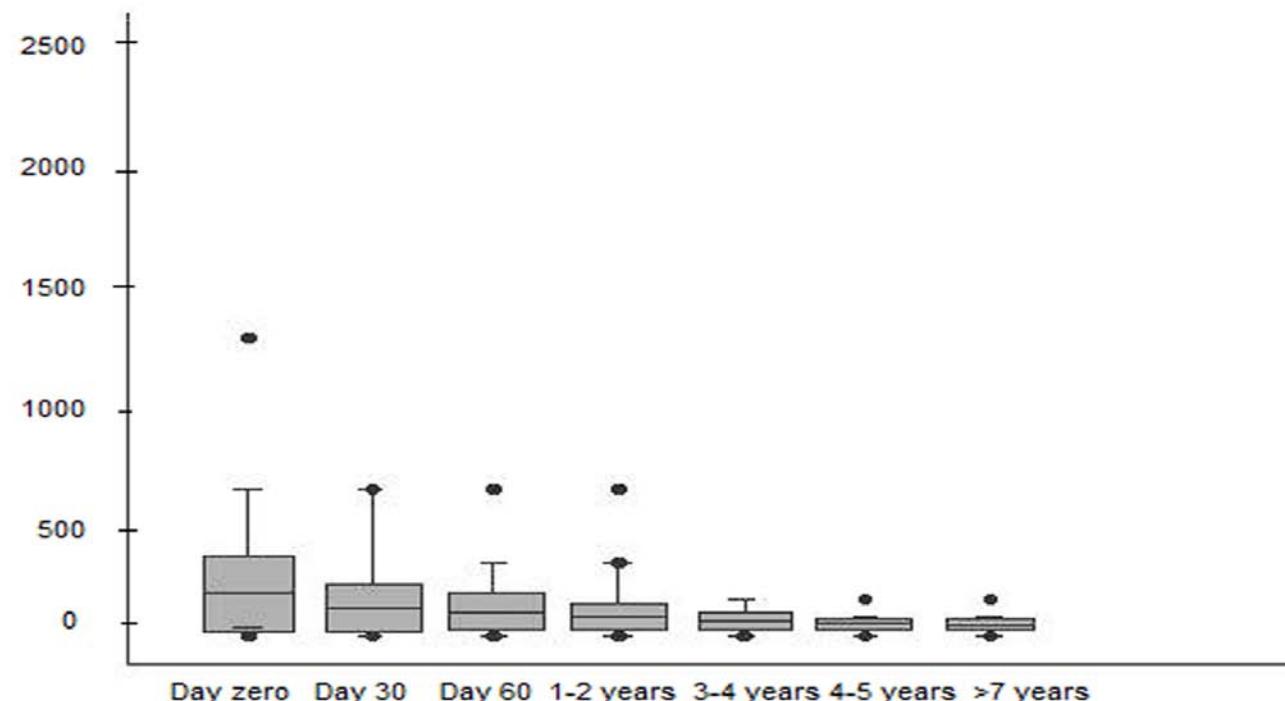
Clinical Follow-Up of Responses to Treatment with Benznidazol in Amazon: A Cohort Study of Acute Chagas Disease

Ana Yecê das Neves Pinto^{1*}, Vera da Costa Valente², José Rodrigues Coura³, Sebastião Aldo da Silva Valente², Angela Cristina Veríssimo Junqueira³, Laura Cristina Santos³, Alberto Gomes Ferreira Jr.⁴, Roberto Cavalleiro de Macedo⁵

1 Clinical epidemiologic Department of Evandro Chagas Institute (SOAMU-IEC)- Secretaria de Vigilância em Saúde/Brazil Ministry Health (SVS/MS), Belém, Pará, Brazil,

2 Parasitology Department of IEC-SVS/MS, Belém, Pará, Brazil, **3** Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Rio de Janeiro, Brazil, **4** Luis Décourt Foundation, Belém, Pará, Brazil, **5** Santa Casa Hospital, Belém, Pará, Brazil

Titers of IgG anti- *T. cruzi* antibodies



Feasibility, Drug Safety, and Effectiveness of Etiological Treatment Programs for Chagas Disease in Honduras, Guatemala, and Bolivia: 10-Year Experience of Médecins Sans Frontières

Oliver Yun¹, M. Angeles Lima^{2*}, Tom Ellman³, Wilma Chambi³, Sandra Castillo³, Laurence Flevaud², Paul Roddy², Fernando Parreño², Pedro Albajar Viñas⁴, Pedro Pablo Palma²

¹Médecins Sans Frontières/Doctors Without Borders, New York, New York, United States of America, ²Médecins Sans Frontières, Operational Center Barcelona-Athens (OCBA), Barcelona, Spain, ³Médecins Sans Frontières/Médicos Sin Fronteras, La Paz, Bolivia, ⁴Laboratory of Parasitological Diseases, Oswaldo Cruz Institute, FIOCRUZ, Rio de Janeiro, Brazil

Table 2. Chagas disease patient diagnosis and treatment results of four Médecins Sans Frontières programs in Central and South America, 1999–2008.

	Yoro (Honduras)	Olopa (Guatemala)	Entre Ríos (Bolivia)	Sucre (Bolivia)
Program duration	1999–2002	2003–2006	2002–2006	2005–2008
Age group (years)	<12	<15	<15	<18
# patients tested	24,771	8,927	7,613	19,400
# patients positive at initial screening	256	124	1,475	1,179
# patients confirmed positive/infected	232	124	1,475	1,145
Seroprevalence (%)	0.9	1.4	19.4	5.9
# patients treated	231	124	1,409	1,040
Seroconversion rate (%)	87.1	58.1	5.4	0

doi:10.1371/journal.pntd.0000488.t002

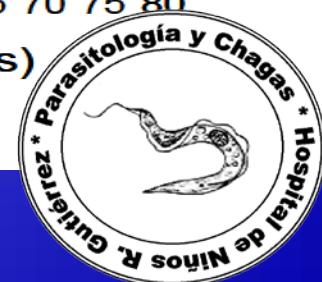
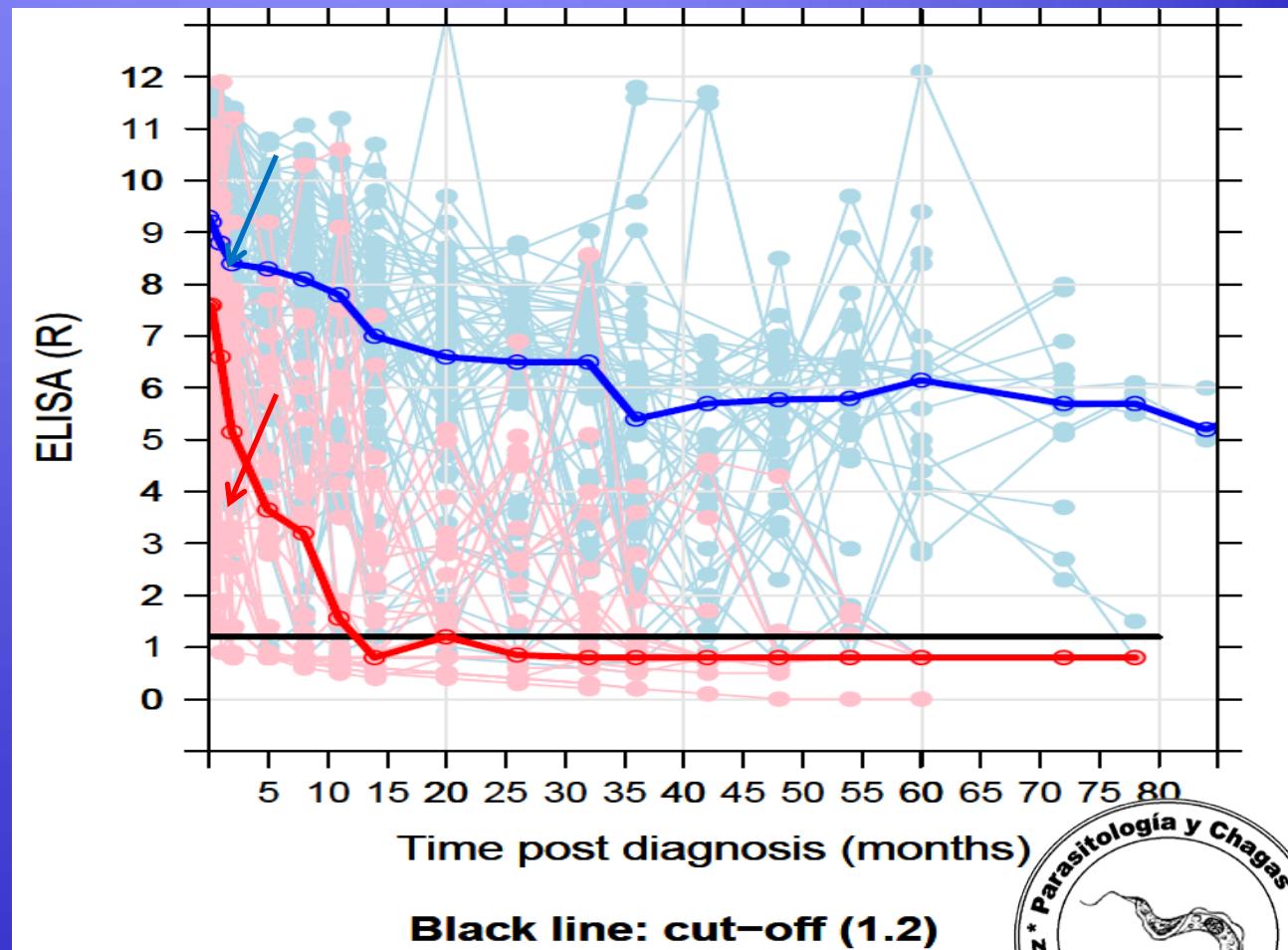
Elisa IgG en niños tratados

Edad <2 años

- Se observa una caída importante luego de 3 a 6 m. Seroconversion en la mayoría a los 12 meses.

Edad > 3 años

- Alguna caída después de 3 a 6 meses.
- Gran variabilidad intra e inter sujetos.
- Solo algunos seroconvierten



Serología no convencional

- Anticuerpos líticos y F29 han sido propuestos como marcadores de curación (de Andrade et al., 1996; Almeida et al., 1999; Sosa Estani et al., 1998).
- Anticuerpos líticos tambien llamados “Anticuerpos anti F2/3” han sido utilizados para evaluar respuesta terapeútica en Chagas congénito (Altcheh et al., 2003).

Desafortunadamente estas técnicas no han sido estandarizadas, son poco reproducibles y muy complejas en su realización.

Puntos a discutir

No es claro el tiempo de tratamiento

¿A que dosis ?

¿Serología como marcador de curación en
fase crónica?

PCR

- n Esta técnica representa un nuevo aporte
- n Varios estudios demuestran una alta sensibilidad de la PCR para detectar fallas terapeúticas.
- n Sin embargo diferentes laboratorios usan diferentes métodos para su realización (Schijman et al., 2011)
- n Solamente Schijman et al. (2003) y Solari et al. (2001) informan datos sobre especificidad.

"Consortium for standardization and validation the clinical use of PCR for *T. cruzi* DNA detection in Chagas disease"

- n Investigadores de diversos laboratorios definieron procedimientos operativos. (Schijman et al, 2011).
- n Cuatro procedimientos fueron establecidos, 2 para PCR convencional y 2 para real time PCR.

Aetiological treatment of congenital Chagas' disease diagnosed and monitored by the polymerase chain reaction

Alejandro G. Schijman^{1*}, Jaime Altcheh², Juan M. Burgos¹, Miguel Biancardi², Margarita Bisio², Mariano J. Levin¹ and Héctor Freilij²

- Conventional PCR targeted to Kinetoplastid (mitochondrial) DNA
 - primers 121-122
- Global results: PCR became negative in 96.8% of treated children (2y of Follow-up) after treatment
- PCR became negative in 95.7% (CI95 78 to 99) in NFTX group and in 100%(CI95 80 to 100) in BZ group (data not shown)

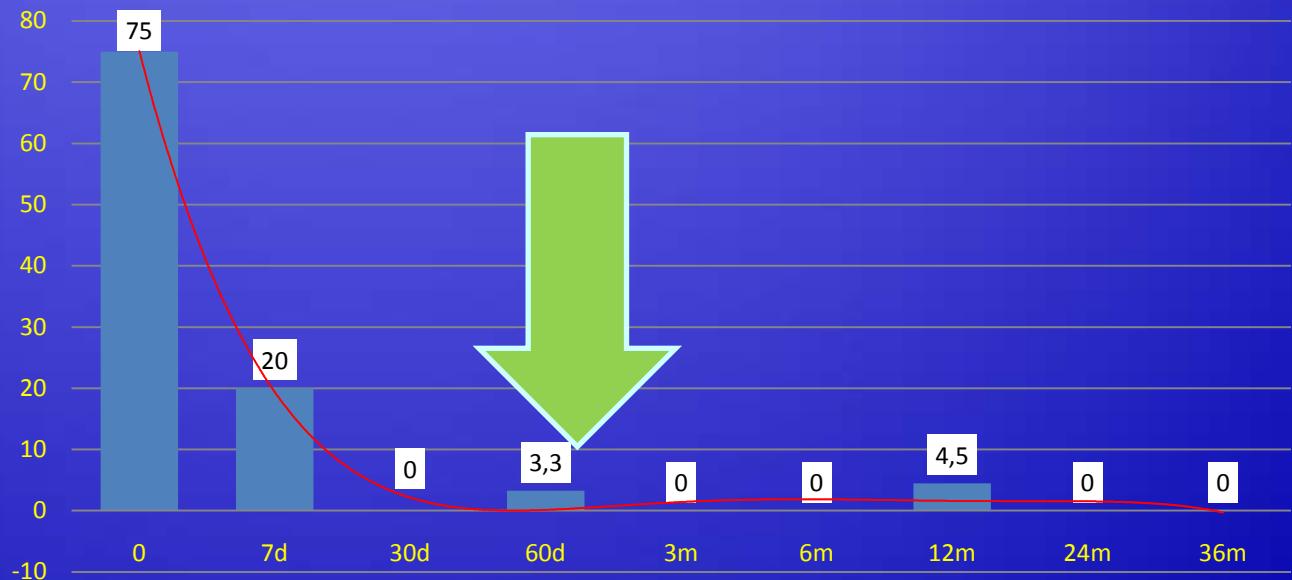
PCR in a cohort of 36 NFTX treated children-

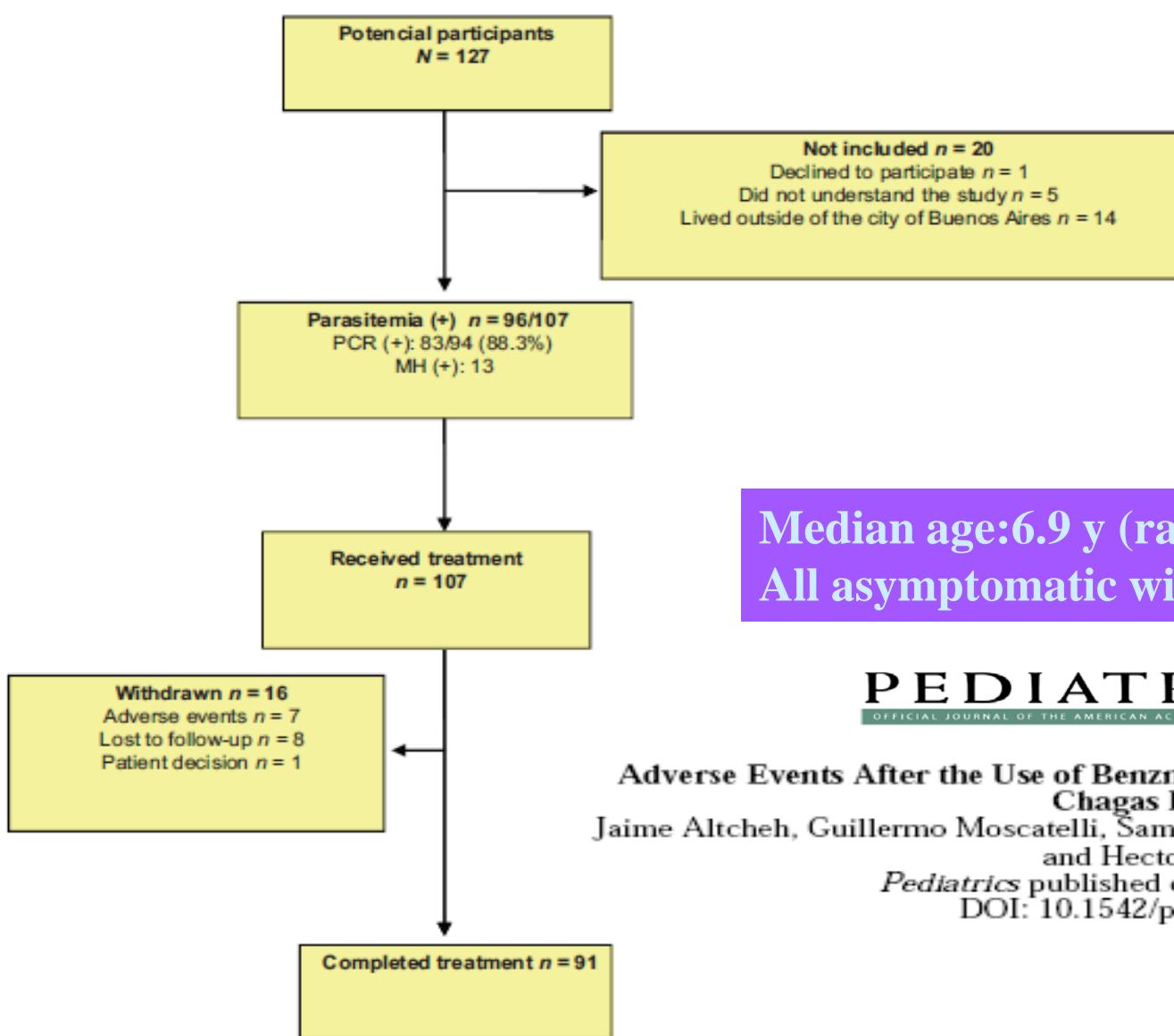
Data not shown in JAC 2003

time	n	+	%	IC95
0	36	27	75	58,9-86,2
7d	5	1	20	36,2-62,2
30d	21	0	0	0-15,4
60d	30	1	3,3	5,9-16,6
3m	15	0	0	0-20,3
6m	12	0	0	0-24,2
12m	22	1	4,5	0,8-21,8
24m	18	0	0	0-17,5
36m	16	1	0	0-39



NFTX- Percentage of positive PCR at follow-up





Median age: 6.9 y (range 10d to 19y)
All asymptomatic with no cardiac involvement

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Adverse Events After the Use of Benznidazole in Infants and Children With Chagas Disease
 Jaime Altcheh, Guillermo Moscatelli, Samanta Moroni, Facundo Garcia-Bournissen and Hector Freilij
Pediatrics published online Dec 20, 2010;
 DOI: 10.1542/peds.2010-1172

FIGURE 1
 Study flowchart.

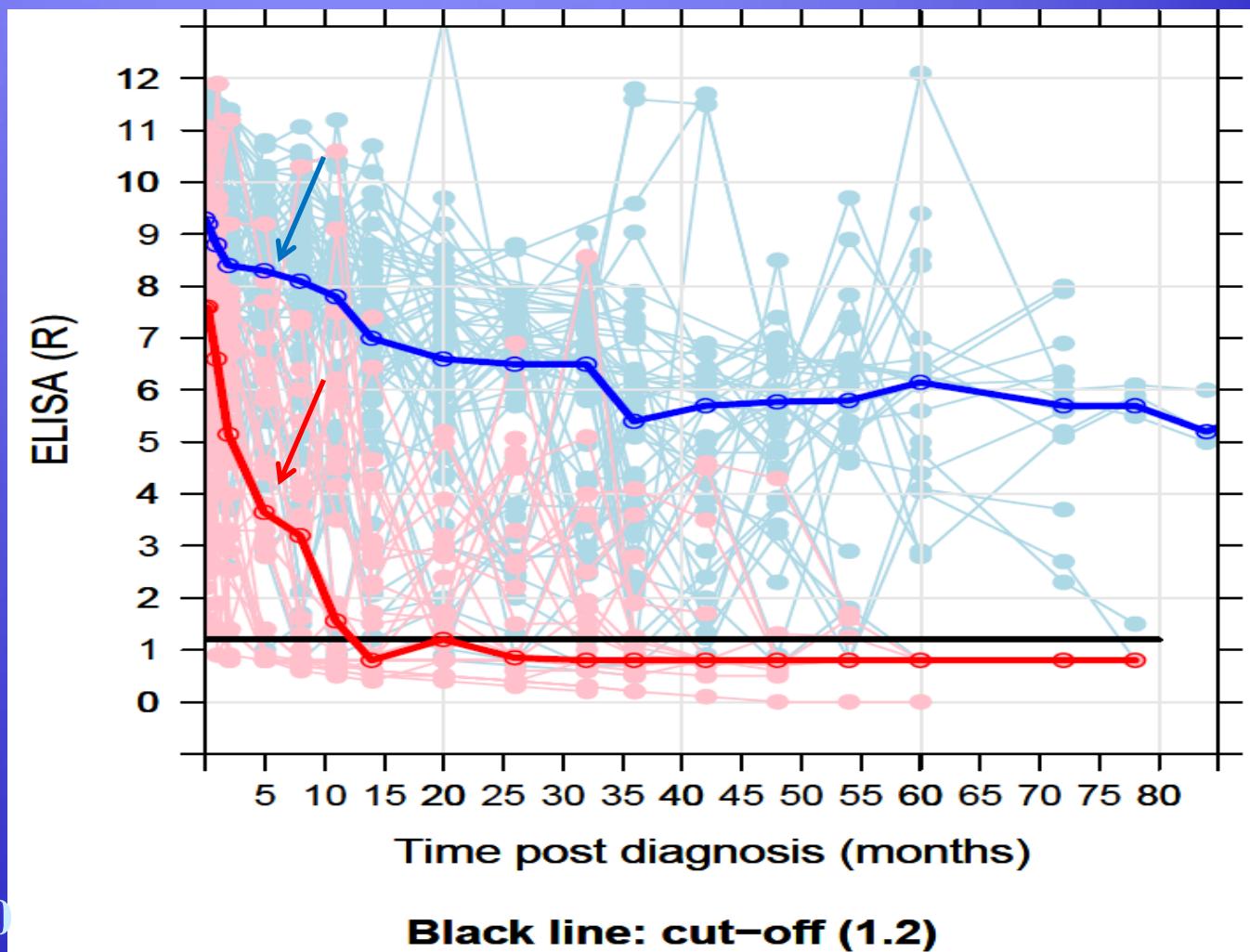
Shorter time course for conventional ELISA in children \leq 2 years

Age <2 y

- Overall good correlation with PCR results
- A significant drop in Elisa titers see after 3-6 months.
- Seroconversion in most patients at 12 months.

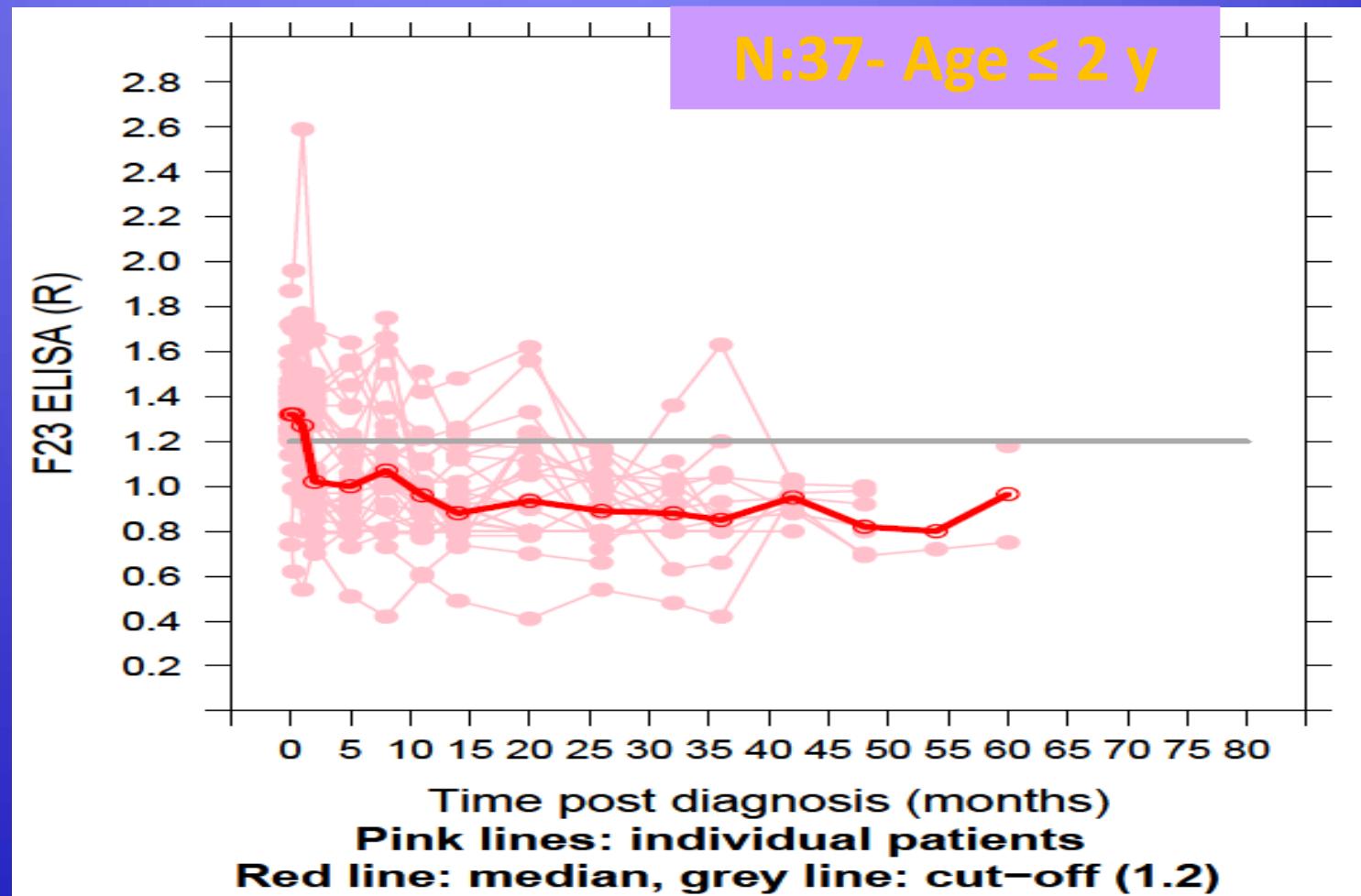
Age >3 y

- Some drop in Elisa titers after 3-6 months.
- Large intra and inter-patient variability
- No seroconversion after 80 months



Elisa antibodies against F2/3 t.cruzi (chemiluminescent ELISA with purified trypomastigote glycoconjugate).

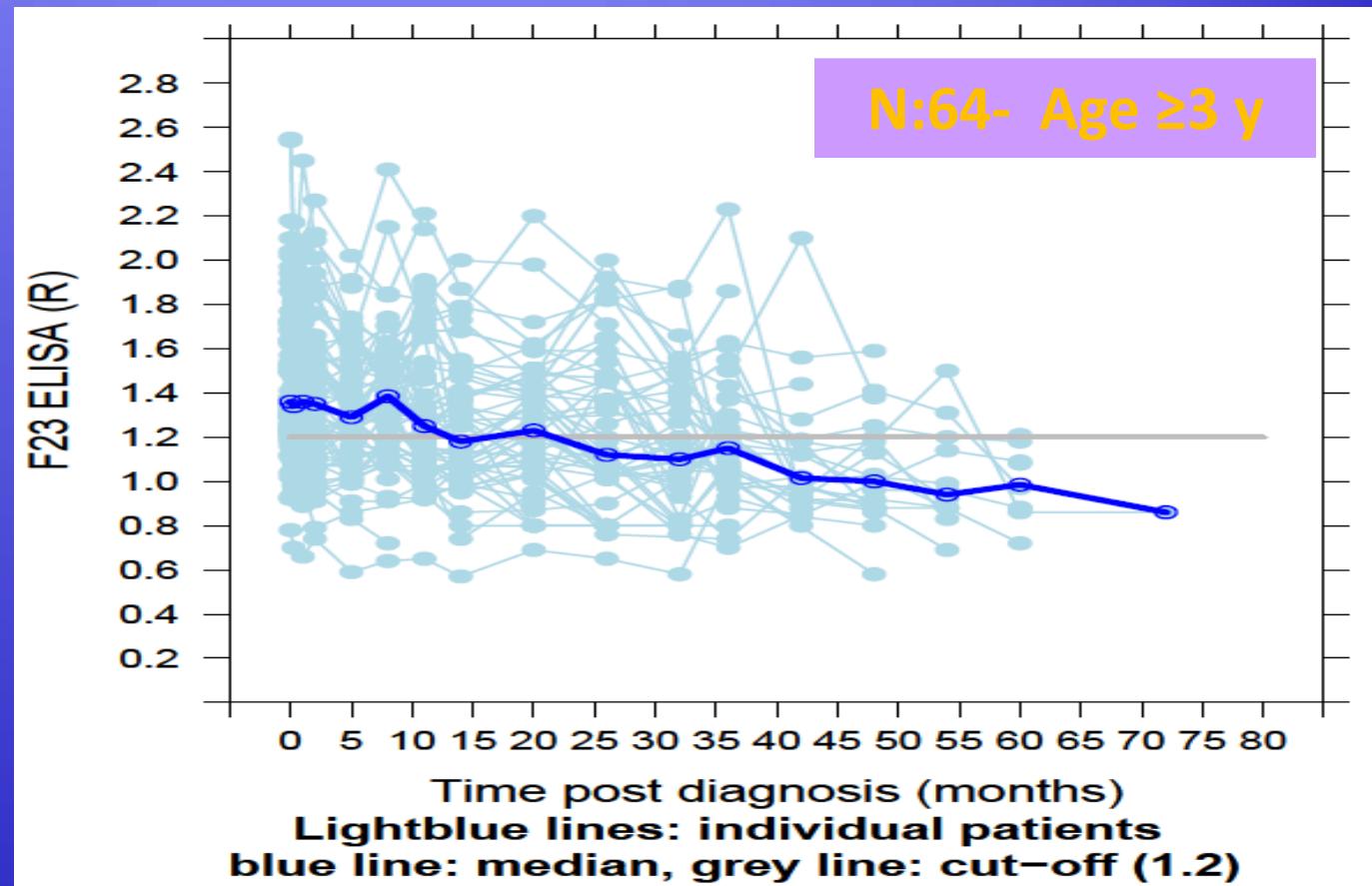
Same methodology of Andrade A. Randomised trial of efficacy of bennidazole.....
Lancet 1996.

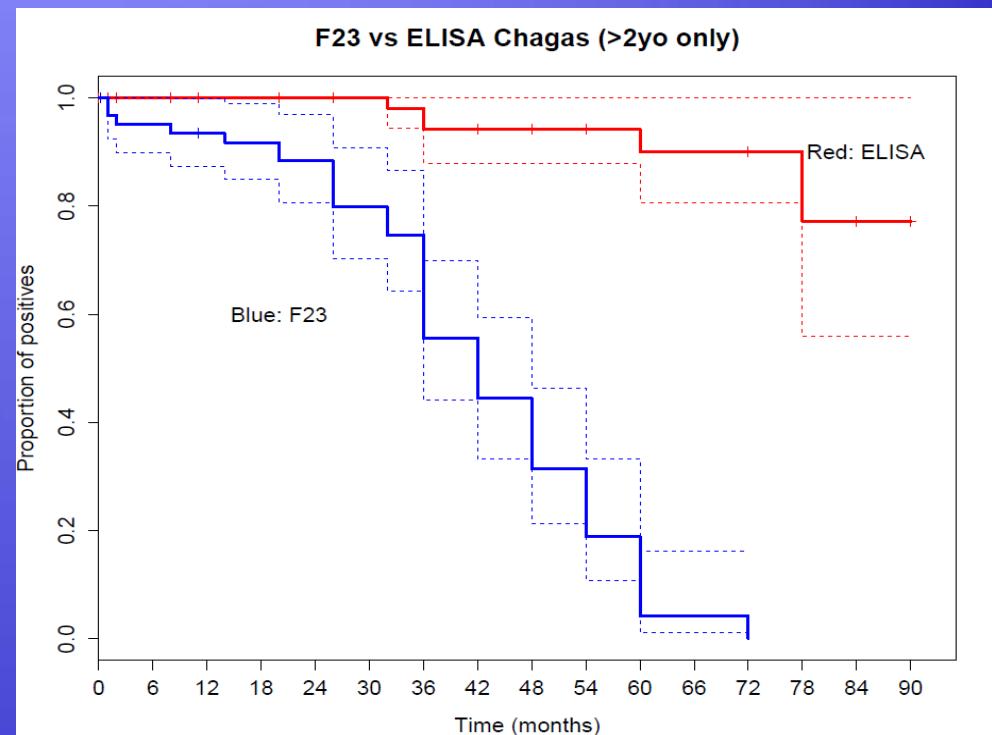
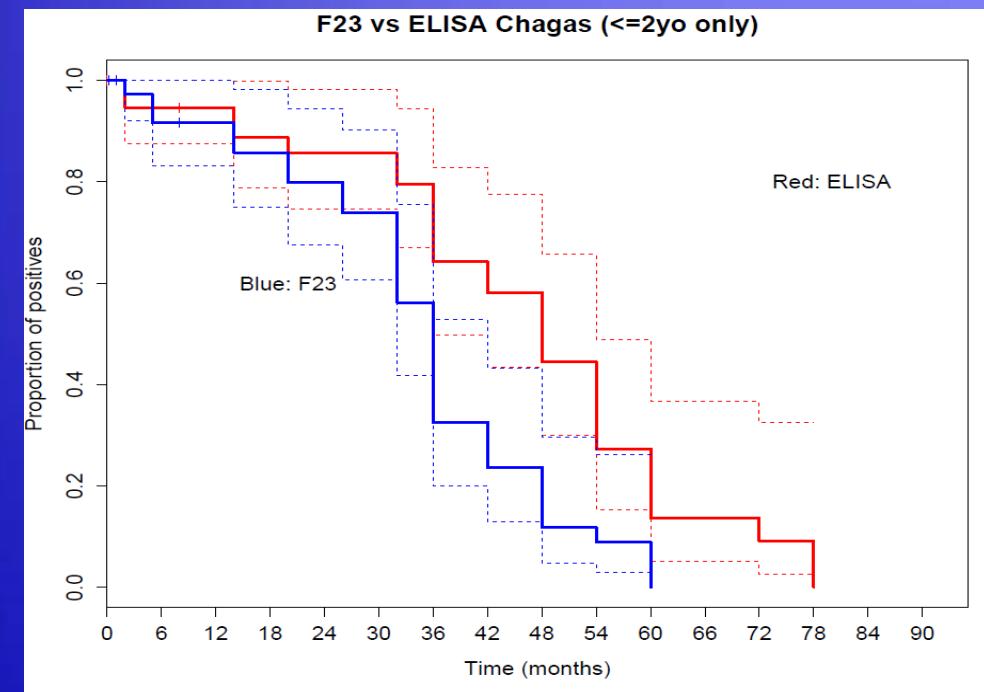


Elisa antibodies against F2/3 t.cruzi (chemiluminescent ELISA with purified trypomastigote glycoconjugate).

Same methodology of Andrade A. Randomised trial of efficacy of bennidazole.....
Lancet 1996.

Elisa F2/3
seroconversion
after 12 months





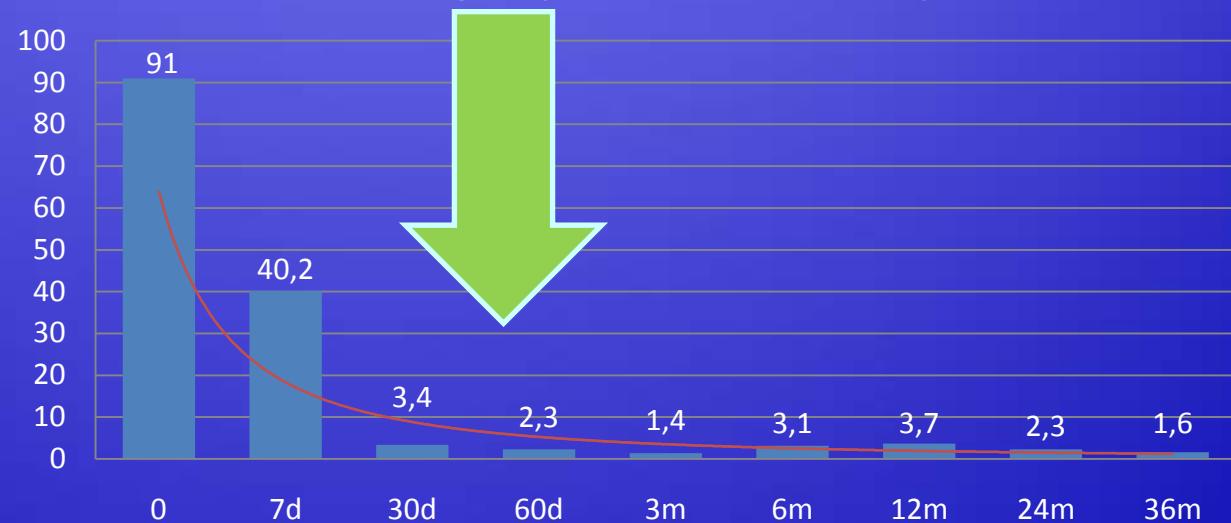
Unpublished Data

PCR in a cohort of 101 BZN - treated children

Time	n	+	%	95 IC
0	101	92	91	83,9- 95,4
7d	92	37	40,2	30,7-50,4
30d	87	3	3,4	1,1-9,9
60d	86	2	2,3	0,6-8
3m	69	1	1,4	0,2-7,7
6m	63	2	3,1	0,8-10,8
12m	53	2	3,7	1,0 -12,7
24m	42	1	2,3	0,4-12,3
36m	59	1	1,6	0,3-9

All asymptomatic,
 Median age: 6.9 y (range 10d to 19y)
 Conventional serology, Lytic antibodies
 Coventional PCR K DNA

Percentage of positive PCR at follow-up



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*}

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

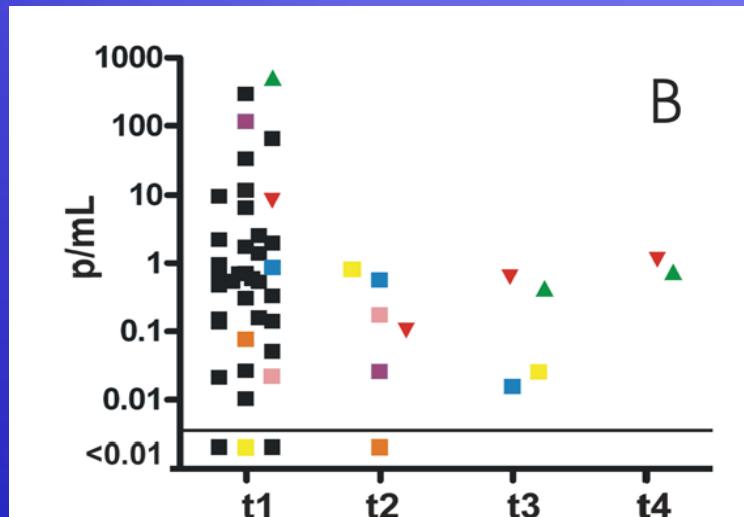


Figure 3. Parasitic loads in peripheral blood samples from pediatric patients. (A) Association between basal parasitic loads and patients' ages in 43 pediatric cases. Coefficient of correlation: -0.5832 ; $P<0.05$. (B) Monitoring of parasitological response to benznidazole therapy in 38 pediatric patients. The evolution of the parasitic loads for patients with more than one positive sample are depicted. Samples were withdrawn at time of diagnosis (t1), after 7 (t2) and 30 (t3) days of treatment, as well as at the end of treatment (t4, 60 days). Only the PCR positive samples are shown. The horizontal line represents the lower limit of the dynamic range of Q-PCR.

Negative Real Time-PCR results after BNZ treatment

- 7 days in 24 out of 31 patients (77%),
- 30 days in 27 out of 31 patients (87%)
- 60 days in 29 out of 31 patients (94%)

Summary of Data from 2 Pop PK cohorts: qPCR in 105 BZN-treated children

time	n	+	%	95IC
0	105	90	85,5	77,7-91,1
7d	10	1	10	17-40,2
30d	9	0	0	0-29,9
60d	97	0	0	0-3,8
3m	15	0	0	0-20,3
6m	9	0	0	0-29,9
12m	26	0	0	0-12,8
24m	4	0	0	0-48,9
36m	17	0	0	0-18,4



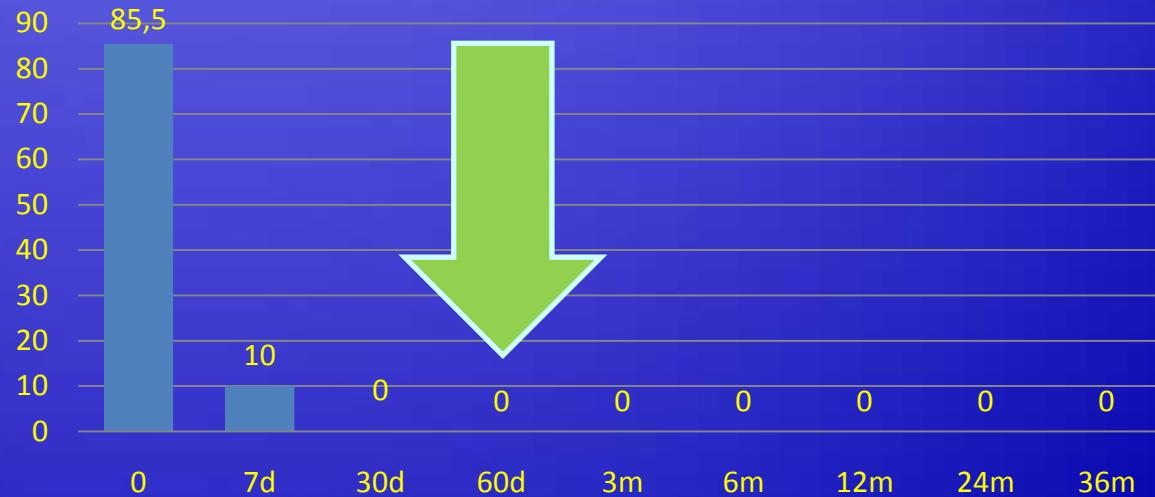
Pediatric network
PEDCHAGAS

DND*i*

Drugs for Neglected Diseases initiative

Multiplex real-time PCR
Taqman^r targeted to satellite
(nuclear) DNA
primers cruzil, cruzi2, cruzi3

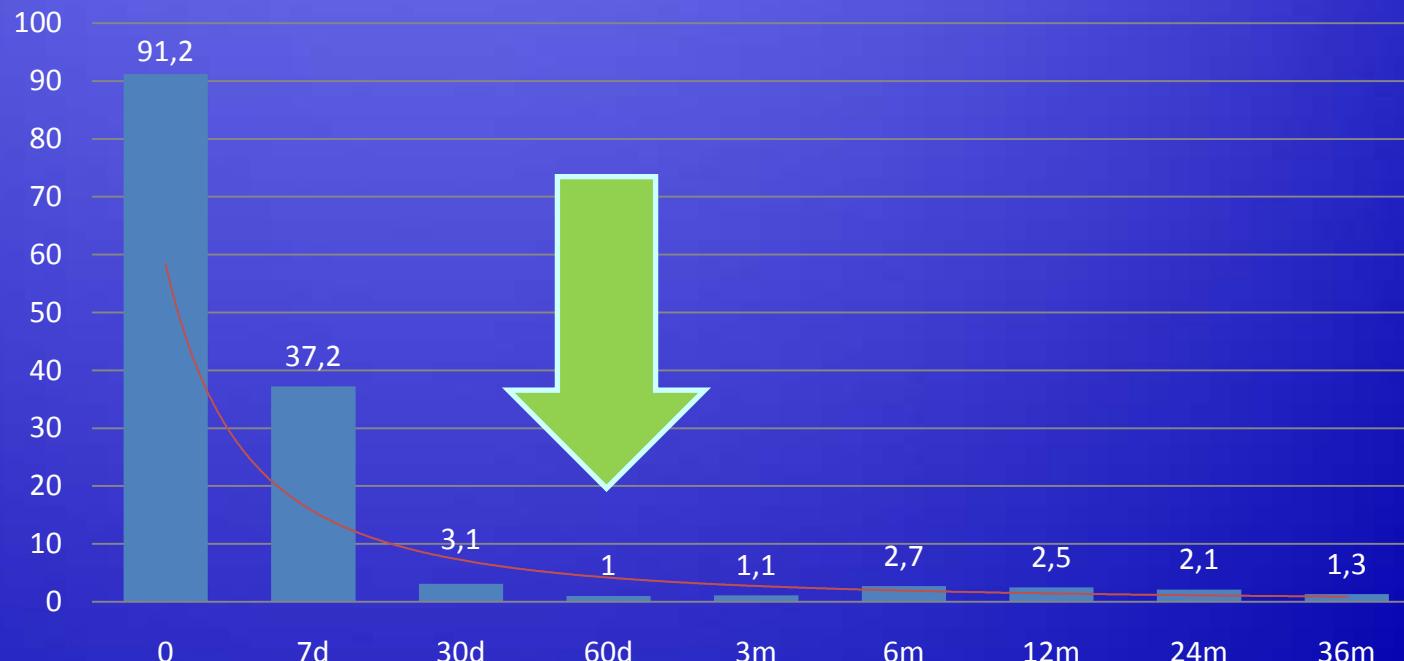
Percentage of positive q PCR at follow-up



PCR in a cohort of 206 BZN- treated children (101 by conventional PCR and 105 by qPCR)

Time	n	+	%	95 IC
0	206	188	91,2	86,6-94,4
7d	102	38	37,2	28,4-46,9
30d	96	3	3,1	1-8,7
60d	183	2	1	0,3-3,9
3m	84	1	1,1	0,2-6,4
6m	72	2	2,7	0,7-9,5
12m	79	2	2,5	0,7-8,7
24m	46	1	2,1	0,3- 11,3
36m	76	1	1,3	0,2-7

Percentage of positive PCR at follow-up



Puntos a discutir

No es claro el tiempo de tratamiento

¿A que dosis ?

Formulaciones pediátricas

¿Serología como marcador de curación en
fase crónica?

PCR como marcador de curación



Avances

El mejor modelo
experimental es el modelo
humano





Limited infant exposure to benznidazole through breast milk during maternal treatment for Chagas disease

Facundo García-Bournissen,¹ Samanta Moroni,¹ María Elena Marson,^{2,3} Guillermo Moscatelli,¹ Guido Mastrantonio,^{2,3} Margarita Bisio,¹ Laura Comou,¹ Griselda Ballering,¹ Jaime Altcheh¹

ARCHIVES OF
DISEASE IN
CHILDHOOD

Resultados

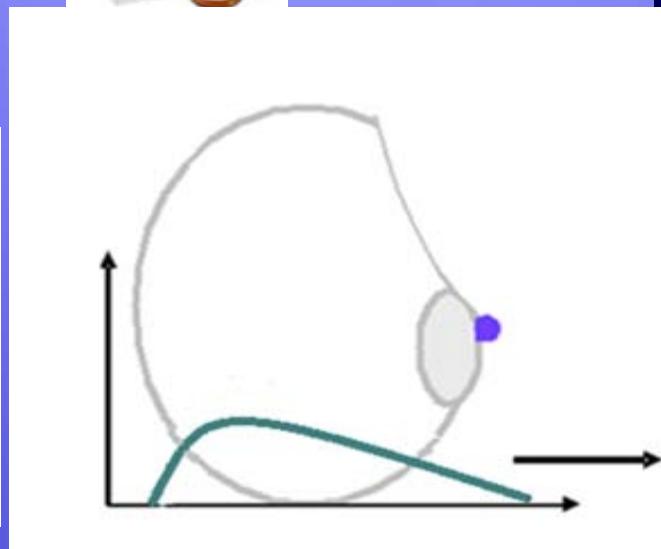
Dosis media de BZ:
5.66 mg/kg/día (3.6-
6.7) máx. 400 mg



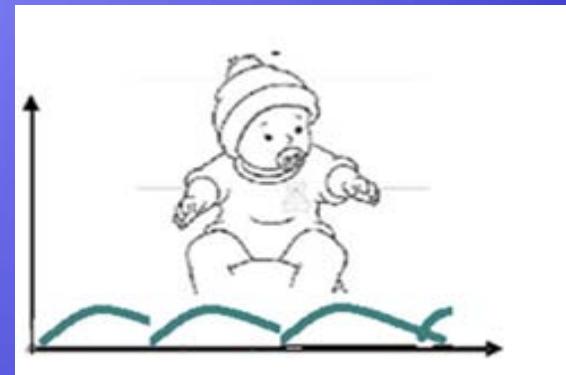
C
O
N
C
E
N
T
R
A
C
I
O
N



Conc. Media BZ: 4.5 mg/l
(SD 4.11, rango 1.3-12.57)



Asumiendo una ingesta diaria
de leche de 150ml/kg la dosis
de BZ es de 0.6 mg/kg



Relación
leche/plasma:

X 0.99 (SD 0.7)

10.9 , SD 3.2 (rango 5.4-
16.8)

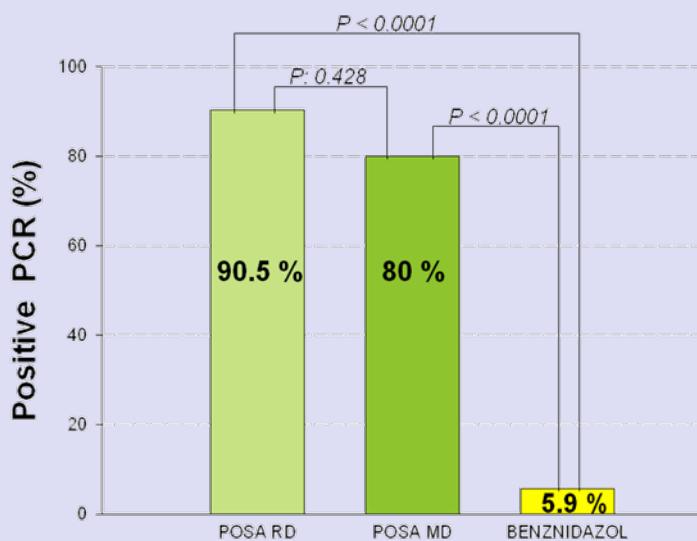
El niño recibe un 10%
de la dosis materna

Nifurtimox en leche

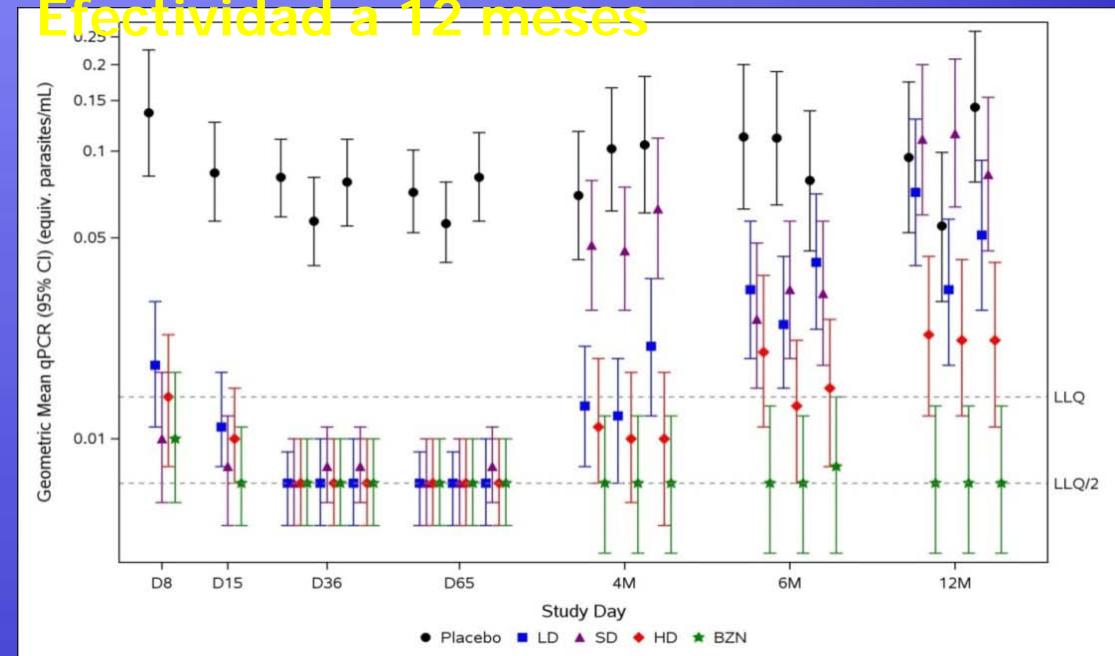
**N = 10 madres tratadas con nifurtimox
(10-15 mg/kg/dia)**

	RID (%)	Dosis/kg bebe
Mean	5.28	0.53 mg
SD	4.37	0.44 mg
Median	5.03	0.50 mg
I _Q	[1.99 - 6.9]	[0.2 - 0.69]

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



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



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

Enfermedad de Chagas

- La enfermedad de Chagas es curable.
- Control del vector + búsqueda de infectados !!!!!
- La mayor parte de los pacientes son asintomáticos.
- Sistema de salud sobrecargado con enfermos, no preparado para buscar asintomáticos.
- Requiere de un manejo infectológico.
- No es solamente una enfermedad cardíaca ó gastrointestinal.
- El tratamiento requiere de una cercana supervisión.
- Si tratamos niños no habrá secuelas.
- Nuevas drogas: las ensayos clínicos de eficacia deben ser evaluadas en niños.



HOSPITAL DE NIÑOS



H N R G

Dr. RICARDO GUTIERREZ

Hospital de Niños, Buenos Aires
Altcheh Jaime
Moroni Samanta
García Bournissen Facundo
Moscatelli Guillermo
Ballering Griselda
Freilij Hector
Bisio Margarita
Fctad química, Univ de La Plata
Marson Elena
Mastrantonio Guido
DNDI
Isabela Ribeiro
Jayme Fernandez
Fabiana Alves



Hospital de Niños, Jujuy
Caruso Martin
Maria Rosa Miranda
Ma Graciela Valdez
Hospital Materno infantil, Salta
Monla Celia
Centro de Chagas, Sgo del Estero
Ledesma Eduardo
Moran Lucrecia
Rodriguez Teresa
Inst.Nac.Parasitología
Riarte Adelina
Ingebi
Alejandro Schijman





Gracias