DRUGS FOR CHAGAS AND LEISHMANIASIS

A brief, and probably skewed, overview from a translational perspective

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Disclaimer

I do not have any potential conflicts of interest to disclose

My opinions are my own and do not necessarily agree with those of my employer(s)

Or anybody else…

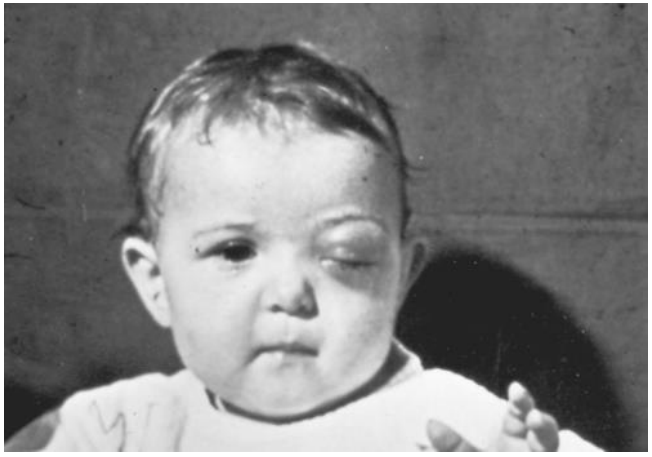
What are Neglected Diseases?

No universally accepted definition

- Prevalent among impoverished and marginalized populations in the developing world
- Insufficient incentives for private or public sector to invest in research and development of drugs or vaccines
- Not adequately addressed nationally and internationally

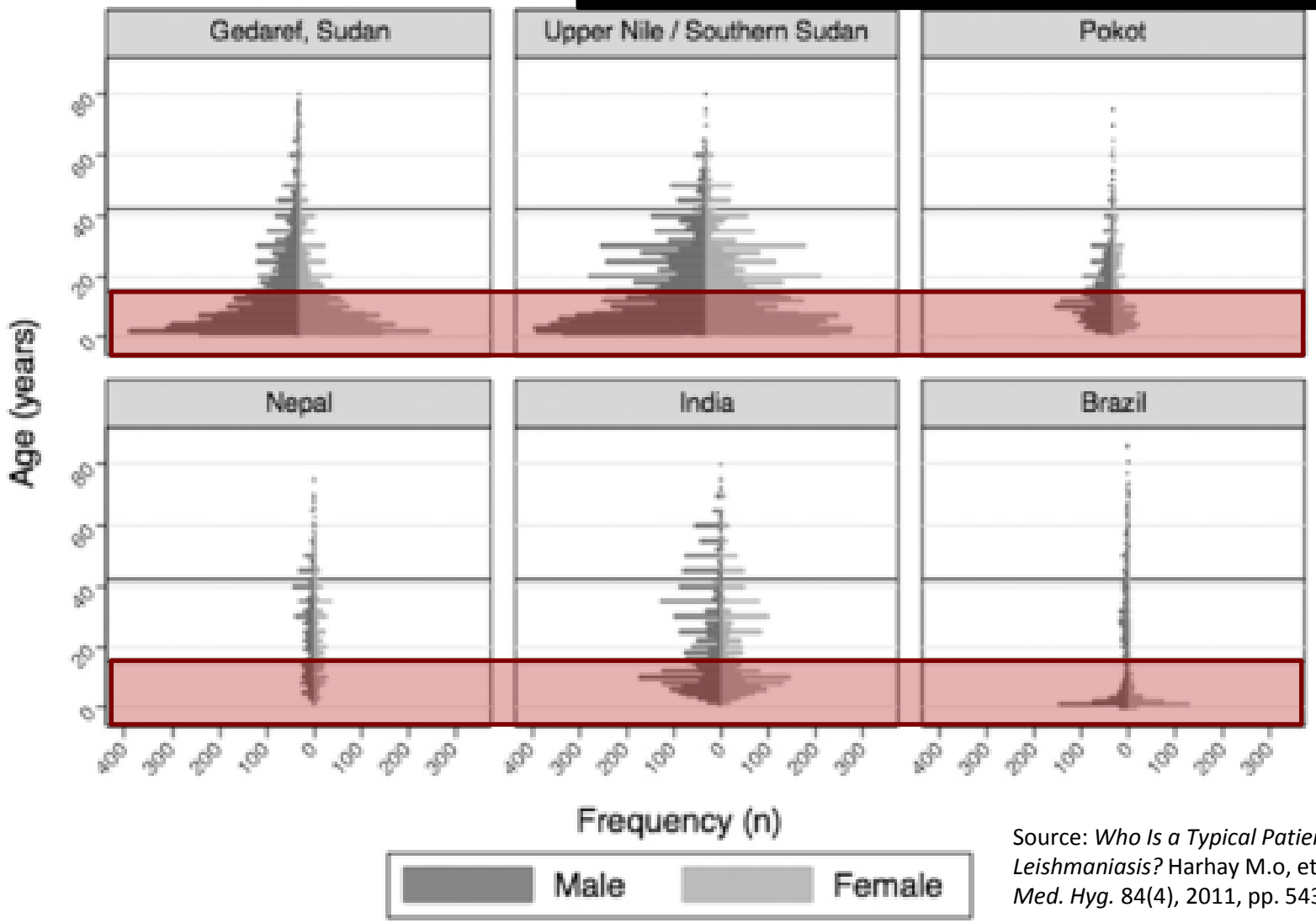
Who is affected?

- Neglected diseases impair or permanently disable a large number of people
- but cause comparatively few deaths, and many have a silent chronic progression
- Neglected diseases mostly affect ***children*** and women (particularly in pregnancy)



Who is affected?

CHILDREN !!



Source: *Who Is a Typical Patient with Visceral Leishmaniasis?* Harhay M.o, et al. *Am. J. Trop. Med. Hyg.* 84(4), 2011, pp. 543–550

Chagas disease

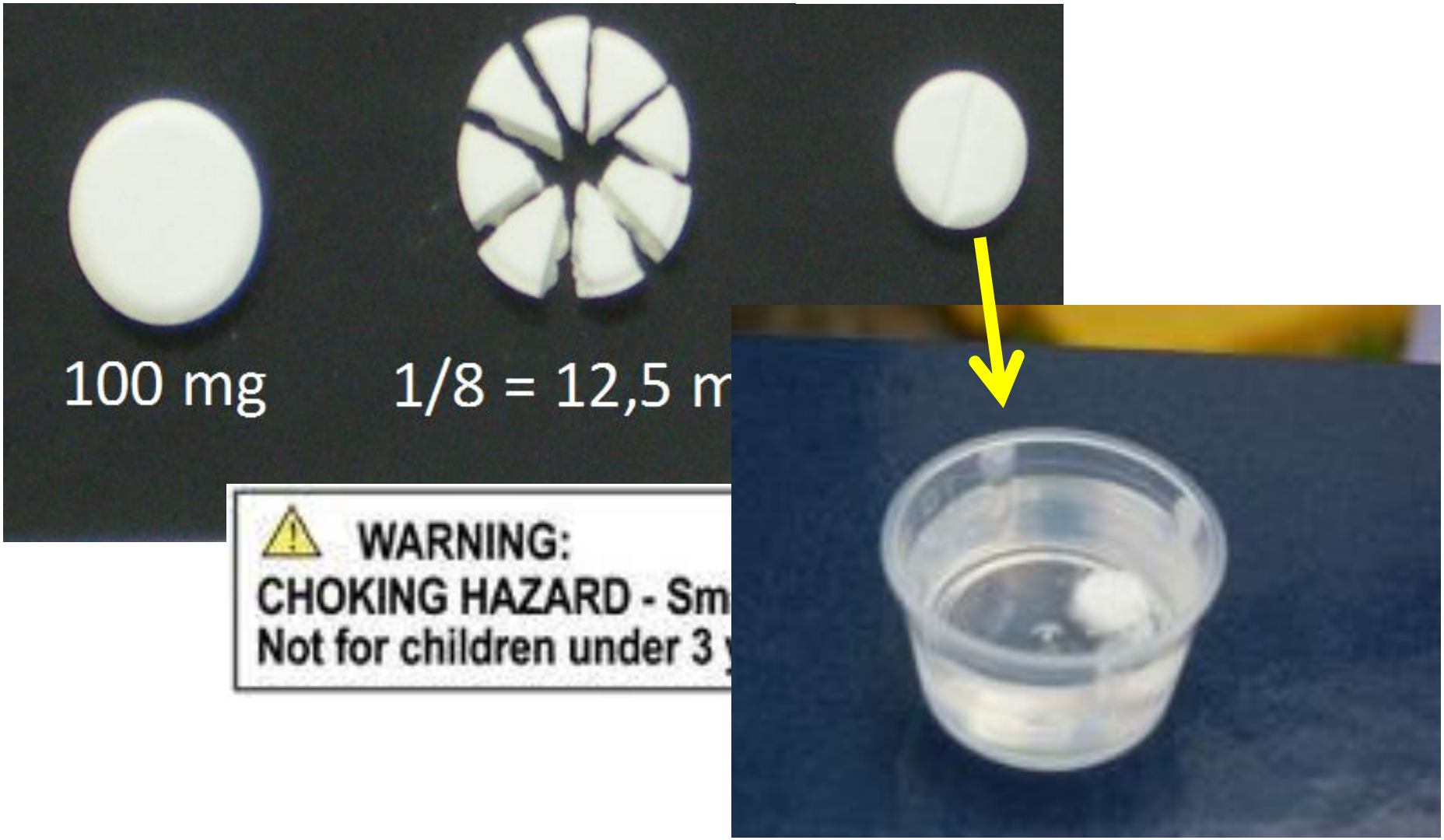
- Caused by the parasite *Trypanosoma cruzi*
- Transmitted by blood-sucking insect vectors, transfusions and **vertical transmission**
- >8 million infected people in the Americas
- >50,000 people die each year of Chagas disease complications
- Economic losses >6 billion U$S/year

Chagas disease - vectors

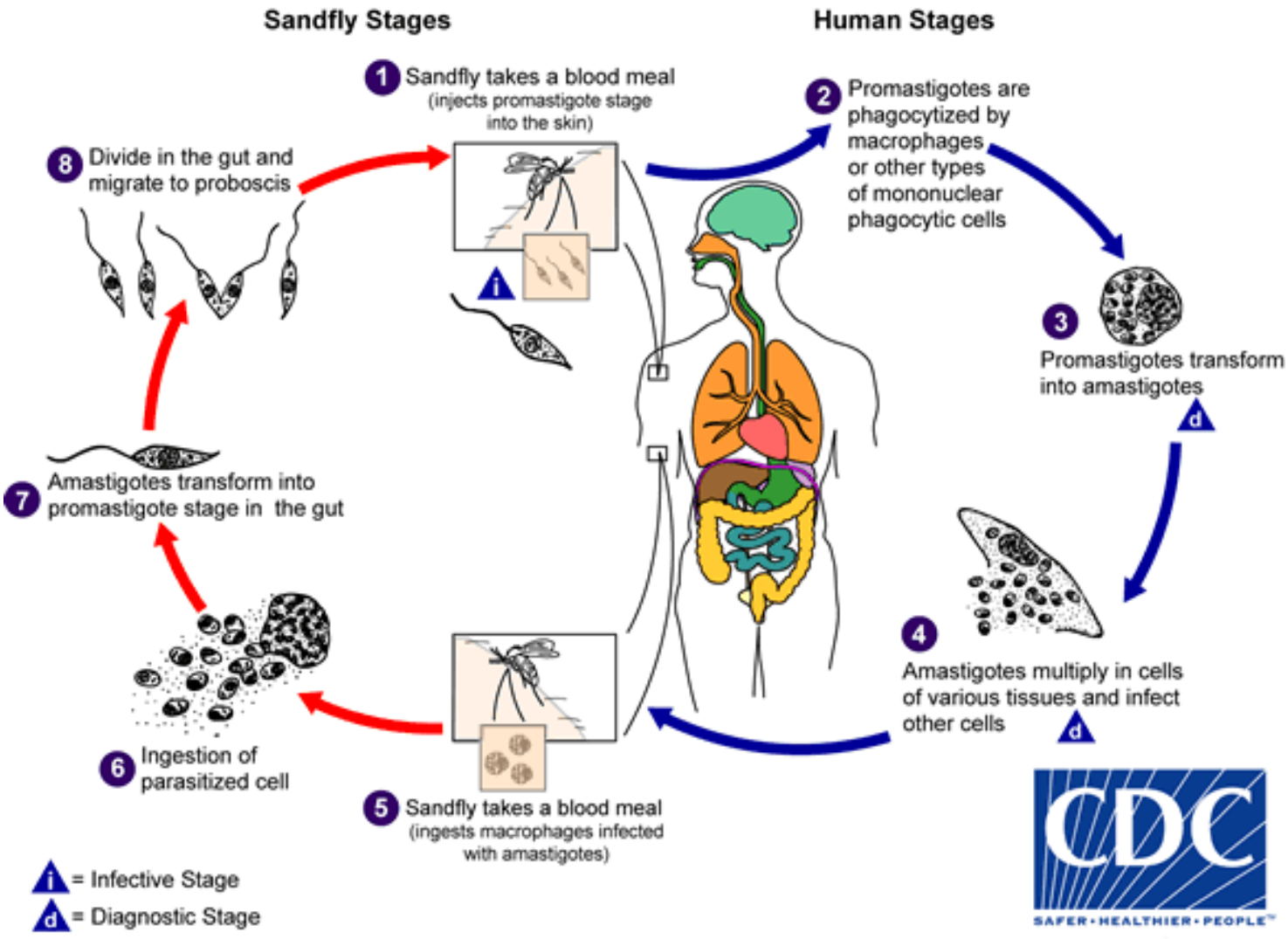
CHAGAS DISEASE

- The infection occurs mostly in **children** by vectorial or congenital route
- The majority of children are **asymptomatic**
- If untreated, CD leads to **cardiac morbidity** years or **decades** after infection
- CD is endemic in Latin America but, due to migration, infected patients have been found in USA, Europe, Australia, Japan

Benznidazole formulation problem



Leishmaniasis



Leishmaniasis

Leishmania taxonomy

Region	Complex	Species	Clinical Manifestation
Old World	*Leishmania donovani*	*L donovani*	CL, VL, PKLD, ML (rare)
		L infantum	CL, VL (children), PKLD, ML (rare)
		L chagasi	CL, VL (children), PKLD, ML (rare)
	Leishmania tropica	*L tropica*	CL, ML (rare), VL (rare)
		L major	CL, ML (rare)
		L aethiopica	CL, DCL
New World	*Leishmania mexicana*	*L mexicana*	CL, DCL (rare)
		L amazonensis	CL, DCL, ML, VL (rare), PKLD (rare)
		L venezuelensis	CL, DCL (rare)
	Leishmania (Viannia) braziliensis	*L braziliensis*	CL, ML, VL
		L guyanensis	CL, ML
		L panamensis	CL, ML
		L peruviana	CL

Leishmaniasis - Treatments

Table 1
The main drugs currently used for treatment of visceral leishmaniasis

Drugs	Regimen	Marketing[a]	Clinical Efficacy	Resistance	Toxicity	Cost/Course	Issues
Pentavalent antimonials	20 mg/kg iv or im daily for 28–30 days	Albert David (SSG); GSK (Pentostam) Sanofi Aventis (Glucantime)	35%–95% (depending geographic area)	As high as 60%	Frequent, potentially Pancreatitis, Nephro + hepatotoxicity	Generic ~ $53	Quality control Toxicity Resistance in India
Amphotericin B	0.75–1 mg/kg iv for 15–20 doses (daily or alternate days)	Bristol Meyers Squibb (Fungizone) Generic companies	>97% all regions	Not documented	Frequent Nephrotoxicity (in-patient care needed)	Generic price:	Need for slow iv Nephrotoxicity Heat stability
Liposomal Amphotericin B	10–30 mg/kg Total dose iv; usually 3–5 mg/kg/dose Single dose (10 mg/kg) in India	Gilead (AmBisome)	Europe and Asia: >95%; Africa: not full established (higher dose required?)	Not documented	Uncommon and mild; Nephrotoxicity	Preferential price: $280 Commercial price: ~ 10x	Price Need for slow iv <25° C)
Miltefosine	2–2.5 mg/kg/d orally daily over 28 days	Paladin (Impavido)	Asia: 94% (India) Africa: single fi study (93% i HIV(-)	Readily obtained	Common, usually mild Nephro + hepatotoxicity Possibly teratogenic	Preferential $150	Price Patient compliance
Paromomycin sulfate	15 mg/kg im daily for 21 days (India only)	IOWH/Gland Pharma	Asia: 95% (India) Africa: 15 mg/ 64% (Sudar <50%) 20 mg/kg: 80% (Sudan)	Readily obtained	Uncommon,	~ $15	Efficacy variable resistance (?)

TOXIC, IM, RESISTANCE

TOXIC, IV

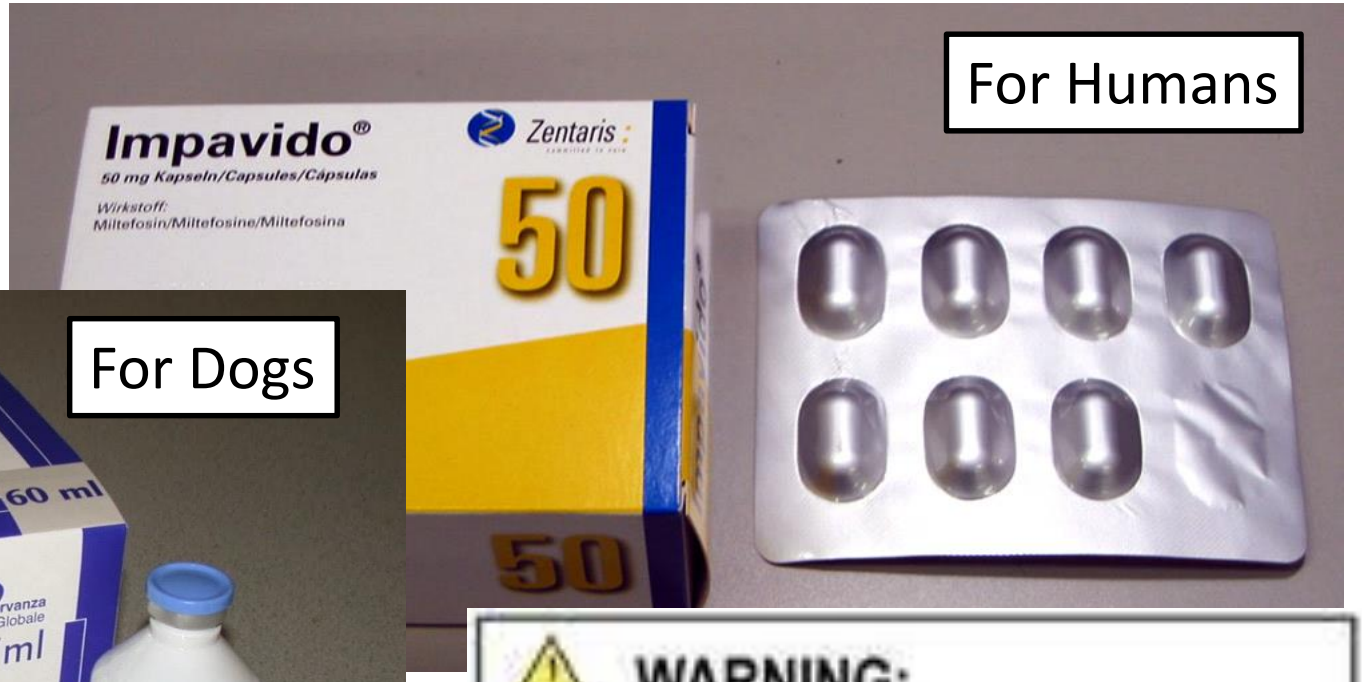
IV, VERY EXPENSIVE

EXPENSIVE, POSSIBLY TERATOGENIC?

IV FOR 21 DAYS, MILDLY TOXIC

Infect Dis Clin N Am 26 (2012) 309–322

Leishmania – miltefosine



For Humans

For Dogs

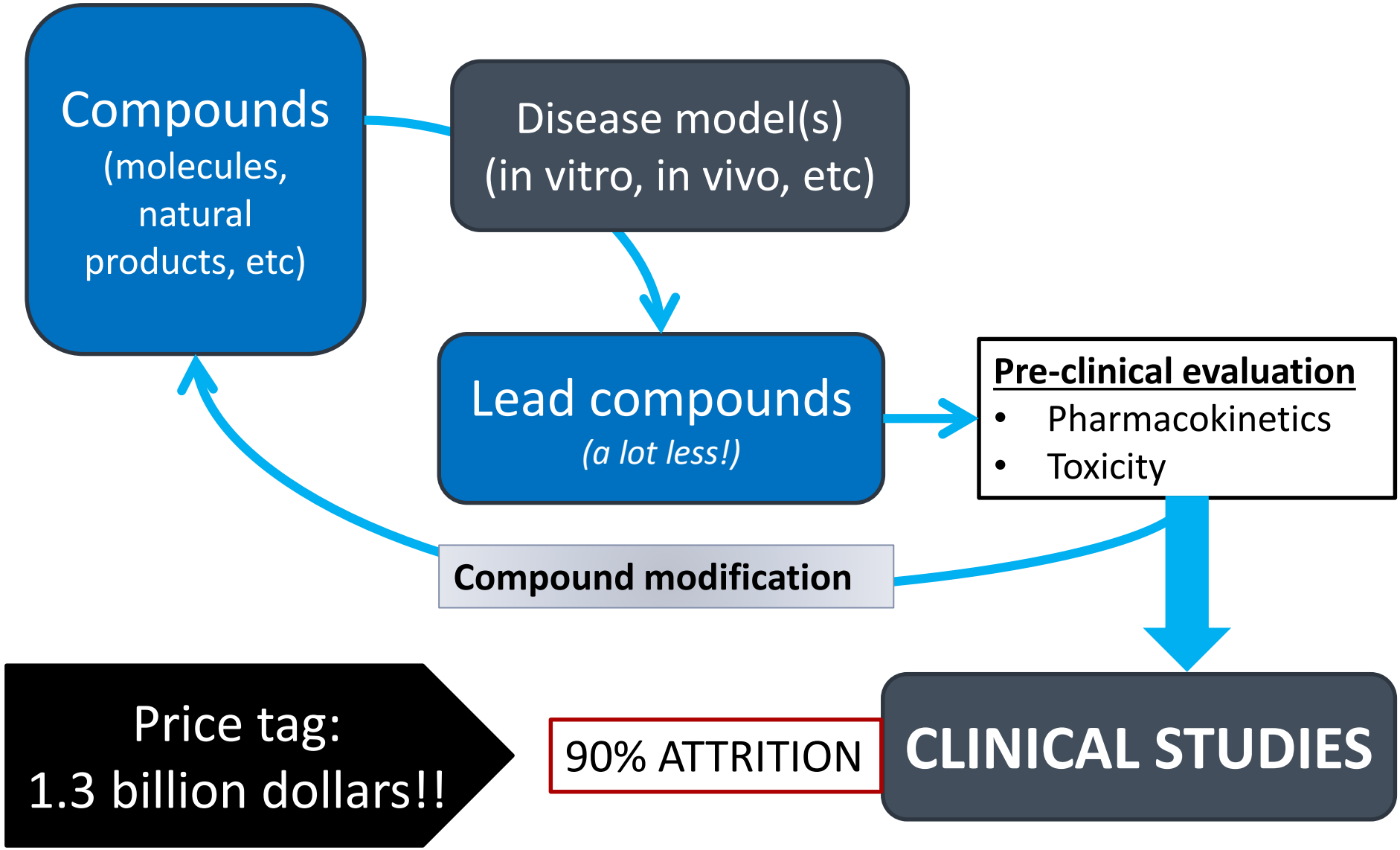
⚠ WARNING:
CHOKING HAZARD - Small parts.
Not for children under 3 years.

Leish –amphotericin B, antimonials, paromomycin

New drugs are needed, **but** they need to be:

- Orally available
- Effective (at least as good as available treatments)
- Rapid action(i.e. short treatments)
- **Appropriate, and safe, for children!**
- And for pregnant women!!
- Affordable…

Drug development - preclinical



Where is big pharma?

- Development costs of a new drug >1B
- These costs include oportunity costs, abandoned projects, marketing…
- Marketing, marketing, marketing…

- NTDs have unattractive socioecononomical characteristics

Why is big pharma not interested?

They can´t really pay much…

What other options are out there?

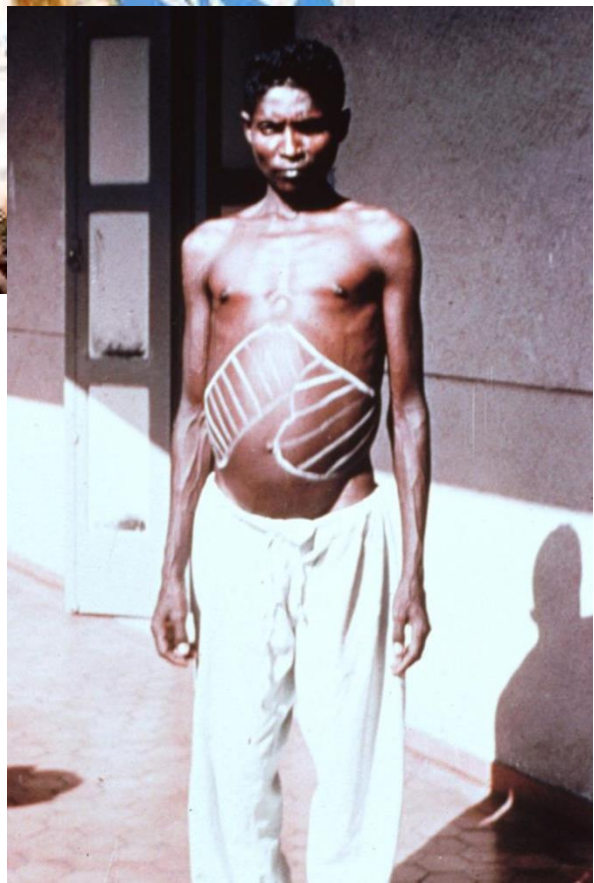
Academic drug development

- Drug development very difficult and expensive
- Academia has very limited compound portfolios
- Limited experience and skills in transitioning from one development phase to the next
- Too often focused on one "miracle" drug, that gets killed off when costs (or toxicity) are actually evaluated
- Very slow to “let go” of ineffective drugs

Public – private partnerships and NGOs can help a lot here! (such as DNDi does)

Disease models

- Many animal models can give insights into parts of the PKPD process
- But it's important to remember that the objective is not to cure mice, rats or dogs…
- **The only accurate animal model is the human model!**



Academic drug development

- Transfer from lead compound to a drug in clinical trials is not easy
- Drug development has about **90%** attrition rate in the CLINICAL TRIALS stage!
- But if you don't get there, your drug will **never** help anyone
- **Let go!**

PHARMACOKINETICS

"What the body does to the drug"

Drug Metabolism and Pharmacokinetics (DMPK)

Pharmacokinetics: "what the body does to the drug"

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

Can be evaluated by *in vitro* techniques and in animals to predict (to some extent…) human pharmacokinetics

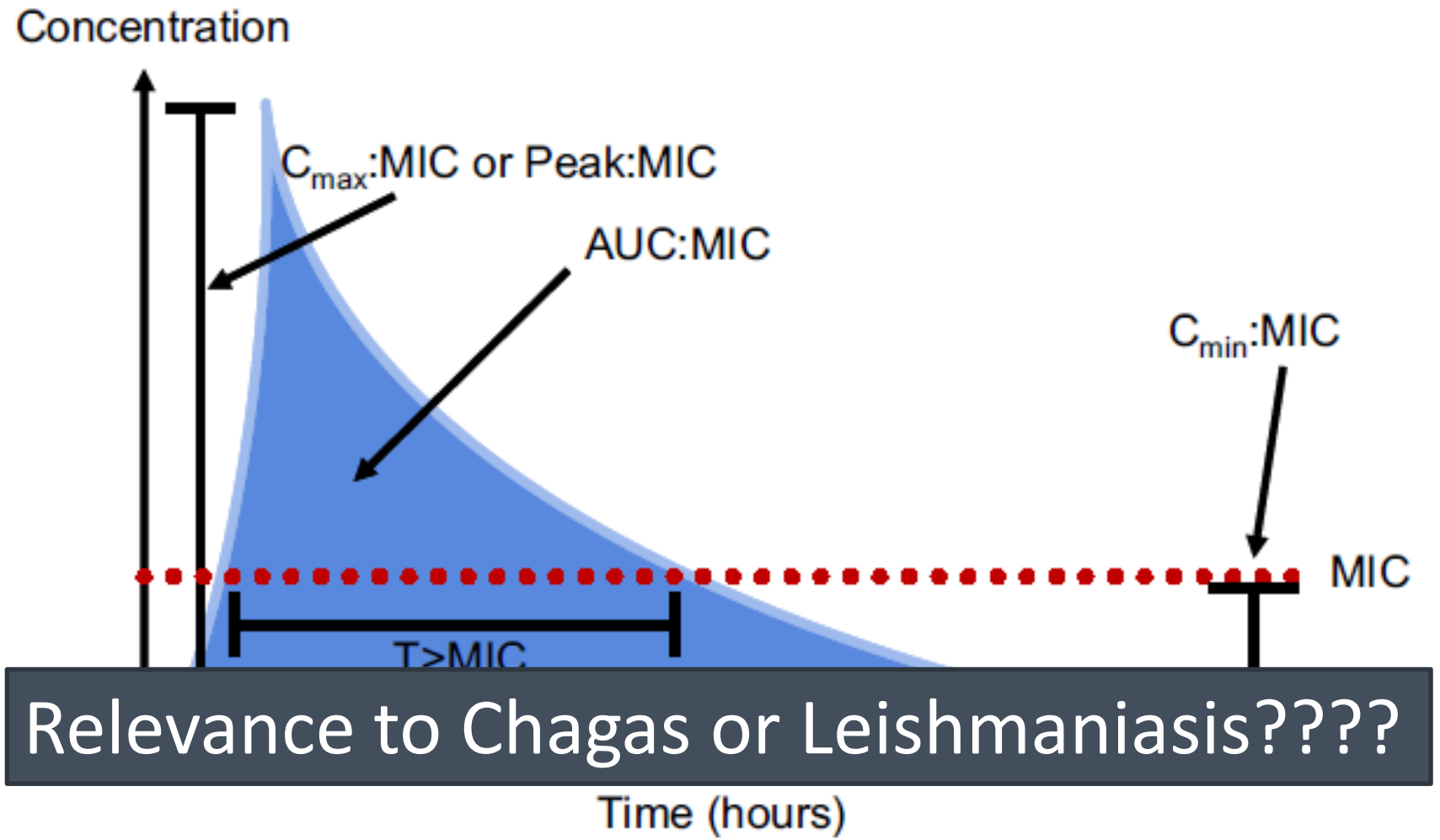
- **T**oxicity (not really pharmacokinetics… pharmacodynamics)

→ **ADMET**

Drug Metabolism and Pharmacokinetics (DMPK)

- **A**bsorption: Dissolution models, monolayer permeability, animal bioavailability, simulation,…
- **D**istribution: protein binding, lipid-water partition, animal studies (radiolabelled drug),…
- **M**etabolism: In vitro CYP studies, microsomes, ex vivo organ perfusion, animal drug metabolism
- **E**xcretion: animal models, simulation, in vitro drug transport, …
- **T**oxicity (not really pharmacokinetics… pharmacodynamics)

PK -> Pharmacodynamics (PKPD)



Relevance to Chagas or Leishmaniasis????

Crit Care Clin 27 (2011) 1–18

TRANSLATIONAL MEDICINE (WHAT CAN WE LEARN FROM HUMAN TRIALS?)

TRANSLATIONAL MEDICINE

- Interdisciplinary branch of medicine
- ***Translates*** clinical observations or findings to basic research (e.g. disease models) to try to find new solutions that can then be brought back to clinical research (and patient treatment)

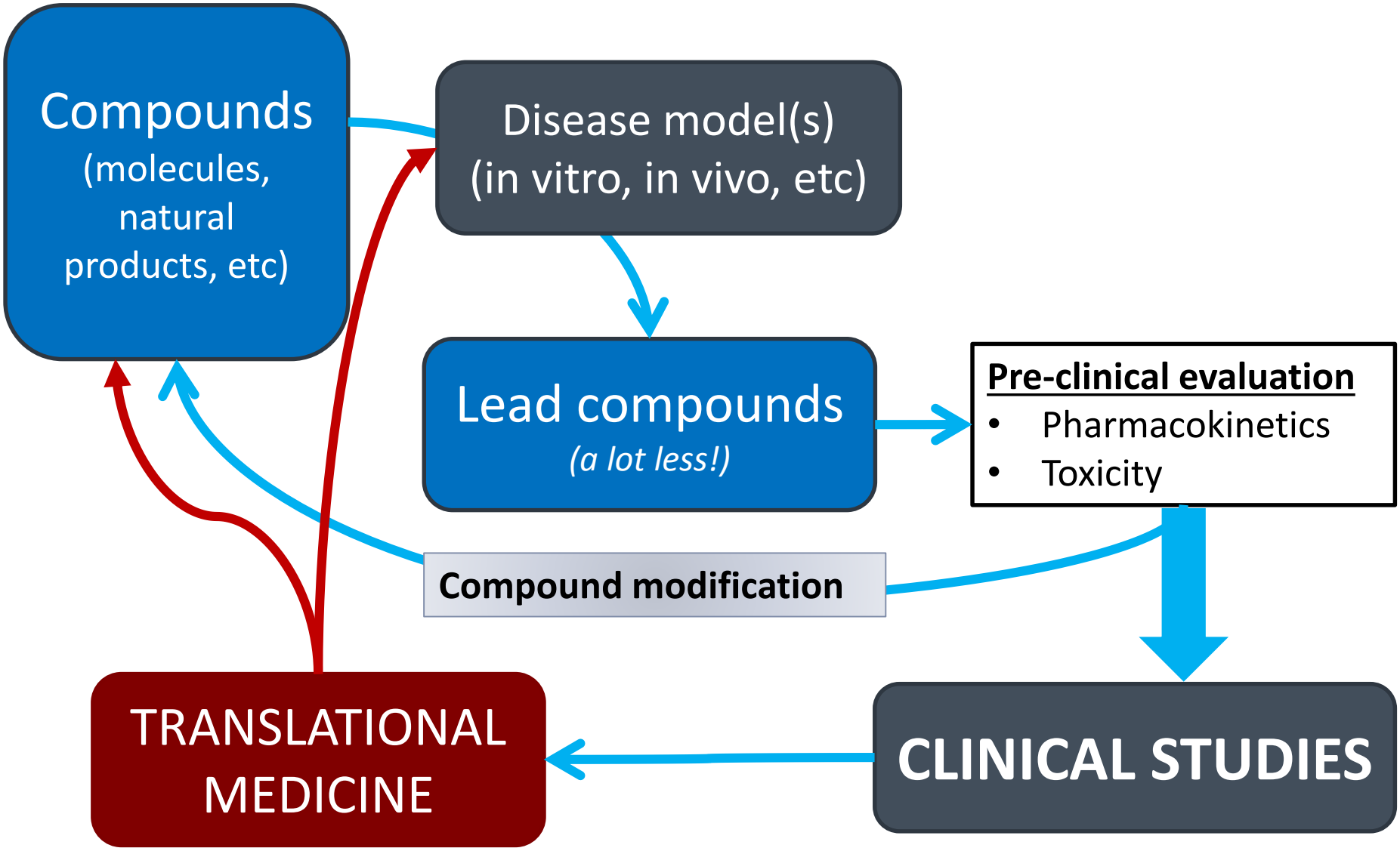
"bench to bedside"

(actually,

bedside to bench,

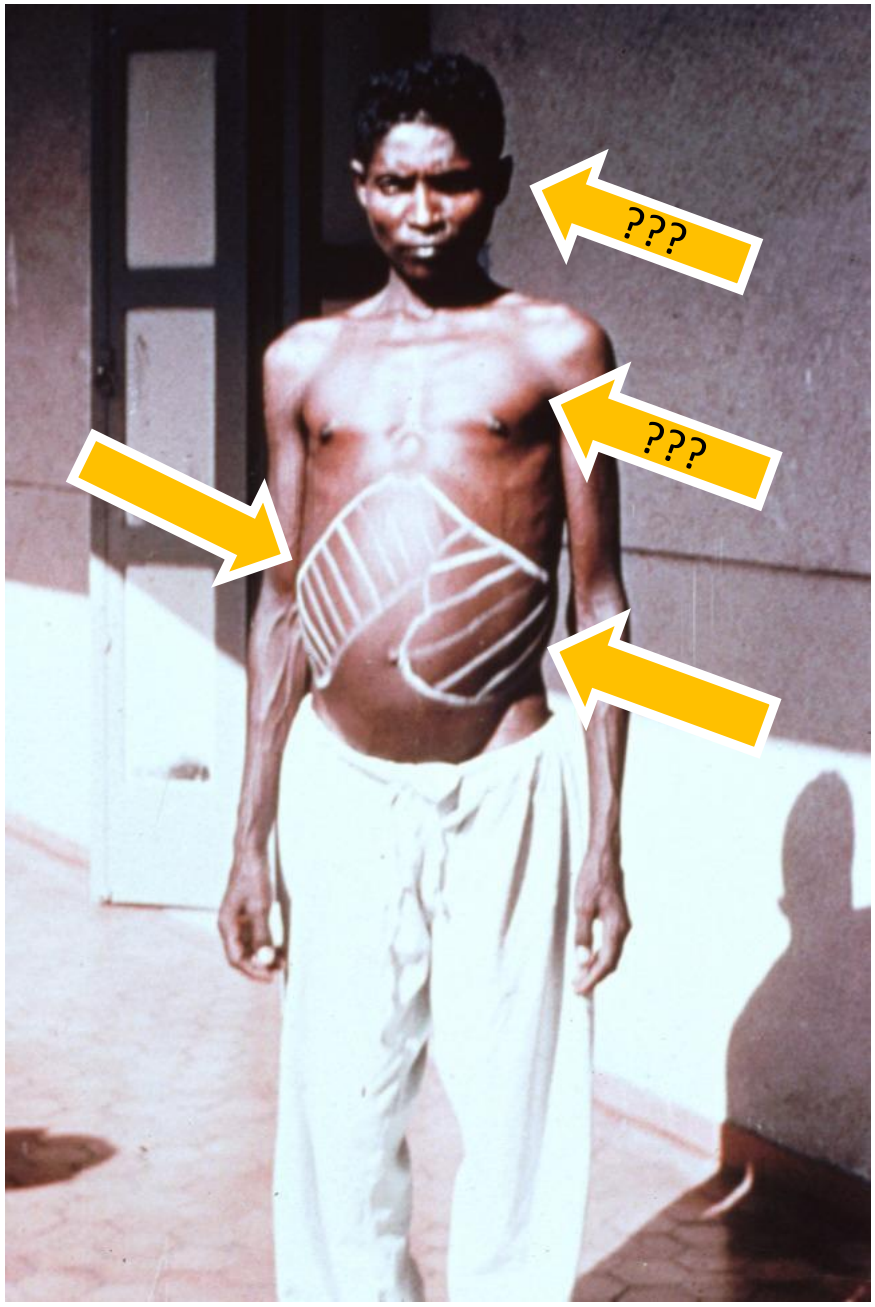
***and back to bedside*)**

Drug development - preclinical



Human model

- Where should the drug go?
- How high should it be?
- How long should it stay there?
- How fast should it clear the infection?
- What effects we don't like to have?
- What effects we don't like but accept as part of the treatment?



PLOS | NEGLECTED TROPICAL DISEASES

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RESEARCH ARTICLE

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

Jaime Altcheh, Guillermo Moscatelli, Guido Mastrantonio, Samanta Moroni, Norberto Giglio, Maria Elena Marson, Griselda Ballering, Margarita Bisio, Gideon Koren, Facundo García-Bournissen

Published: May 22, 2014 • DOI: 10.1371/journal.pntd.0002907

HOSPITAL DE NIÑOS H N R G Dr. RICARDO GUTIERREZ

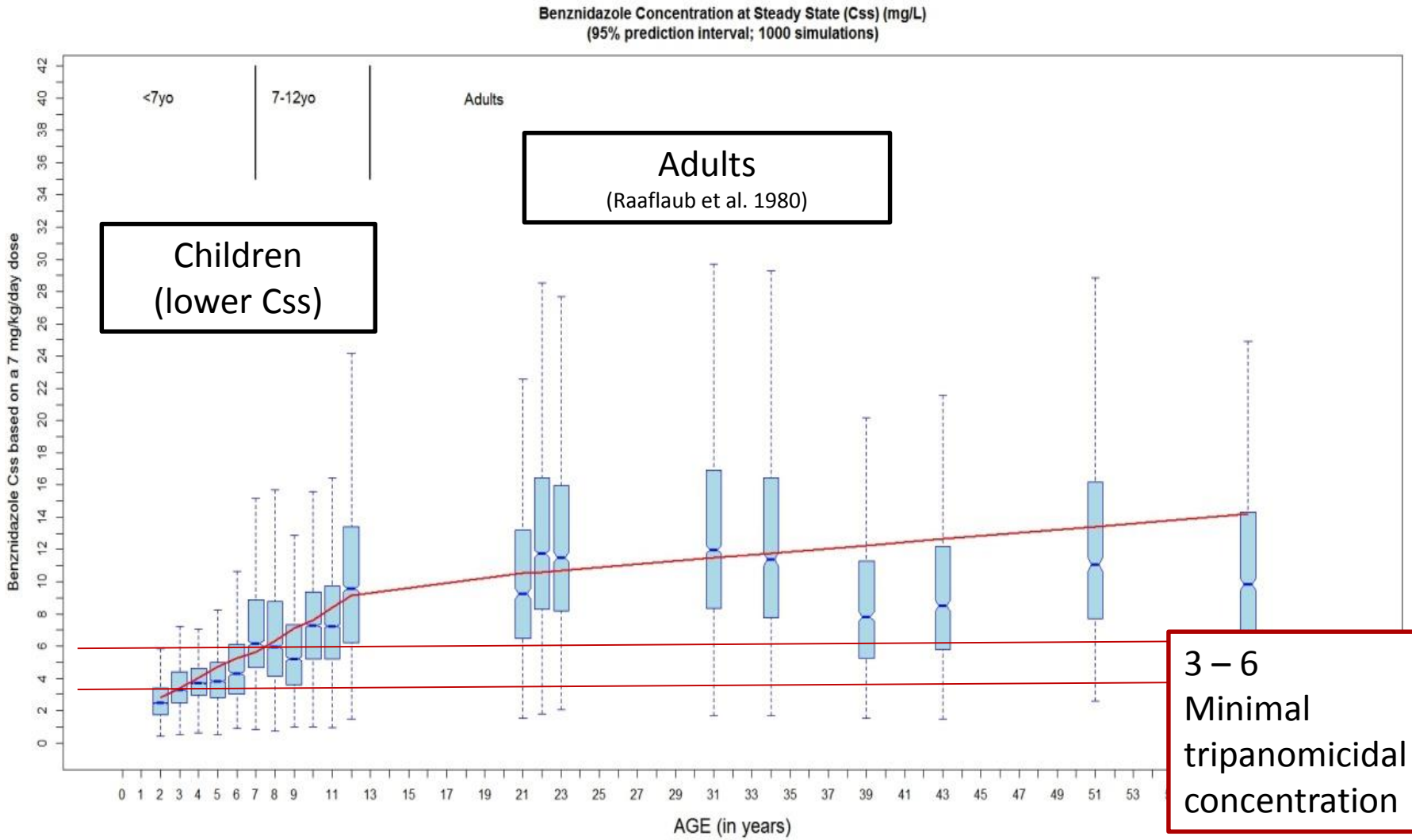
Parasitología y Chagas * Hospital de Niños R. Gutiérrez *

SickKids

UNIVERSITY OF TORONTO

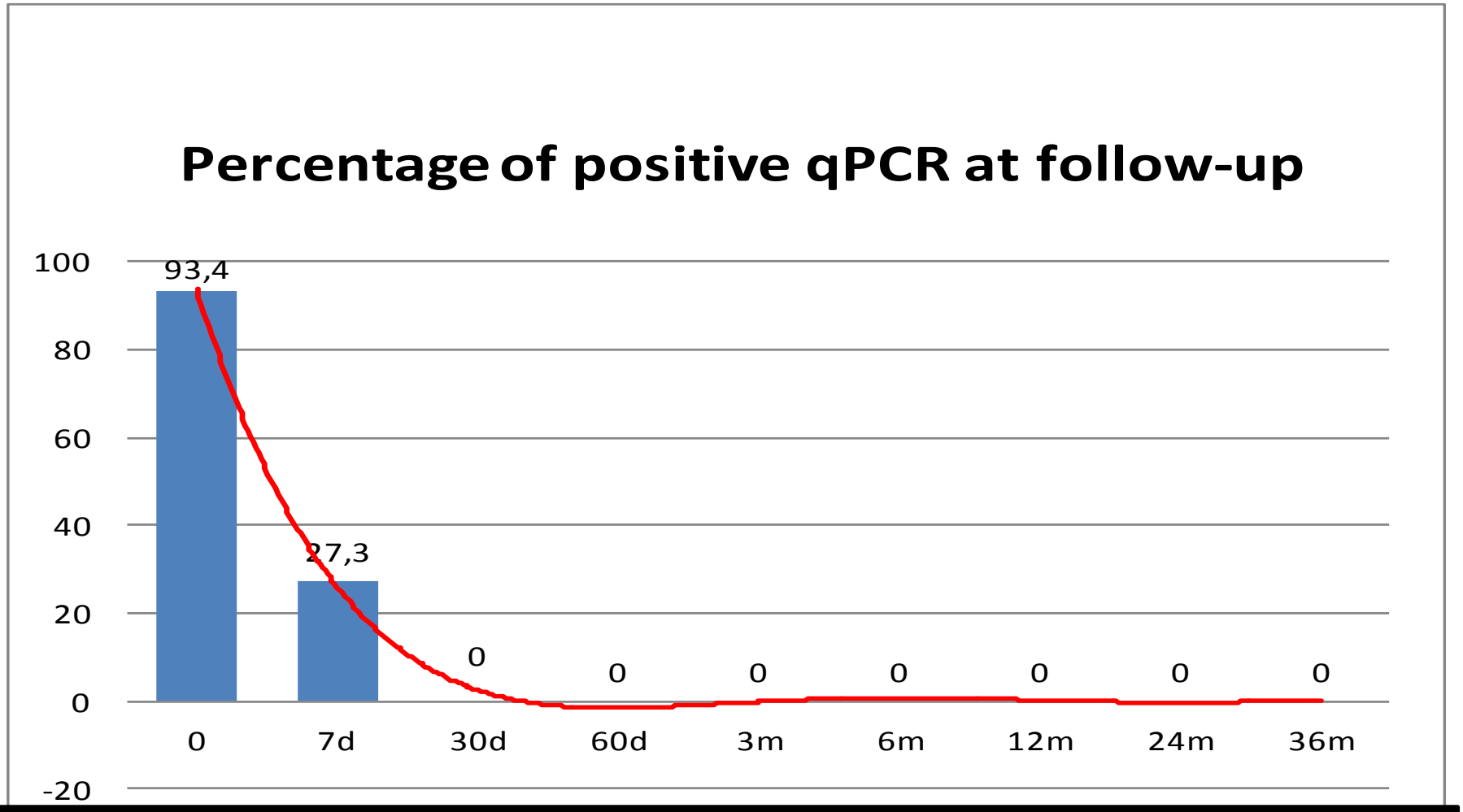
Clinicaltrials.gov registry # NCT00699387

Steady state concentrations (popPK)



Altcheh et al. Population pharmacokinetics of benznidazole in children with Chagas disease. Clinicaltrials.gov registry # NCT00699387

Blood parasitemia by qPCR in treated children



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

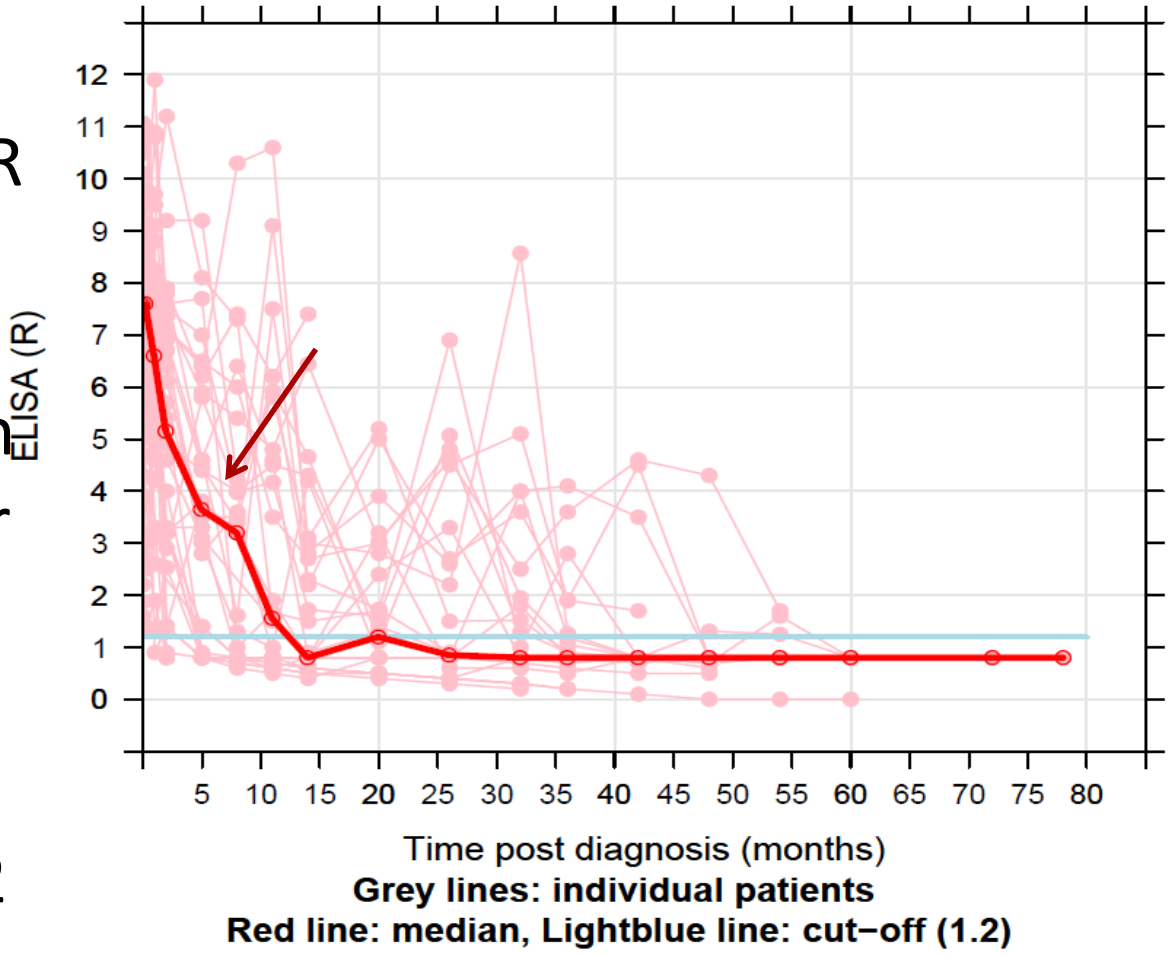
T.cruzi ELISA

N:37- 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.



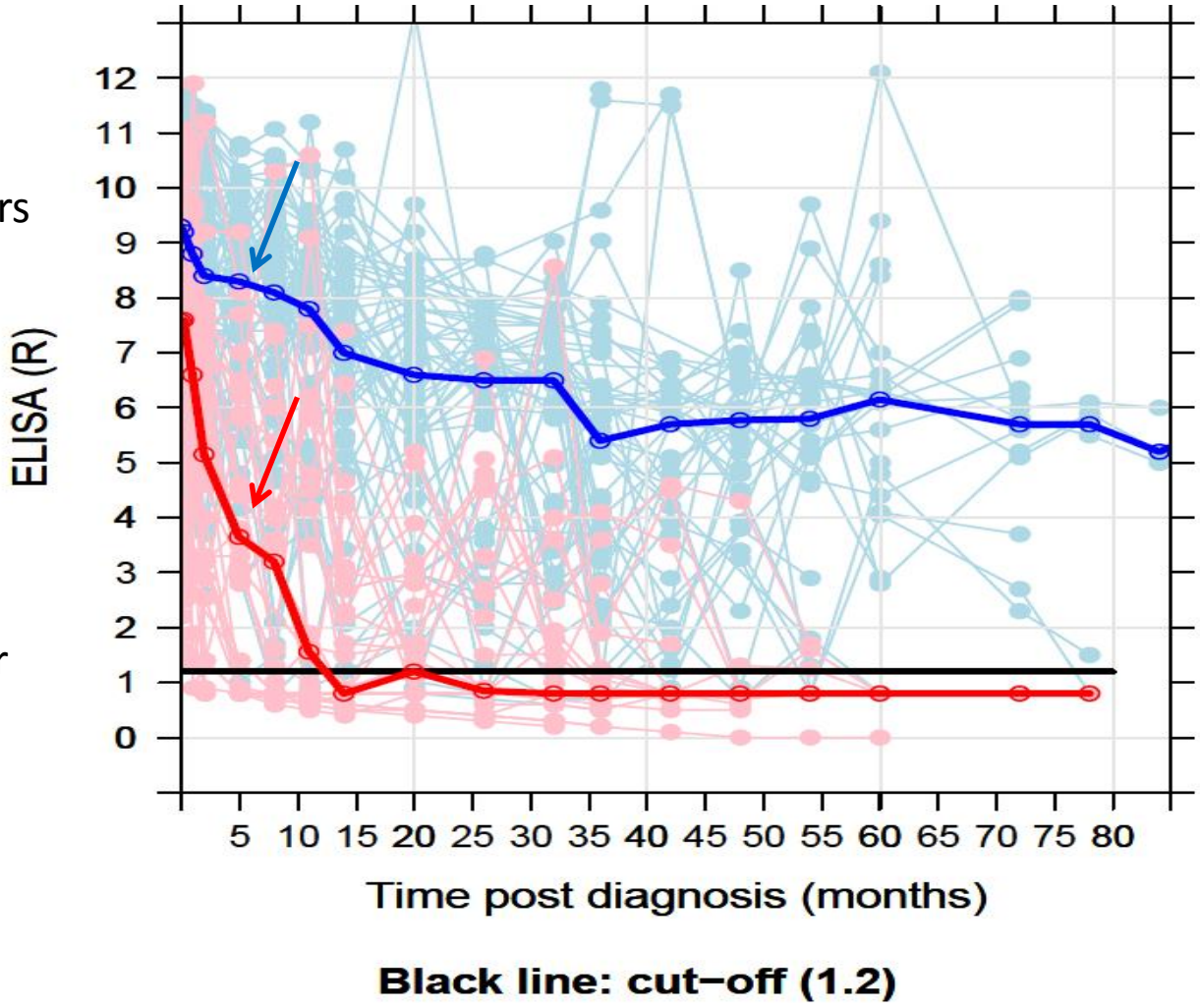
T.cruzi ELISA

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



BNZ – Children

- Benznidazole concentrations in children were significantly lower than those reported in adults (treated with comparable mg/kg doses)
- In spite lower plasma concentrations, children responded well to the treatment, and had a low incidence of ADRs
- If these results are confirmed, dose reduction of benznidazole in adults should be explored

Mem Inst Oswaldo Cruz, Rio de Janeiro, Vol. *110*(4): 507-509, June 2015

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 Altcheh

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

Trypanocide Treatment of Women Infected with *Trypanosoma cruzi* and Its Effect on Preventing Congenital Chagas

Diana L. Fabbro, Emmaria Danesi, Veronica Olivera, Maria Olenka Codebó, Susana Denner, Cecilia Heredia, Mirtha Streiger, Sergio Sosa-Estani

Published: November 20, 2014 • DOI: 10.1371/journal.pntd.0003312

BNZ & POSACONAZOLE ADULTS

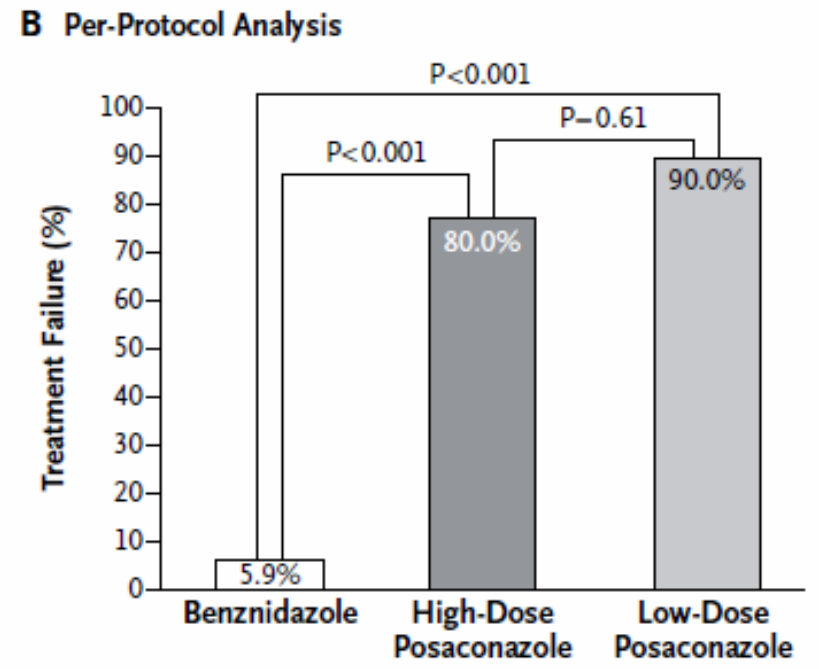


Figure 2. Efficacy End Points.

The intention-to-treat analysis included all patients who underwent randomization; the per-protocol analysis included patients who completed treatment and follow-up. Patients who were lost to follow-up were excluded from the per-protocol analysis unless rt-PCR testing after the end of the treatment period was positive.

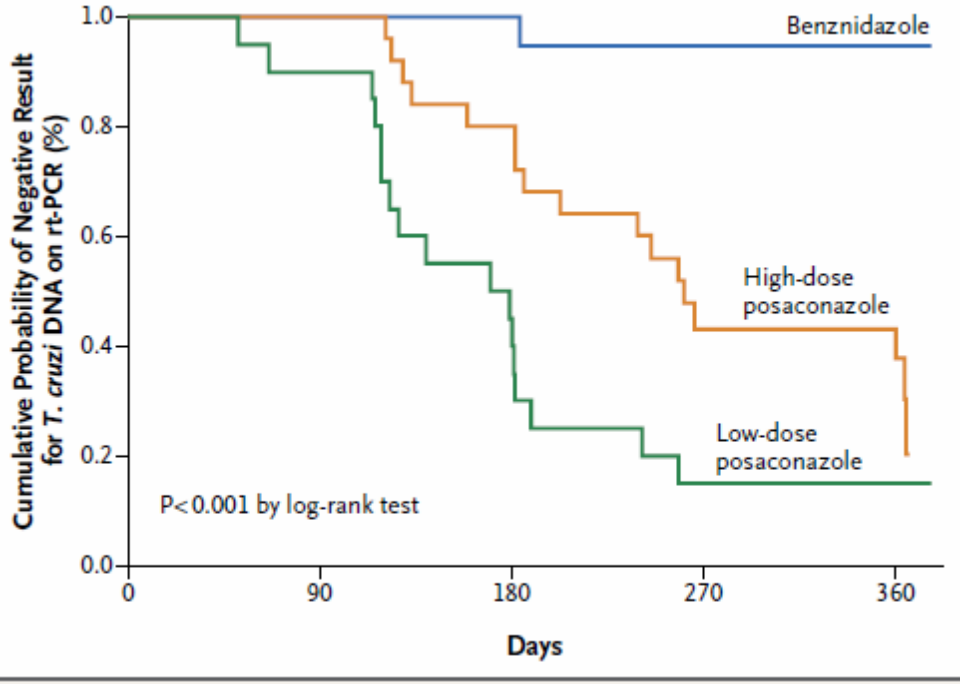
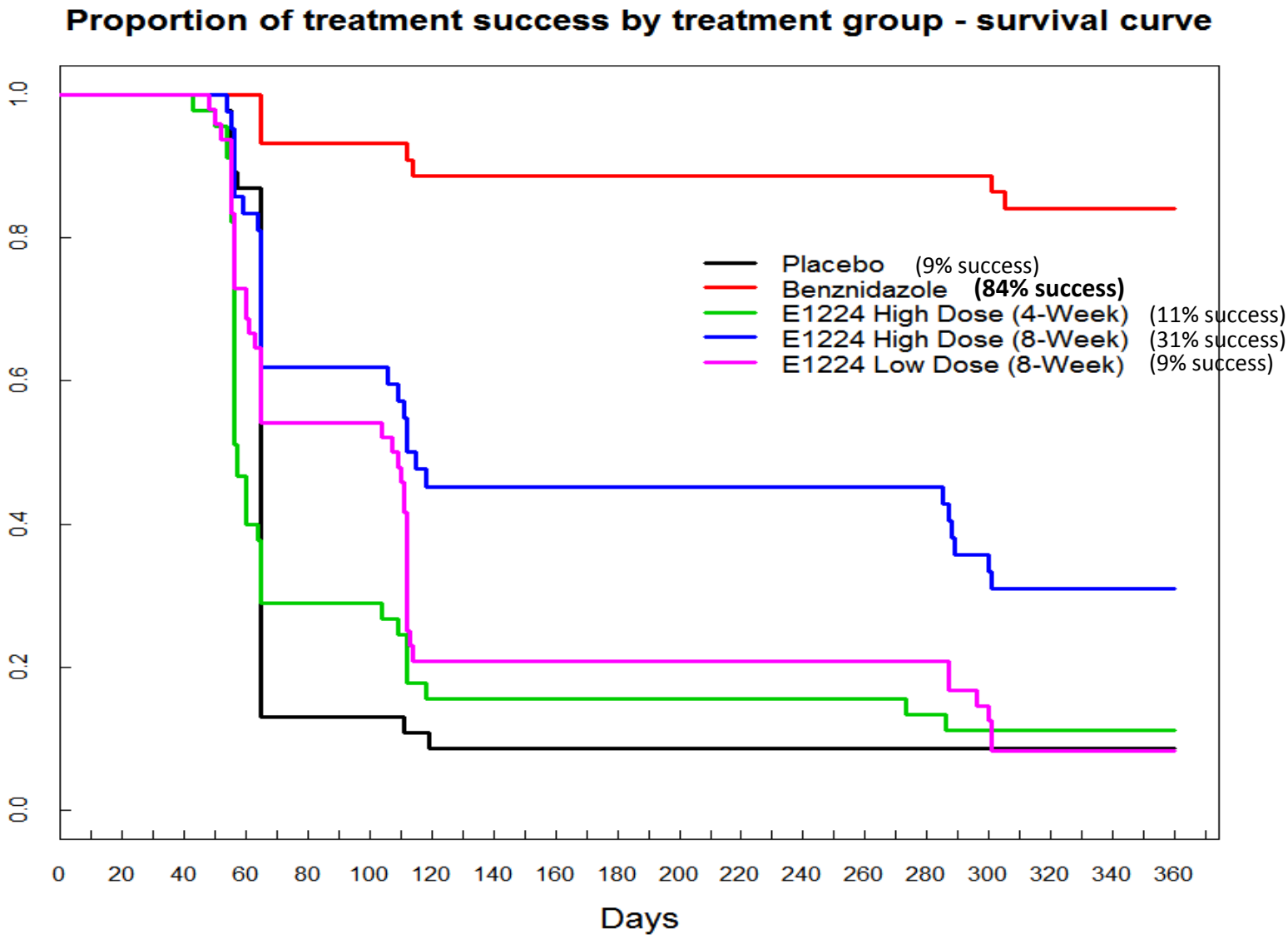


Figure 3. Time to Treatment Failure.

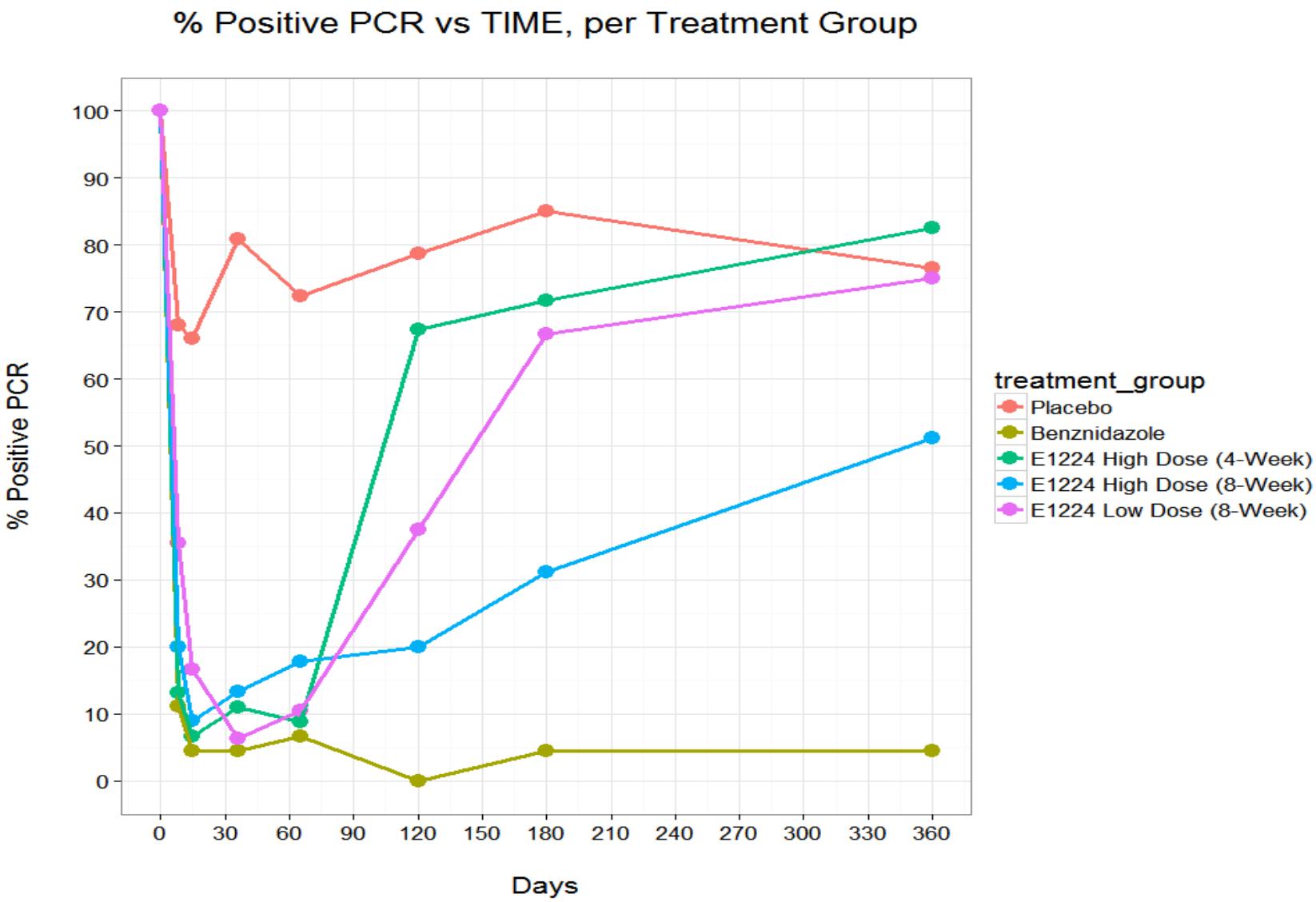
Randomized Trial of Posaconazole and Benznidazole for Chronic Chagas' Disease

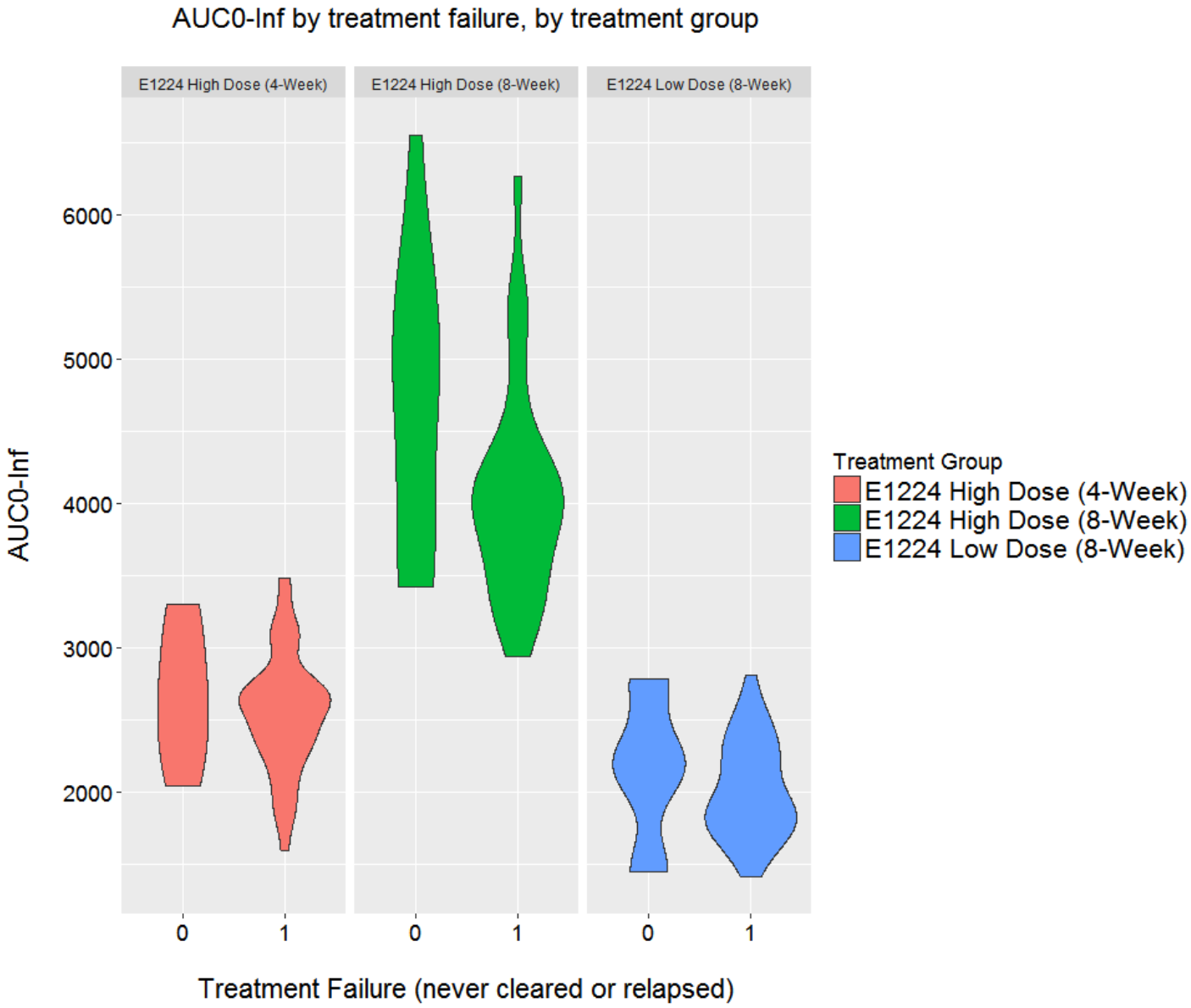
Israel Molina, M.D., Jordi Gómez i Prat, M.D., Fernando Salvador, M.D., Begoña Treviño, M.D., Elena Sulleiro, M.D., Núria Serre, M.D., Diana Pou, M.D., Sílvia Roure, M.D., Juan Cabezos, M.D., Lluís Valerio, Ph.D., Albert Blanco-Grau, M.D., Adrián Sánchez-Montalvá, M.D., Xavier Vidal, Ph.D., and Albert Pahissa, Ph.D.

E1224 & BENZNIDAZOLE



E1224 & BENZNIDAZOLE



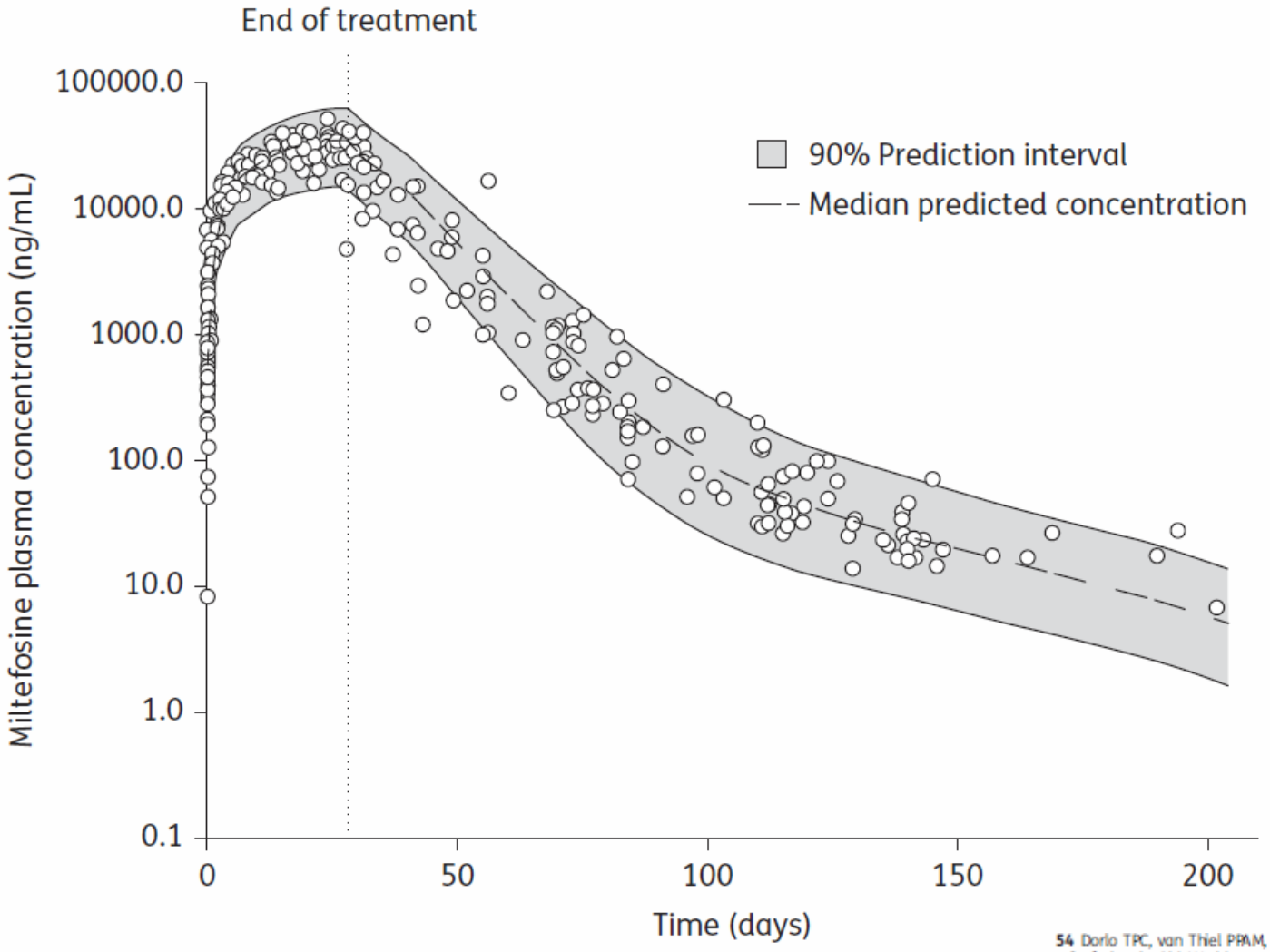

AUC0-Inf by treatment failure, by treatment group
E1224 High Dose (4-Week)
E1224 High Dose (8-Week)
E1224 Low Dose (8-Week)
AUC0-Inf
6000
5000
4000
3000
2000
0
1
0
1
0
1
Treatment Failure (never cleared or relapsed)
Treatment Group
E1224 High Dose (4-Week)
E1224 High Dose (8-Week)
E1224 Low Dose (8-Week)

Chagas translational medicine lesson

- Antifungals (CYP 51 inhibitors at least) are not particularly good for treatment of Chagas disease…
- Screening (in vitro) and animal models should incorporate this knowledge
- New approaches may still have potential (e.g. combinations)

- Back to the drawing board!

MILTEFOSINE TRIALS ADULTS



54 Dorlo TPC, van Thiel PPAM, Huitema ADR *et al.* Pharmacokinetics of miltefosine in Old World cutaneous leishmaniasis patients. *Antimicrob Agents Chemother* 2008; **52**: 2855–60.

MILTEFOSINE TRIALS - FAILURES

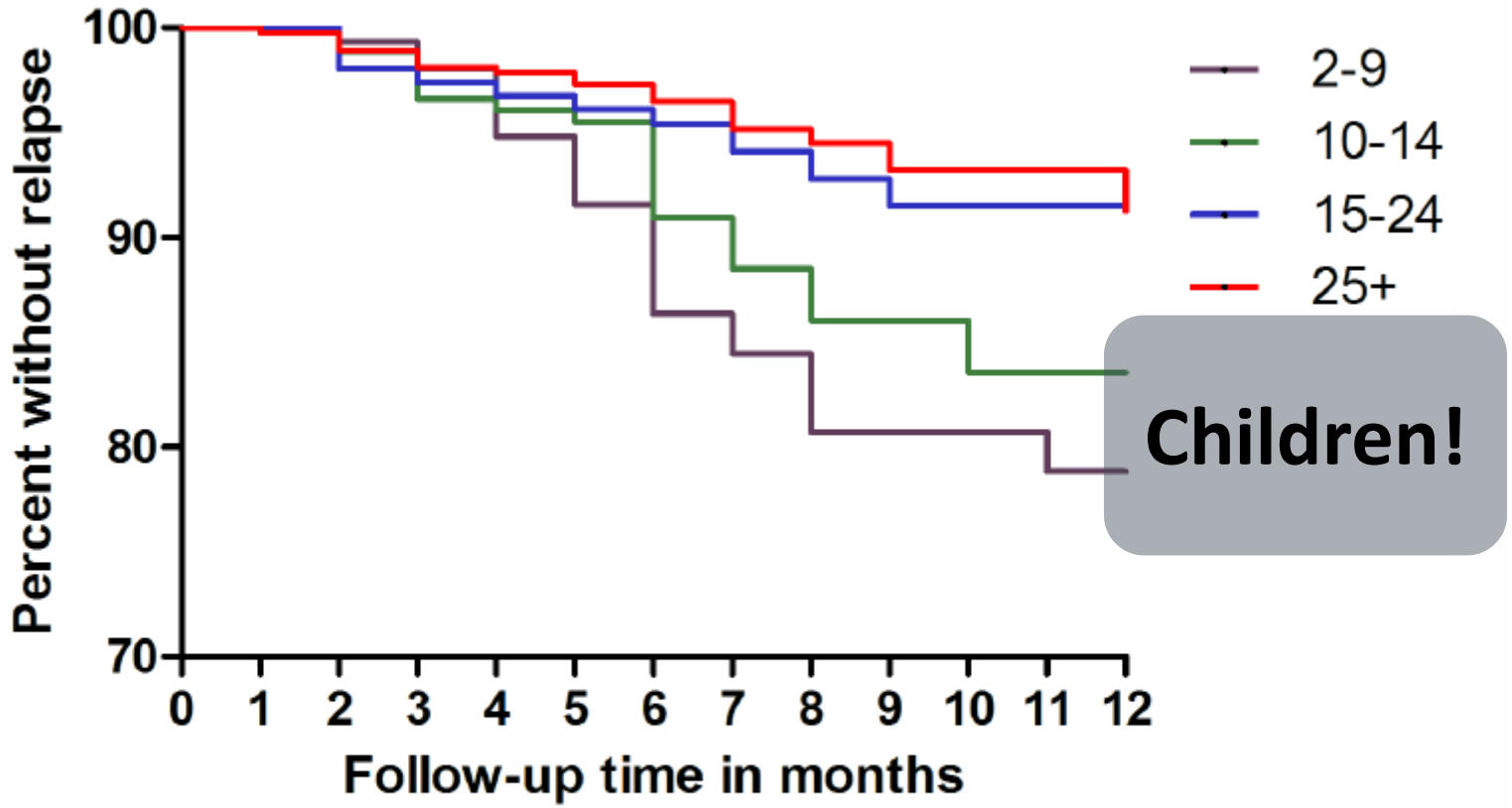


Figure 1. Kaplan-Meier Survival plot for relapse per age group.

doi:10.1371/journal.pone.0100220.g001

Citation: Ostyn B, Hasker E, Dorlo TPC, Rijal S, Sundar S, et al. (2014) Failure of Miltefosine Treatment for Visceral Leishmaniasis in Children and Men in South-East Asia. PLoS ONE 9(6): e100220. doi:10.1371/journal.pone.0100220

MILTEFOSINE TRIALS CHILDREN

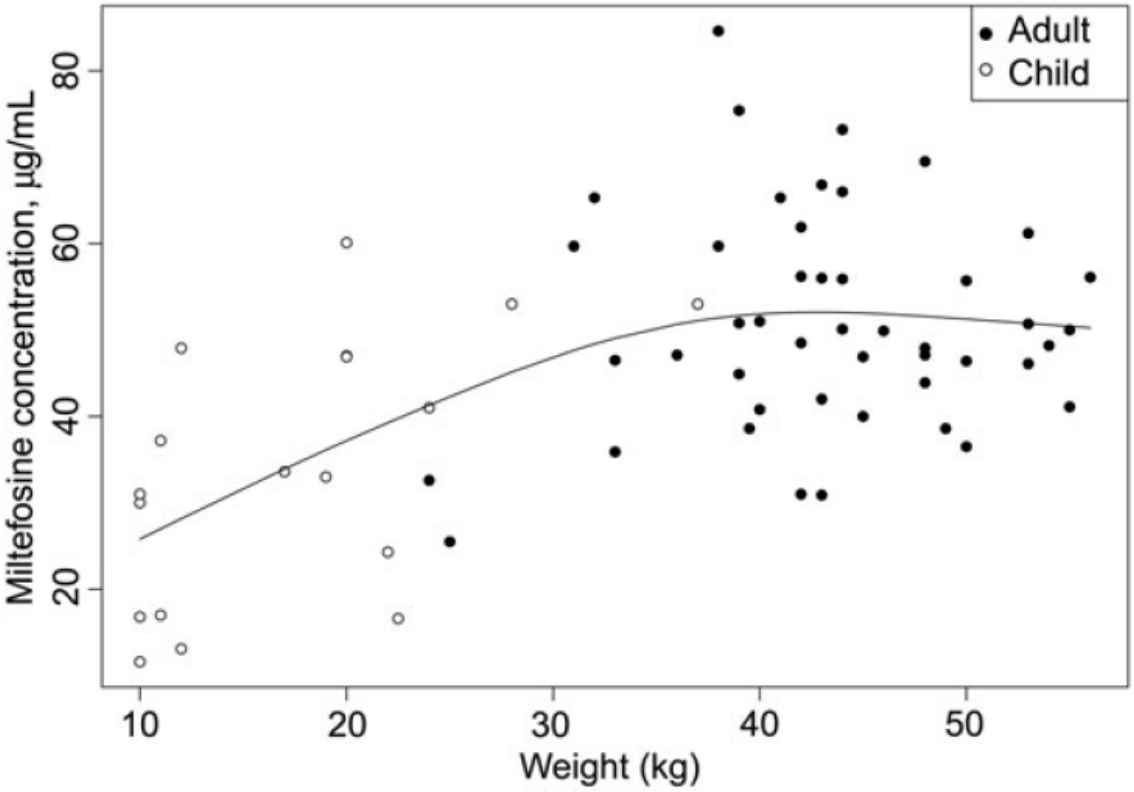


Figure 2. Observed miltefosine end-of-treatment (EOT) concentrations among children and adults, by body weight. Adults are individuals aged ≥12 years, and children are individuals aged <12 years. The solid line shows a fitted polynomial smoothed regression line. For comparability, only observed concentrations within 7 days of EOT were included here

Leishmaniasis translational medicine lesson

- No matter how effective in animal models, studies in humans will need adjustments
- Children will need even more adjustments
- Children are not small adults…
- Or big mice…
- And they have more rights than dogs do to have a liquid formulation!!

DISCUSSION

- Drug development, particularly from an academic perspective, should be viewed as a iterative process
- Data from clinical trials and clinical observations can inform the drug development process
- Animal and in vitro models can help refine knowledge and select drugs that address clinical problems
- New compounds with potential should evaluated for clinical testing as soon, and as often, as possible provided safety data is reasuring
- Drug combinations have a still untapped potential in Chagas disease and Leishmaniasis

Thank you very much!

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