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Training Network

ACCESS TO QUALITY-ASSURED MEDICINE FOR NEGLECTED TROPICAL DISEASES:

A case study of miltefosine for leishmaniasis

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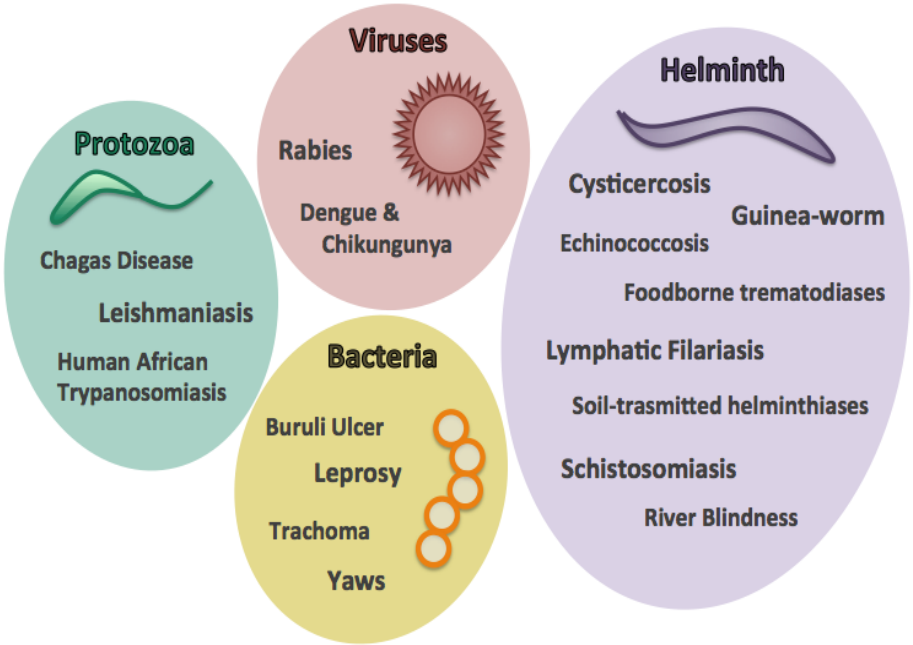
ACCESS CAMPAIGN
MEDECINS SANS FRONTIERES

Neglected Tropical Diseases

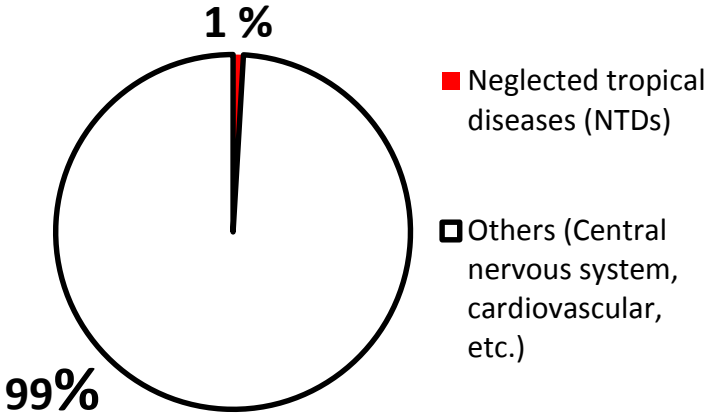


- WHO: a diverse group of communicable diseases that prevail in tropical and subtropical conditions
- = diseases of poverty

- Repackaging of global health
- Several milestones: Berlin meeting 2003, London Declaration 2012, NTD summit 2017

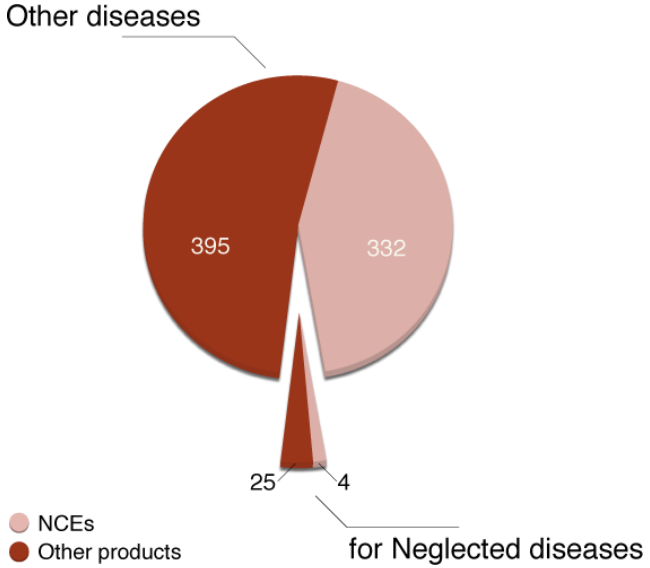
+ Mycetoma, chromoblastomycosis and other deep mycoses
+ Snakebite envenoming
+ Scabies and other ectoparasites

Fatal imbalance in R&D



Source: Trouiller et al., (2002) Drug development for neglected diseases: a deficient market and a public-health policy failure. The Lancet.

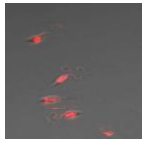
756 products developed
(excluding vaccines & biologicals) (2000-2011)*

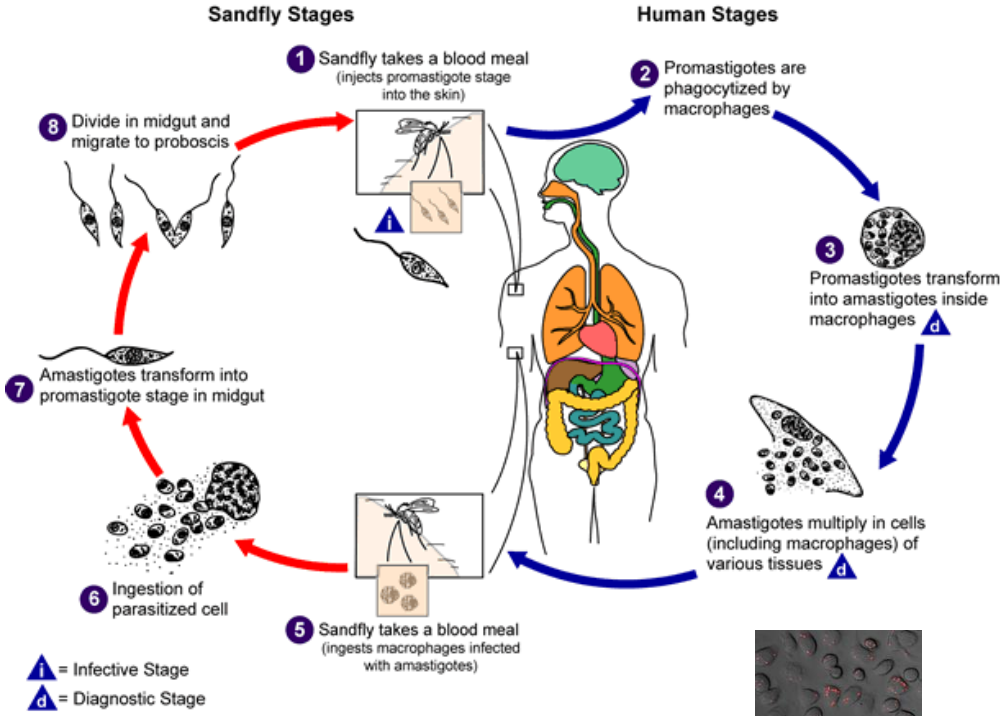


* Source: Pedrique B et al. The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment. *Lancet Global Health*, 2013.

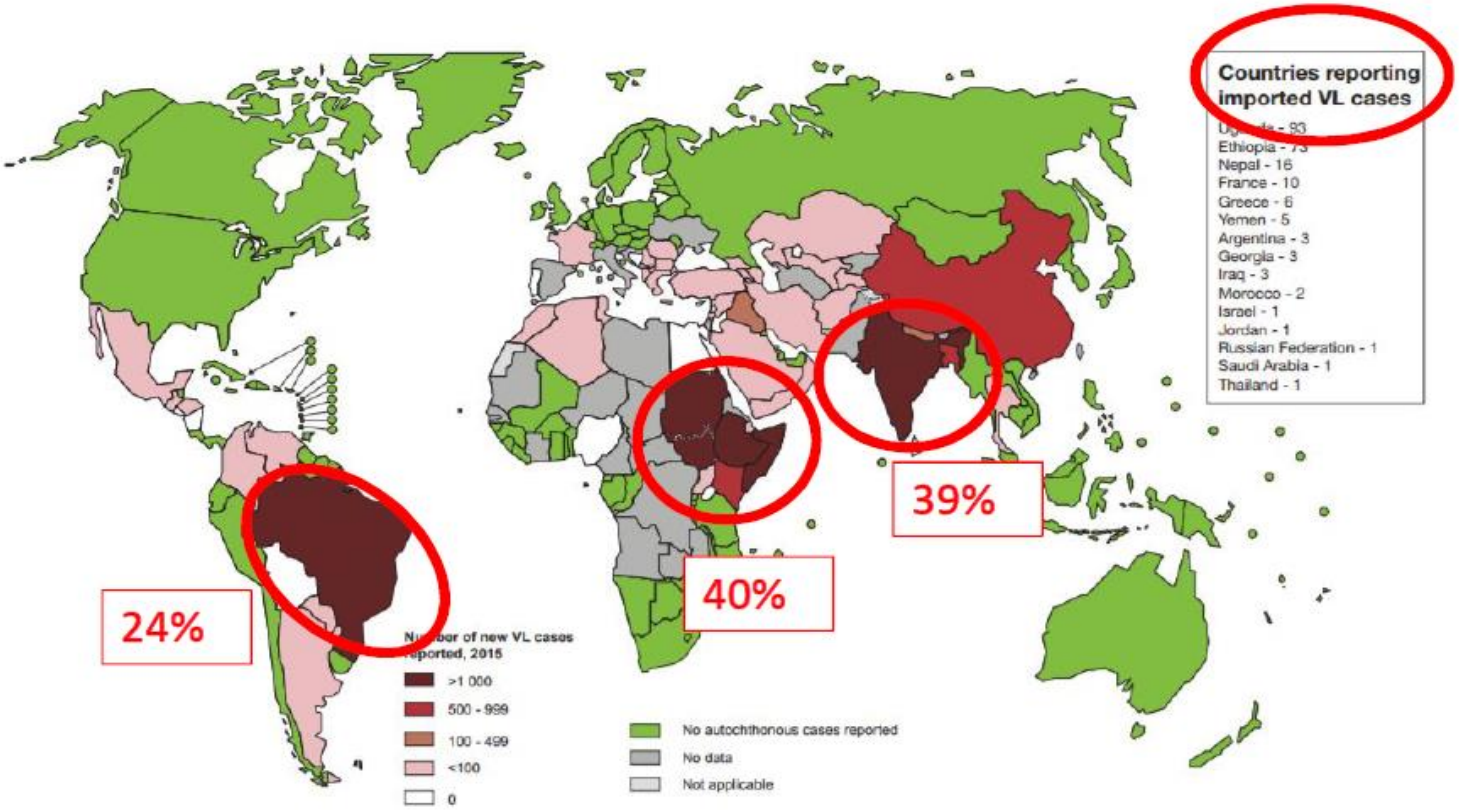
Leishmaniasis

- A parasitic Neglected Tropical Disease
- Caused by >20 Leishmania parasite
- Transmitted by Phlebotomine sandflies
- Anthroponootic or zoonotic
- Clinical spectrum: CL, MCL, VL or Kala azar – fatal without treatment





Global burden of VL 2015



Control (and elimination) of VL

- Control options for VL:
  - Early diagnosis and treatment
  - Vector control
  - Control of animal reservoir
  - Environmental measures
  - (Vaccination)

- 2005 MoU: Bangladesh, India & Nepal elimination **by 2015**
- 2014 MoU: Bangladesh, Bhutan, India, Nepal, Thailand & SEAR elimination **by 2017**

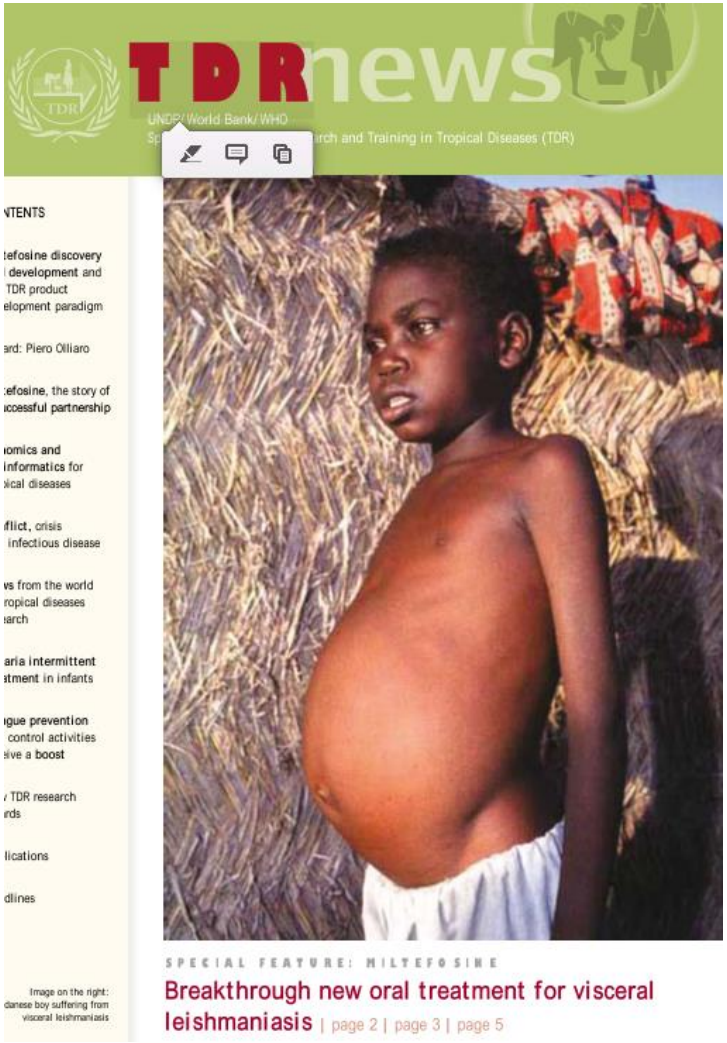
WHO Regional Strategic Framework for Elimination of Kala-azar from the South-East Asia Region (2005–2015). http://apps.who.int/iris/bitstream/10665/205825/1/B0211.pdf [Last accessed May 2017]; WHO Press Release: Health Ministers commit to eliminating kala-azar http://www.searo.who.int/mediacentre/releases/2014/pr1581/en/ [Last accessed May 2017].

Drug	Commercial names and manufacturer	Unit	Price information	Limitations
Sodium stibogluconate	Pentostam®: GSK Generic: Albert David	30 ml vial of 100 mg/ml	$6.45	Injectable, high toxicity, resistance
Meglumine antimoniate	Glucantime®, Aventis	5 ml vial of 81 mg/ml	WHO-negotiated price: $1.2	As above
Amphotericin B deoxycholate	Various	50 mg vial	Variable ~$ 7.5 per 50-mg vial	Injectable, high toxicity
Liposomal amphotericin B	AmBisome®: Gilead	50 mg vial	Access price $18	Low toxicity, requires cold chain - stable up to 25°C
Miltefosine	Impavido®: Knights Therapeutics	50 mg and 10 mg tablet-pack of 56	€100-140	Adverse effect, teratogenicity
Paromomycin	Generic: Gland Pharma	2 ml vial of 375 mg/ml	€1.3	Injectable, side effects

A PPP success story

- Miltefosine (Impavido®)
- Originally developed as **anti-cancer agent**
- 1987: discovery *in vitro* anti-leishmanial activity
- Excellent oral bioavailability in mouse models
- Candidate compound for human VL
- 1995: **Public Private Partnership**:

WHO/TDR - Asta Medica – Indian researchers



Drug discovery and development

Drug R&D phase

Pre-clinical development by academia in Germany and UK

From 1998-2002: Ph I – II - III trials of MLF for VL

1980 **1990** **1995** **2002**

Milestones

MLF – discovered to have anti-leishmanial activity *in-vitro* and *in vivo*

MoU between WHO/TDR-AstaMEDICA India to develop MLF for VL

March 2002: MLF registered as the first oral drug for VL in India

Ownership

ASTA MEDICA

Zentaris AG

Zentaris

Æterna Zentaris

Transaction

Access issue #1: Cost

- Orphan drug status obtained in EU (2002) and US (2006), WHO EML in 2011
- Public health needs: **cost should not exceed US$50-60/treatment**
- Miltefosine first became available in private market in India for US$150-200/ tx
- Long negotiation over public price – known as WHO-negotiated price
- **BUT:** minimum order quantity was imposed (75,000 caps and later 200,000 caps or equal to 3500 treatment courses)
- Price keeps increasing

Access issue #1: Cost

Price policy	Price per full course	Period covered	Remark
Preferential price for public or non-for-profit sector in developing countries	€45,3-54,9 (US$54-64)[a]	2002 – 2008	Price varied based on quantity purchased; minimum order quantity/MOQ was imposed
	€80-110 (US$94-130)	2009 – 2014	
	€100-140 (US$117-164)[b]	2016 onwards	No MOQ, but price still varied based on quantity
Market price EU	€3000-12000	2012	Direct order to the producer/distributor
Market price US	US$16,712[c]	2016	

*One full adult course of miltefosine monotherapy uses one pack containing 56 caps. The recommended dose is 2.5 mg/kg daily for 28 days (roughly 50 mg capsule bid for adults weighing >25 kg).

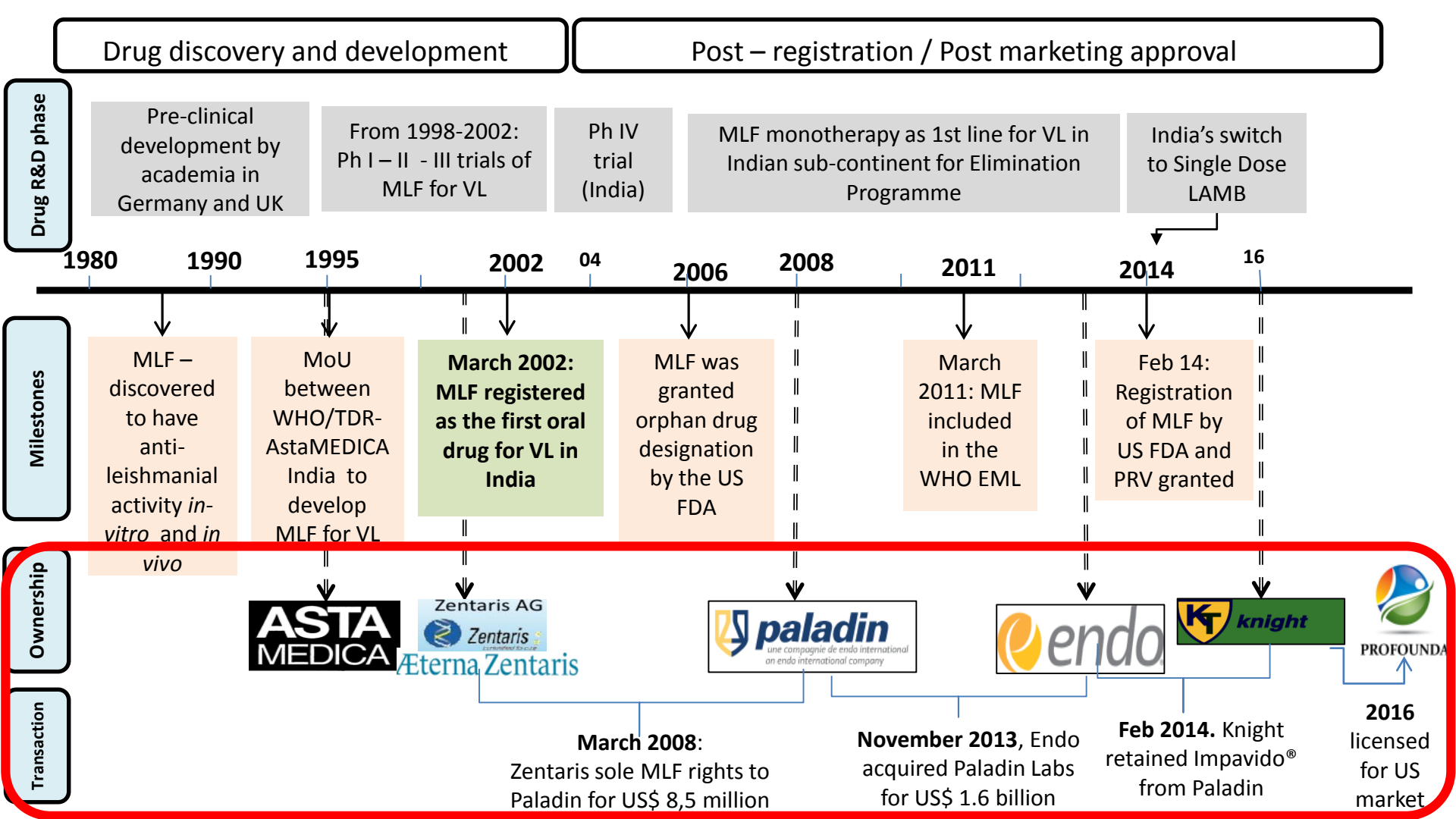
[a] This is the original price aimed for in the agreement between WHO and AstaMedica (1995) and published officially in the latest WHO Control of Leishmaniasis guidelines (2010)

[b] Price quoted by Knight Therapeutics for purchase by non-profit organizations Médecins Sans Frontières (MSF)

[c] For 28 caps, see https://www.drugs.com/price-guide/impavido

Access issue #2 : Availability

- Difficulties to obtain preferential price impacts availability in endemic countries
- Minimum order quantity led to oversupply and wastage
- Long production lead-time at the manufacturer
- Insecure supply – frequent stock-outs
- Bureaucratic tender mechanisms for public procurement
- Access difficulties in each region (Asia, Africa, Europe, North America, Latin America)
- Compassionate use or donation exist, yet little known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India's switch to Single Dose LAMB
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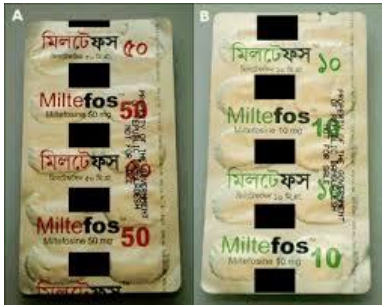
March 2008: Zentaris sole MLF rights to Paladin for US$ 8,5 million
November 2013, Endo acquired Paladin Labs for US$ 1.6 billion
Feb 2014. Knight retained Impavido® from Paladin
2016 licensed for US market

Access issue #3 : Quality

- Often forgotten
- Procurement and accessibility issues led Bangladeshi program to opt for locally sourced and less expensive product
- Cluster of VL deaths followed
- On investigation, it was counterfeit, without active ingredients



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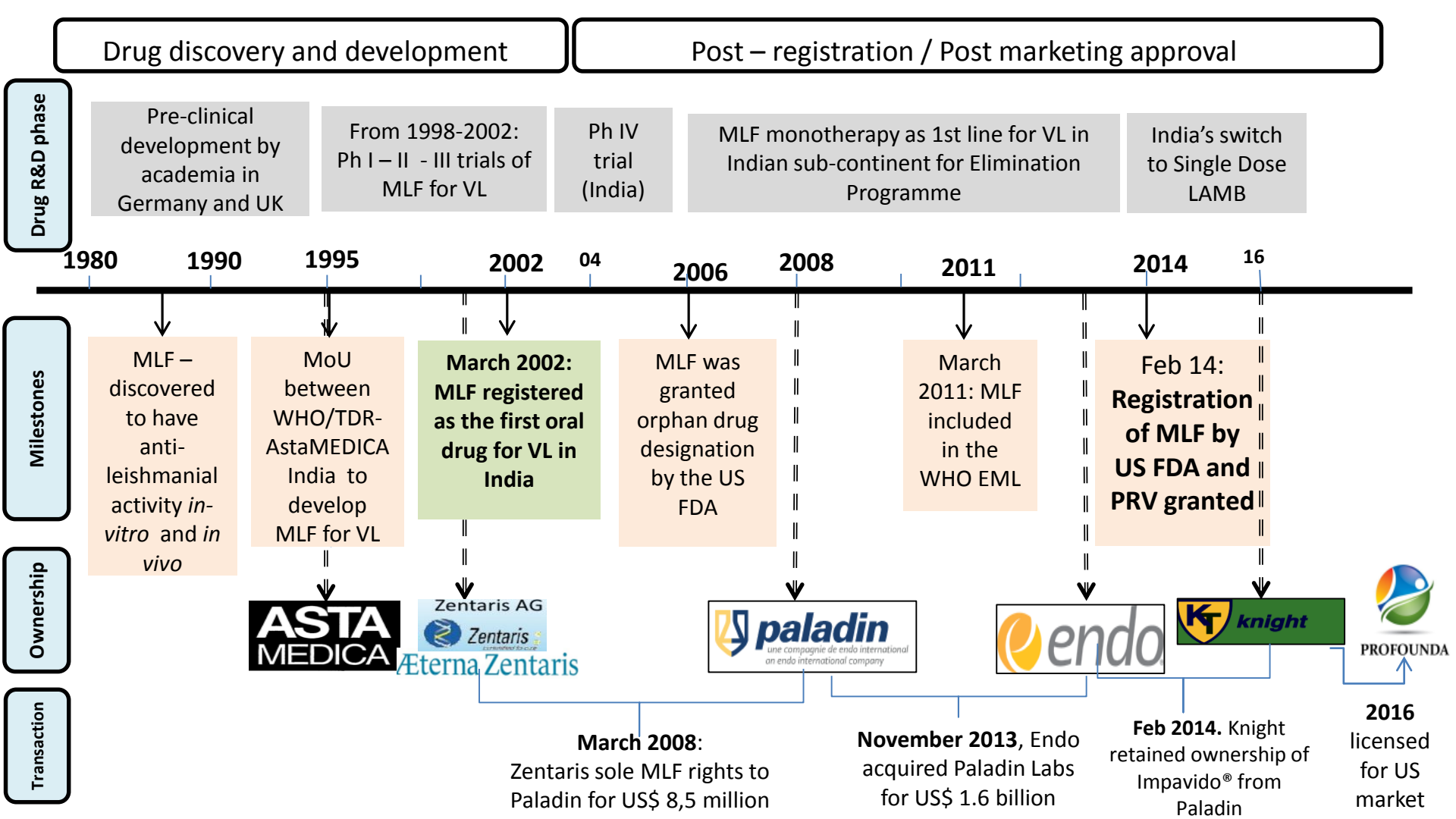
PLOS TROPICAL DISEASES

Viewpoints

A Poor-Quality Generic Drug for the Treatment of Visceral Leishmaniasis: A Case Report and Appeal

Dorlo TPC, Eggelte TA, Schoone GJ, de Vries PJ, Beijnen JH (2012) A Poor-Quality Generic Drug for the Treatment of Visceral Leishmaniasis: A Case Report and Appeal. PLoS Negl Trop Dis 6(5): e1544. doi:10.1371/ journal.pntd.0001544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Priority Review Voucher

A US law created in 2007 as incentive for R&D for NTD and rare pediatric diseases

- Some loopholes:
  - ❑ Drugs that have been used outside the US for some time
  - ❑ Recipient may have no role in R&D
  - ❑ No guarantee for better access

Table. Awarded Priority Review Vouchers, September 2008 to August 2015[a]

Drug	Year	Sponsor	Disease	Sold	Used
Neglected tropical diseases					
Artemether-lumefantrine	2009	Novartis	Malaria	No; used internally	Canakunimab for gouty arthritis in 2011 (indication rejected)
Bedaquiline	2012	Johnson &	Multidrug-resistant		
Miltefosine	2014	Knight Therapeutics	Leishmaniasis	$125 million to Gilead Sciences, 2014	
Rare pediatric diseases					
Elosulfate alfa	2014	BioMarin	Morquio A syndrome	$67.5 millionto Regeneron and Sanofi, 2014	Alirocumab for high cholesterol (approved July 2015)
Cholic acid	2015	Asklepion[a]	Bile acid synthesis disorders involving single-enzyme defects and peroxisomal disorders	$245 million to Sanofi, 2015	
Dinutuximab	2015	United Therapeutics	High-risk neuroblastoma	$350 million to Abbvie, 2015	

JAMA. 2015 Oct 27;314(16):1687-8. doi: 10.1001/jama.2015.11845. Experience With the Priority Review Voucher Program for Drug Development. Kesselheim AS, Maggs LR, Sarpatwari A.

Lessons learned

- Miltefosine is a **major therapeutic advance** for leish - will remain valuable
- Its development showed that PPP is a **viable** model for R&D for NTDs
- However, **access to this drug is limited**
  - ✓ even in a context where preferential pricing should apply
  - ✓ *de facto* monopoly of a drug as **the only quality-assured source.**
- Miltefosine availability affected by changes in ownership rights over the years
- Despite existing MoU, dependency on the goodwill of company (which changes)
- Not all NTDs can be tackled with big pharma donation

Lessons learned

- **PPP or PDP should not only target the registration of the product**
  - ❑ Improve mechanism(s) to enforce framework and legal agreements between partners
  - ❑ Access plan imperative

- **Transparency** in drug pricing structures

- **PRV as incentive to enhance R&D for NTD need fixing**
  - ❑ Applicants seek regulatory approval and demonstrate appropriate access strategies
  - ❑ Signs of change: **2017 PRV for benznidazole for Chagas diseases** (Chemo Group, DNDi, Mundo Sano)

- **Develop short-mid-long term strategies for Leish drugs:**
  - ❑ Consolidate coordination and approach through coalition e.g WHO Working Group
  - ❑ Pooled procurement and establishment of common buffer stock

THANK YOU
Questions?

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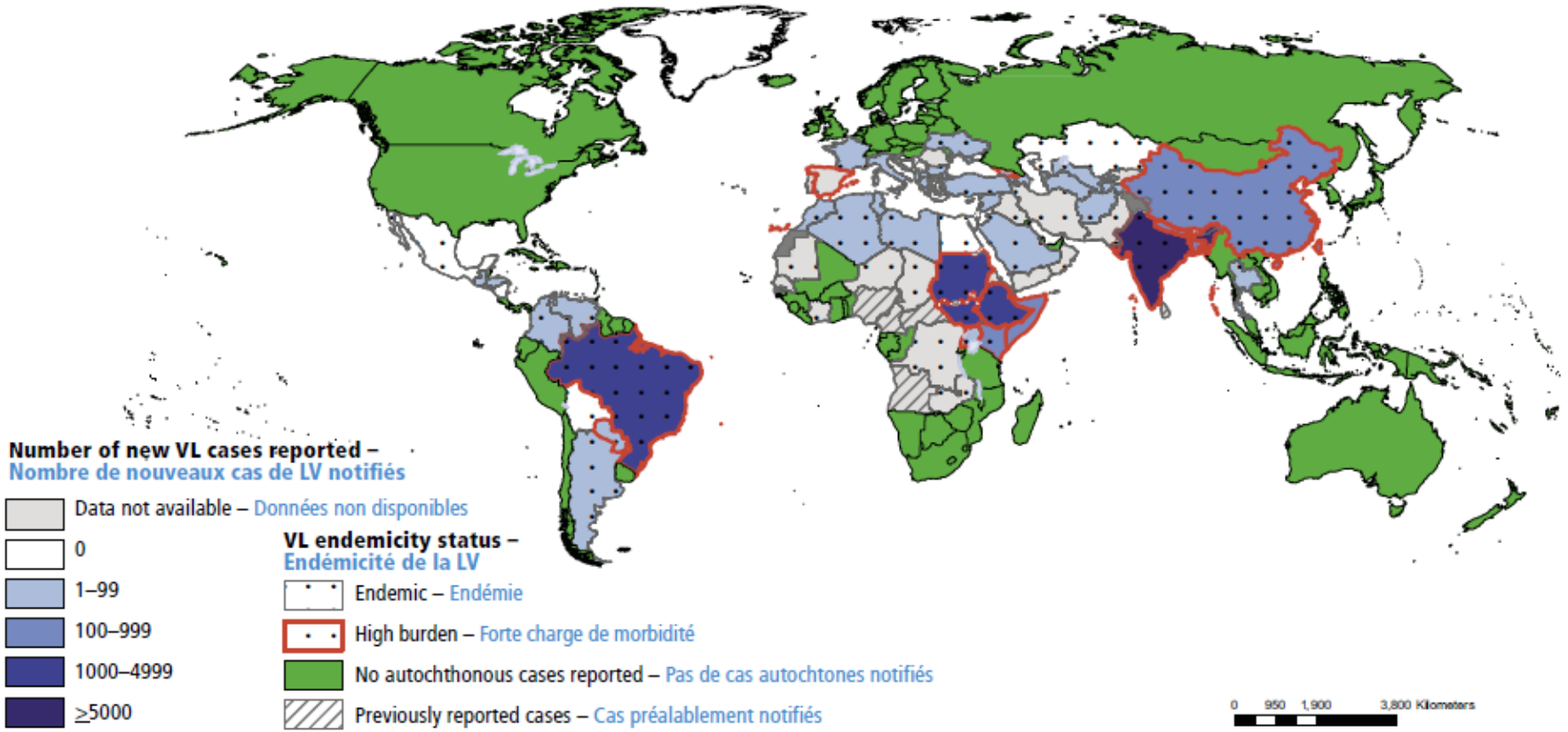

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The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or

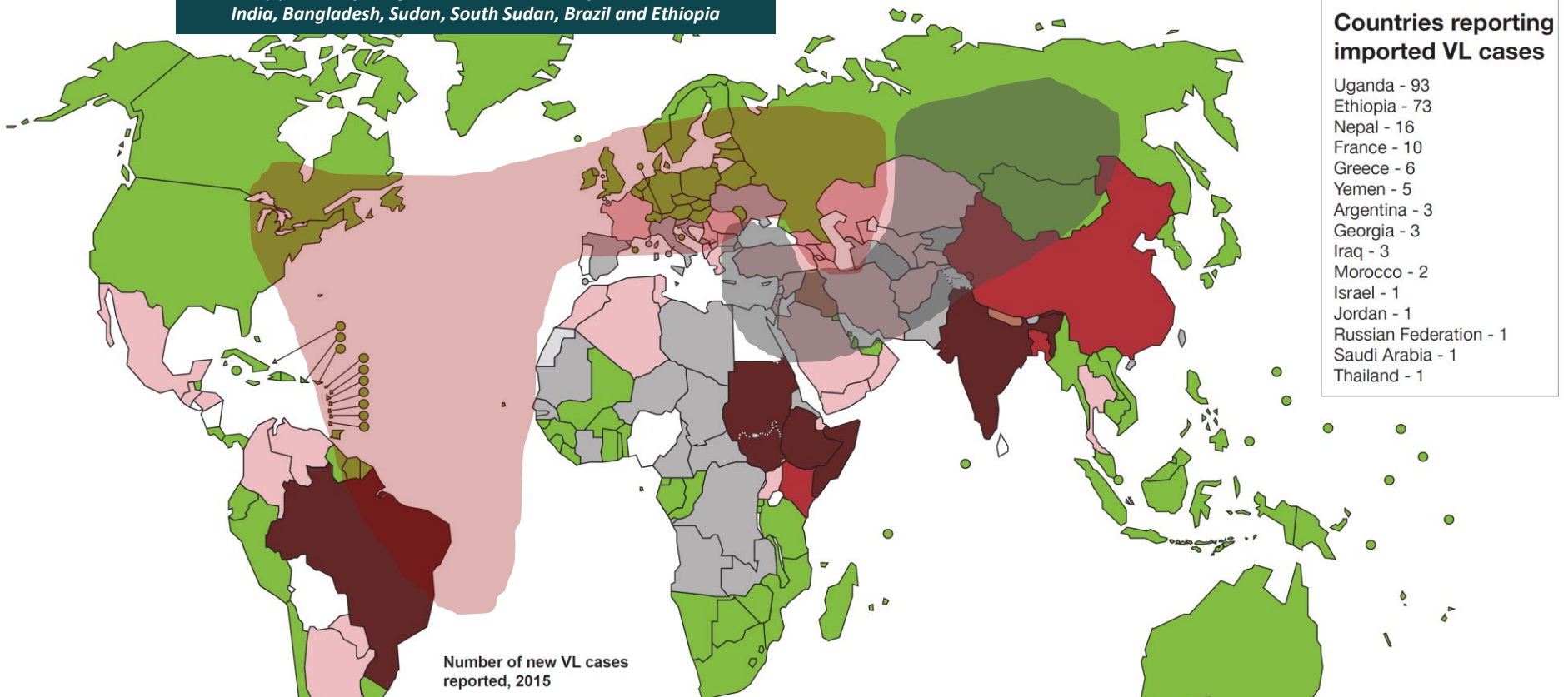
***L infantum*: ZOONOTIC**

- ✓ Middle East/ Central Asia
- ✓ Mediterranean
- ✓ Latin-America

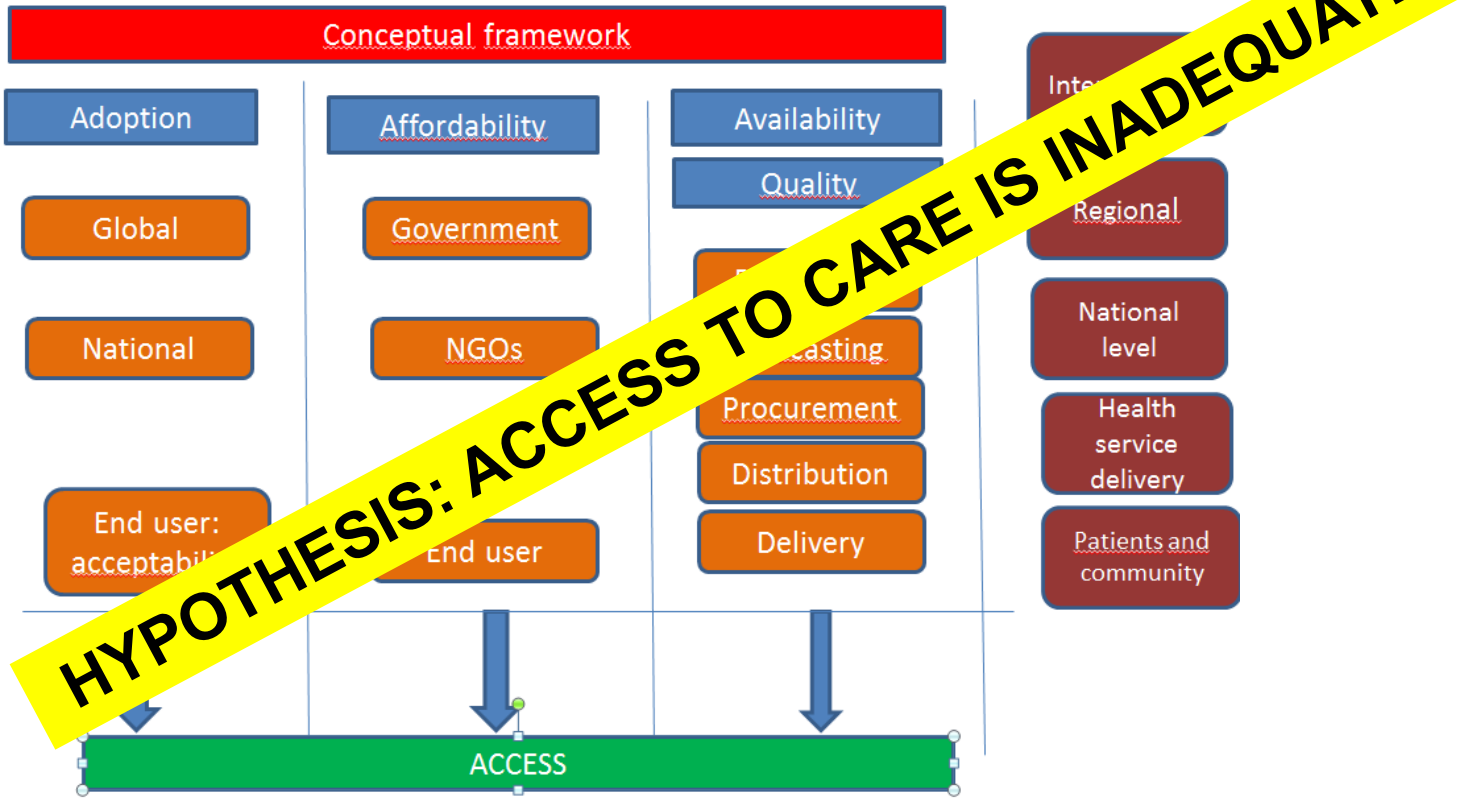
***L donovani*: ANTHROPONOTIC**

- ✓ Indian subcontinent
- ✓ East Africa

Ninety percent of the global burden occurs in just six countries:
India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia



Significance of access problems



HYPOTHESIS: ACCESS TO CARE IS INADEQUATE