



# Pour un accès global aux médicaments antiinfectieux

Dr. Bernard Pécoul, Executive Director

**DNDi**

Drugs for Neglected Diseases *initiative*

L'inégalité devant les maladies infectieuses, Collège de France  
23 janvier 2013

# OUTLINE

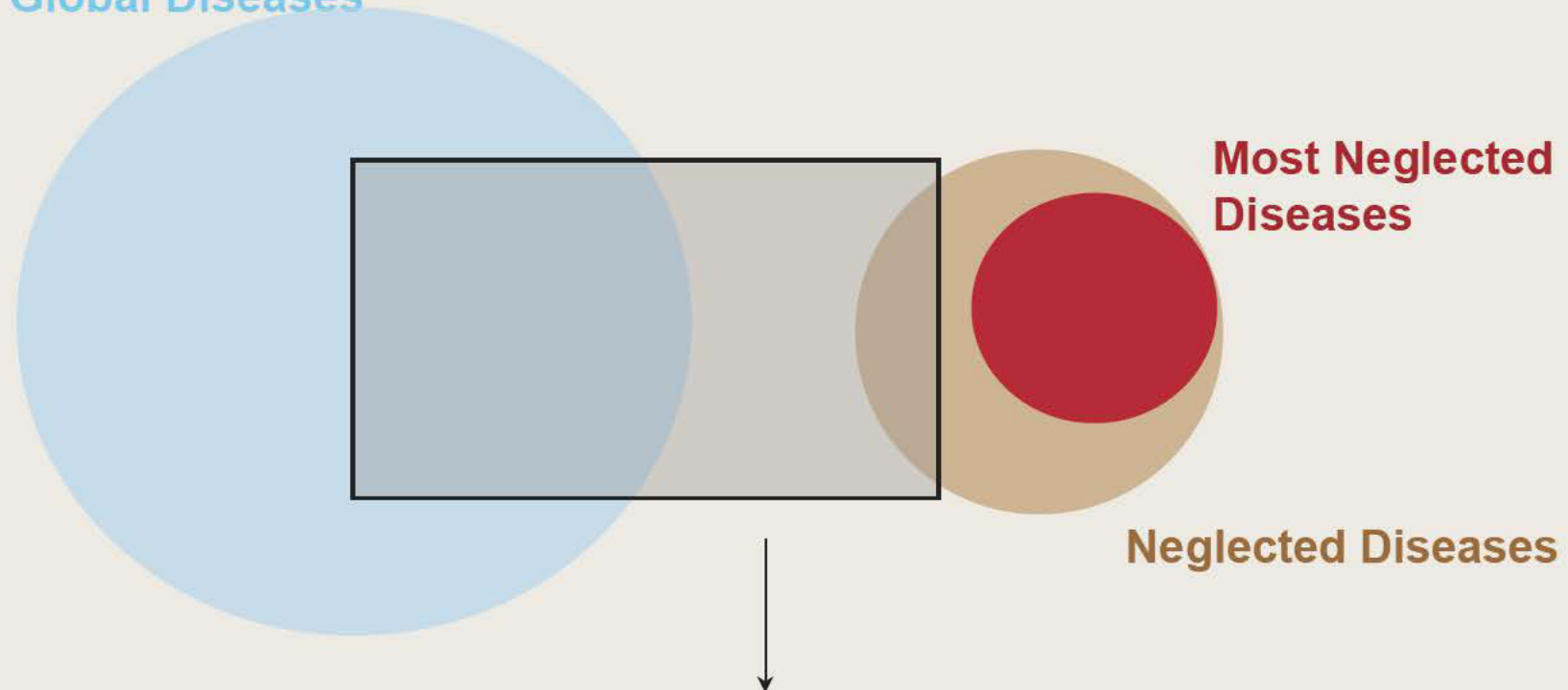
- ❑ The Landscape
- ❑ Neglected Diseases
- ❑ DNDi's Model
- ❑ DNDi's Portfolio
- ❑ Challenges



# The Landscape

# Neglected Diseases: Primarily Affect Developing Countries & Lie Outside the World Market

Global Diseases



Most Neglected Diseases

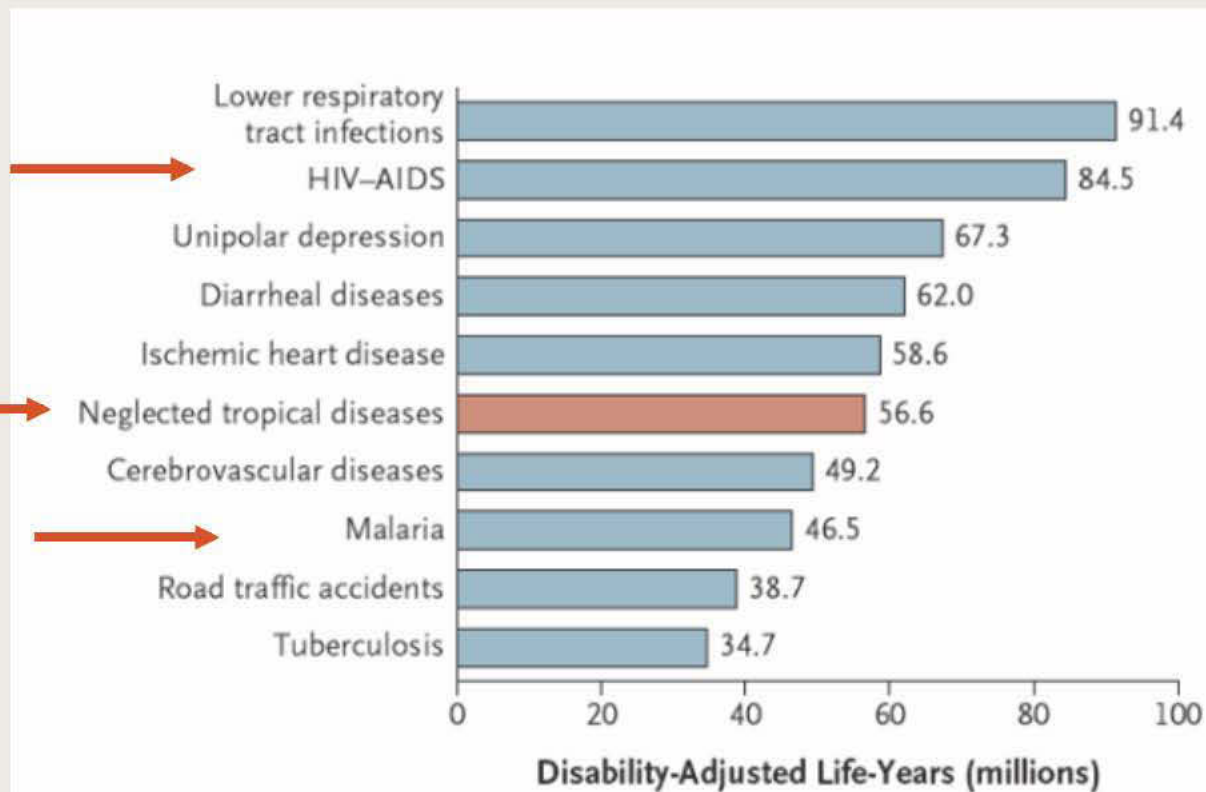
Neglected Diseases

World pharmaceutical market  
\$856 bn in 2010\*  
nearly \$1,100 bn forecast by 2015

\*Source: IMS Health

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# Burden of the Diseases



**Figure 1. The 10 Leading Causes of Life-Years Lost to Disability and Premature Death.**

## CURRENT CONCEPTS

### Control of Neglected Tropical Diseases

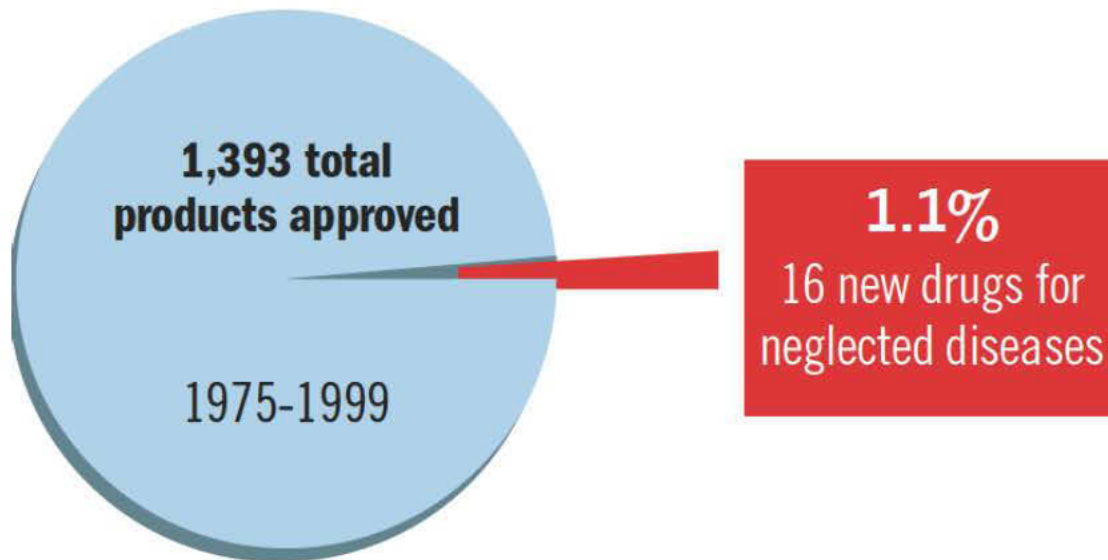
Peter J. Hotez, M.D., Ph.D., David H. Molyneux, Ph.D., D.Sc., Alan Fenwick, Ph.D., Jacob Kumaresan, M.B., B.S., Dr.P.H., Sonia Ehrlich Sachs, M.D., Jeffrey D. Sachs, Ph.D., and Lorenzo Savioli, M.D.

N ENGL J MED 357;10 WWW.NEJM.ORG SEPTEMBER 6, 2007

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# A Decade Ago, Pipeline Virtually Empty for Neglected Diseases

## Health R&D (1975 – 1999)



## A Fatal Imbalance

From 1975-1999:

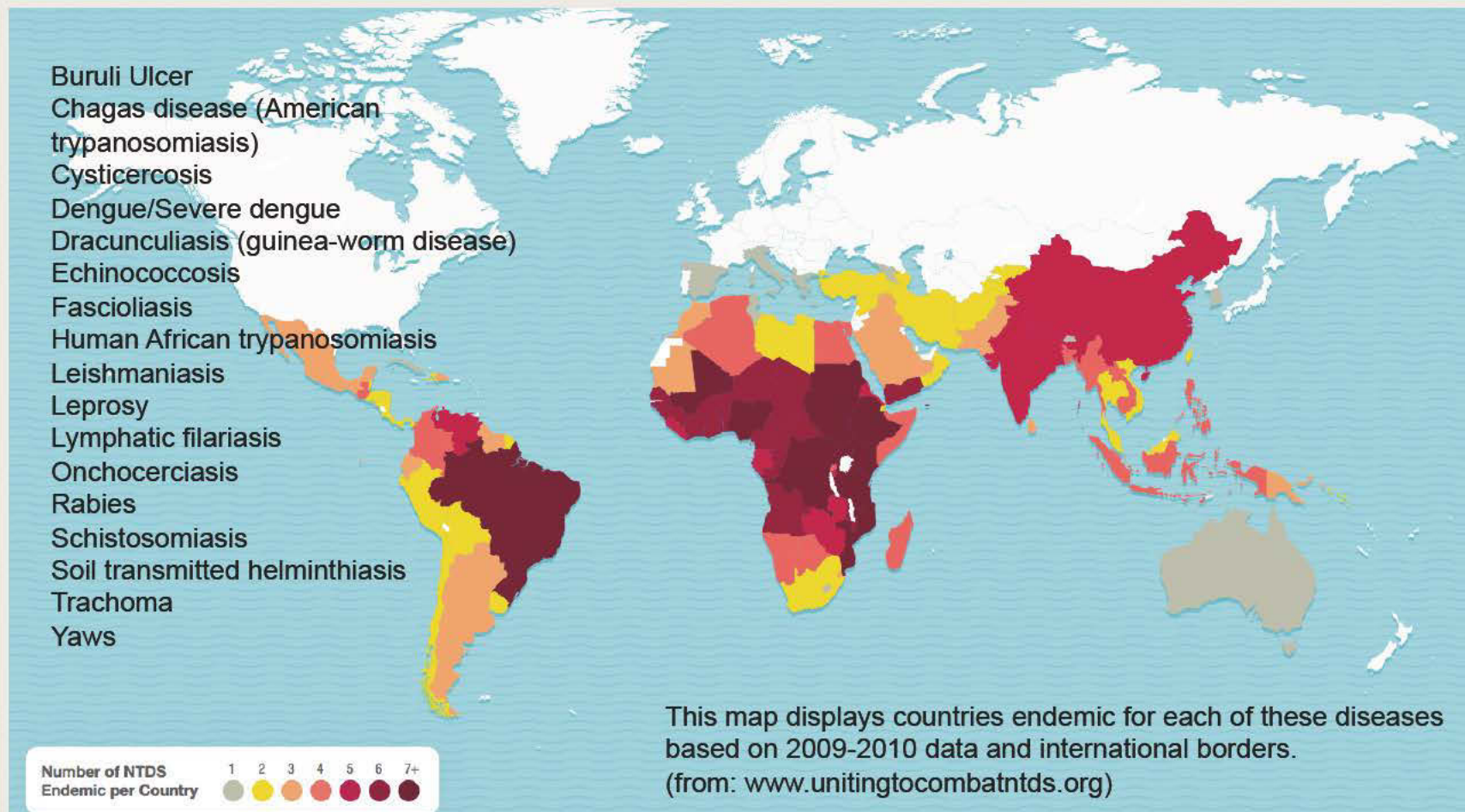
-16 of 1393 new products for neglected tropical diseases + malaria and TB (1.1%) despite these diseases representing 12% of global disease burden

-approx. 10% of R&D dedicated to illnesses that affect 90% of global disease burden ('10/90 gap')

Source: Fatal Imbalance: The Crisis in Research and Development for Neglected Diseases, MSF, 2001



# Burden of Neglected Tropical Diseases



# Responding to the Needs of Patients Suffering from Neglected Diseases...



Malaria



Leishmaniasis



Paediatric HIV



Sleeping Sickness (HAT)



Chagas Disease



Helminth infections



# But for Neglected Patients, 10 Years Later Reality Remains the Same...

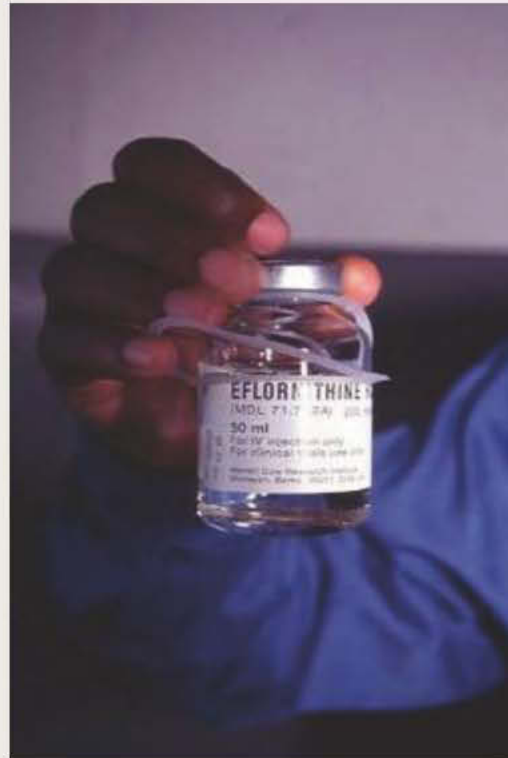
- ❑ Poorest of the poor
- ❑ Living in remote areas
- ❑ Socioeconomic burden on family and community
- ❑ Marginalized & voiceless patients



# Neglected Diseases: Current Treatment Limitations



Melarsoprol

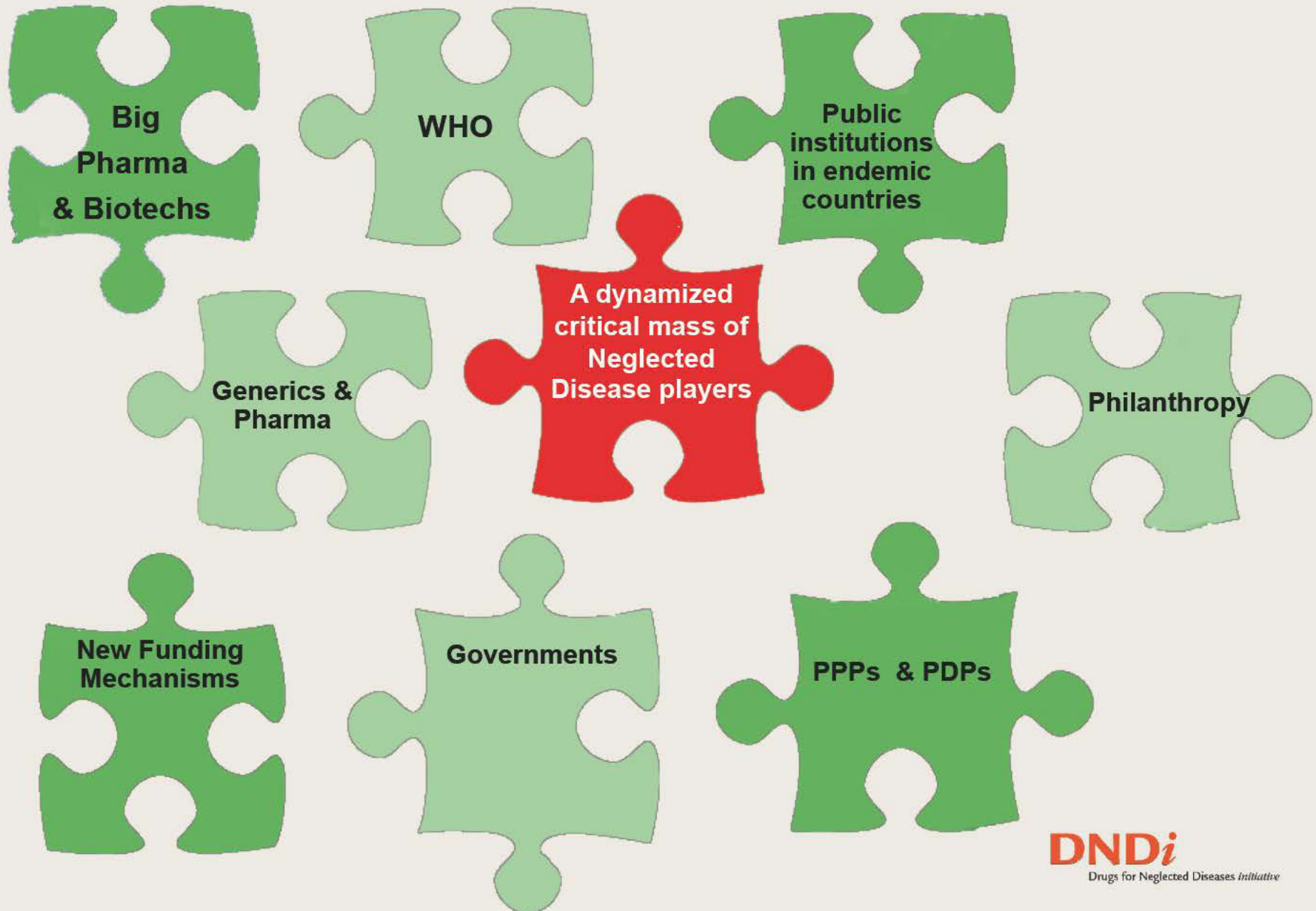


Eflornithine

- ❑ Ineffective (resistance)
- ❑ Toxic
- ❑ Expensive
- ❑ Painful when delivered
- ❑ Difficult to use
- ❑ Not registered in endemic regions
- ❑ Restricted by patents

We Need Safe, Effective, Easy-to-Use Drugs

# A Changing Landscape for Neglected Disease R&D



# Neglected Diseases



# Human African Trypanosomiasis (HAT) or Sleeping Sickness

- ❑ 36 countries at risk in sub-Saharan Africa; estimated current cases: 30,000
- ❑ Transmitted by the tsetse fly
- ❑ Difficult to diagnose; many patients go undiagnosed until late stage of disease
- ❑ Fatal if untreated
- ❑ Needs:
  - ❑ A safe, effective, and orally administered stage 2 treatment



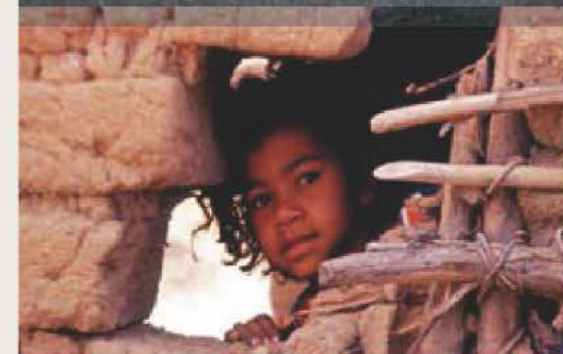
# Leishmaniasis

- ❑ 350 million at risk worldwide (in 98 countries)
- ❑ Transmitted by the sandflies
- ❑ 2 types of leishmaniasis:
  - ❑ Visceral (VL): fatal without treatment
  - ❑ Cutaneous (CL): has a spectrum of presentations; typically with self-healing or chronic lesions on the skin.
- ❑ Symptoms of VL: prolonged fever, enlarged spleen & liver, substantial weight of loss, progressive anemia
- ❑ Treatments needs for VL:
  - ❑ Oral, safe, effective, low-cost and short-course treatment



# Chagas Disease

- ❑ 100 million at risk in Latin America
  - ❑ Kills more people in region than malaria
  - ❑ Patient number growing in non-endemic, developed countries
- ❑ Transmitted by 'kissing bug', blood transfusion, organ transplantation, as congenitally or orally
- ❑ Majority of patients undiagnosed until late stage
- ❑ Needs:
  - ❑ An affordable, age-adapted, safe, and efficacious paediatric strength
  - ❑ A new drug for early chronic stage





# Malaria

- Transmitted by the *Anopheles* mosquito
- *Plasmodium falciparum* responsible for most deaths
- 350-500 million new cases, 1 million deaths
  - 1 child dies of malaria every 45 seconds
  - Malaria causes 20% of child deaths in Africa
- Highly dangerous for pregnant woman and foetus
- Widespread drug resistance
- Existing treatments too expensive

## Needs:

- Artemisinin-based fixed-dose combinations  
Affordable, safe, effective, with paediatric formulations



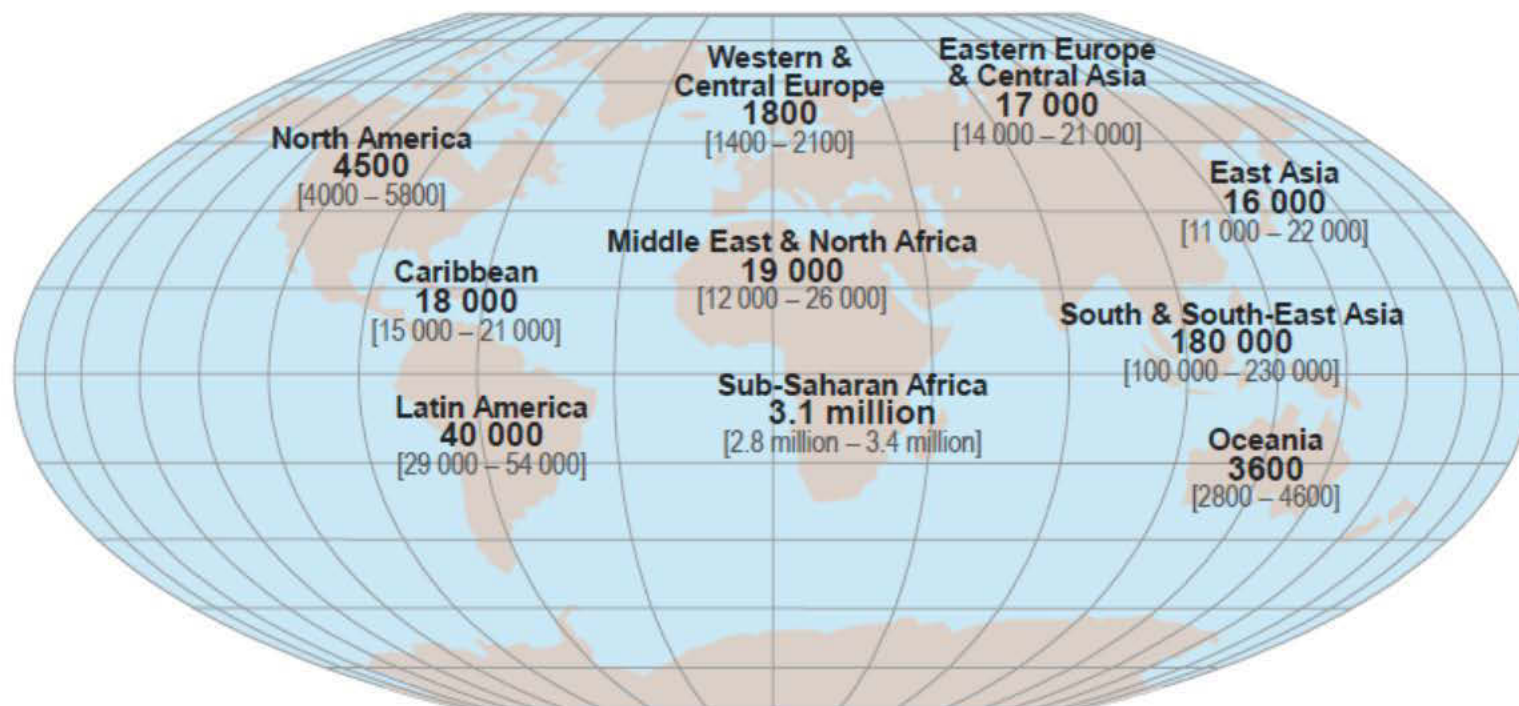


# Paediatric HIV

- Virtual elimination of paediatric HIV in high-income countries...
- ...but 330,000 new infant infections each year and 3.4 million children with HIV/AIDS (91% in sub-Saharan Africa)
  - ▣ > 900 new pediatric HIV infections daily
  - ▣ > 600 deaths in HIV+ children daily
- HIV disease progression in children more rapid than in adults if no treatment is given
  - ▣ 1/3 of HIV+ infants will die by 1 yr old
  - ▣ 50% of HIV+ children will die by 2 yrs old
  - ▣ 80% of HIV+ children will die by 5 yrs old



## Children (<15 years) estimated to be living with HIV | 2011

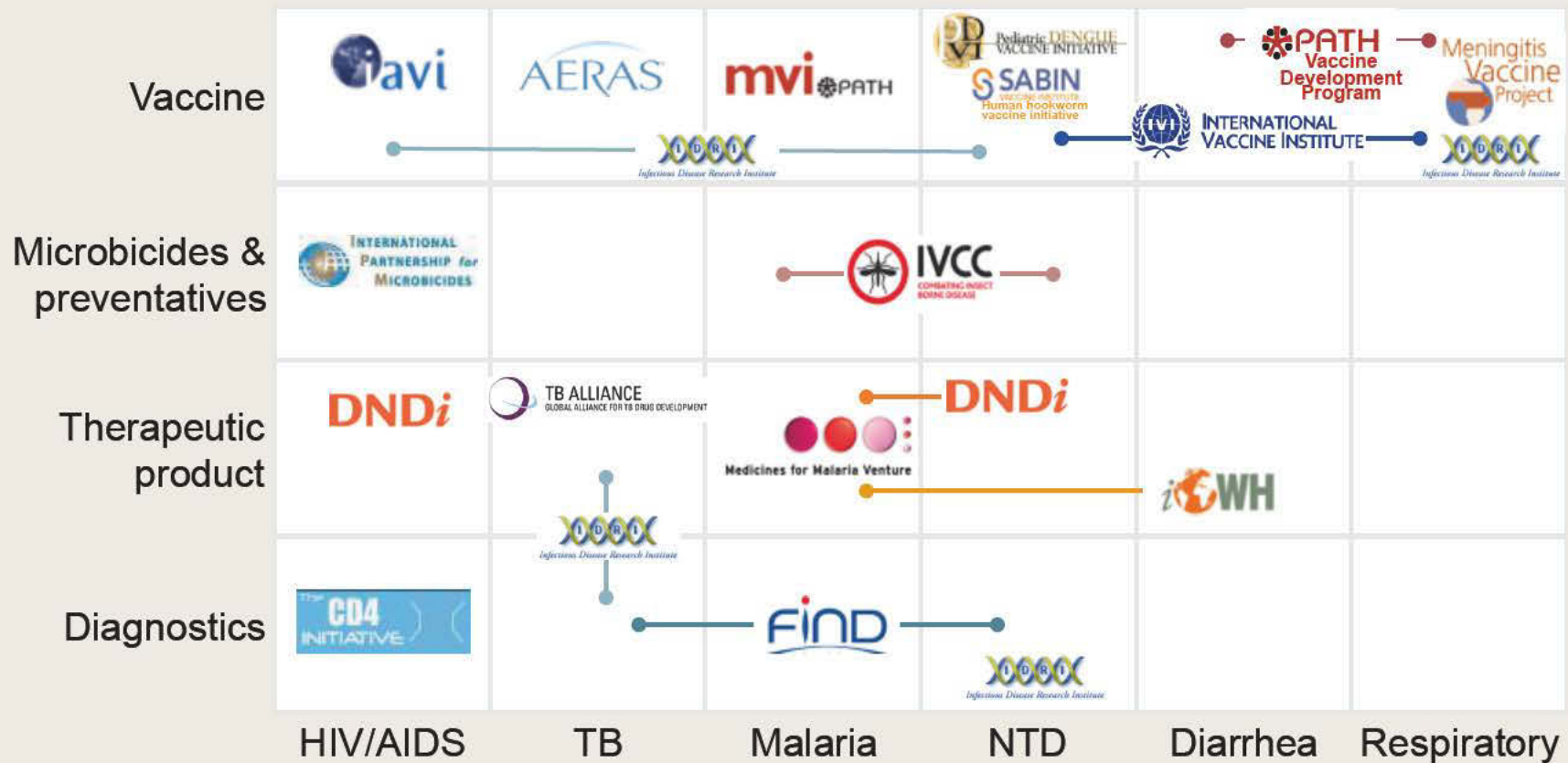


**Total: 3.4 million** [3.1 million – 3.9 million]

# DNDi's Model

# Product Development Partnerships (PDPs): Filling the Gaps in Translational Research and Product Development

PDPs work across different diseases and modalities



Source:

BILL & MELINDA  
GATES foundation

&

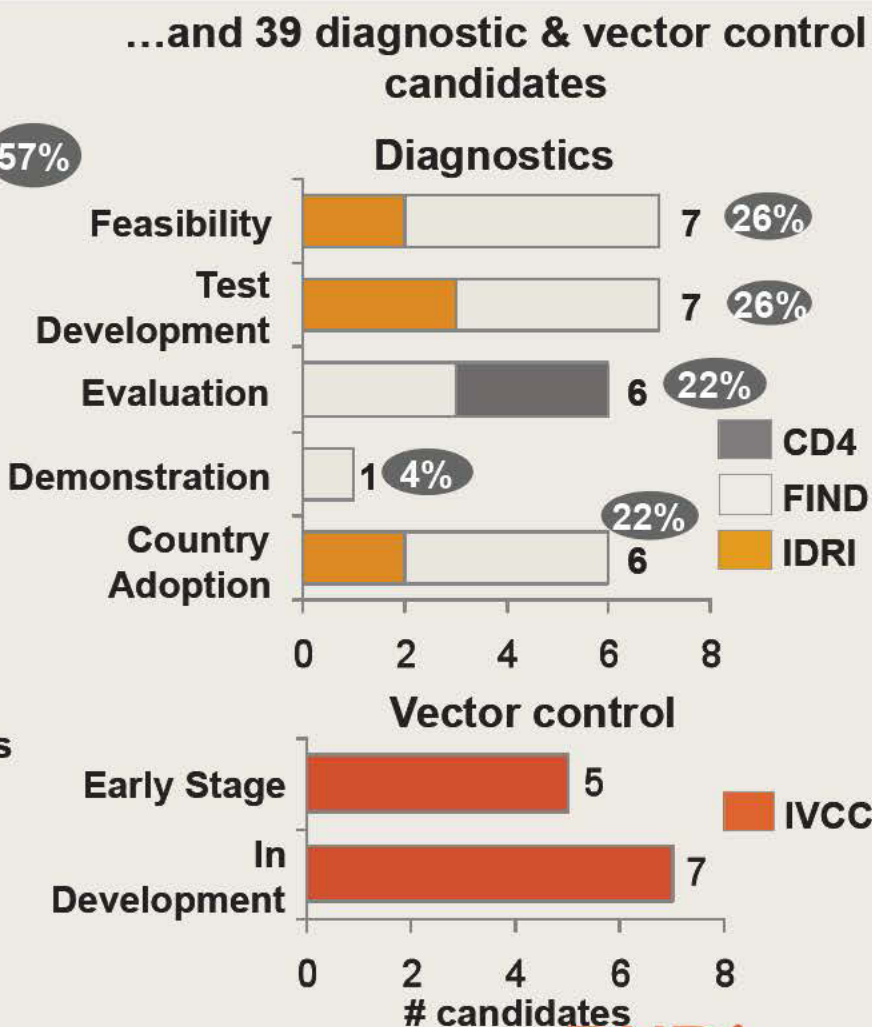
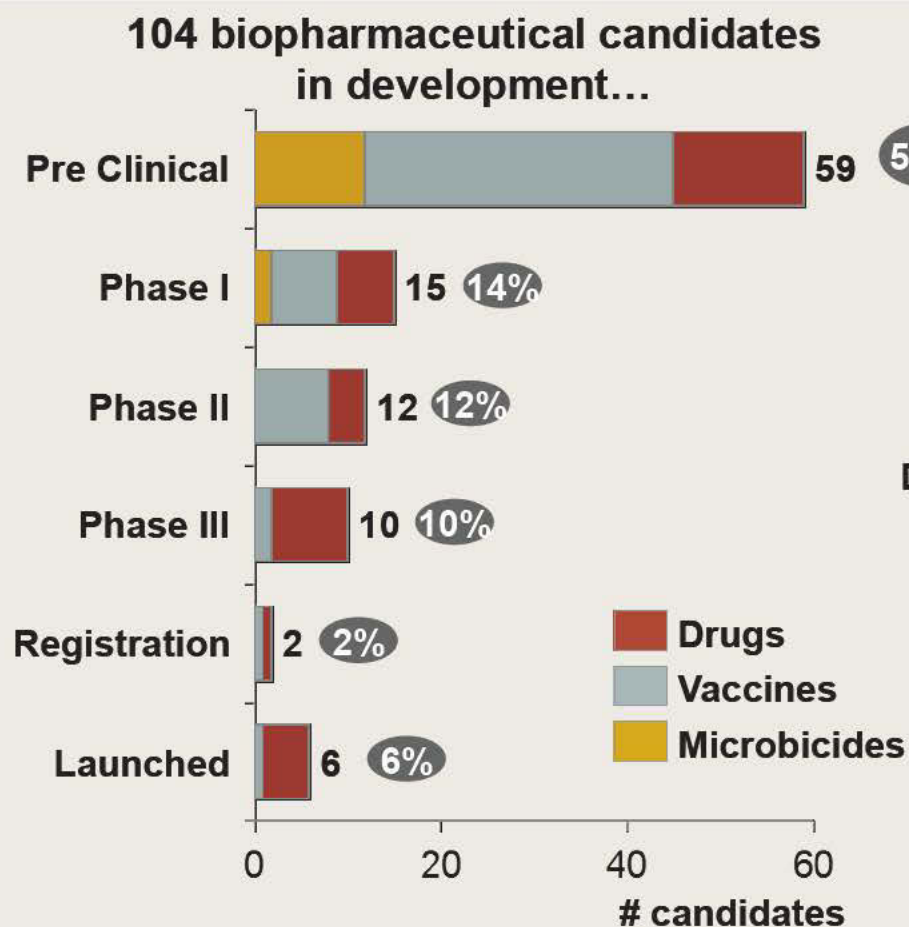
BCG  
The Boehringer-Ingelheim Group

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# Pipeline Now Begins to Be Filled

## 143 Candidates



Notes: Includes products not funded by Gates Foundation.

Biopharmaceutical candidates in development Include: IAVI, IPM, IVI, GATB, Aeras, MMV, MVI, MVP, PVS, DNDi, iOWH, PDVI, HHVI.

Source: PDPs

Source:

BILL & MELINDA  
GATES foundation

&

BCG  
The Boston Children's Group

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# Since 1999, from ideas to realization ...

- ❑ 1999
  - ❑ First meeting to describe the lack of R&D for neglected diseases
  - ❑ MSF commits the Nobel Peace Prize money to the DND Working Group
  - ❑ JAMA article: 'Access to essential drugs in poor countries - A Lost Battle?'
- ❑ July 2003
  - ❑ Creation of DNDi (7 founding members)
- ❑ 2007
  - ❑ First DNDi treatment registered...



# DNDi: Patient Needs-Driven & Innovative R&D Model

- ❑ Deliver **11 to 13 new treatments by 2018**
- ❑ Establish a **robust pipeline**
- ❑ Use and strengthen existing **capacity in disease-endemic countries**
- ❑ **Raise awareness** and advocate for increased **public leadership**

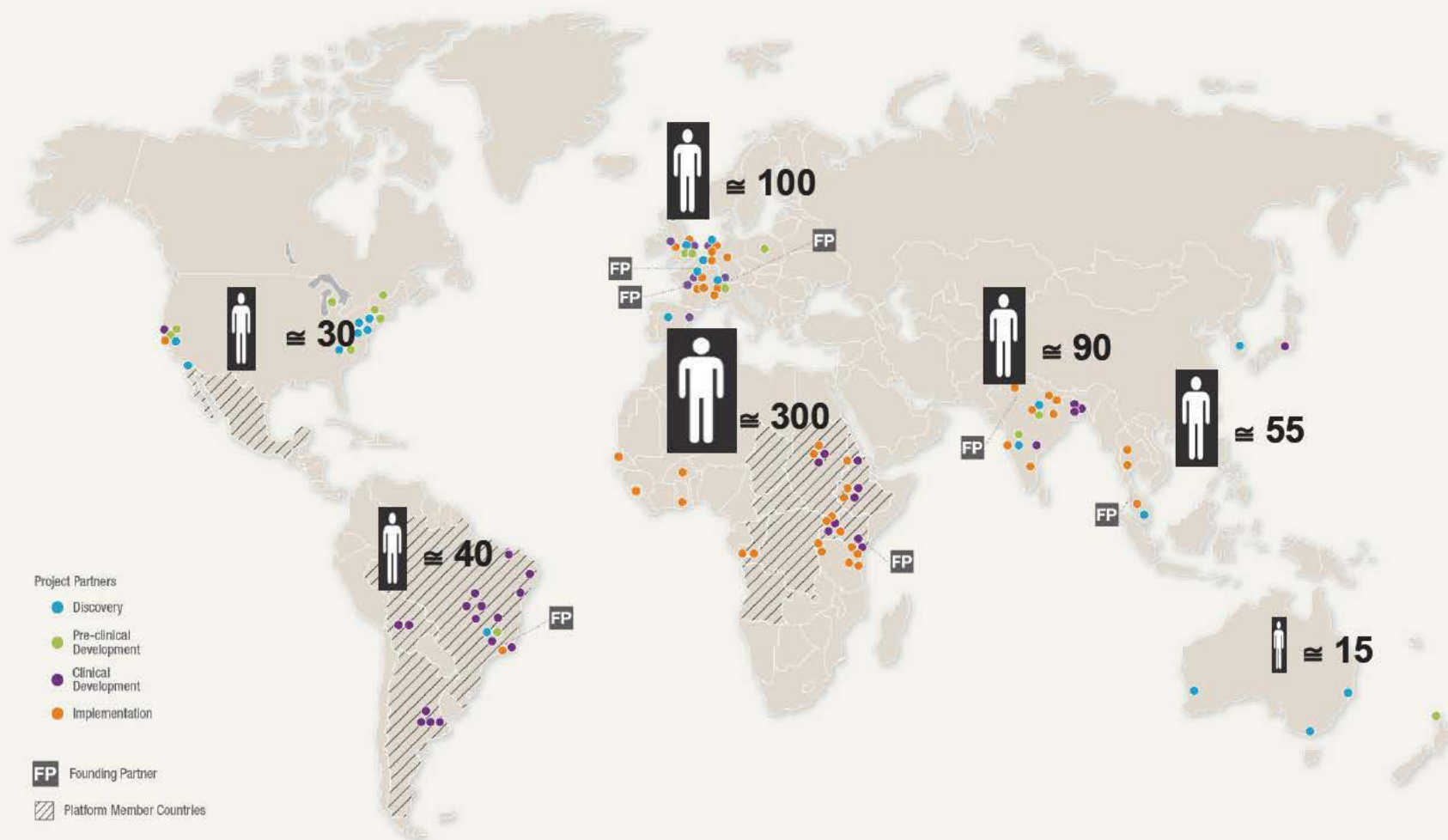
## Founding Partners

- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation, Brazil
- Médecins Sans Frontières (MSF)
- Institut Pasteur France
- TDR (permanent observer)



# Dedicated Teams Worldwide

Over 630 People Committed to DNDi's Vision

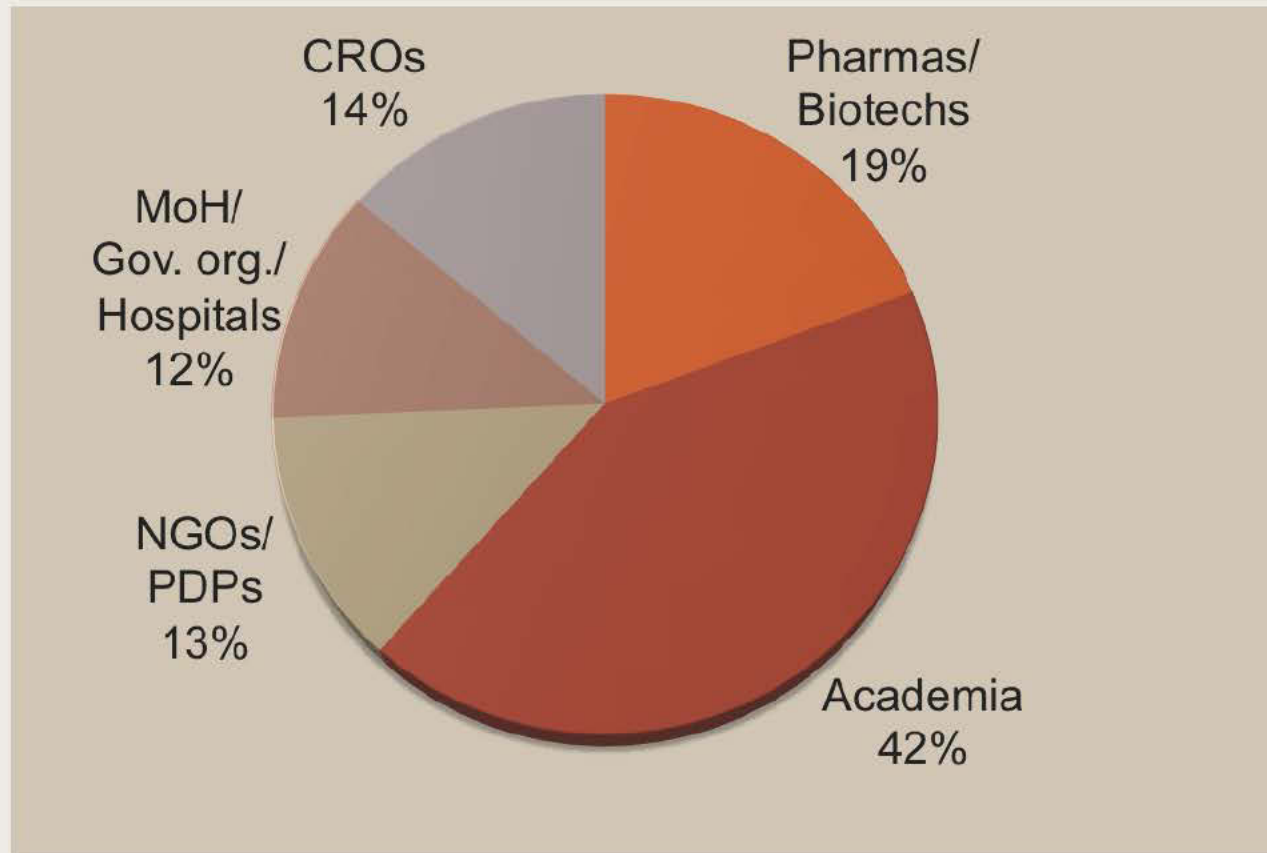




# A Global Network to Leverage Resources

More Than 100 R&D Partners

- Balance of public and private partnerships worldwide



# 30 January 2012, London: 'Uniting to Combat NTDs' A Turning Point in the NTD Landscape

Global actors form a coalition to support WHO's 2020 NTD Roadmap:

- ❑ Pharmaceutical companies
- ❑ World Bank
- ❑ Donor Countries (UK, USA, UAE)
- ❑ BMGF and other private donors (Mundo Sano, Brazil)
- ❑ Endemic country MoHs
- ❑ DNDi



The outcome for DNDi?

-New, renewed, or expanded commitments from 12 major pharmaceutical companies.

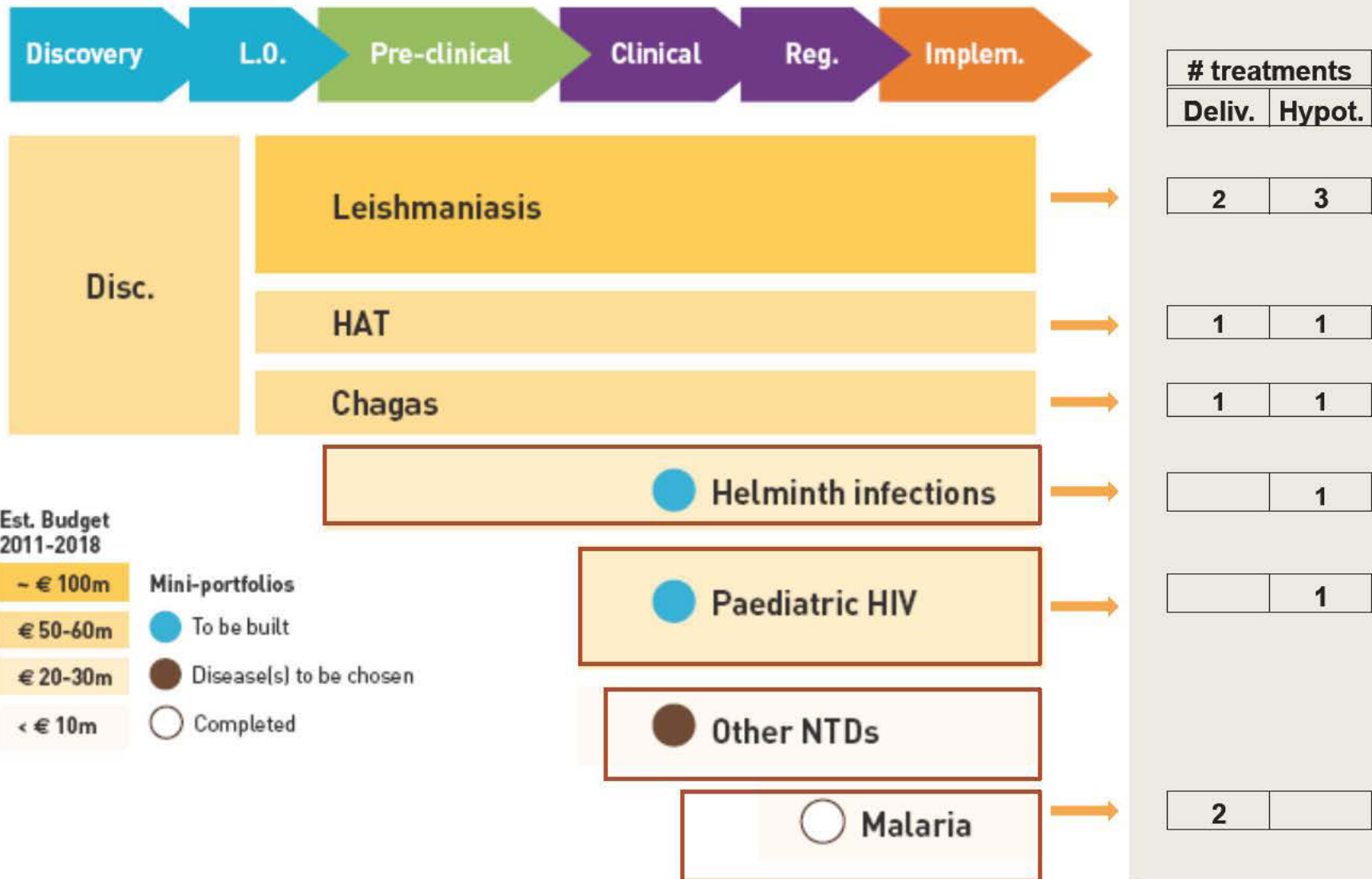
-Greatest ever access to compound libraries for DNDi.



# Scope of Disease & Level of Investment

€ 400M for 2003-2018

=> 11 to 13 Treatments

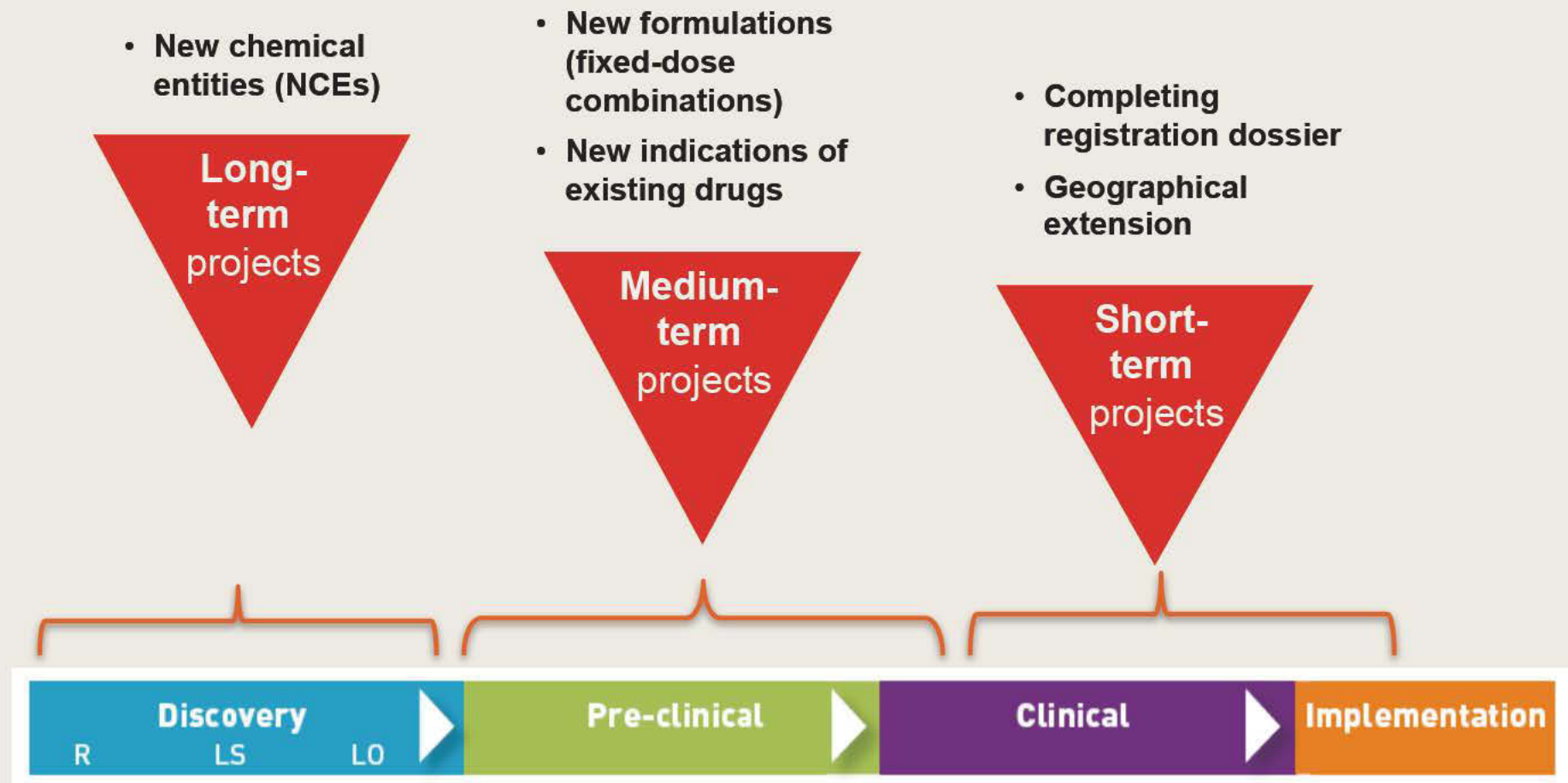


# DNDi's Portfolio

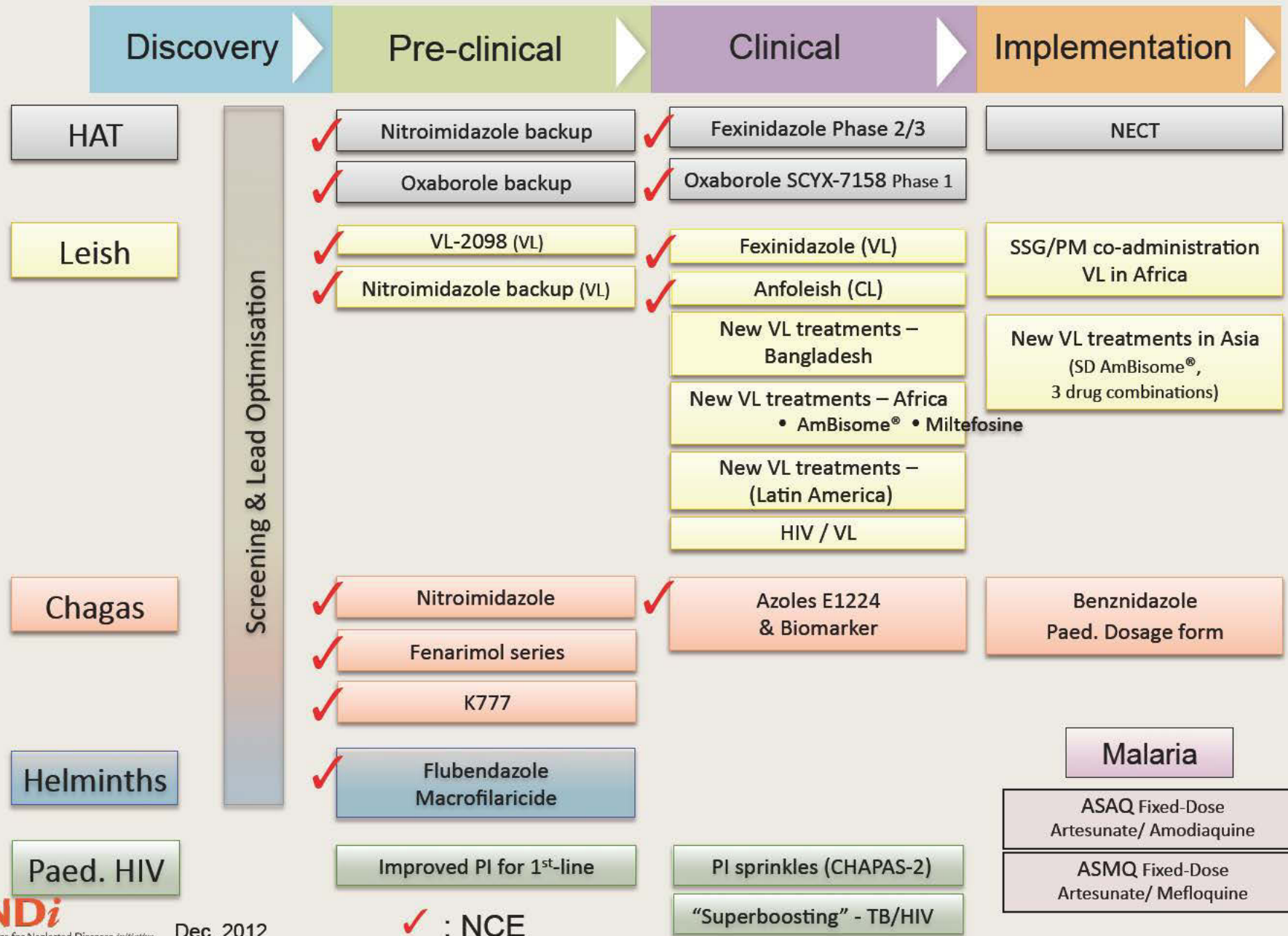


# DNDi Portfolio-Building Model:

Address Immediate Patient Needs & Deliver Innovative Medicines

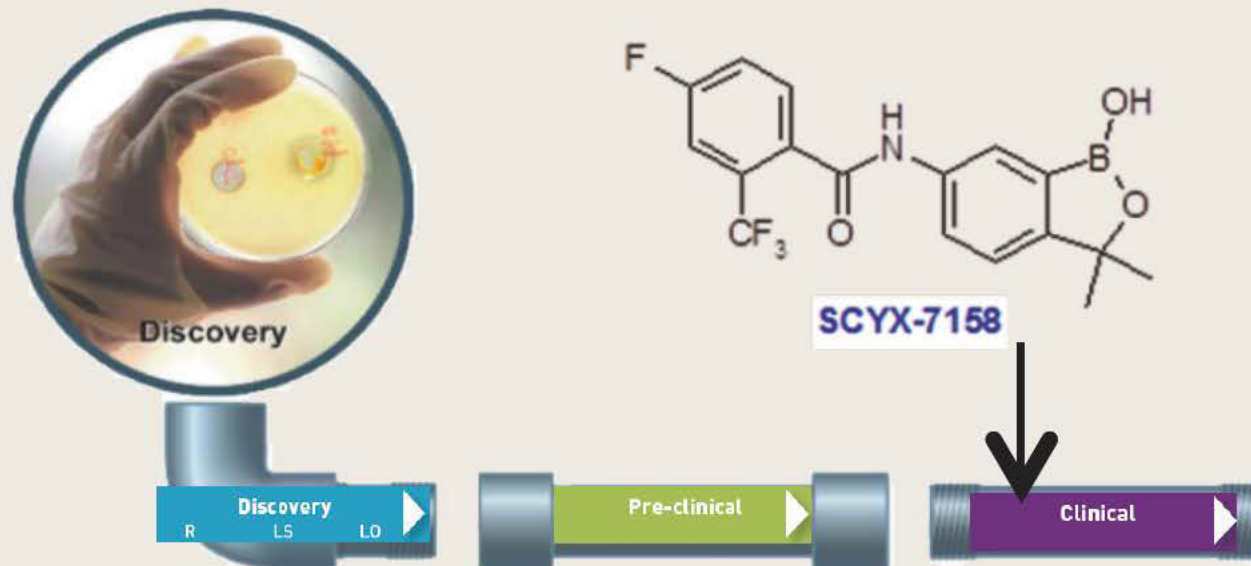


# DNDi Portfolio: A Mix of Existing Drugs & NCEs



# Oxaboroles SCYX-7158 for HAT

## From Lead Optimization to Clinical Candidate



Potential to be oral,  
effective against  
both stages 1 and 2

Key partners:

Scynexis, Anacor, Pace University,

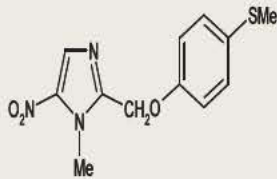
Sandler Center UCSF, Swiss TPH

- Identified as hits against *T. brucei* at Sandler Center, showed activity in animal models of HAT
- Innovative US partnership with 2 biotechs and 1 university
- First candidate issued from DNDi Lead Opt. Programme
- Start of Phase I in March 2012

# Fexinidazole

Phase I Clinical Study Completed and Phase II Started in DRC

Objective: Drug candidate to become an oral, short course treatment for stage 1+ 2 sleeping sickness treatment, caused by either *T.b. gambiense* or *T.b. rhodesiense*




- ❑ Preclinical development including ADME-PK, GLP-toxicology and safety pharmacology
- ❑ Phase I clinical trials in Paris - completed
- ❑ Agreement to co-develop with Sanofi
- ❑ Phase II started with Sanofi in DRC and CAR




# 6 New Treatments Developed Since 2007

**ASAQ** 2007  
(Fixed-dose combination of artesunate + amodiaquine)  
**malaria**



**ASMQ** 2008  
(Fixed-dose combination of artesunate + mefloquine)  
**malaria**



**NECT** 2009  
(Nifurtimox-eflornithine combination therapy)  
**sleeping sickness stage 2**




✓ Easy to Use    ✓ Affordable    ✓ Field-Adapted    ✓ Non-Patented

**SSG&PM** 2010  
(Sodium stibogluconate & paromomycin combination therapy)  
**VL**



**NEW VL TREATMENTS IN ASIA** 2011  
(SD AmBisome® / PM+M / A®+M /)  
**VL**



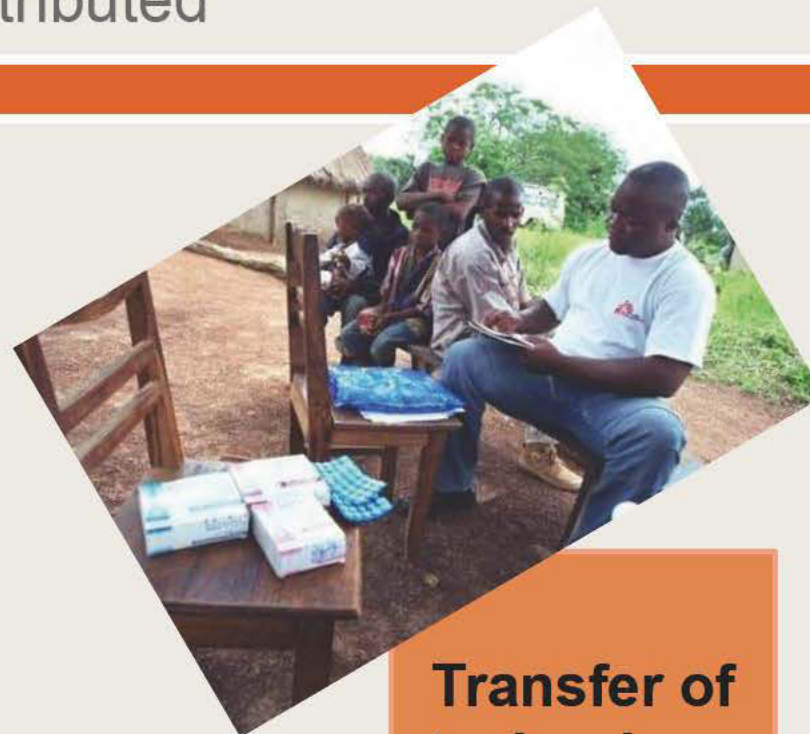
**LAFEPE** 2011  
Benznidazol 12.5 mg  
(Paediatric dosage form of benznidazole)  
**Chagas disease**



# ASAQ Implemented in Partnership with Sanofi

## More than 170M Treatments Distributed

- ❑ Registered in 2007, prequalified by WHO in 2008
- ❑ Registered in 30 sub-Saharan African countries, in India, Bangladesh and Colombia
- ❑ Only FDC with a 3 year shelf life
- ❑ Ambitious risk management plan (Pharmacovigilance)



**Transfer of  
technology  
to  
Zenufa  
Tanzania**





# ASMQ Developed with Farmanguinhos

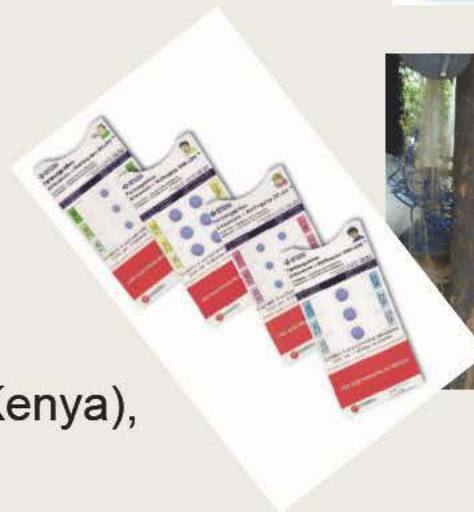
## Small Tablets - Paediatric Strengths & Easy to Use

- ❑ Registered in Brazil in 2008 and implemented by the Brazilian national programme
- ❑ Successful technology transfer to Cipla (India)
  - ❑ WHO pre-qualification (Sept 2012)
  - ❑ ASMQ registered in India (2011), in Malaysia and in Myanmar (2012)
- ❑ Donations to Bolivia and negotiations in Peru and Venezuela
- ❑ Positioning ASMQ
  - ❑ Clinical studies completed: Latin America (Brazil), Asia (India, Myanmar)
  - ❑ Clinical studies ongoing: Africa (Tanzania, Burkina Faso, Kenya), Asia (Malaysia)

**ASMQ FDC**  
as easy to use  
**as 1 2 3!**

**1** dose    **2** products    **3** days

One single daily dose of 1 or 2 tablets of two highly effective combined products for three days of affordable medicine



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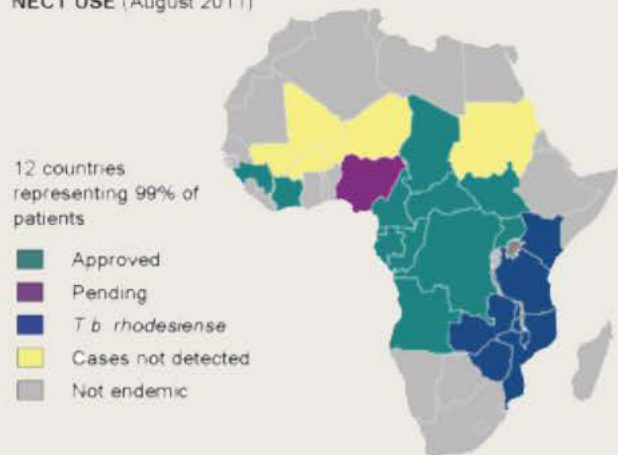
# NECT, an Improved Therapy Option for HAT Implemented in 12 Countries (99% of reported cases)

Nifurtimox-eflornithine combination therapy

- ❑ A simplified, safe & effective treatment for stage 2 HAT
- ❑ WHO Essential Medicines List (2009)
- ❑ > 60% of stage 2 HAT patients treated with NECT in 2010
- ❑ ↘ melarsoprol use (36% to 12%)



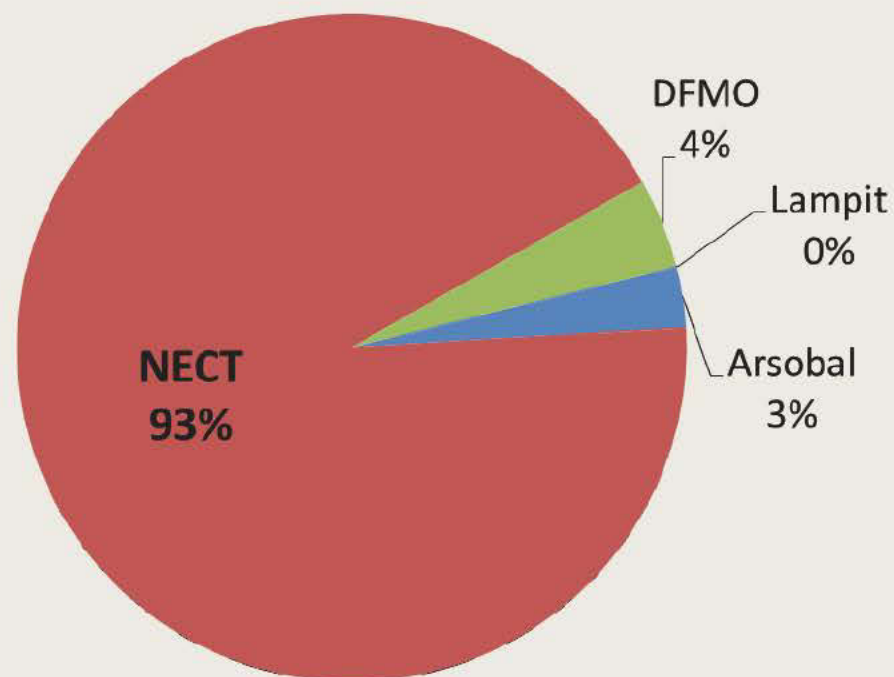
NECT USE (August 2011)





# HAT Treatments in 2011 in DRC

## Treatments for stage 2 HAT



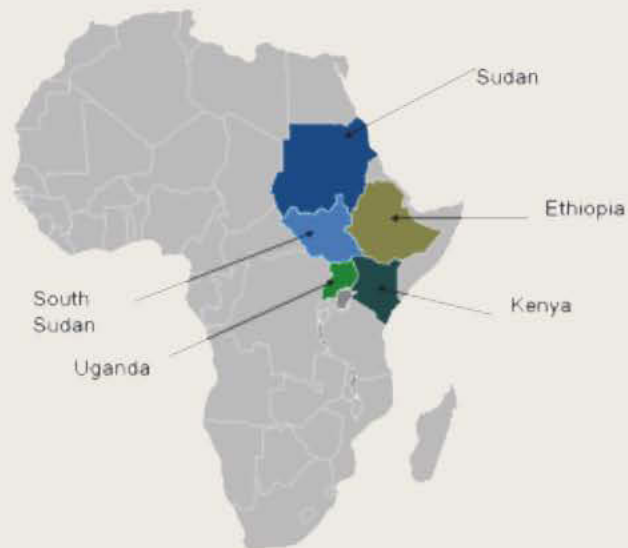
# treatments 2011

ARSOBAL	NECT	DFMO	LAMPIT
37	1'171	55	0

# SSG&PM for Visceral Leishmaniasis in East Africa

Recommended by WHO in 2010

- ❑ Multi-centre study started in 2004
- ❑ SSG&PM used in Sudan in 2010
  - ❑ approx. 10 000 patients treated in South Sudan
- ❑ Pharmacovigilance studies in 3 countries: Sudan, Uganda, and Kenya (end 2011)



# Visceral Leishmaniasis in Asia

## Implementation of New Treatment Modalities

- ❑ Single Dose AmBisome® and 3 VL combination therapies
- ❑ Consortium coordinated by DNDi including TDR & OWH, in collaboration with MSF, NCPs, Bihar State Health Society, and ICMR
- ❑ Focus on Pharmacovigilance and effectiveness
- ❑ 10,000 patients involved (2011-2014)



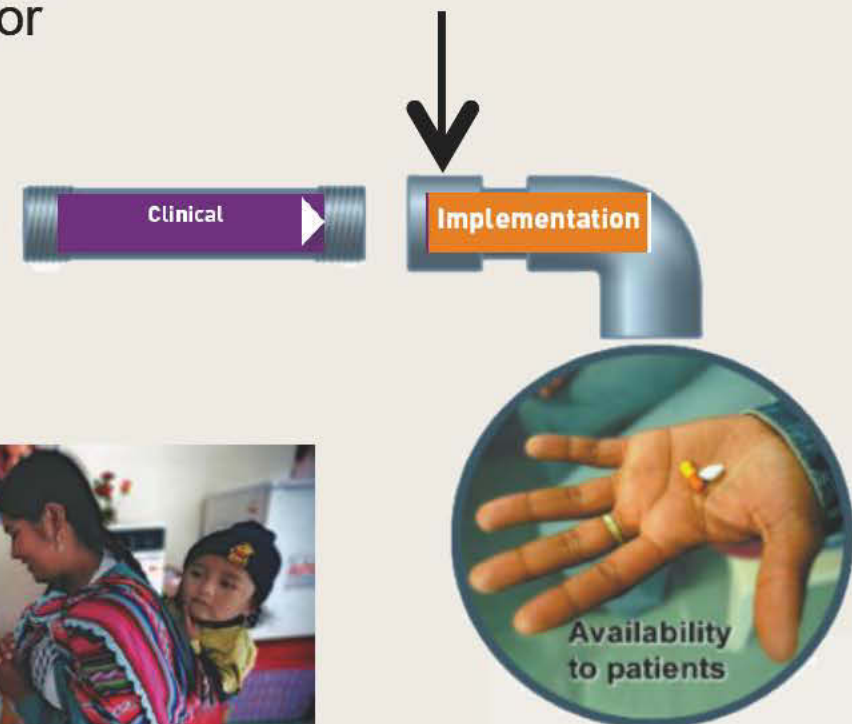


# Paediatric Dosage Form of Benznidazole

## Successful Collaboration with LAFEPE

- ❑ No adapted treatment for children
  - ❑ 100 mg tablet fractionated or macerated for administration
  - ❑ High risk of delivering improper dosages
- ❑ Objective: An affordable, age-adapted, easy to use, paediatric formulation for Chagas disease (12.5 mg tablets for <20 kg children)
- ❑ DNDi-LAFEPE agreement in 2008 to develop paediatric formulation
- ❑ Registered in Brazil (Dec. 2011)

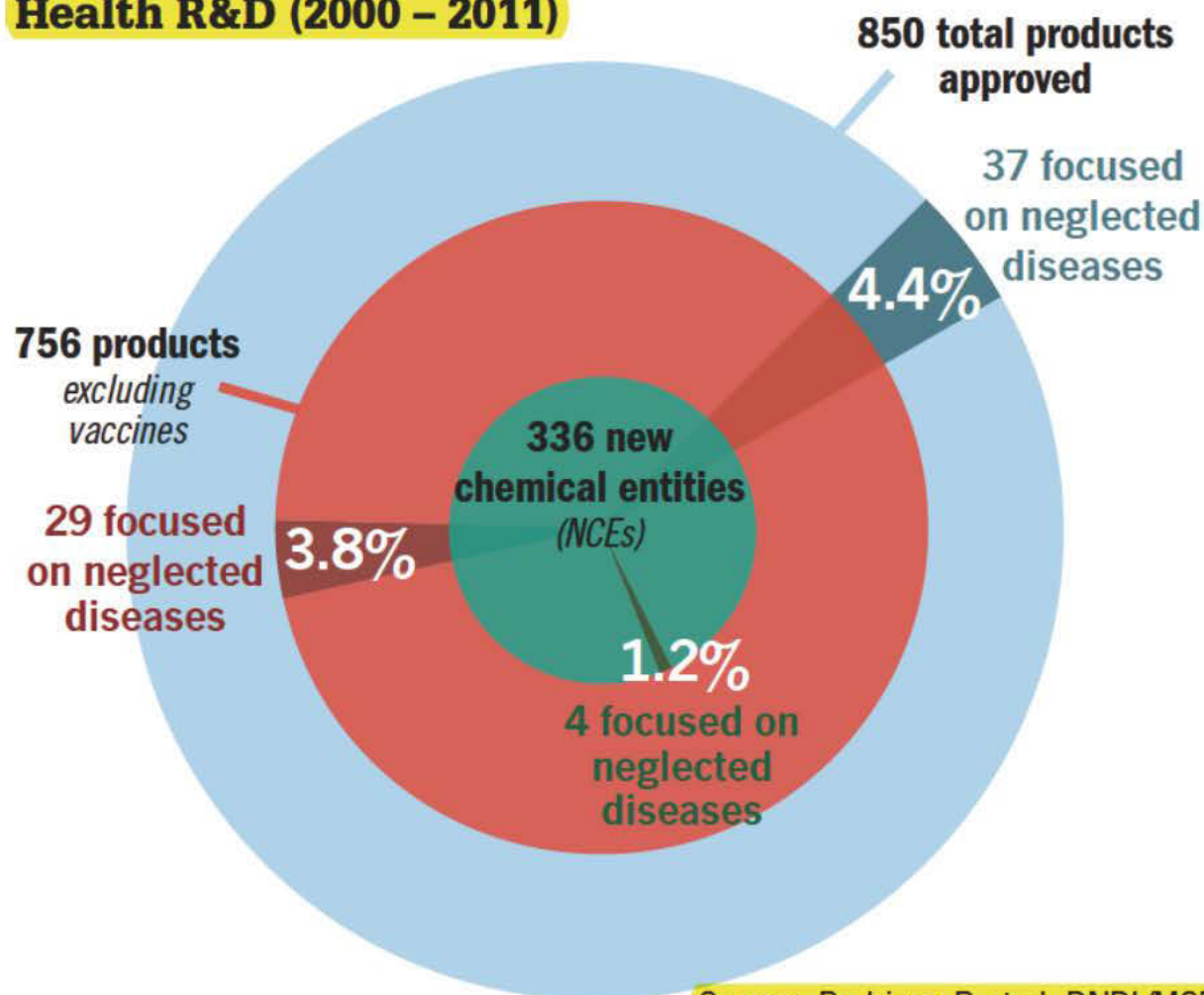
Paediatric  
Dosage Form  
of Benznidazole





# Today, More Robust Pipeline but Imbalance Remains

## Health R&D (2000 – 2011)



Source: Pedrique B et al, DNDI/MSF forthcoming publication, 2013'

From 2000-2011

-29 of 756 new drugs for neglected diseases (3.8%) whereas the diseases represent 10.5% of global burden

-As per Dec. 2011, only 1.4% clinical trials (of nearly 150,000 trials) focus on neglected diseases – and very few for NCEs

Trend

-Coming years, an average of 4.7 new products (exc. Vaccines) compared to 2.4 products from 2000 to 2011

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# Challenges

# Main Challenges for Sustainable R&D for Neglected Patients

IP & Open  
Innovation  
Platforms

Overcoming  
Regulatory  
Barriers

Sustainable  
Financing &  
New  
Incentives  
for R&D

# IP & Open Innovation Practices

- ❑ Access to compounds, know-how and knowledge
- ❑ Increase access to innovation
- ❑ Ensure equitable access to all patients & affordable treatment



=> Medicines Patent Pool,  
WIPO Re:Search, open &  
equitable licensing.....

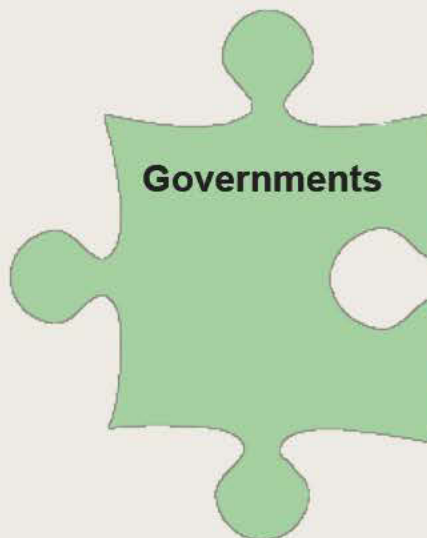
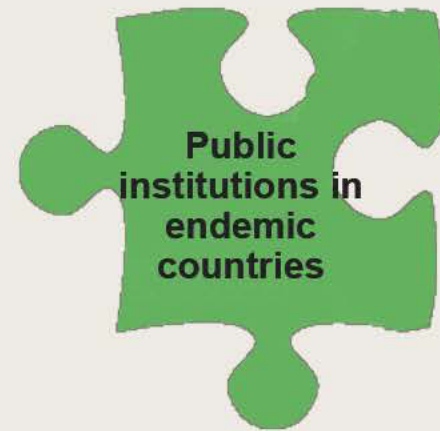


# Overcoming Regulatory Barriers

- ❑ New Chemical Entities (NCEs): now being developed to respond to specific needs in endemic countries
- ❑ Need to strengthen regulatory agencies in endemic regions (regional collaboration)
- ❑ Regulatory assessment of new treatments through collaboration of endemic countries, WHO and stringent regulatory agencies

# Innovative Mechanisms to Sustain Innovation for Neglected Diseases

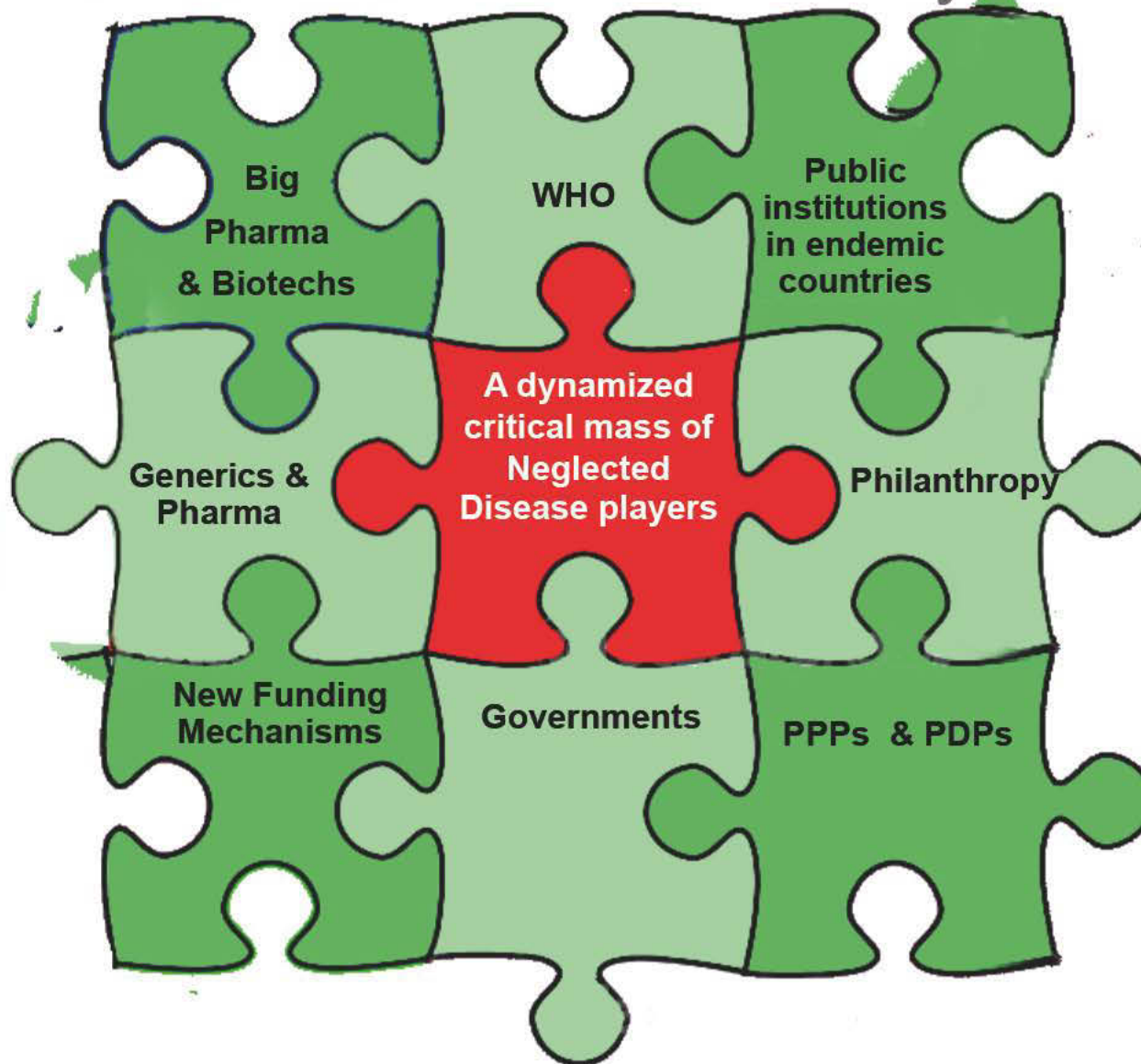
- ❑ Sustainable Funding to Ensure Predictability & Secure Development and Access
- ❑ New Incentives to Maintain and Develop Pipelines with New Compounds



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# A Global Framework to Secure Coordination and Sustainability





# Thank You to All Our Partners & Donors



BEST  
SCIENCE  
FOR THE MOST  
NEGLECTED



BILL & MELINDA  
GATES foundation



Ministry of Foreign Affairs



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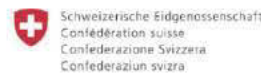


Federal Ministry  
of Education  
and Research

by



wellcome trust



via the 4<sup>th</sup> Sector Health  
Project implemented by Abt  
Associates, Inc.



medicor foundation



THE STARR FOUNDATION



WELLSPRING ADVISORS



[www.dndi.org](http://www.dndi.org)

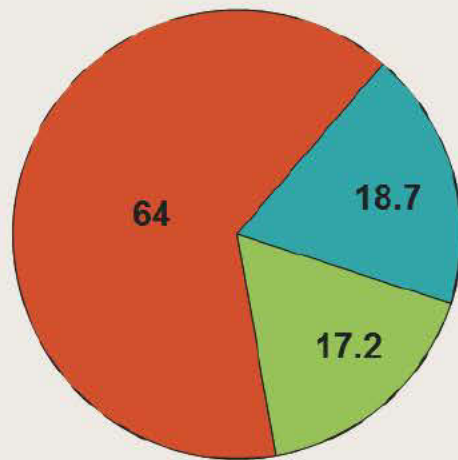
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# Additional slides

# DNDi's Funding Strategy

# Global R&D Funding for Neglected Diseases

## Neglected Diseases \$3.045 billion (US)



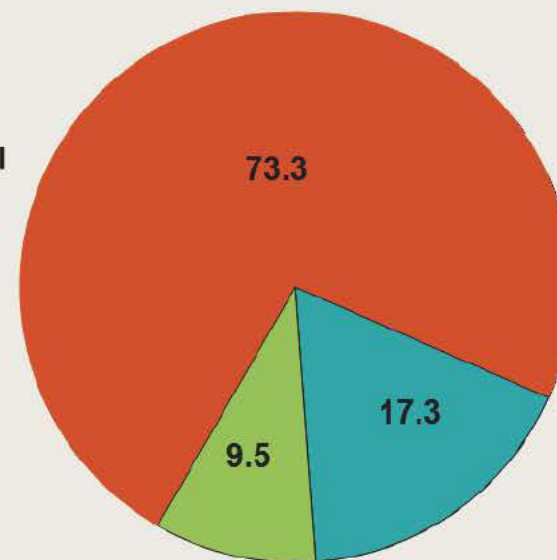
Public (LMIC\* and HIC\*\* governments) - 95% from HIC gov.)

Philanthropic

Private (multi-pharmas & small pharmas and biotechs)

## Kinetoplastids \$131.7 million (US)

=> 4.3% of the total!



Public

Philanthropic

Private

Source: Moran et al., G-Finder report 2012, Dec. 2012 **Data 2011**

\*LMIC= Low- and Middle-Income Countries

\*\*HIC= High-Income Countries



# Our Donors

## Private Donors

- Médecins Sans Frontières (€49M)
- Bill & Melinda Gates Foundation (€43.72M)
- Wellcome Trust (€5M)
- Other Private Foundations (incl. Starr and Medicor, €1.7M)

## Public Donors

- United Kingdom – DFID (€40M)
- Netherlands – DGIS (€17M)
- Spain – AECID (€12M)
- France – AFD & MAEE (€9.3M)
- Germany – KFW & GTZ (€9M)
- Switzerland – SDC & Geneva (€ 4.2M)
- USA – NIH/NIAID (€2M)
- European Union – FP5,6,7& EDCTP (€4.2M)
- The Global Fund – AMFm (€0.5M)



# Public Leadership is Still Needed for Neglected Patients

DNDi campaigns

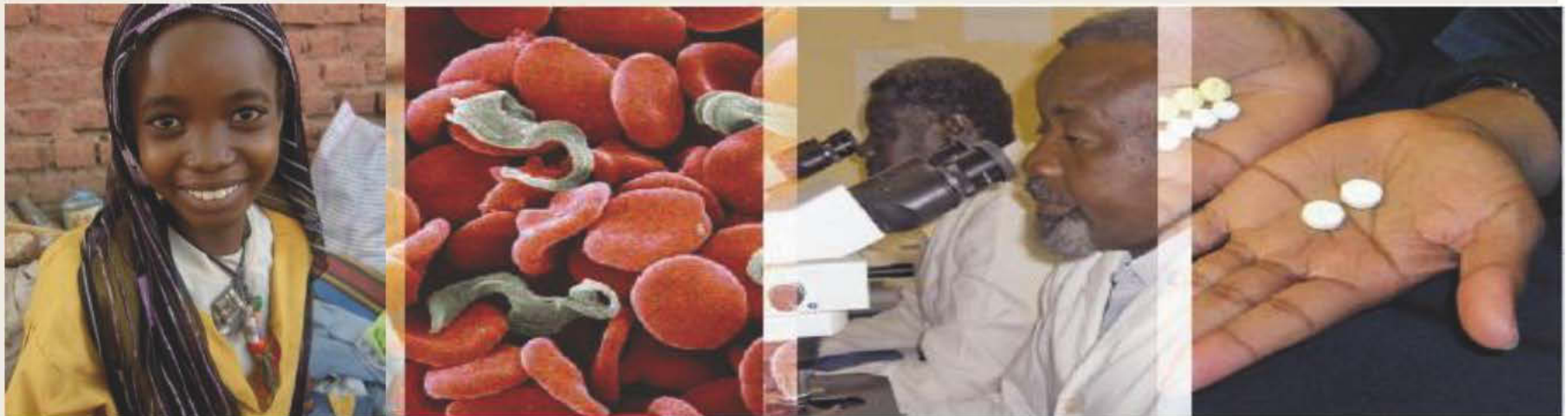
**2005:** Global  
Call for Research

**2009:** Call for  
Innovation & Access  
for Chagas Disease

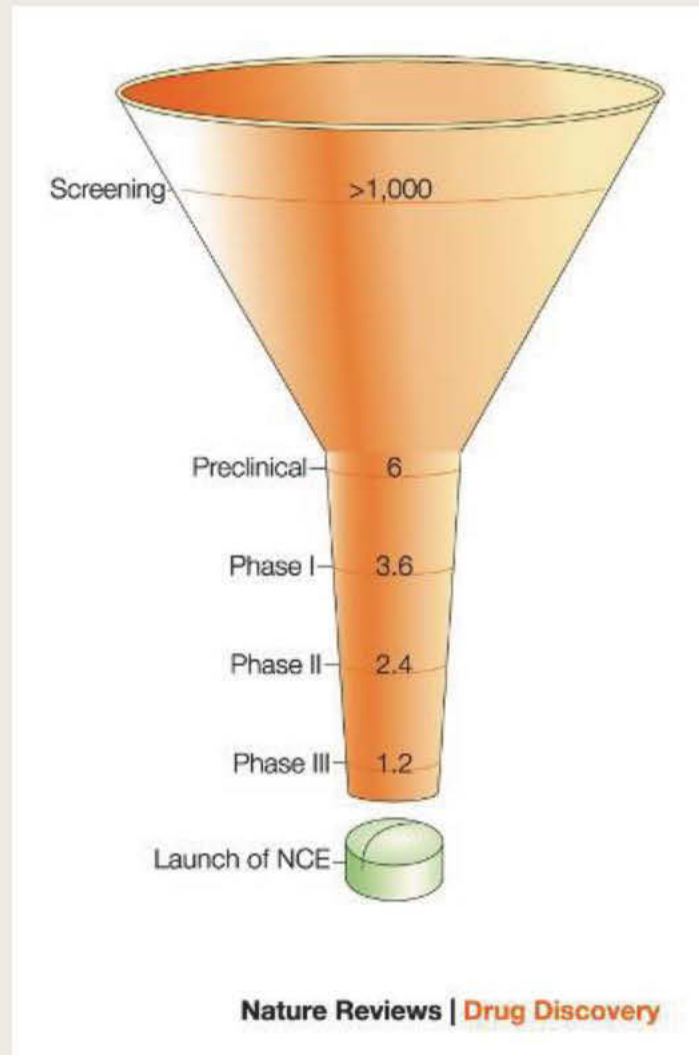


# 9-Year Results

- ❑ **2 new malaria treatments**
- ❑ **1 new sleeping sickness combination**
- ❑ **1 new visceral leishmaniasis combination for Africa**
- ❑ **1 set of VL treatment modalities for Asia**
- ❑ **1 Chagas paediatric dosage form**
- ❑ **Largest pipeline ever for the kinetoplastid diseases**
- ❑ **Clinical research platforms in Africa**
- ❑ **€218M of €400M needed raised**
- ❑ **On track to deliver new treatments per business plan**



# Risks in R&D of Pharmaceutical Drugs



(Preziosi, P. 2004, Nature Reviews in Drug Discovery 3, 521-526)

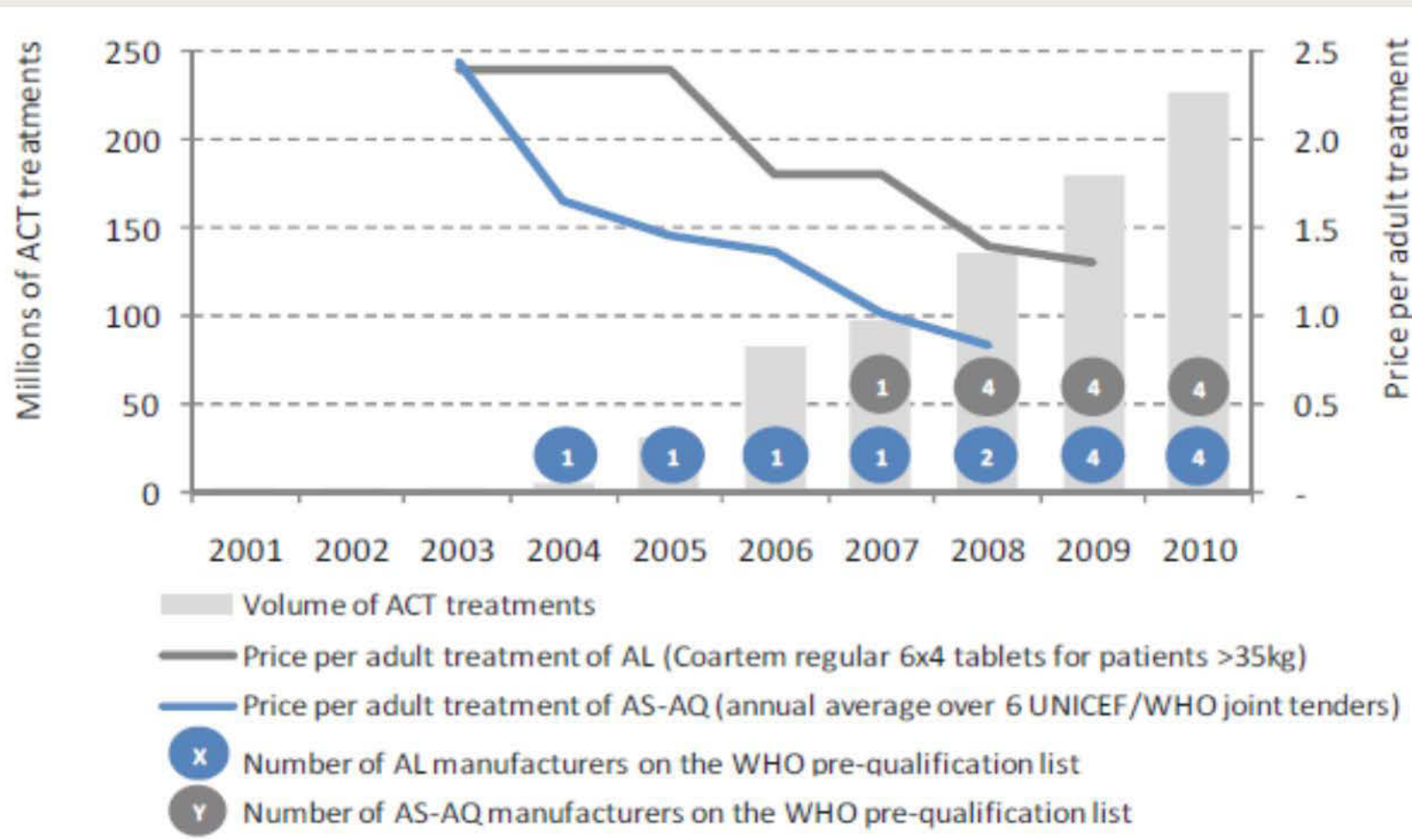


# The PDP Model

- Non-profit organizations, created around a decade ago
- Advance global health goals by accelerating the development of products that may not otherwise be developed
- Strategic collaborations with public and private sectors from developed and developing countries
- Develop research networks
- Capacity-building in developing countries

=> This innovative organizational model proves to be successful

# ACTs: Competition Down Prices



Source: The Global Fund 2011

# Artesunate-Amodiaquine Fixed Dose Combination: FACT Partnership

Industrial Partners:  
Sanofi-Aventis



DNDi/TDR:  
scientific coordination  
& project management



Funding: EU's INCODEV,  
France, Netherlands,  
Spain, UK, MSF



# Artesunate-Mefloquine Fixed Dose Combination: FACT Partnership

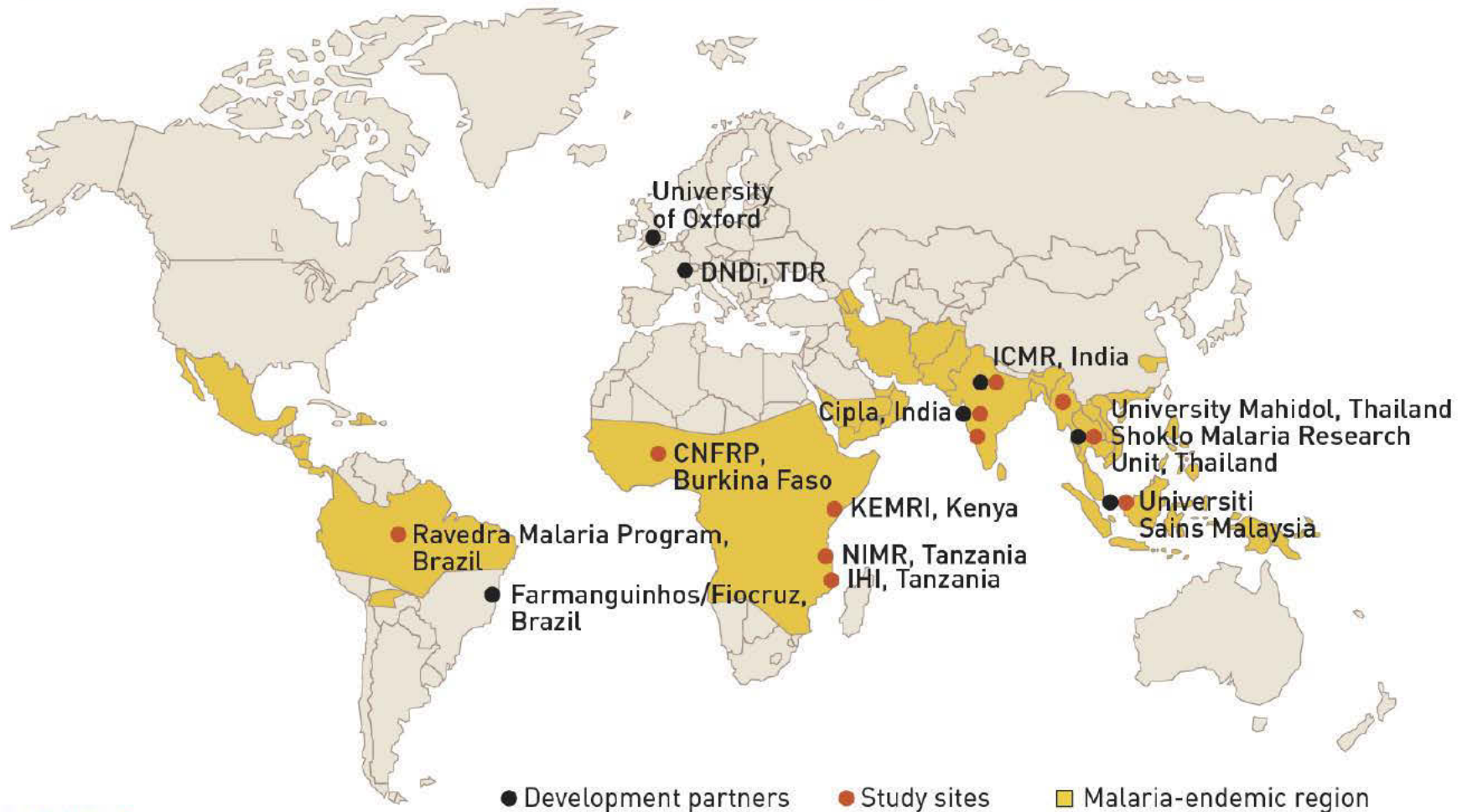
Industrial Partners:  
Farmanguinhos  
Cipla



DNDi/TDR:  
scientific coordination  
& project management



Funding: EU's INCODEV,  
France, Netherlands,  
Spain, UK, MSF





# Simplified 3-Day Dose Regimen of ASAQ

## NEW Fixed-dose ASAQ Artesunate/amodiaquine

3 dosage strengths available

Infants (4.5-8 kg)



AS: 25 mg  
AQ: 67.5 mg

Young  
Children (8-17 kg)



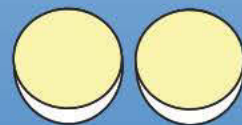
AS: 50 mg  
AQ: 135 mg

Children (17-35 kg)



AS: 100 mg  
AQ: 270 mg

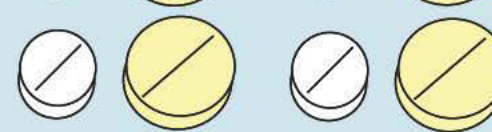
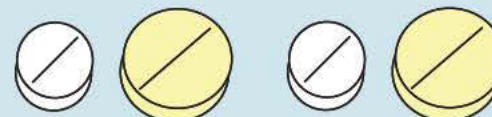
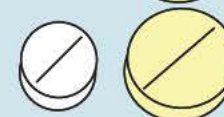
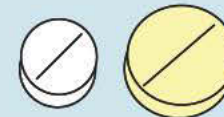
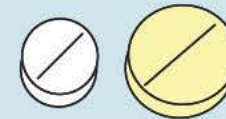
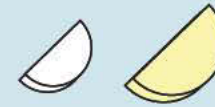
Adults ( $\geq 36$  kg)



AS: 100 mg  
AQ: 270 mg

## Co-blistered non-fixed AS+AQ Artesunate-amodiaquine

AS: 50 mg; AQ 135 mg



# ASMQ

## Small Tablets-Paediatric Strengths & Easy to use

**ASMQ FDC**  
as easy to use  
**as 1 2 3!**

**1** dose    **2** products    **3** days

One single daily dose of 1 or 2 tablets of two highly effective combined products for three days of affordable medicine

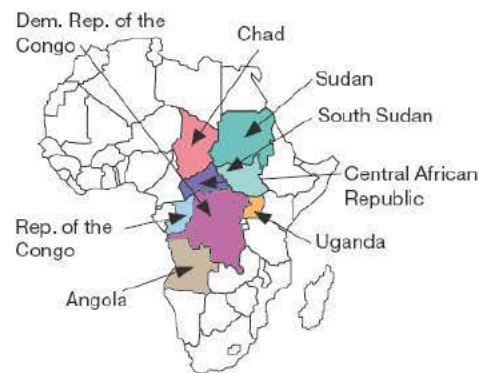


	New FACT ASMQ	NON-FIXED AS and MQ
<b>INFANT DOSE &lt; 1 YEAR</b>	AS: 100mg MQ(salt): 220mg	AS: 50mg MQ(salt): 250mg
	Once a day	Once a day
Day 1		
Day 2		
Day 3		

# Utilizing and Strengthening Research Capacities in Disease-Endemic Countries



VL



HAT



CHAGAS

## Major Role of Regional Disease Platforms:

- ❑ Defining patients' needs and target product profile (TPP)
- ❑ Strengthening local capacities
- ❑ Conducting clinical trials (Phase II/III studies)
- ❑ Facilitating registration
- ❑ Accelerating implementation of new treatments (Phase IV & pharmacovigilance studies)



# Challenge to Conduct Clinical Trials in Very Difficult Settings



- ❑ Access to Sites
- ❑ Status of Infrastructure
- ❑ Staff Limitations





## DR CONGO

**Katanda HAT center**



**Lab before rehabilitation**



**HAT ward**



**New lab**



# ETHIOPIA

**Gondar, Clinical Trial Center  
before rehabilitation**



**Arba Minch,  
before rehabilitation**



**Gondar New Site**



**Arba Minch new lab**

