Challenging Issues for Research and Development in Neglected Diseases

Isabela Ribeiro

June 28, 2011

DNDi
Drugs for Neglected Diseases *initiative*

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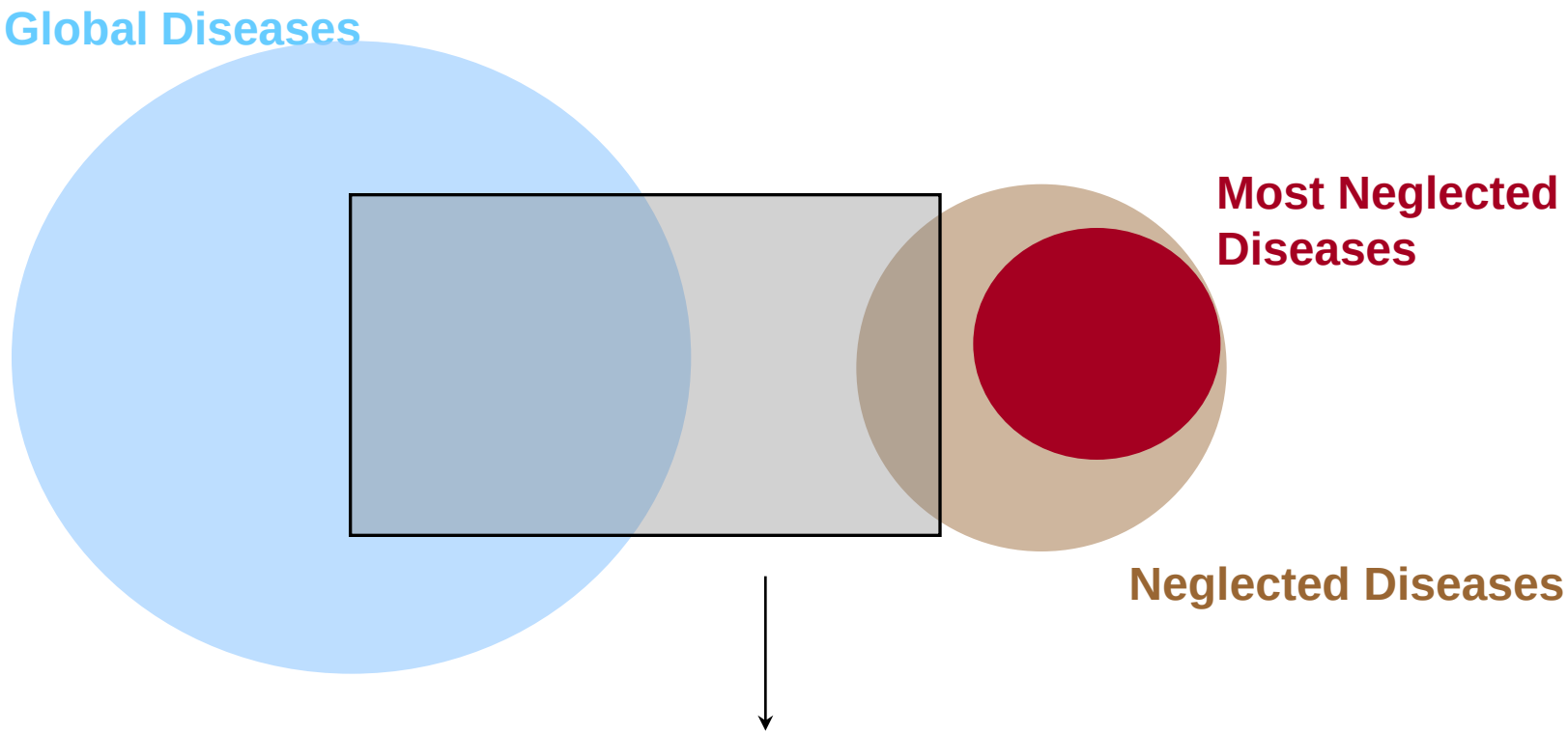
Neglected Diseases:
- primarily affect developing countries
- lie outside the world market



*Source: IMS Health, 20.04.2010

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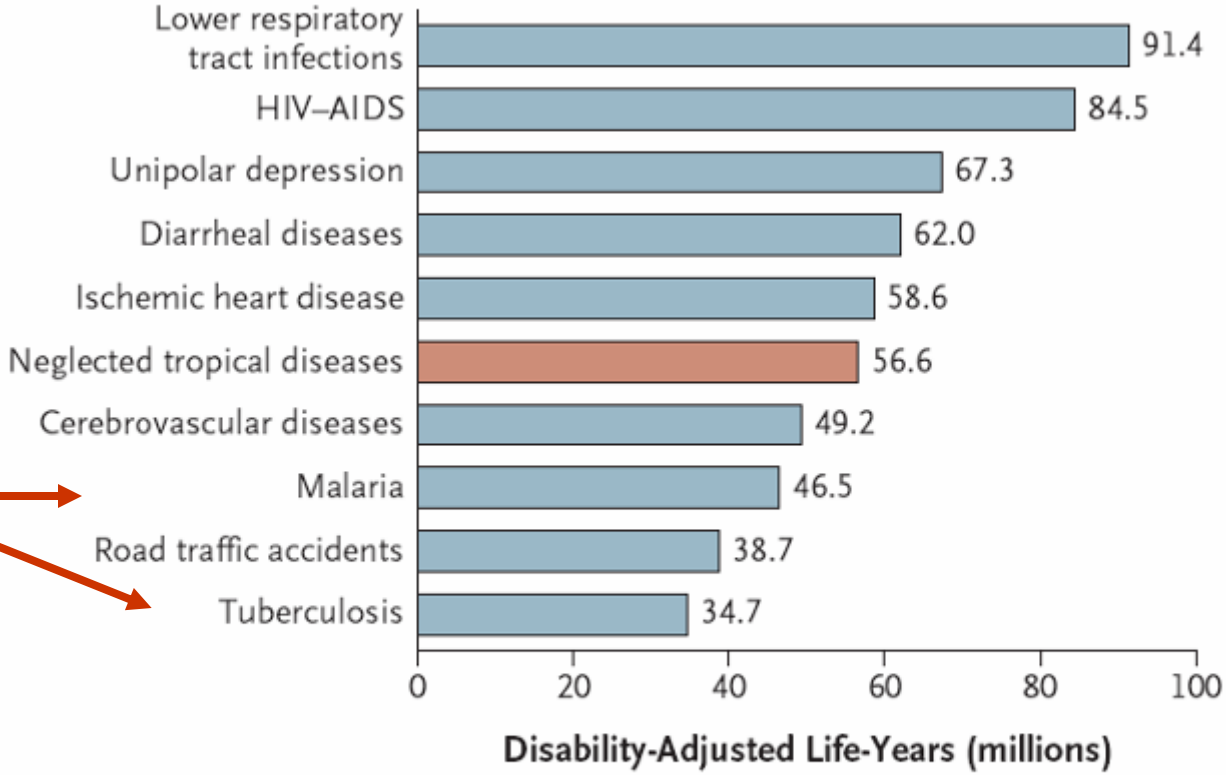
CURRENT CONCEPTS

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.



~ 139 Millions

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

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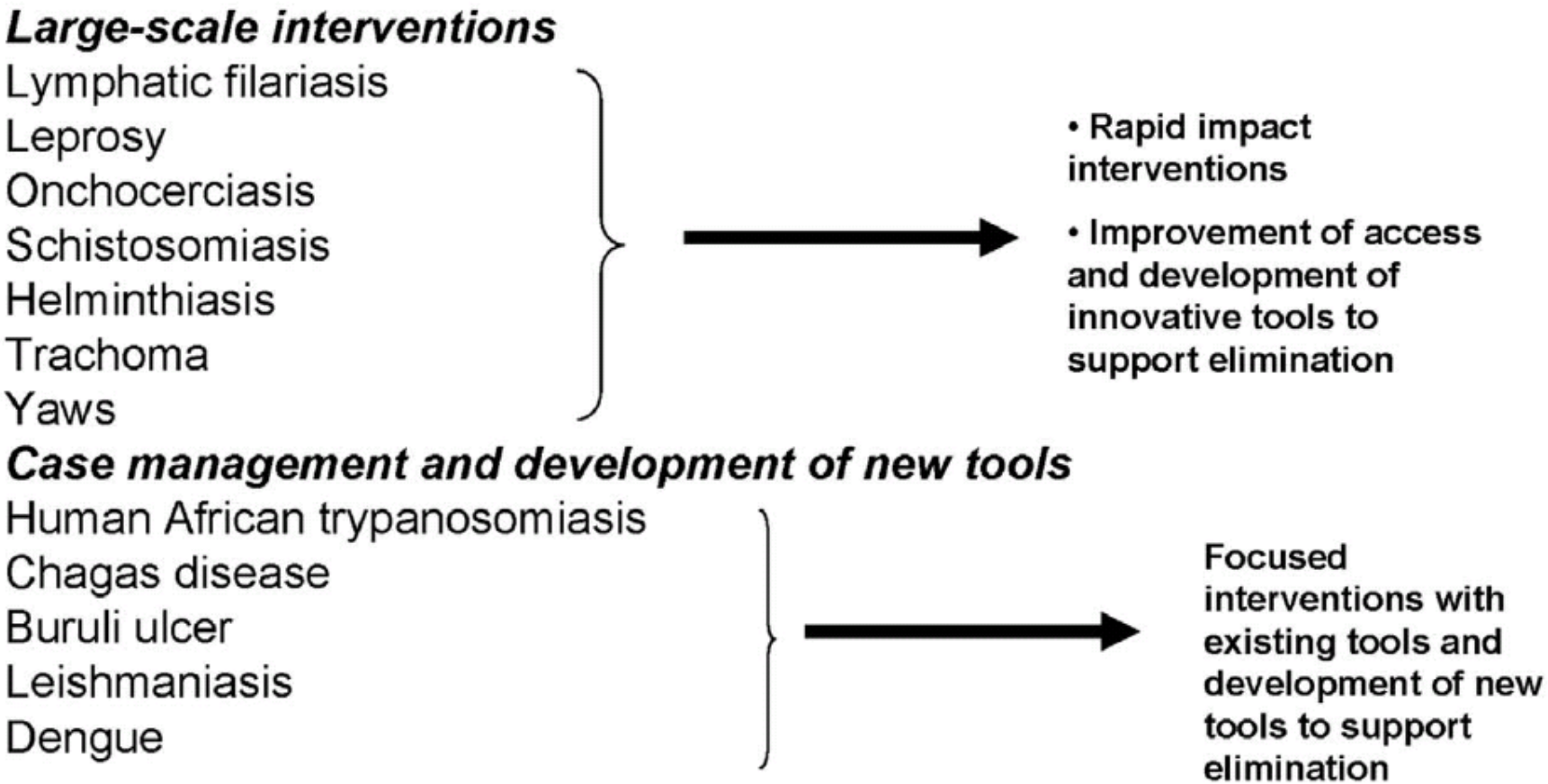
What's Needed to Combat NTDs?



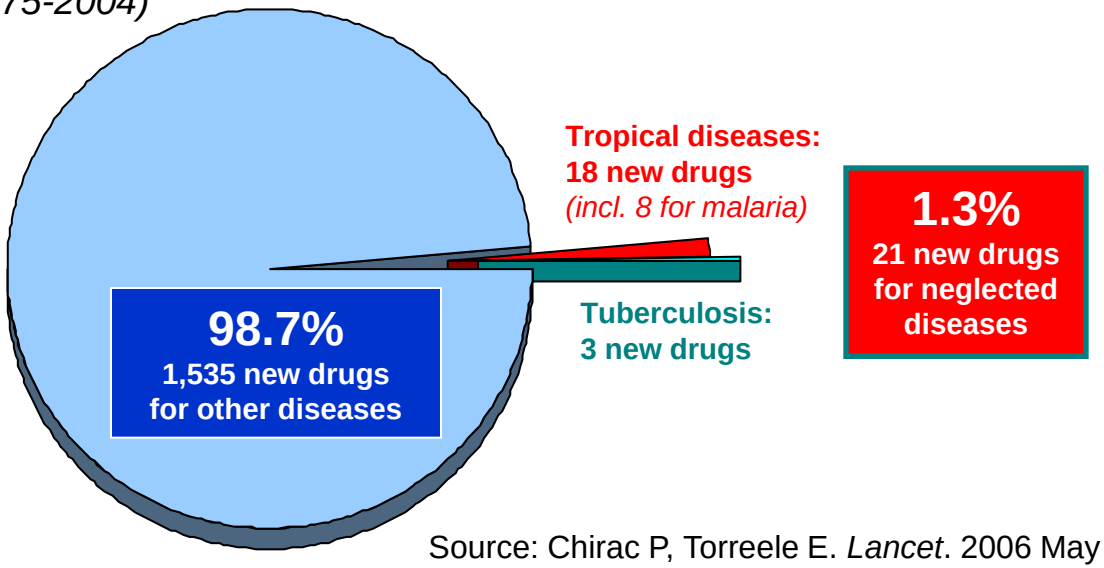
Hotez P, Pecoul B. "Manifesto" for Advancing the Control and Elimination of Neglected Tropical Diseases, *PLoS NTDs*, May 2010, Vol 4, 5, e718

15 years ago – a fatal imbalance and virtual standstill

Tropical diseases (including malaria) and tuberculosis account for:

- **12% of the global disease burden**
- **Only 1.3% of new drugs developed**

(1975-2004)



Source: Chirac P, Torreele E. *Lancet*. 2006 May 12; 1560-1561.

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

AERAS

iAVWH

Meningitis Vaccine Project

The CD4 INITIATIVE

INTERNATIONAL VACCINE INSTITUTE

mvi PATH

DNDi

IVCC COMBATING INSECT BORNE DISEASE

PATH Vaccine Development Program

FIND

INTERNATIONAL PARTNERSHIP for MICROBICIDES

PDVI Pediatric DENGUE VACCINE INITIATIVE

iavi

Medicines for Malaria Venture

SABIN VACCINE INSTITUTE HHVI

IDRI Infectious Disease Research Institute

TB ALLIANCE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

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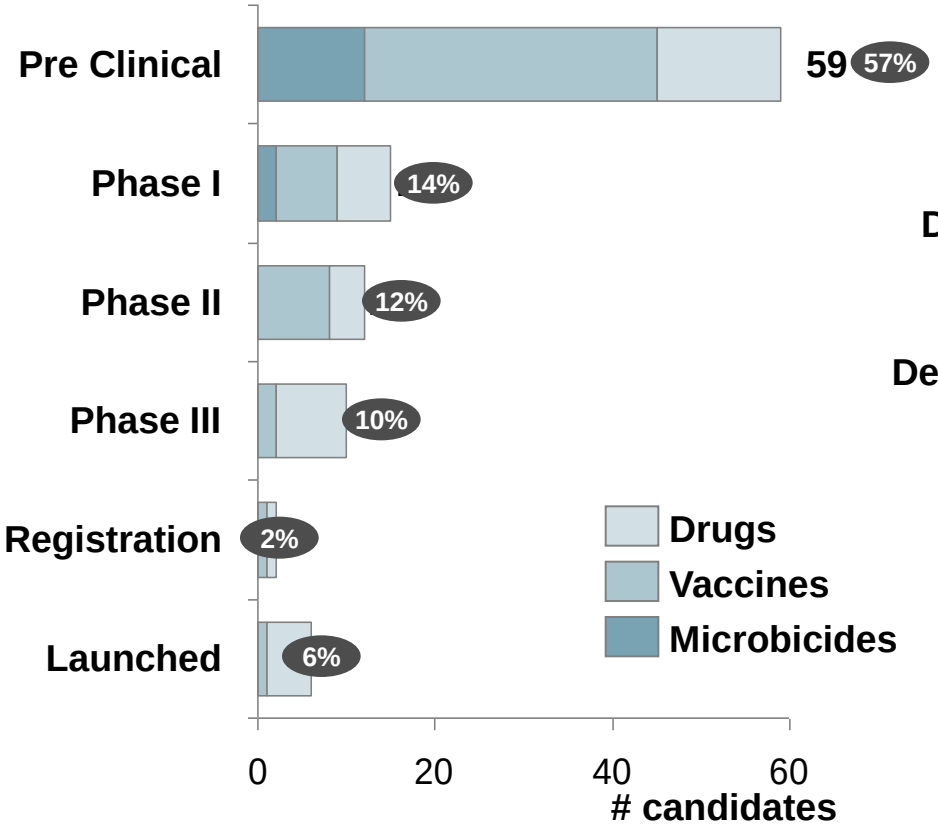
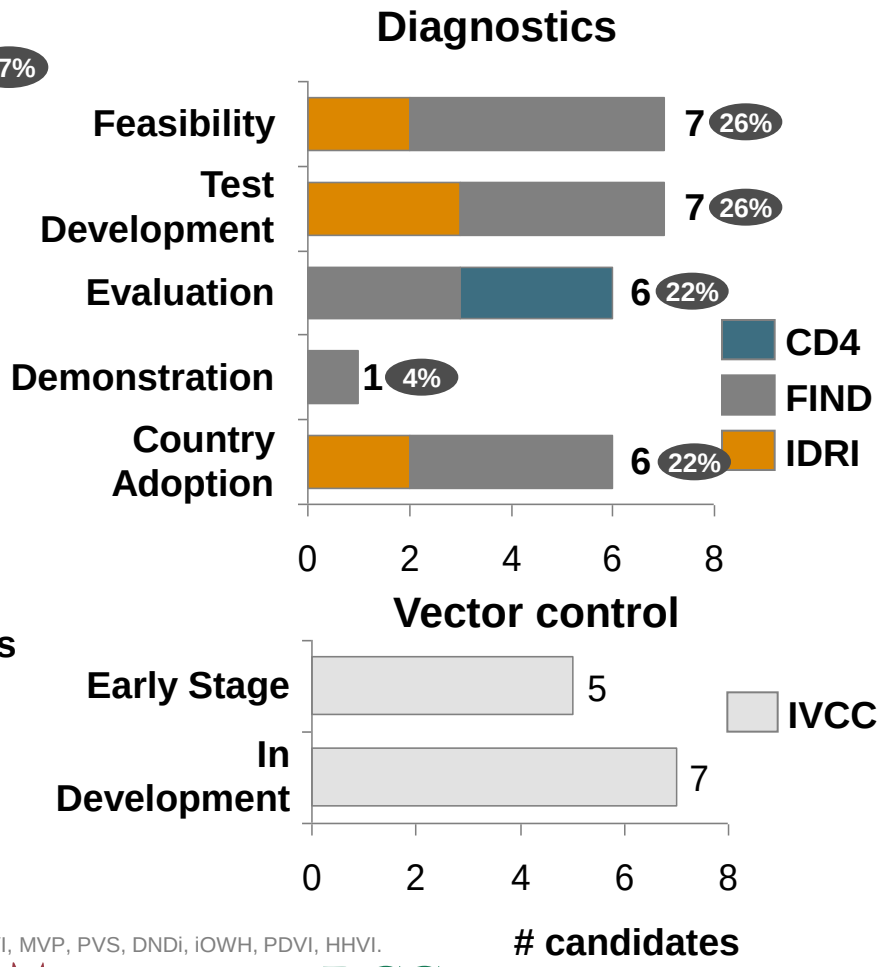
Combined PDP pipeline today includes 143 candidates

104 biopharmaceutical candidates in development...



... and 39 diagnostic & vector control 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

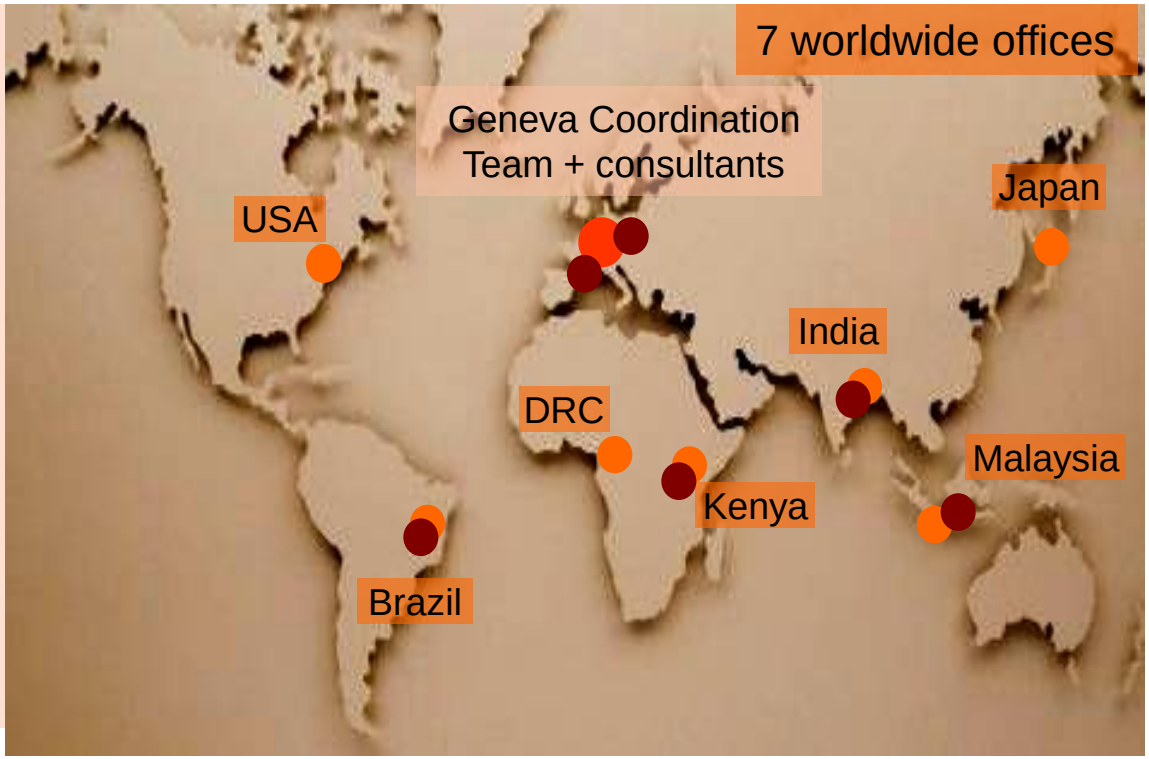
Slides source from: Bill & Melinda Gates foundation & BCG The Boston Consulting Group

DNDi: An innovative R&D model

- Non-profit drug research & development (R&D) organization founded in 2003
- Addressing the needs of the most neglected patients
- Harnessing resources from public institutions, private industry and philanthropic entities

7 Founding Partners

- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation Brazil
- Medecins Sans Frontieres (MSF)
- Institut Pasteur France
- WHO/TDR (permanent observer)



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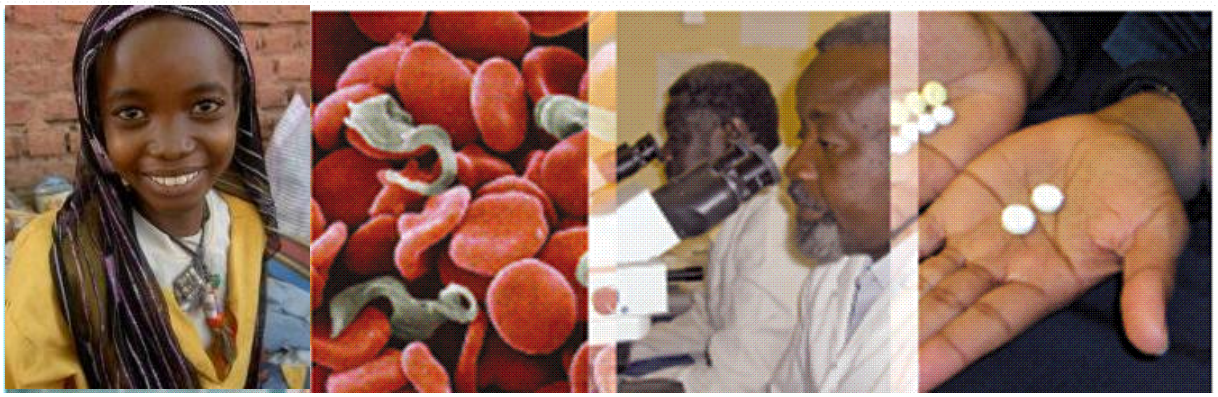
Drugs for Neglected Diseases initiative

Vision

A collaborative, patients' needs-driven, virtual, non-profit drug R&D organisation to develop new treatments against the most neglected communicable diseases

DNDi's Main Objectives

- Deliver **6 - 8 new treatments by 2014** for sleeping sickness, Chagas disease, leishmaniasis and malaria
- Establish a **robust pipeline** for future needs
- Use and strengthen existing **capacity in disease-endemic countries**
- Raise awareness and advocate for increased **public responsibility**



DNDi Portfolio-Building Model

- Existing chemical libraries
- New lead compounds

Long-term projects

- New formulations (fixed-dose combinations)
- New indications of existing drugs

Medium-term projects

- Completing registration dossier
- Geographical extension

Short-term projects

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Project Portfolio – June 2011

Discovery	Pre-clinical	Clinical	Implementation
HAT LO Consortium - *Scynexis* - *Pace Univ.*	Nitroimidazole backup (HAT)	Fexinidazole (HAT)	ASAQ (Malaria) Fixed-Dose Artesunate/ Amodiaquine
VL LO Consortium - *Advinus* - *CDRI*	Oxaborole SCYN7158 (HAT)	New VL treatments – Bangladesh	ASMQ (Malaria) Fixed-Dose Artesunate/ Mefloquine
Chagas LO Consortium - *CDCO* - *Epichem* - *Murdoch Univ.* - *FUOP*	Alternative formulations of Amphotericin B (VL)	New VL treatments – Africa	NECT (Stage 2 HAT) Nifurtimox – Eflornithine Co-administration
Major Collaborators: - Sources for hit and lead compounds: *GSK, Anacor, sanofi aventis, Merck, Pfizer, Novartis (GNF, NITD), TB Alliance,…* - Screening Resources: *Eskitis, Institut Pasteur Korea, Univ. Scynexis, U. Dundee,…* - Reference screening centres: *LSHTM, Swiss Tropical & Public Health, University of Antwerp*	Nitroimidazole (VL)	New VL treatments – Latin America	SSG&PM co-administration VL in Africa
	Drug combination (Chagas)	Benznidazole Paediatric dosage form (Chagas)	New VL treatments in Asia (SD AmBisome®, PM+M / A®+M / PM+ A®)
	K777 (Chagas)	Azoles E1224 & Biomarker (Chagas)	
	Flubendazole Macrofilaricide (Helminth)	Paediatric HIV (exploratory)	
	Exploratory	*Exploratory*	

a robust pipeline

6 to 8 new treatments by 2014

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Available

Five Products Making a Difference

Main Partners

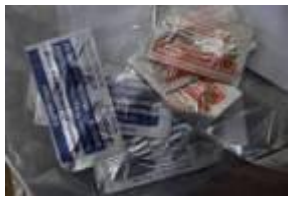
2007

ASAQ *(Malaria)*
Fixed-Dose Artesunate/ Amodiaquine

sanofi-aventis
(France)

2008

ASMQ *(Malaria)*
Fixed-Dose Artesunate/ Mefloquine



Farmanguinhos
(Brazil)
Cipla
(India)

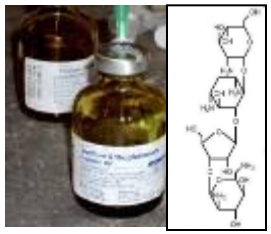
2009

NECT
Nifurtimox - Eflornithine Co-Administration (HAT)

National Control Programs
MSF / Epicentre
Bayer / sanofi-aventis
WHO

2010

Paramomycin + SSG
(VL)



LEAP
National Programs
iOWH

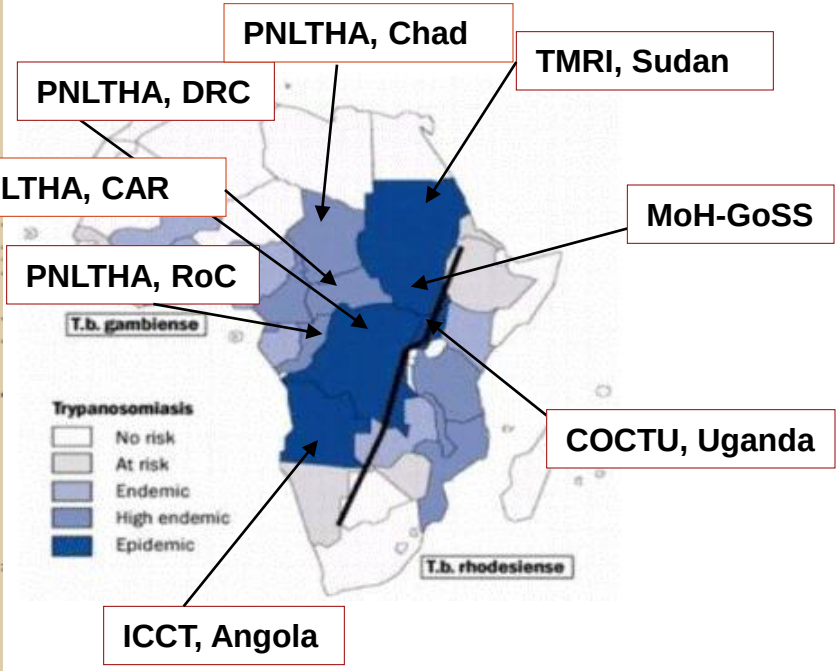
2011

New VL treatments in Asia
(SD AmBisome®, PM+M / A®+M / PM+ A®)

National Programs
ICMR, iOWH, TDR

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

HAT Strengthening Clinical Trial Capacity Platform



Objectives:

- To strengthen clinical trial capacity for sleeping sickness
- To overcome health system challenges for clinical research
- To share information on HAT research progress
- To improve HAT clinical trial methodologies

Partners:

- **National HAT control programmes of most affected endemic countries**
- **DNDi, STI**
- **Research institutes like ITMA, INRB, CDC, KARI-TRC**
- **NGOs like MSF, Epicentre**
- **FIND, WHO**
- **Regional networks - eg. EANETT, PABIN, AMANET**

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HAT

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Challenge to conduct clinical trials in very difficult settings

- Access to Sites
- Status of Infrastructure
- Staff Limitations


TB


GP


JS


Dr. Jannin, WHO

HAT

DR OF CONGO

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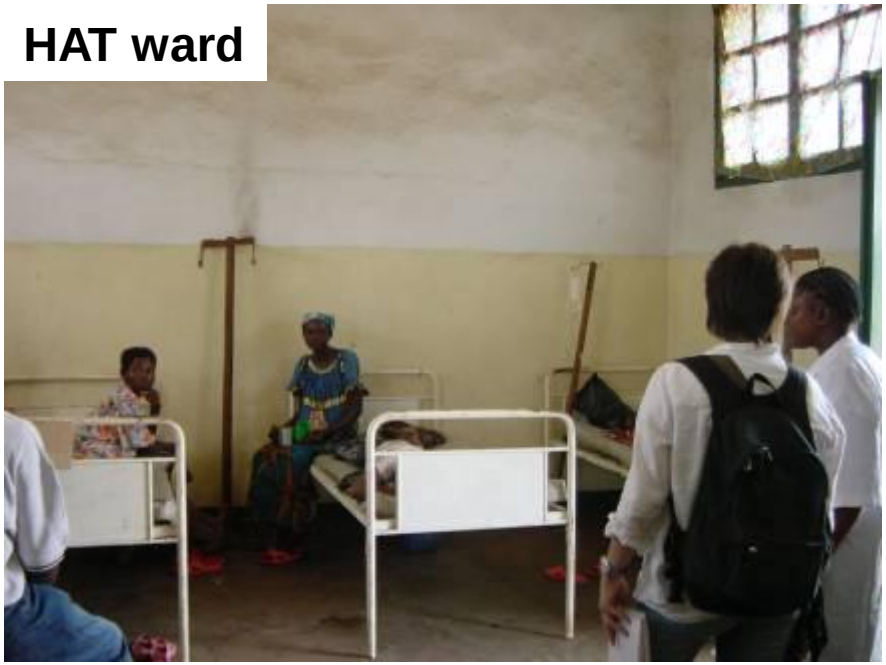
Katanda HAT center

Lab before rehabilitation

HAT ward

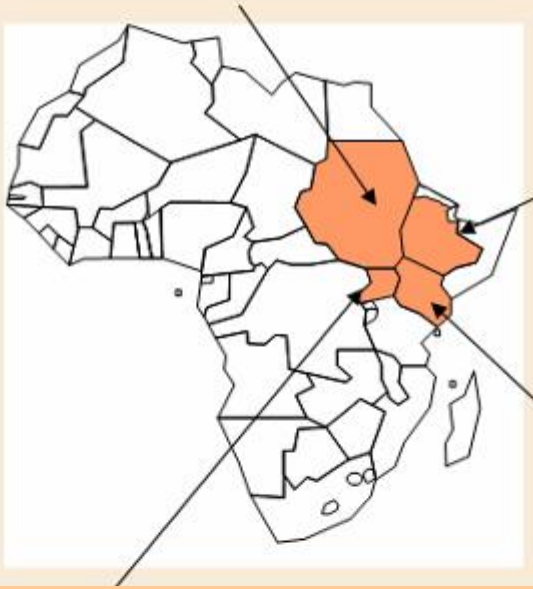


New lab, Feb06

VL

Leishmaniasis East Africa Platform (LEAP)

SUDAN: 2 sites (Kassab, Dooka)
Univ. of Khartoum
Federal Ministry of Health



ETHIOPIA: 2 sites (Gondar, Arba Minch)
Addis Ababa Univ.
Gondar Univ.
Ministry of Health

UGANDA: 1 site (Amudat)
- Makerere Univ.
- Ministry of Health

KENYA: 2 sites (Nairobi, Kimalel)
KEMRI
Ministry of Health

Objectives:

A group of scientists and institutions working on developing clinical trial capacity to bring new treatments to patients

DNDi

Partners:

MSF
I+ solutions
LSH&TM
AMC/ SU/ KIT (ASK)
IOWH - India
Industry partners

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LEAP
Leishmaniasis East Africa Platform

VL

ETHIOPIA

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Gondar, Clinical Trial Center before rehabilitation

Arba Minch, before rehabilitation

Gondar New Site, May 08

Arba Minch new lab

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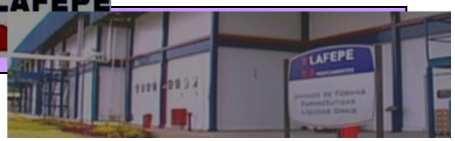
Chagas: Consolidating our Portfolio

Discovery | **Preclinical** | **Clinical** | **Available to patients**

Lead opt. Consortium

Azoles E1224 Phase 2

Paediatric Benznidazole



Azoles
E1224

- License signed with the Japanese pharma Eisai for clinical development of **Ravuconazole** for treatment of Chagas disease funded by DNDi (September 29, 2009)
  - E1224, pro-drug of ravuconazole, an anti-fungal drug discovered by Eisai
  - Implementation of Phase II clinical trial in adult patients with chronic indeterminate Chagas disease (Bolivia, 2 sites in 2011)
    - Study initiation in June 2011

Chagas

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Biomarkers in Chagas

- PCR study: optimization of sampling procedures in chronic Chagas Disease (n=220)
  - Collaboration with MSF Spain, Bolivia Mission (MSF-OCBA) and UMSS
  - Study initiation – April 13th (102 patients recruited)
- RT-PCR lab optimization and validation for clinical studies
  - Collaboration with UMSS, CEADES, CONICET
- NHEPACHA network for long term evaluation of candidate biomarkers
- Coordination of activities with different partners
  - Work towards the integration of data on candidate markers
  - Participation in PAHO/TDR PCR meeting in B. Aires
  - Collaboration with Univ. of Georgia and TBRI– non-human primate study

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Chagas

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DNDi Drugs for Neglected Diseases initiative

Pediatric Benznidazole

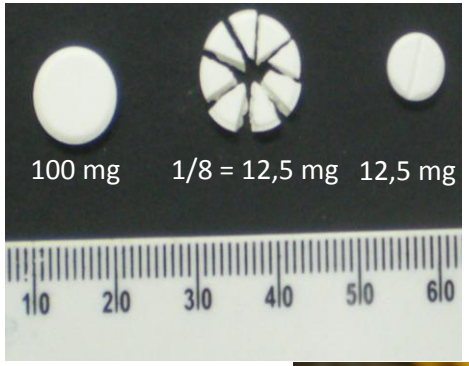
A pediatric formulation available in 2011

Benznidazole registered by Roche in 1971, licensed to Brazilian government in 2003

Objective:
An affordable, age-adapted, easy to use, pediatric formulation for Chagas disease

Current ways to administer in children

- 100 mg tablet fractionated or macerated for administration
- High risk of delivering improper dosages
  - **40-160% of Target BZ content**



Target: 12.5 mg tablets for <20 kg children

DNDi-Lafepe agreement in 2008 for development of pediatric formulation

Chagas

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Chagas Clinical Research Platform

Objectives:

- Facilitate effective and efficient trials to deliver improved treatment for Chagas disease
- Strengthen institutional research capacity
- Support an environment conducive to quality research
- Develop a critical mass of expertise
- Define priority areas for clinical evaluation of new treatments in Chagas disease
- Conduct periodic review and update of Target Product Profile in Chagas Disease
- Articulate with other initiatives

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7-Year Results

- **2 new malaria treatments**
- **1 new sleeping sickness** combination
- **1 new visceral leishmaniasis** combination for Africa
- **1 new visceral leishmaniasis** combination for Asia
- **Largest pipeline** ever for the kinetoplastid diseases
- Clinical research platforms in Africa and Latin America
- On track to deliver new treatments per business plan




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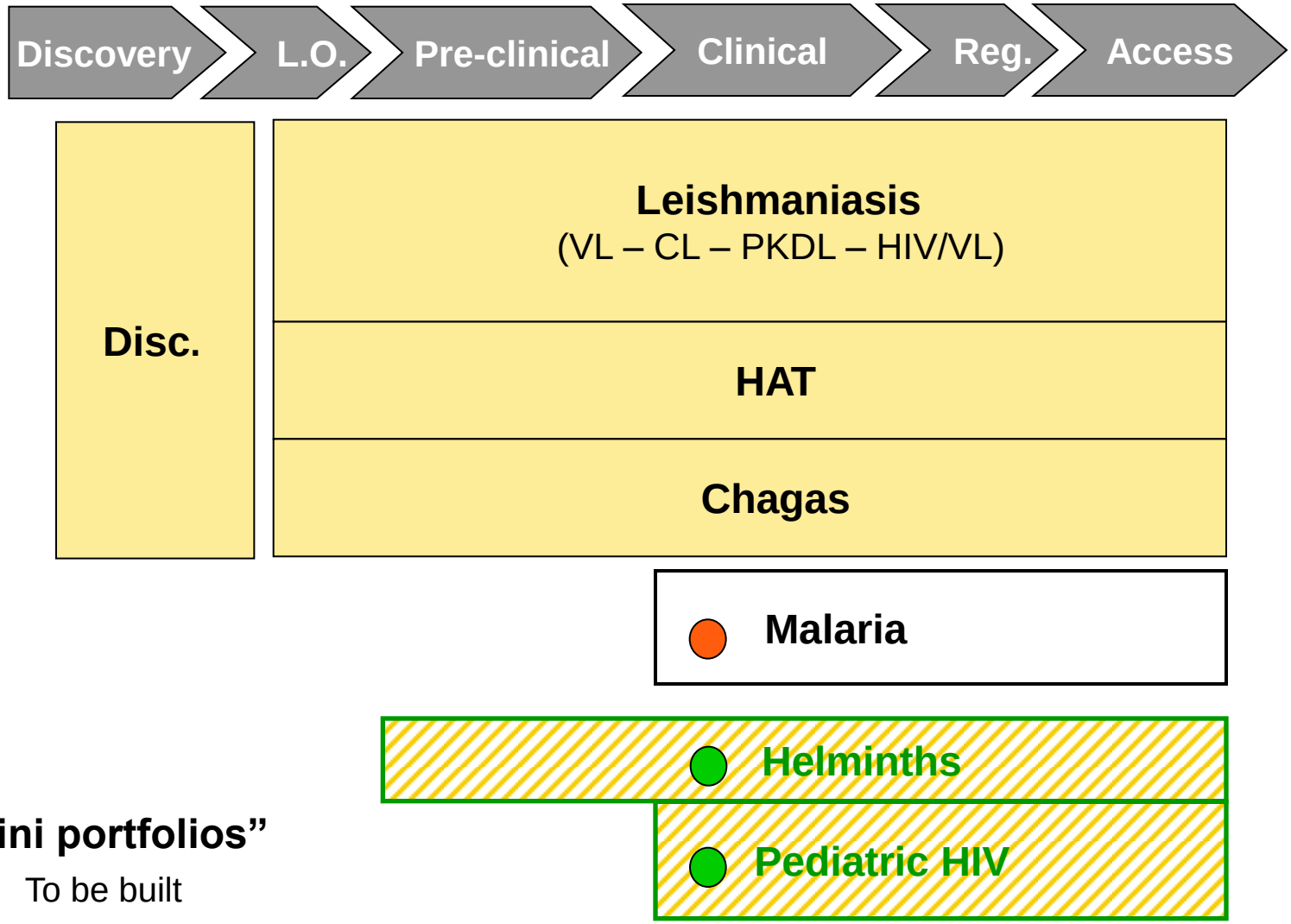
Evolution of DNDi Disease Portfolio



"Mini portfolios"

- To be built
- To complete

Several gaps along the R&D process remain

- New knowledge on drug targets and lead compounds may be published but preclinical research does not begin
- Validated candidate drugs may not enter clinical development because of commercial company choices
- New or existing drugs may not reach patients due to economically unsustainable production or high prices, lack of registration in all endemic countries, or lack of adapted formulations to the local conditions of use

Global R&D funding for neglected diseases

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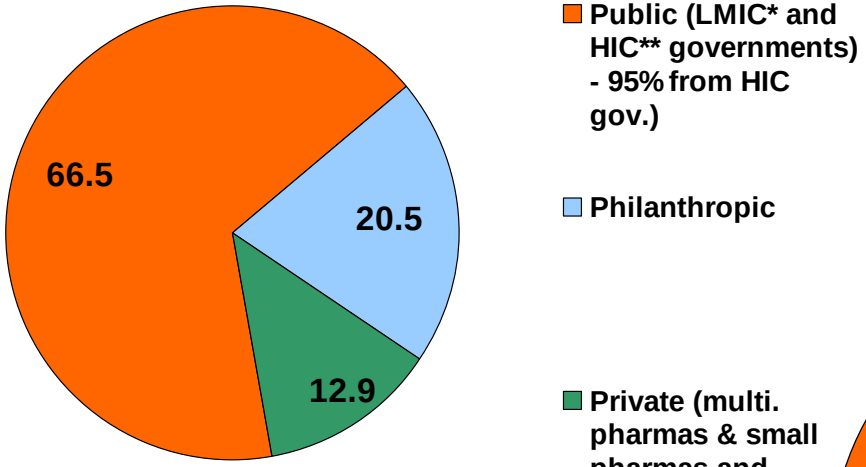
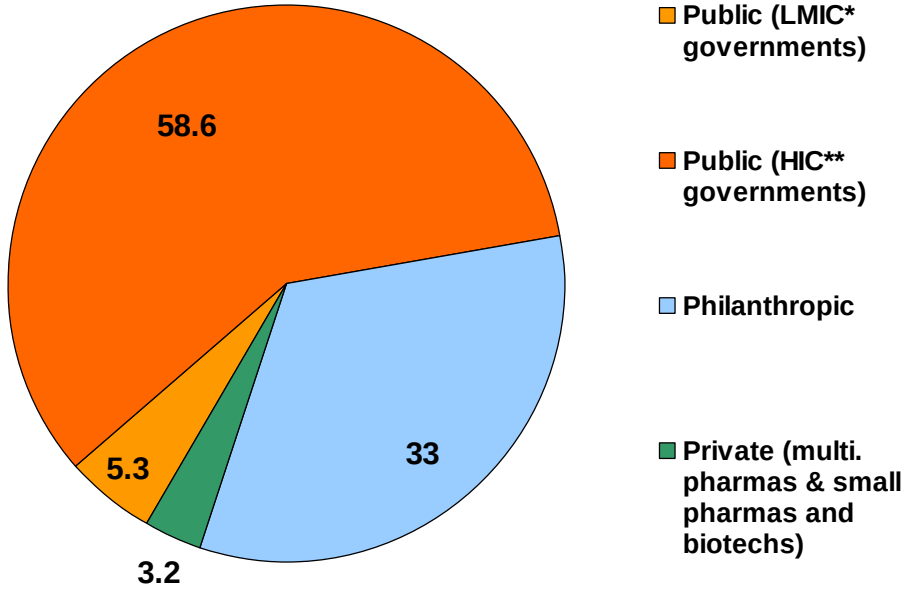
Neglected Diseases
$3.2 billion (US)



Kinetoplastids
$162 million (US)

=> 5% of the total!



Source: Moran et al., G-Finder report, Feb. 2011 **Data 2009**

*LMIC= Low- and Middle-Income Countries
**HIC= High-Income Countries

DNDi Portfolio – ~100 M spent since 2003

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	Exploratory	*Exploratory*	

a robust pipeline

6 to 8 new treatments by 2014

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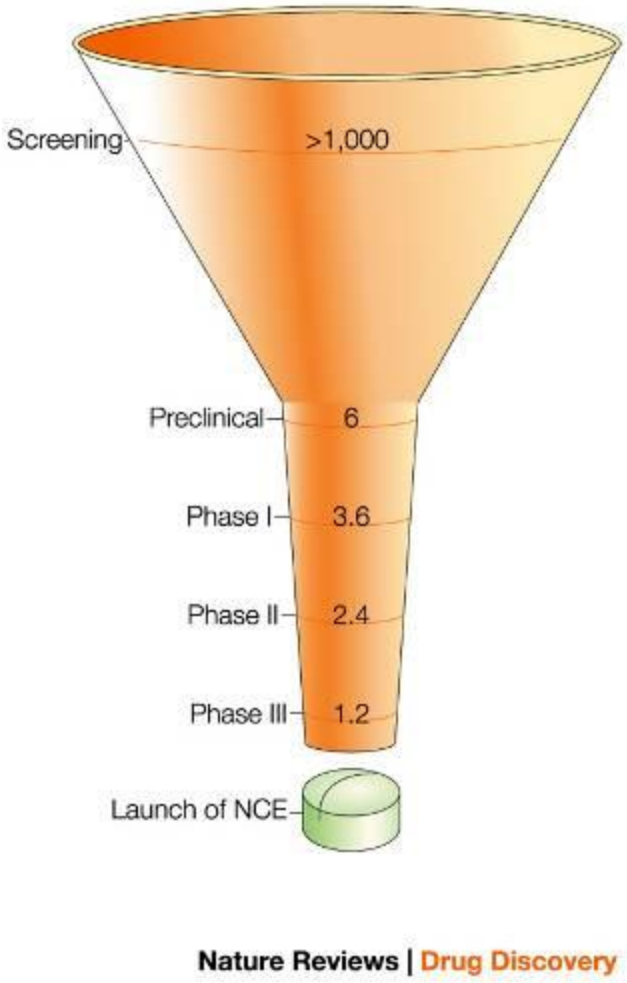
PDP costs will likely increase in the next years



Risks in research and development of pharmaceutical drugs

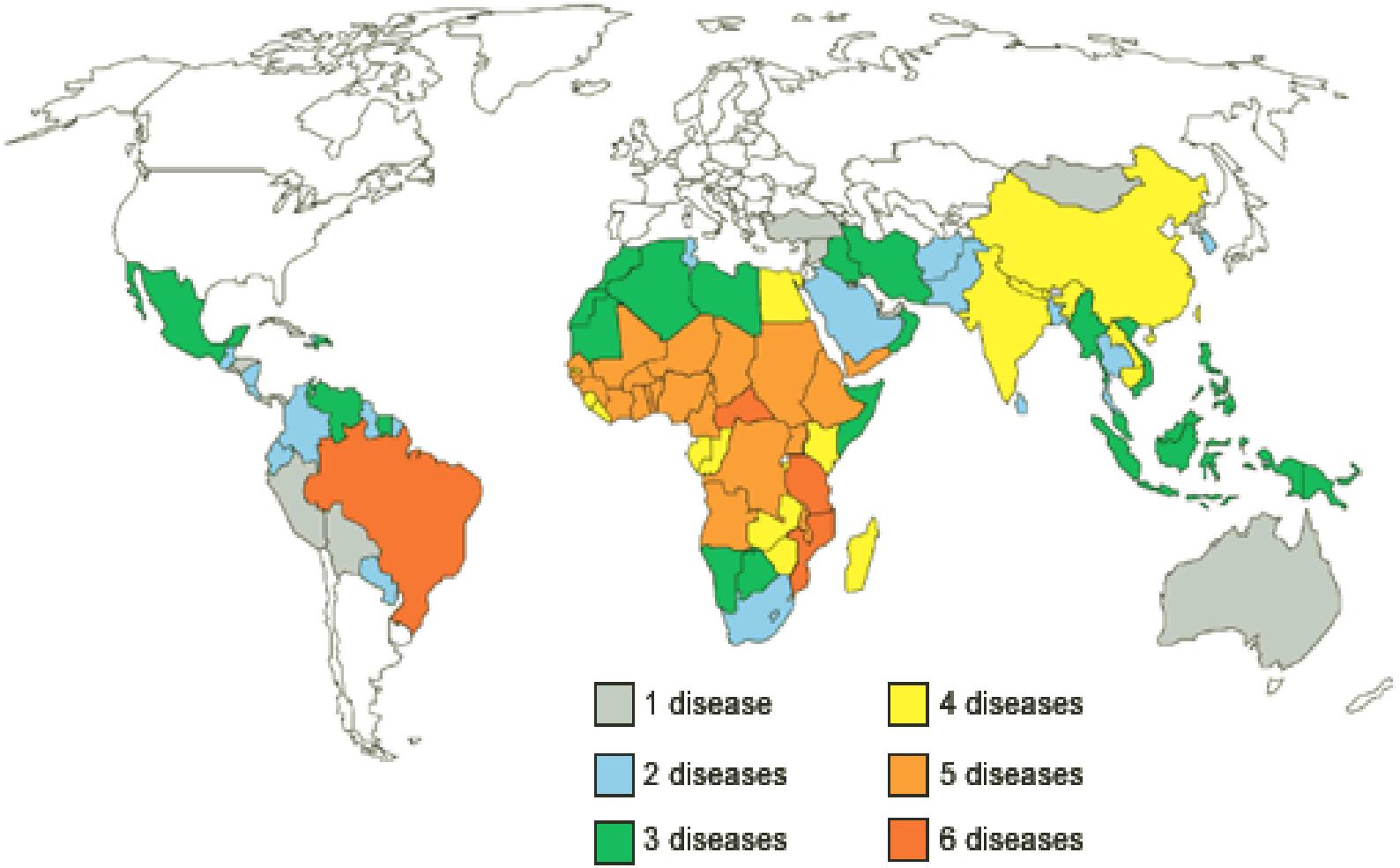
(Preziosi, P. 2004, Nature Reviews in Drug Discovery 3, 521-526)

Access

- Need to facilitate equitable access to new treatments
- Unmet medical needs == often non-existing procurement and distribution mechanisms and lack of traditional commercial partners
- Important to full transition, in long term, new treatments to natural implementers, i.e., Ministry of Health, National Control Programmes, WHO, NGOs

Access strategy: pragmatic and focused on most pressing "actionable" access barriers

Countries Burdened with Neglected Tropical Diseases



WHO, 2010

Brazil and the PDPs

- The role of PDPs in R&D not yet fully considered or recognized
- Existing innovative policy initiatives (Innovation Law, strengthenening of the Health Industrial Complex, organisation of research networks, focus on public private parternships) open and consistent to new R&D management models, such as PDPs
- However, PDPs often not eligble for existing funding opportunities which are based on the traditional R&D development model (and which works for non-neglected diseases, but not applicable for neglected disease R&D)

Towards a global public health & equitable access framework for R&D

WHO Global Strategy on Public Health, Innovation and Intellectual Property

Incentives and financing mechanisms tailored to particular stages of R&D, types of diseases and health technologies are necessary to address existing gaps and the unmet needs of neglected patients

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Public Leadership
Waking Up to «Essential Health R&D»

- Public leadership to define R&D priorities
- Significant investment with sustainable funding
- Ensure better access to knowledge and promote innovative IP management policies
- Enable more adapted regulatory environment
- Transfer technology and strengthen research capacities in developing countries

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Increasing resources for neglected disease R&D

- Investigate innovative sustainable funding for product development and access
- Pilot milestone prizes to stimulate discovery of new clinical candidates

Reducing the costs of R&D for neglected diseases

- IP management, open innovation and sharing of knowledge
  - *Accessing compounds and annotated data*
  - *Negotiating freedom to operate, paving the way for access*
  - *Pushing for transparency and sharing of knowledge*
- Innovative regulatory pathways to expedite access in endemic regions and strengthening local regulatory capacity

By working together in a creative way, PDPs, large and small pharma, and the public sector can bring innovation to neglected patients!

www.dndi.org

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