



## R&D for Neglected Patients: Evolution over a Decade and Future Perspectives on Access & Innovation

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ICOPA Opening Ceremony – August 10, 2014

## Outline

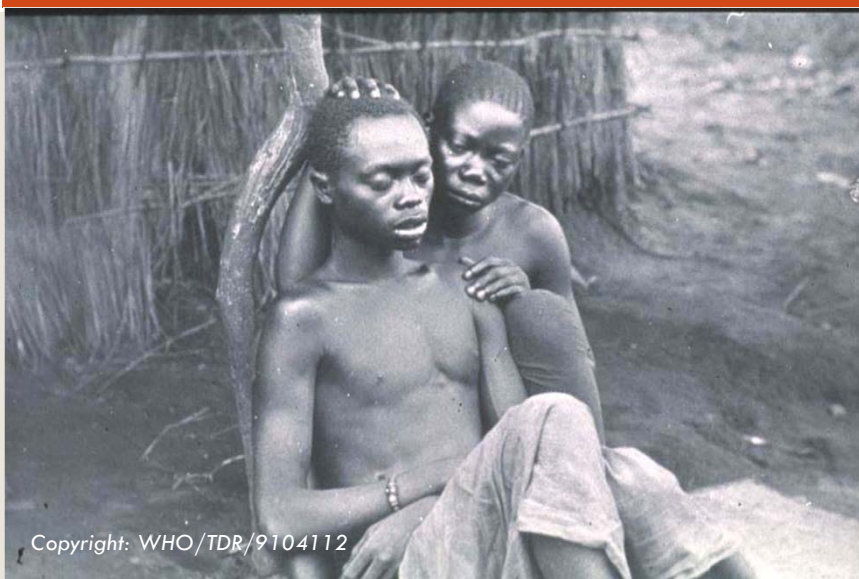
- ❑ Where it all Started: Background
- ❑ Change over the Past 10-15 Years
- ❑ Chagas Disease: How Far Have We Come?
- ❑ Gaps and Challenges: Innovation & Access



## Where It All Started – In the Field



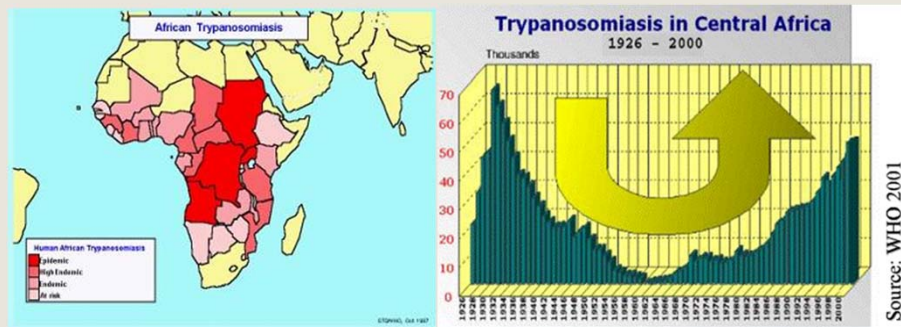
## HAT-Sleeping Sickness: Patients and Health Professionals Scourged



Copyright: WHO/TDR/9104112

## Despite Near Elimination: HAT Re-Emerges in The 1990s

- ❑ 55 million at risk in sub-Saharan Africa
- ❑ Estimated 300,000 infected
- ❑ Difficult, even dangerous, to diagnose and stage
- ❑ Fatal if untreated
- ❑ Existing drugs: old, toxic, resistance, difficult to use, expensive

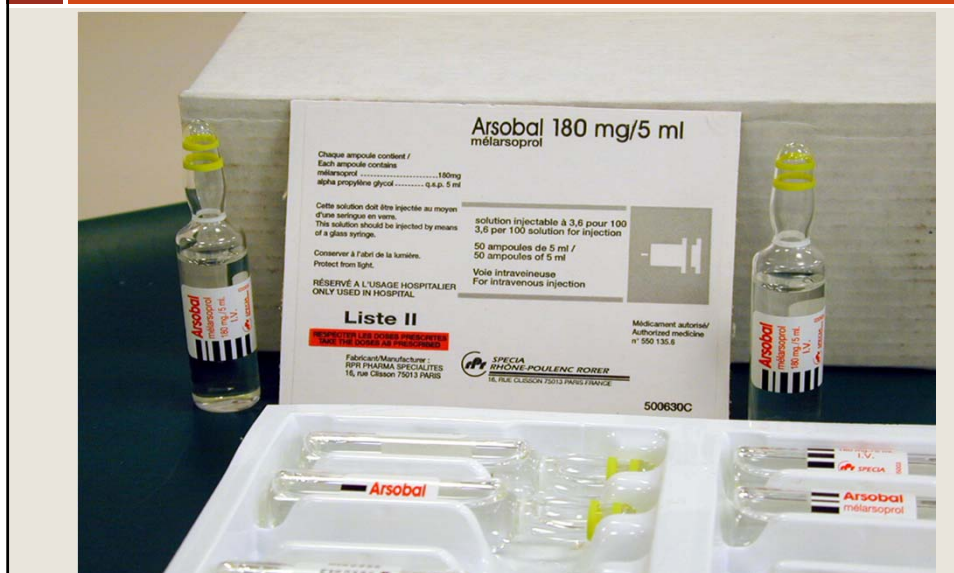


## Complex Diagnostic Algorithm with Lumbar Puncture to Define Disease Stage & Monitor Efficacy





## First Choice Treatment Was Toxic: Melarsoprol



## Only Alternative Treatment Complex & Unavailable: Eflornithine



## Reality In The Field: Treatment Limitations for Neglected Diseases

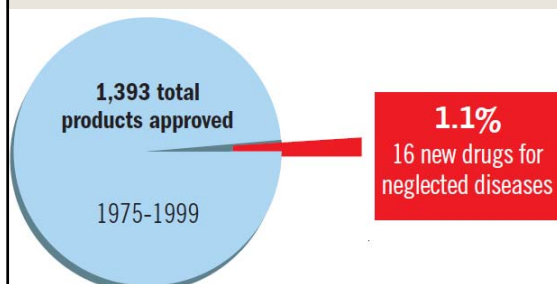


- ❑ Ineffective (resistance)
- ❑ Toxic
- ❑ Expensive
- ❑ Painful when administered
- ❑ Difficult to use
- ❑ Not registered in endemic regions
- ❑ Restricted by patents

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

## A Decade Ago, Neglected Disease R&D at A Standstill: The 'Fatal Imbalance' Documented

### Health R&D (1975 – 1999)



### A Fatal Imbalance

From 1975-1999:

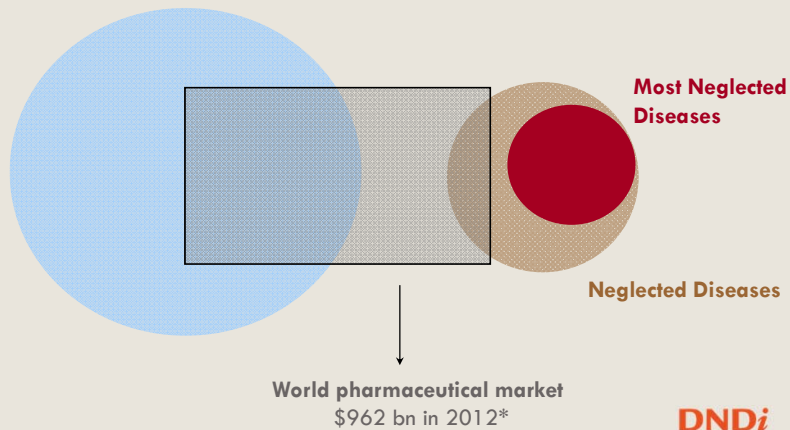
- ❑ 16 of 1393 new products for NTDs + malaria & TB (1.1%) despite their global disease burden of 12%
- ❑ Illustration of the '10/90 Gap'

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

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

Global Diseases



\*Source: IMS Health

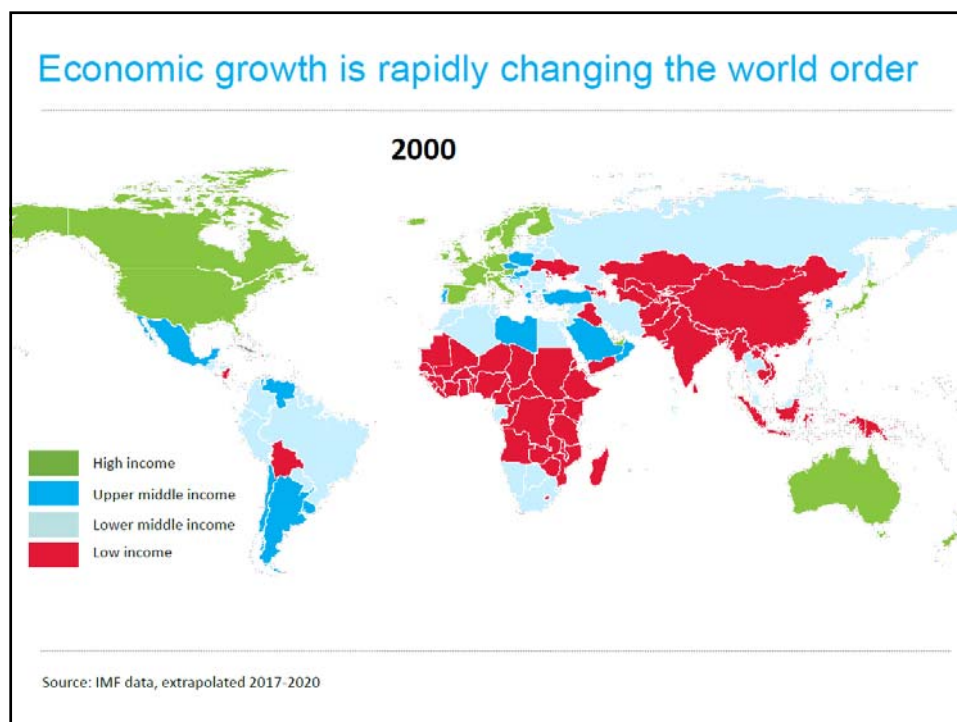
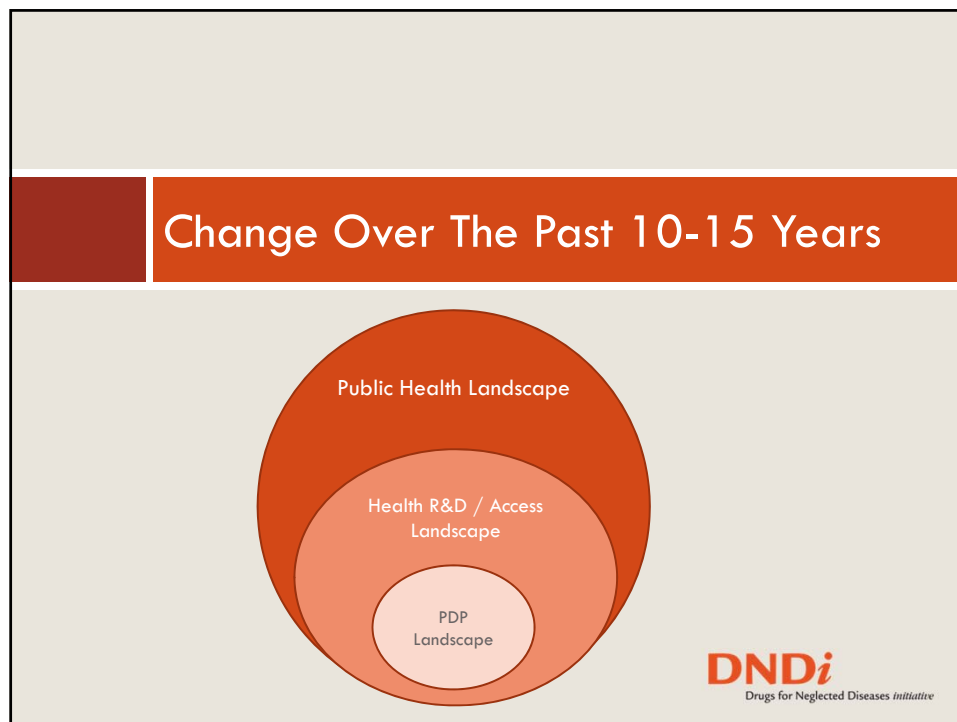
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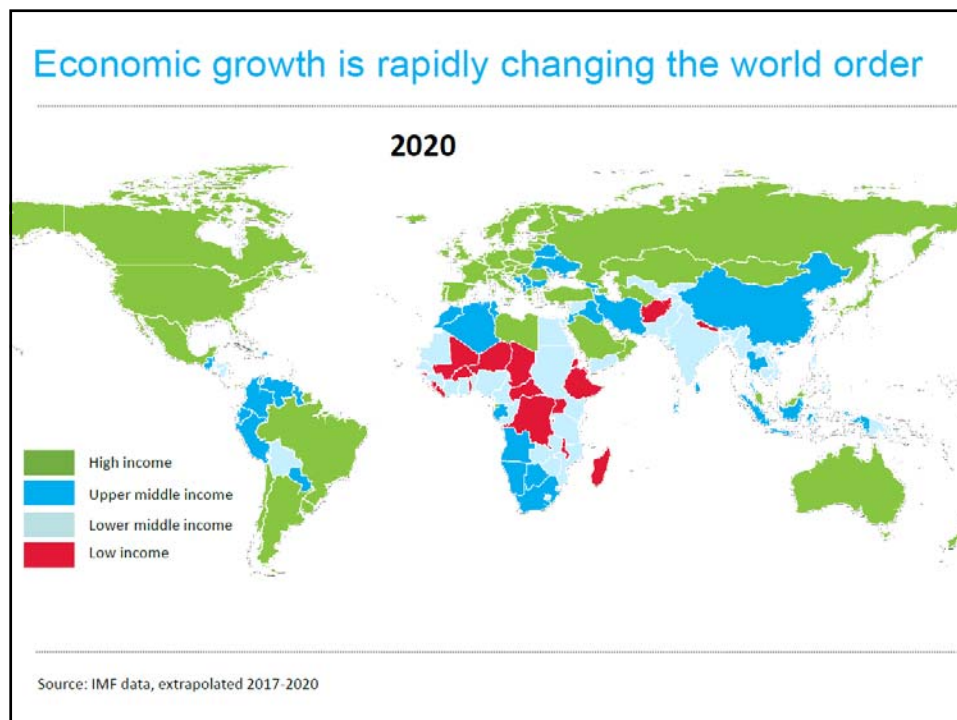
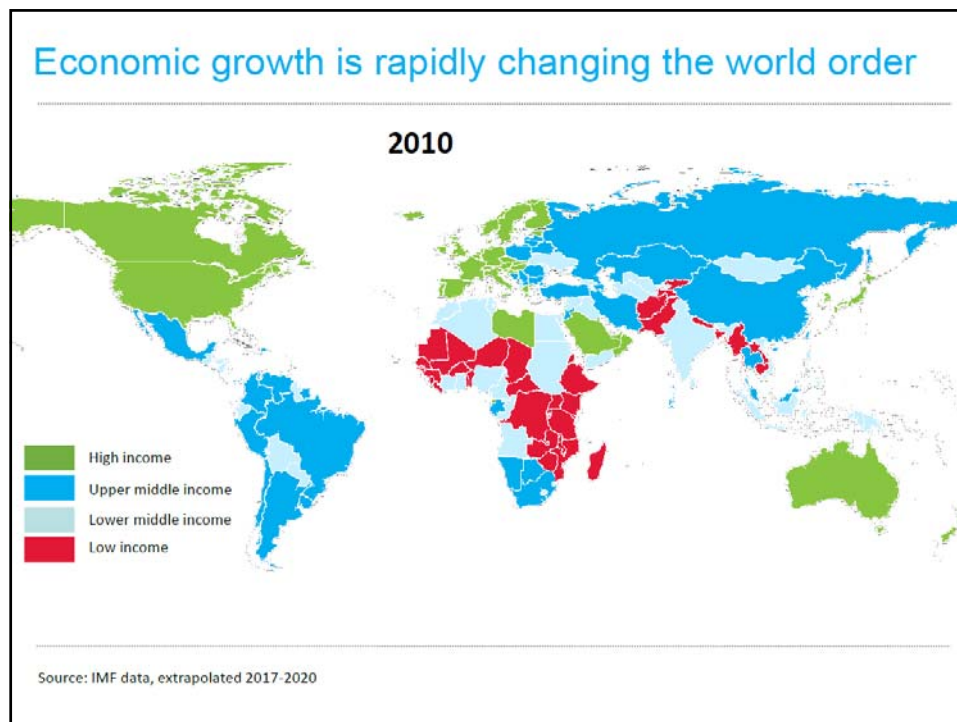
## Vicious Cycle of Poverty and Disease

- ❑ Disease is both cause and consequence of poverty
- ❑ Poorest of the poor
- ❑ Living in remote areas
- ❑ Socioeconomic burden on family and community
- ❑ Marginalized & voiceless patients



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## Two-Thirds of the World's Poor are in Emerging Economy Countries

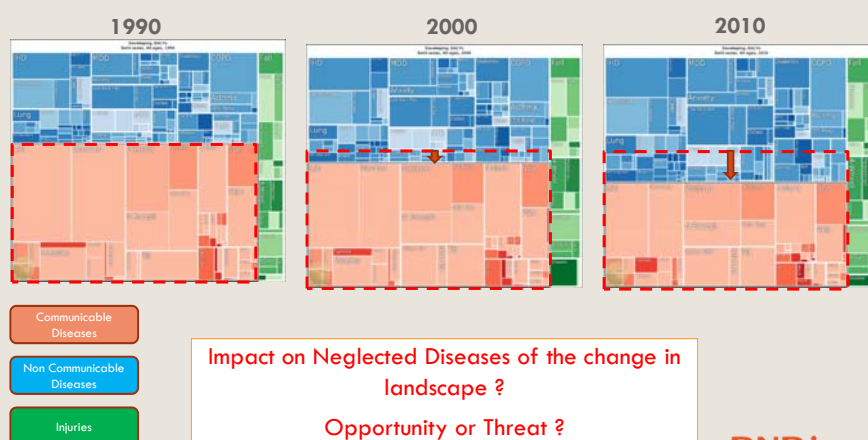
Nearly twice as many poor people are living in emerging economies than in low-income countries today

|                           | Total population (in millions) | People living with less than 2\$ a day (in percentage) | People living with less than 2\$ a day (in millions) |
|---------------------------|--------------------------------|--|--|
| Least Developed Countries | 1000                           | 74%  | 755  |
| Emerging economies        | 4420                           | 57%  | 1,536  |

Source: Michel Kazatchkine, DNDi-Institut Pasteur meeting, Dec. 2013

## Shift towards Non-Communicable Diseases But Communicable Diseases Remain a Major Burden in MICs & LICs

Middle-Income and Low-Income Countries : Shifting disease burden



Source: Healthdata.org, Global Disease Burden. 20 May 2014

## Increased Investment in Global Health through New Actors

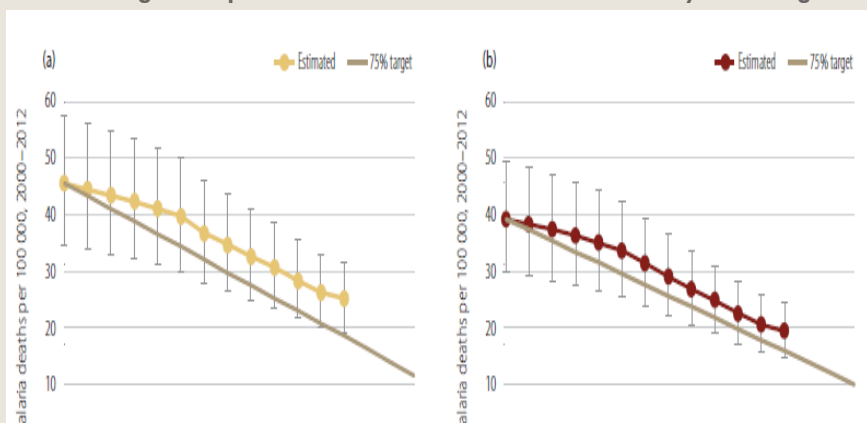


... and many others!



## Impact: Overall Malaria Mortality Rates Have Fallen by More than 25% Since 2000

Estimated malaria mortality rates 2000-2012  
All Age Groups Under five years of age



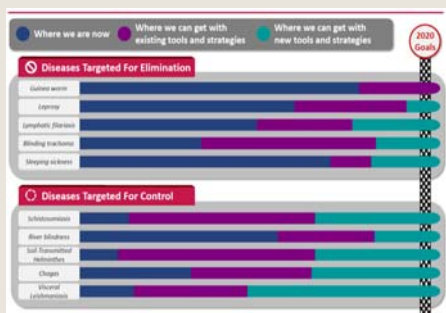
Source: World Malaria Report 2013



## Joining Forces to Achieve NTD Control and Elimination

### WHO Roadmap

Reaching the 2020 WHO  
NTD Goals



Source: United to Combat NTDs ([www.unitedtocombatntds.org](http://www.unitedtocombatntds.org))

### London Declaration (2012)

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

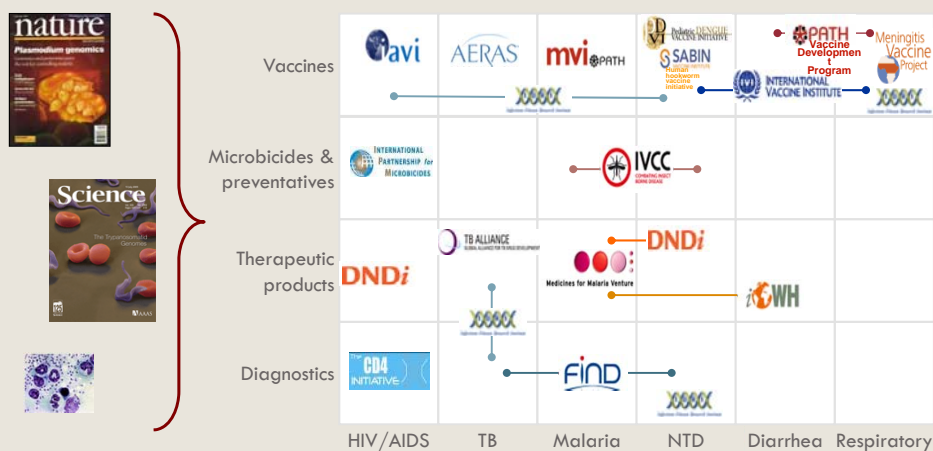
In addition, endemic country and regional actors play an increasingly important role...

- Carlos Slim, Mundo Sano, Emirates
- BNDES (Brazil)

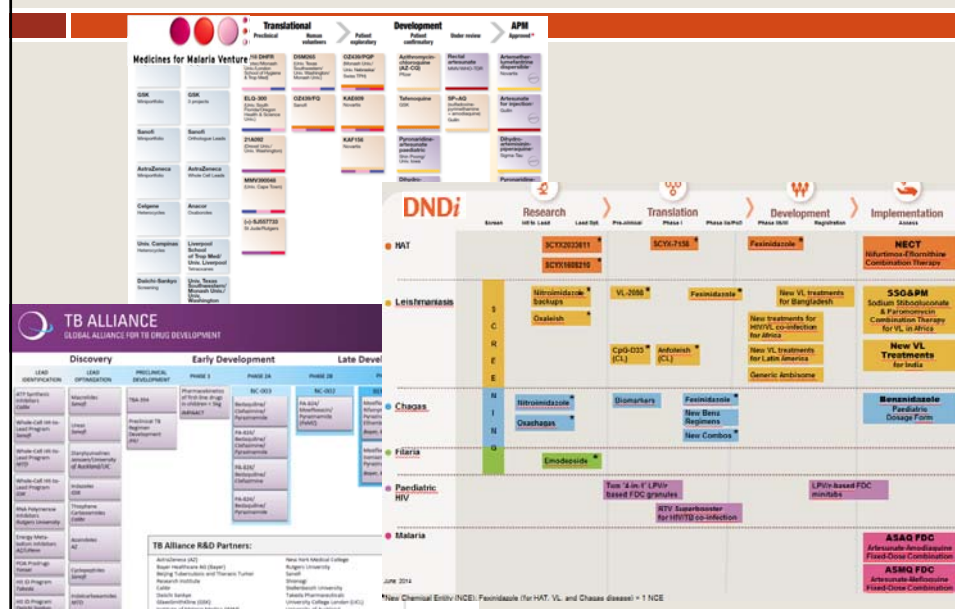
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## Product Development Partnerships: Filling Gaps in Translational Research and Product Development

PDPs work across different diseases and modalities



## R&D Pipelines Begin to Replenish for Neglected Diseases

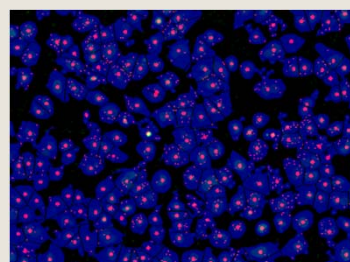


## Accessing Advanced Technology to Accelerate Compound Identification for NTDs

- High-Throughput / High Content Screening capacity
- Increasing access to large pharma libraries and screening factories
- NTD-focused screening centres applying new technologies (Institut Pasteur Korea, Dundee University)

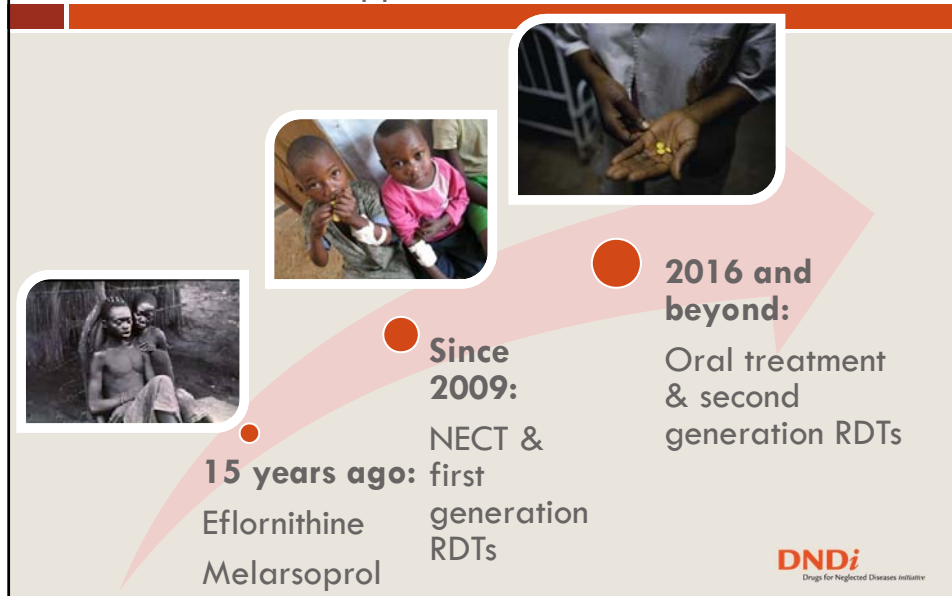


Removes the bottleneck of drug screening for *Leishmania* and *T. cruzi*

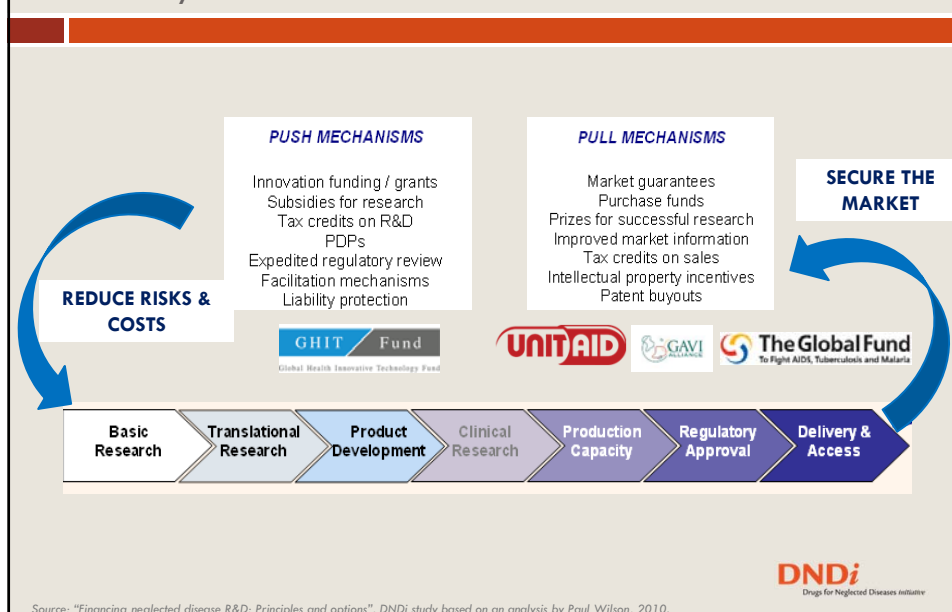




## Sleeping Sickness: From Unacceptable To Better, Towards Tools to Support Elimination



## New Financing Mechanisms & Incentives Begin to Change R&D Dynamics



## Overcoming Intellectual Property Barriers: TRIPS Implemented in All Major Countries

### Some flexibilities:

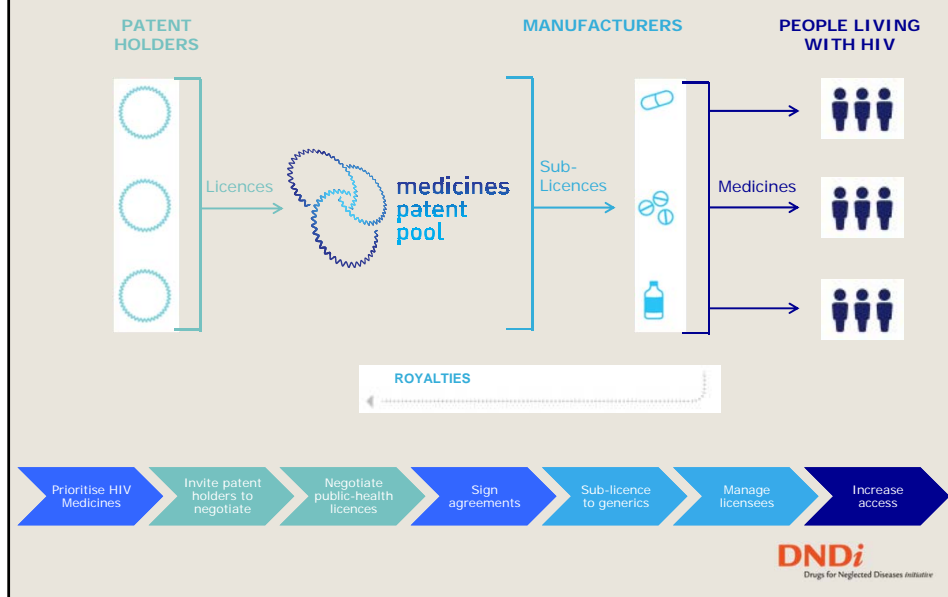
- Compulsory Licensing
  - Some use of TRIPS flexibility (e.g. compulsory licensing in Brazil, India, Indonesia, Thailand)
- Voluntary licensing
  - Creation of the Medicines Patent Pool (MPP) for HIV
  - Bi-lateral agreements between innovators and endemic countries (i.e. Innovators with South Africa & India)

### Open innovation to support drug discovery, but limited:

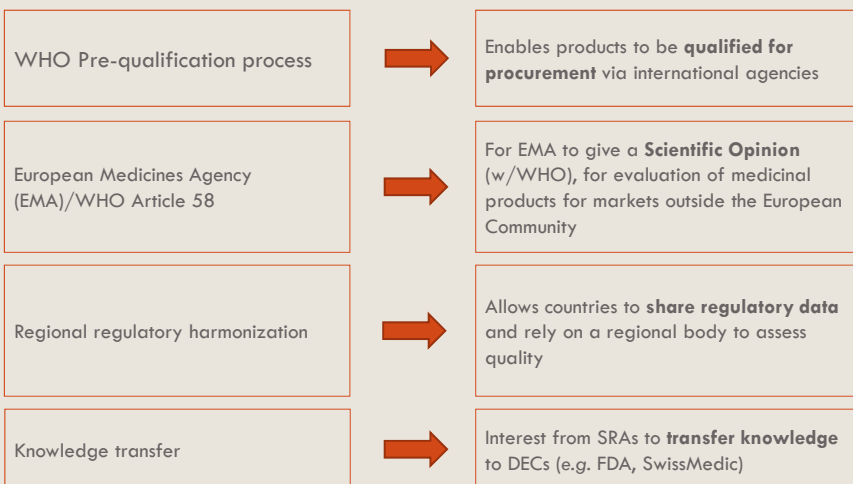
- Open Source Lab
- WIPO Re:Search
- Pathogen Box



## Medicines Patent Pool



## Overcoming Regulatory Obstacles



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## A Successful Model: MenAfriVac

### MenAfriVac licensure, and WHO pre-qualification



- Marketing authorization for export to African meningitis belt countries : 21<sup>st</sup> Jan 2010
- WHO accepted the dossier for review: Feb 2010
- WHO Pre-qualification Inspection : 8<sup>th</sup> to 12<sup>th</sup> March 2010
- WHO Pre-qualification certificate on : 23<sup>rd</sup> June 2010
  - African countries Registration in:
    - Mali : August 2010
    - Niger: August 2010
    - Burkina Faso: September 2010



MPV IS A PARTNERSHIP BETWEEN WHO AND PATH

Confidential & Proprietary Information

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## Chagas Disease: How Far Have We Come?







## Chagas Disease Burden

- ❑ **100 million at risk** in Latin America (21 countries)
  - ❑ Kills more people in the region than malaria
- ❑ Transmitted by 'kissing bug', blood transfusion, organ transplantation, and congenitally or orally
- ❑ Majority of **patients undiagnosed** until late stage
- ❑ Patient **numbers growing** in non-endemic, developed countries
- ❑ Mexico
  - ❑ Ranks 3rd in number of people infected
  - ❑ Approx. 30 million people at risk and 1.1 million people infected



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## Success of Control Efforts: Endemicity Is Reduced

### Overall prevalence of Chagas Disease



## It is Time to Test and Treat with Existing Tools

**Today, still less than 1% of the targeted patient population has access to treatment! Despite...**



- Availability of Product
  - Two sources of Benznidazole: LAFEPE and ELEA/Mundo Sano
  - One source of nifurtimox: Bayer/WHO
  - Rapid Diagnostic Tests
- More evidence on efficacy and safety of treatments through clinical trials
- Increasing role of patients' associations

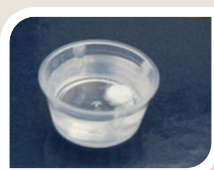
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## R&D Must Push On For Better Tools



### 10 years ago:

- No paediatric formulation
- No drug recommended for chronic phase



### Since 2010:

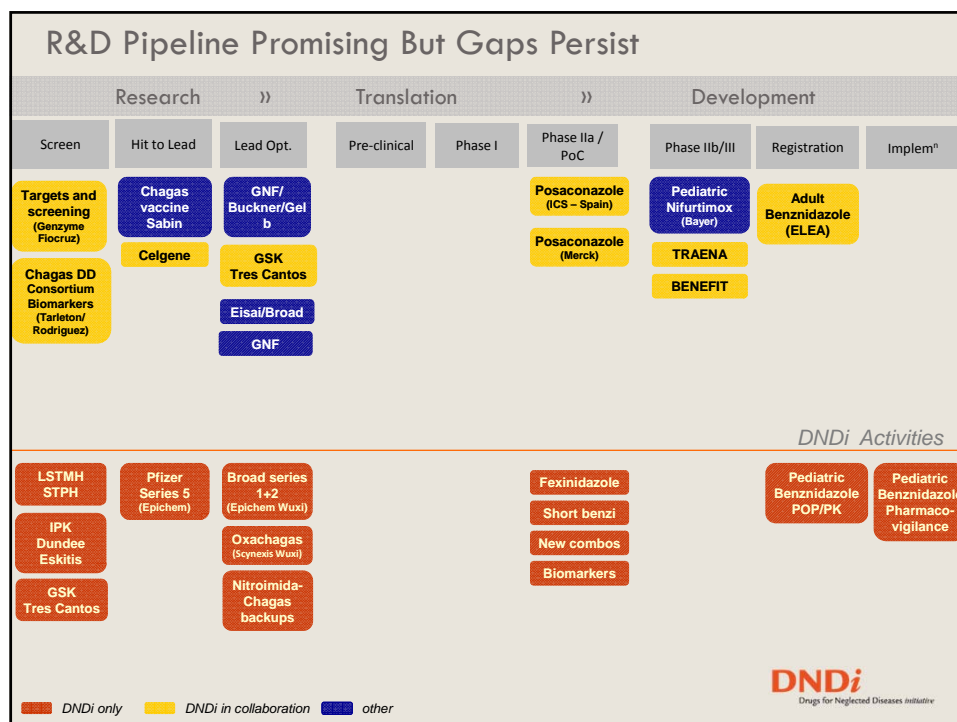
- Paediatric Dosage Form of benznidazole
- WHO recommendation treatment of chronic patients



### Future:

Simple and better-tolerated oral treatment for chronic stage and acute form of the disease

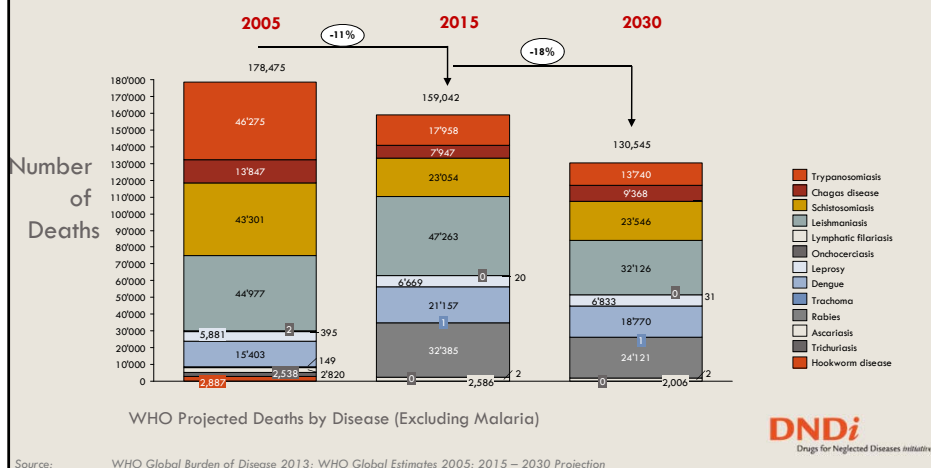
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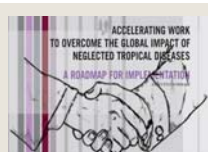
## Gaps & Challenges To Overcome: Innovation and Access

## Reduction in Global Disease Burden for Neglected Tropical Diseases: But There Are Still Unmet Needs

Deaths due to neglected diseases are projected to decrease over the next 15 years ... but **will not be eliminated and others are still unaddressed**



## Public Health Goals Shifting Towards Elimination Goals But Not Without Risk...



The London Declaration



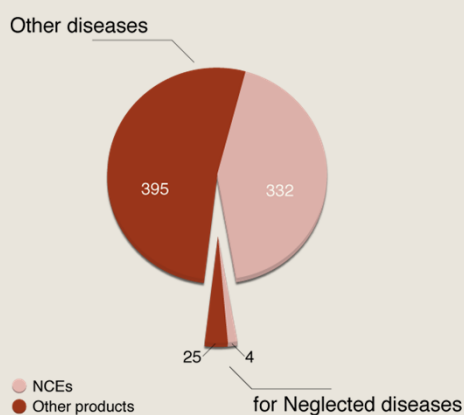
**Beware!**

Decreasing R&D efforts & diverting resources from remaining needs



## Fatal Imbalance Remains Despite Progress Over A Decade

756 products developed (excluding vaccines) (2000-2011)



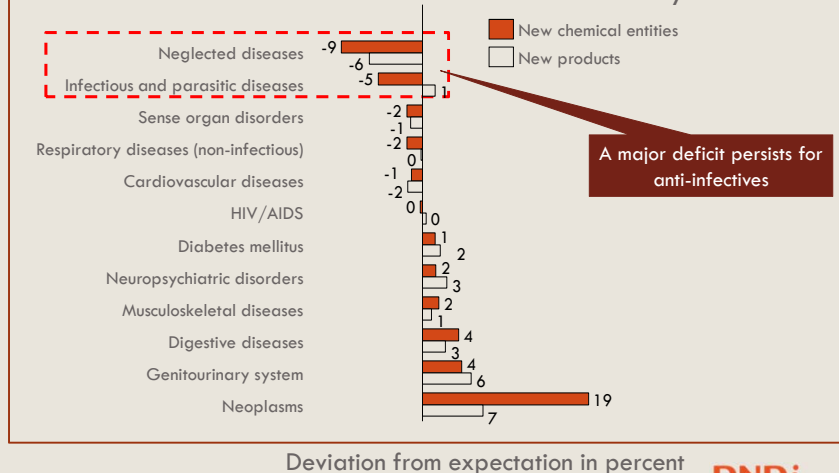
- 3.8% of new products for neglected diseases (reformulations, combinations)
- 1.2% of NCEs for neglected diseases
- Only 1.4% clinical trials (of nearly 150,000 trials) focus on neglected diseases
- Only 1% of global health investment for neglected diseases\*

Source: 'The drug and vaccine landscape for neglected diseases (2000-2011): a systematic assessment' Pedrique B et al. Lancet, Oct 2013

\*Source: 'Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory?' Rottingen et al. Lancet, May 2013

## Still a Major R&D Deficit for Anti-Infectives

### NCEs and New Products Deficit Analysis



Source: The drug and vaccine landscape for neglected diseases (2000-11): a systematic assessment; Dr Belen Pedrique et al; the Lancet 2013. Deficit analysis was not part of the published version.

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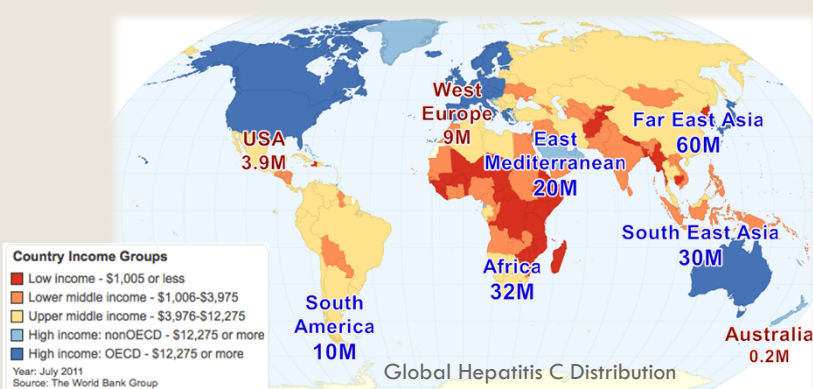
## Broader Challenge in Discovery

### Multi-Resistant Bacteria: Needs Are Clearly Recognized!



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## Major Progress on Hep C But Will Not Benefit Majority of Patients



Could progress in virology benefit other viral neglected diseases?

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## Among the Neglected in R&D, Children All the More

Paediatric HIV: Still in need of R&D for the right formulation, dose and taste

| Nucleoside Reverse Transcriptase Inhibitors (NRTIs) | Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) | Protease Inhibitors (PIs)            | Integrase Inhibitor          | Fusion Inhibitor          | CCR5 Antagonist                      |
|---|--|--------------------------------------|------------------------------|---------------------------|--------------------------------------|
| Abacavir (ABC)/ Zigen                               | Delavirdine (DLV)/ Rescriptor                            | Atazanavir (ATV)/ Reyataz            | Raltegravir (RAL)/ Isentress | Enfuvirtide (T20)/ Fuzeon | Maraviroc (MVC)/ Selzentry           |
| Didanosine (ddI)/ Videx EC                          | Efavirenz (EFV)/ Sustiva                                 | Darunavir (DRV)/ Prezista            |                              |                           |                                      |
| Emtricitabine (FTC)/ Emtriva                        | Etravirine (ETR)/ Intelence                              | Fosamprenavir (FPV)/ Lexiva **       |                              |                           |                                      |
| Lamivudine (3TC)/ Epivir                            | Nevirapine (NVP)/ Viramune                               | Indinavir (IDV)/ Crivian             |                              |                           |                                      |
| Stavudine (d4T)/ Zert                               | Etravirine (ETR)/ Intelence                              | Lopinavir + Ritonavir (LPV)/ Kaletra |                              |                           |                                      |
| Tenofovir Disoproxil Fumarate (TDF)/ Viread         |  | Nelfinavir (NFV)/ Viracept           |                              |                           |                                      |
| Zidovudine (ZDV)/ AZT/ Retrovir                     |  | Ritonavir (RTV)/ Norvir              |                              |                           |                                      |
|   |  | Sacquinavir (SQV)/ Invirase          |                              |                           |                                      |
|   |  | Tipranavir (TPV)/ Aptivus            |                              |                           | Not approved in neonates and infants |



FDA approved ARVs

Limitations of LPV/r

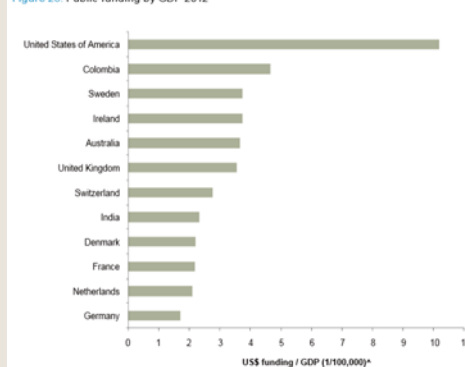
- ❑ Solution contains over 40% alcohol
- ❑ Unstable in tropical climates (not heat-stable)
- ❑ Horrible taste
- ❑ Up to 50% of children co-infected with TB, and need anti-TB therapy – with major negative DDI with LPV/r
- ❑ Liquid formulations (not just of LPV/r) extremely complex for caregivers to administer

## Lack of Sustainable Funding

- ❑ The 'big three' account for 58% of overall R&D
- ❑ BMGF & Wellcome Trust responsible for +85% of all R&D funding by philanthropic donors
- ❑ Insufficient investment from emerging economies
- ❑ New funding mechanisms not yet developed (Transaction Tax, etc.)

### Neglected Diseases Public Funders

Figure 26. Public funding by GDP 2012




Source: G-Finder 2013 report

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## Research Efforts Must Stay Focused on Real Patient Needs to Deliver Adapted Tools

|                          | Fixed-dose ASAQ (w/ Sanofi)<br>Artesunate/amodiaquine<br>3 dosage strengths available | Co-biestered non-fixed AS+AQ<br>Artesunate-amodiaquine<br>AS: 50 mg; AQ 135 mg |
|--------------------------|---|--|
| Infants (4.5-8 kg)       | AS: 25 mg<br>AQ: 67.5 mg  |  |
| Young Children (8-17 kg) | AS: 50 mg<br>AQ: 135 mg   |  |
| Children (17-35 kg)      | AS: 100 mg<br>AQ: 270 mg  |  |
| Adults (≥36 kg)          | AS: 100 mg<br>AQ: 270 mg  |  |






## Best Science For The Most Neglected



Give a voice to  
neglected  
patients.

They exist, they  
must be heard.

Carmen Rosa,  
Bolivia

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