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

Dr Bernard Pécoul, Executive Director

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

Presented at ICOPA conference, August 2014
First Choice Treatment Was Toxic: Melarsoprol

Only Alternative Treatment Complex & Unavailable: Eflornithine

Administration:
- 400mg/kg/day
- 1 infusion every 6 hours during 14 days
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)

- 1,393 total products approved
- 1975-1999

A Fatal Imbalance

From 1975-1999:

- 16 of 1,393 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
Neglected Diseases: Primarily Affect Developing Countries & Lie Outside the World Market

![Diagram showing the relationship between Global Diseases, Most Neglected Diseases, and Neglected Diseases. The world pharmaceutical market is $962 bn in 2012.]

*Source: IMS Health

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
Change Over The Past 10-15 Years

Public Health Landscape

Health R&D / Access Landscape

PDP Landscape

Economic growth is rapidly changing the world order

2000

Source: IMF data, extrapolated 2017-2020
Economic growth is rapidly changing the world order

2010

High income
Upper middle income
Lower middle income
Low income

Source: IMF data, extrapolated 2013-2020

Economic growth is rapidly changing the world order

2020

High income
Upper middle income
Lower middle income
Low income

Source: IMF data, extrapolated 2013-2020
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.

<table>
<thead>
<tr>
<th></th>
<th>Total population (in millions)</th>
<th>People living with less than 2$ a day (in percentage)</th>
<th>People living with less than 2$ a day (in millions)</th>
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<tbody>
<tr>
<td>Least Developed Countries</td>
<td>1000</td>
<td>74%</td>
<td>755</td>
</tr>
<tr>
<td>Emerging economies</td>
<td>4420</td>
<td>57%</td>
<td>1,536</td>
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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

Impact on Neglected Diseases of the change in landscape ?
Opportunity or Threat ?

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

- 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)

**London Declaration (2012)**

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<th>Disease Targeted for Elimination</th>
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<tr>
<td>Schistosomiasis</td>
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<td>Filariasis</td>
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<td>Pinworms</td>
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Source: United to Combat NTDs (www.unitedtocombatntds.org)

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

PDPs work across different diseases and modalities

- Vaccines
- Microbicides & preventatives
- Therapeutic products
- Diagnostics

R&D Pipelines Begin to Replenish for Neglected Diseases

- 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)

Accessing Advanced Technology to Accelerate Compound Identification for NTDs

Removing the bottleneck of drug screening for Leishmania and T. cruzi
Sleeping Sickness: From Unacceptable To Better, Towards Tools to Support Elimination

15 years ago:
Eflornithine
Melarsoprol

Since 2009:
NECT & first generation RDTs

2016 and beyond:
Oral treatment & second generation RDTs

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

PUSH MECHANISMS
Innovation funding / grants
Subsidies for research
Tax credits on R&D
PPRs
Expediting regulatory review
Facilitation mechanisms
Liability protection

FULL MECHANISMS
Market guarantees
Purchase funds
Prizes for successful research
Improved market information
Tax credits on sales
Intellectual property incentives
Patent buyouts

SECURE THE MARKET

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

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**Medicines Patent Pool**

- **Patent Holders**
  - Licences
  - Patent holders to negotiate
  - Sign agreements
  - Patent pool

- **Manufacturers**
  - Sub-licences
  - Negotiate public health licences
  - Sub-licence to generics

- **People Living with HIV**
  - Medicines
  - Prioritize HIV
  - Health crisis
  - Increase access
  - Sub-licences
  - Manage licences

- **Royalties**
  - Incentive payment

**Note:** Presented at ICOPA conference, August 2014
Overcoming Regulatory Obstacles

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<th>WHO Pre-qualification process</th>
<th>Enables products to be qualified for procurement via international agencies</th>
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<tr>
<td>European Medicines Agency (EMA)/WHO Article 58</td>
<td>For EMA to give a Scientific Opinion (w./WHO), for evaluation of medicinal products for markets outside the European Community</td>
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<tr>
<td>Regional regulatory harmonization</td>
<td>Allows countries to share regulatory data and rely on a regional body to assess quality</td>
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<td>Knowledge transfer</td>
<td>Interest from SRAs to transfer knowledge to DECs (e.g. FDA, SwissMedic)</td>
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A Successful Model: MenAfriVac

MenAfriVac licensure, and WHO pre-qualification

- Marketing authorization for export to African meningitis belt countries: 21st Jan 2010
- WHO accepted the dossier for review: Feb 2010
- WHO Pre-qualification Inspection: 8th to 12th March 2010
- WHO Pre-qualification certificate on: 23rd June 2010
- African countries Registration in:
  - Mali: August 2010
  - Niger: August 2010
  - Burkina Faso: September 2010
10-Years of Political Debate at WHO Begin to Point Towards a Sustainable Solution

2003
Resolution WHA56.27
Intellectual property rights, innovation and public health

2006
Resolution WHA59.24
Public health, innovation, essential health research and intellectual property rights: towards a global strategy and plan of action

2008
Resolution WHA61.11
Global strategy and plan of action on public health, innovation and intellectual property

2010
Resolution WHA63.28
Establishment of a consultative expert working group on research and development, financing and coordination

2013
Governments agree to set up a global R&D observatory and experiment demonstration projects

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

Success of Control Efforts: Endemicity Is Reduced

Overall prevalence of Chagas Disease

- **1990**
  - 30 million cases
- **2001**
  - 9.8 million cases
- **2010**
  - 6-8 million cases
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

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
R&D Pipeline Promising But Gaps Persist

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<th>Research</th>
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**DNDi Activities**

**Chagas DD Consortium Biomarkers**
- Chagas vaccine Sabin
- Caligene
- GSK Tres Cantos
- Eisa/IBP
- GNF

**LSTMH**
- STPH
- IPK Dundee
- Edinburgh
- GSK Tres Cantos

**Pfizer**
- Series 1-2
- Sabin (Phase Ia)

**Broad series**
- 1+2
- Sabin (Phase IIb/III)

**Nitroimidazoles**
- Chagas backups

**Fexinidazole**
- Short benzi
- New combos
- Biomarkers

**Pediatric Benznidazole**
- POP/PK
- Pharmaco-vigilance

**DNDi only**

**Gaps & Challenges To Overcome:**
Innovation and Access

**DNDi**
Drugs for Neglected Diseases initiative

Presented at ICOPA conference, August 2014
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

- 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*


Still a Major R&D Deficit for Anti-Infectives

NCEs and New Products Deficit Analysis

- A major deficit persists for anti-infectives

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.
Broader Challenge in Discovery
Multi-Resistant Bacteria: Needs Are Clearly Recognized!

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

Could progress in virology benefit other viral neglected diseases?
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

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- 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

Limitations of LPV/r

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.)

source: G-Finder 2013 report
Research Efforts Must Stay Focused on Real Patient Needs to Deliver Adapted Tools

Best Science For The Most Neglected

Give a voice to neglected patients.
They exist, they must be heard.

Carmen Rosa, Bolivia