NEGLECTED DISEASES: THE ORPHANEST DISEASES OF ALL

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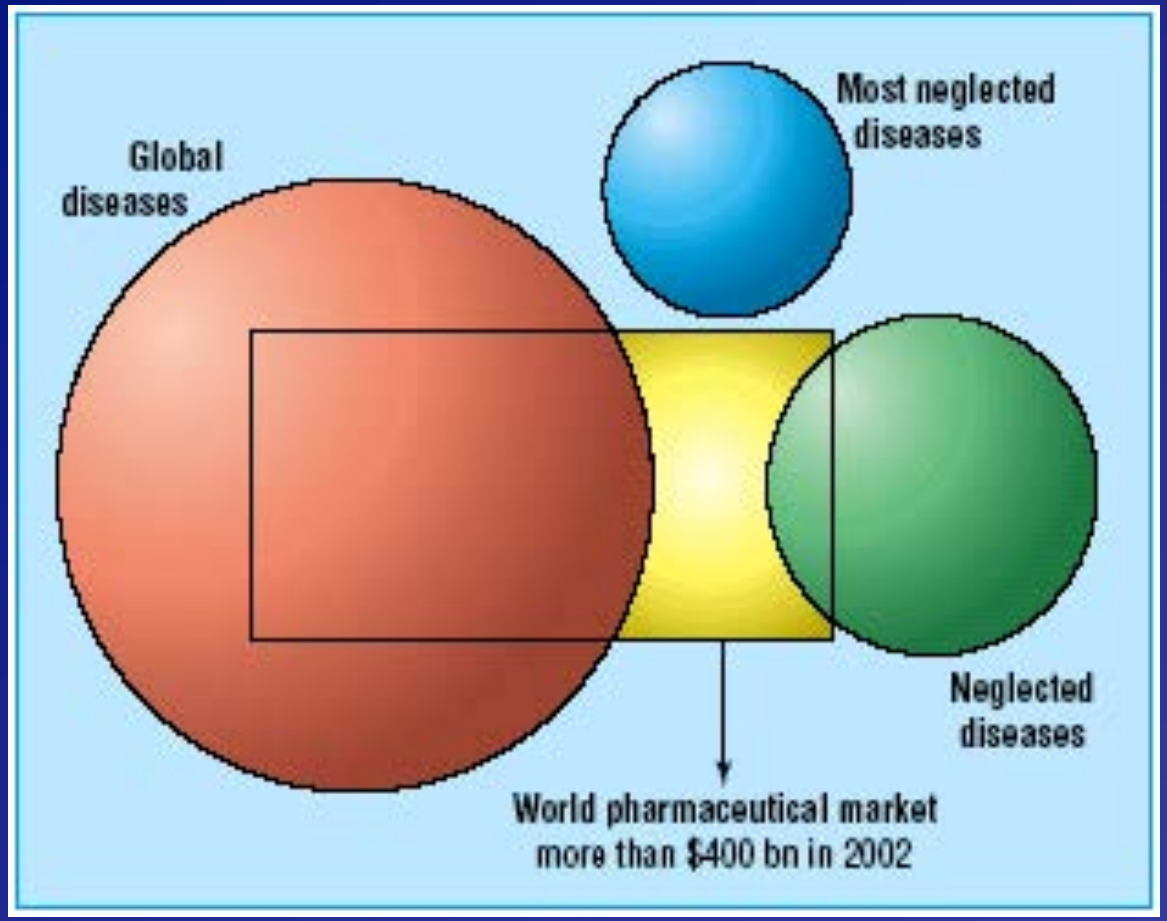
What is a neglected disease?



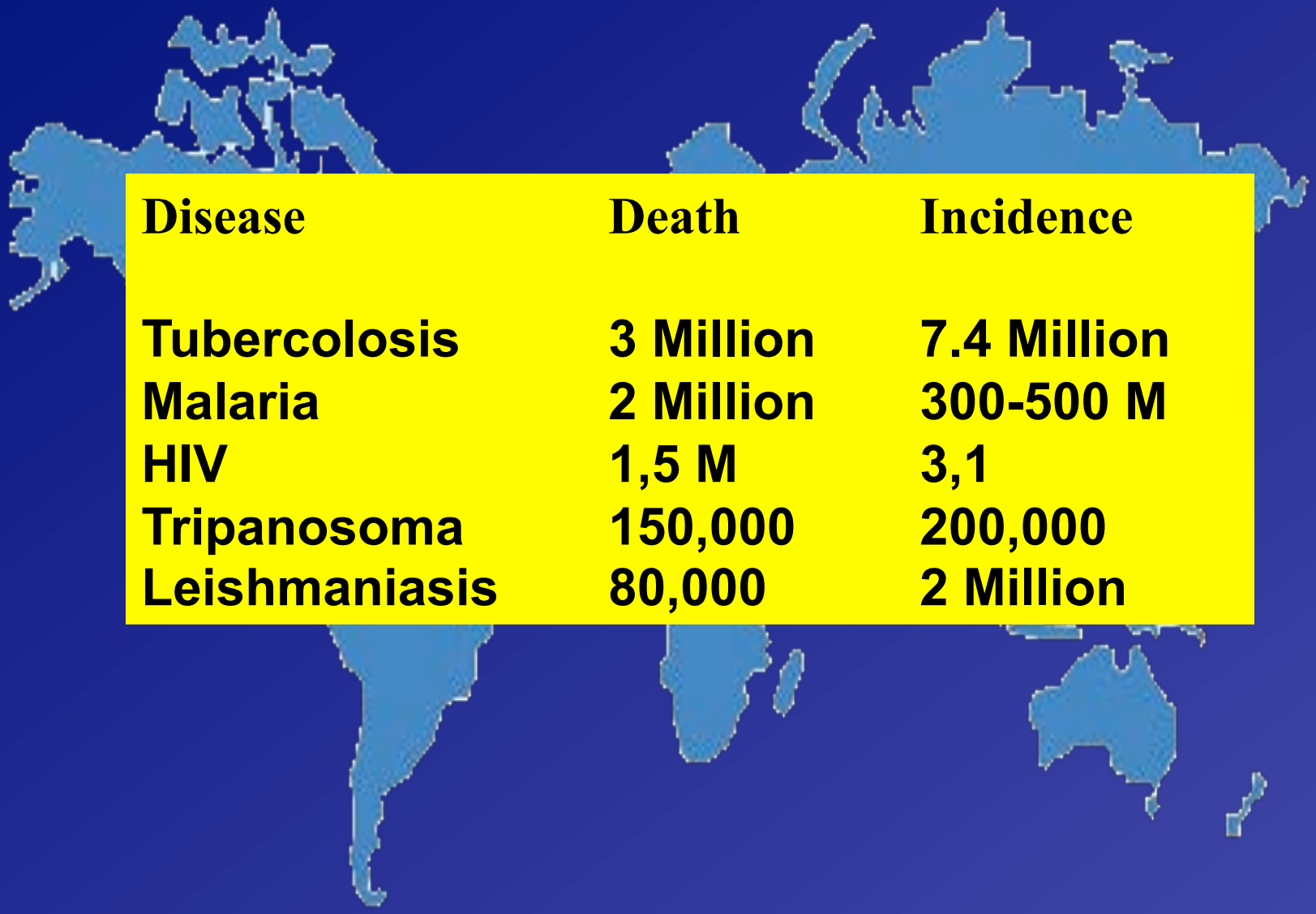
- Disproportionate effect on LMI countries
- Gap in attention from global R&D
- Shortage of safe, effective treatments

Yamey, Brit. Med. J. 2002

Operational definition of neglected diseases

- From the U.S. Orphan Drug Act
- Any disease that either:
  - affects less than 200,000 persons in the United States OR
  - for which there is no reasonable expectation that the cost of developing and making available in the U.S. a treatment...can be recovered from sales of the treatment.

Neglected diseases



Disease	Death	Incidence
Tubercolosis	3 Million	7.4 Million
Malaria	2 Million	300-500 M
HIV	1,5 M	3,1
Tripanosoma	150,000	200,000
Leishmaniasis	80,000	2 Million

Neglected disease: unresolved issues

Tubercolosis	⇒	**Resistance, no compliance**
Malaria	⇒	**Resistance, no new drugs farmaci**
HIV	⇒	**Cost of treatment**
Tripanosomiasis	⇒	**Only old, toxic drug available**
Leishmaniasia	⇒	**Old drugs, unreliable distribution**

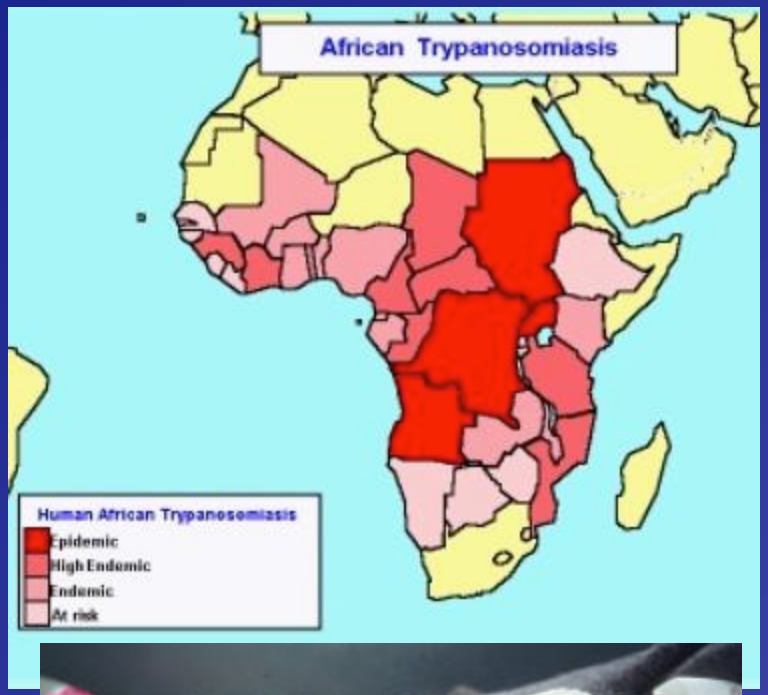
Examples – Lymphatic Filariasis

40 million people permanently debilitated or disfigured by the disease.
1/3 of cases in India, 1/3 in Africa, the rest scattered around LMI regions
Worms are transmitted by mosquito bite. Most obvious manifestation is elephantitis. Debilitating and stigmatizing disease
Treatment options are limited.

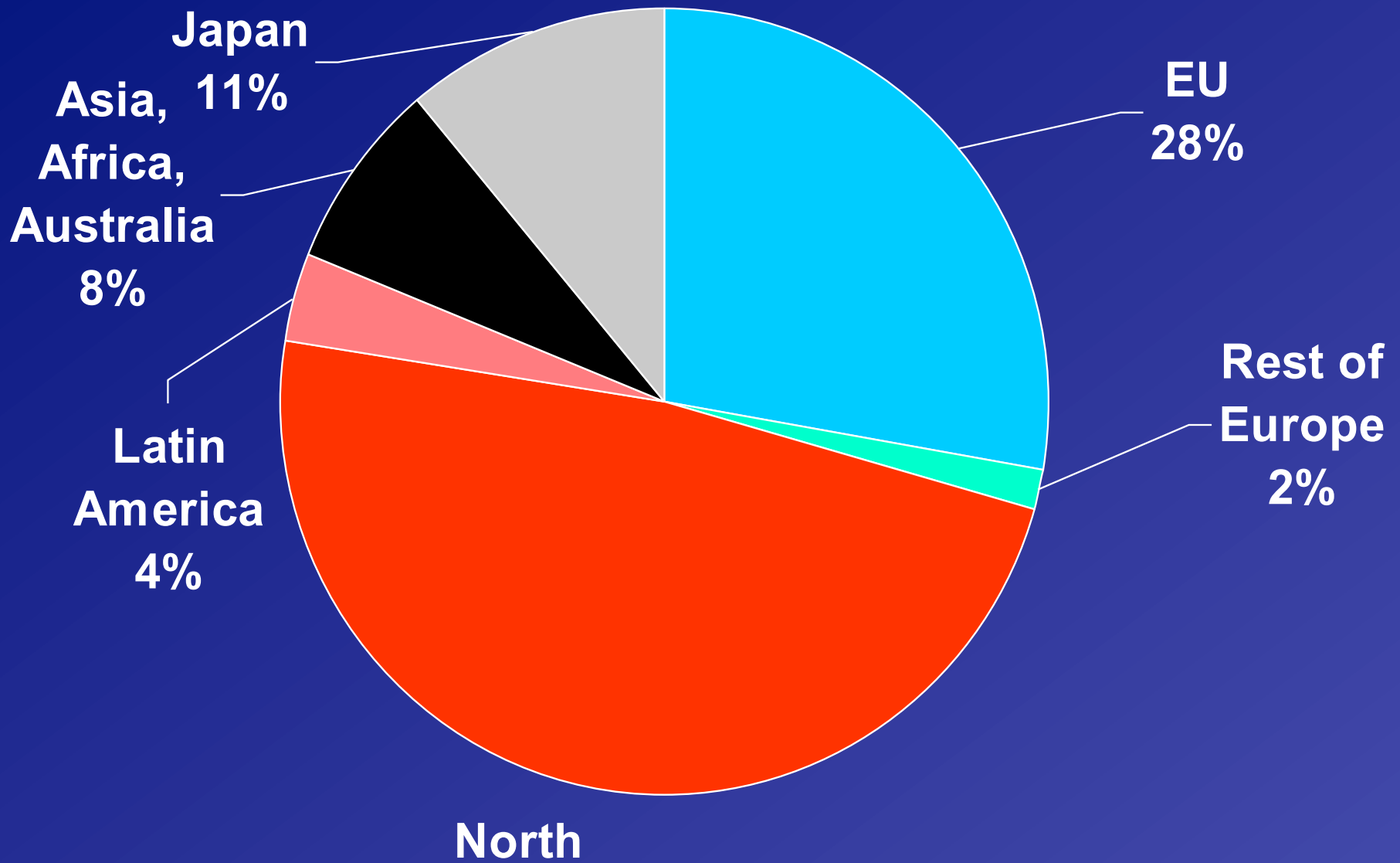
www.who.int

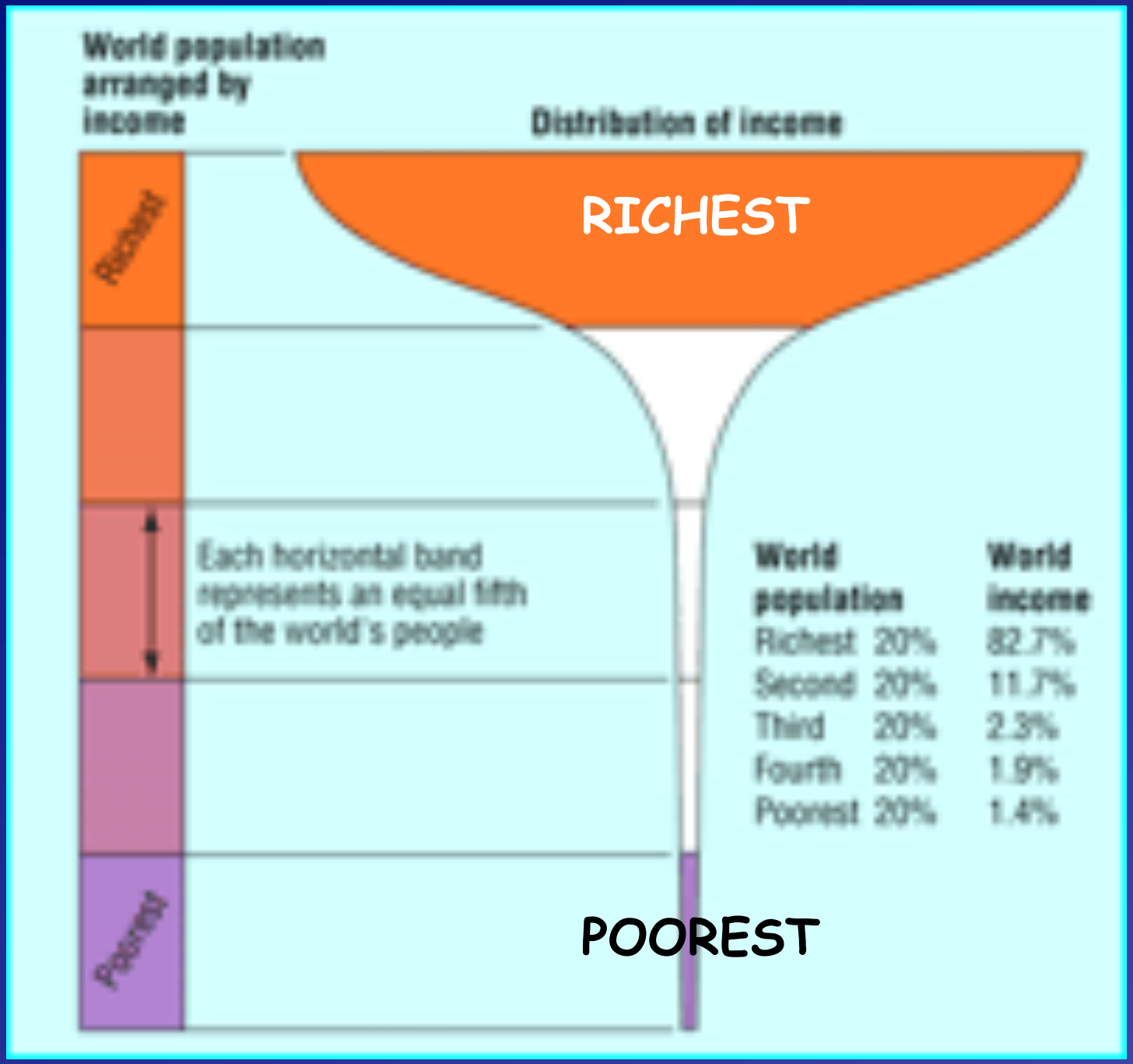
Examples – African Trypanosomiasis

- **Sleeping Sickness**
- **Between 300-500K deaths each year in Africa**
- **A local disease – prevalence as high as 20-50% in some areas**
- **Causes pain, headaches in its first phase, severe neurological disease – confusion, sleep cycle disruption, etc.**
- **Without treatment – fatal.**



No cash, no cure. The drug market share

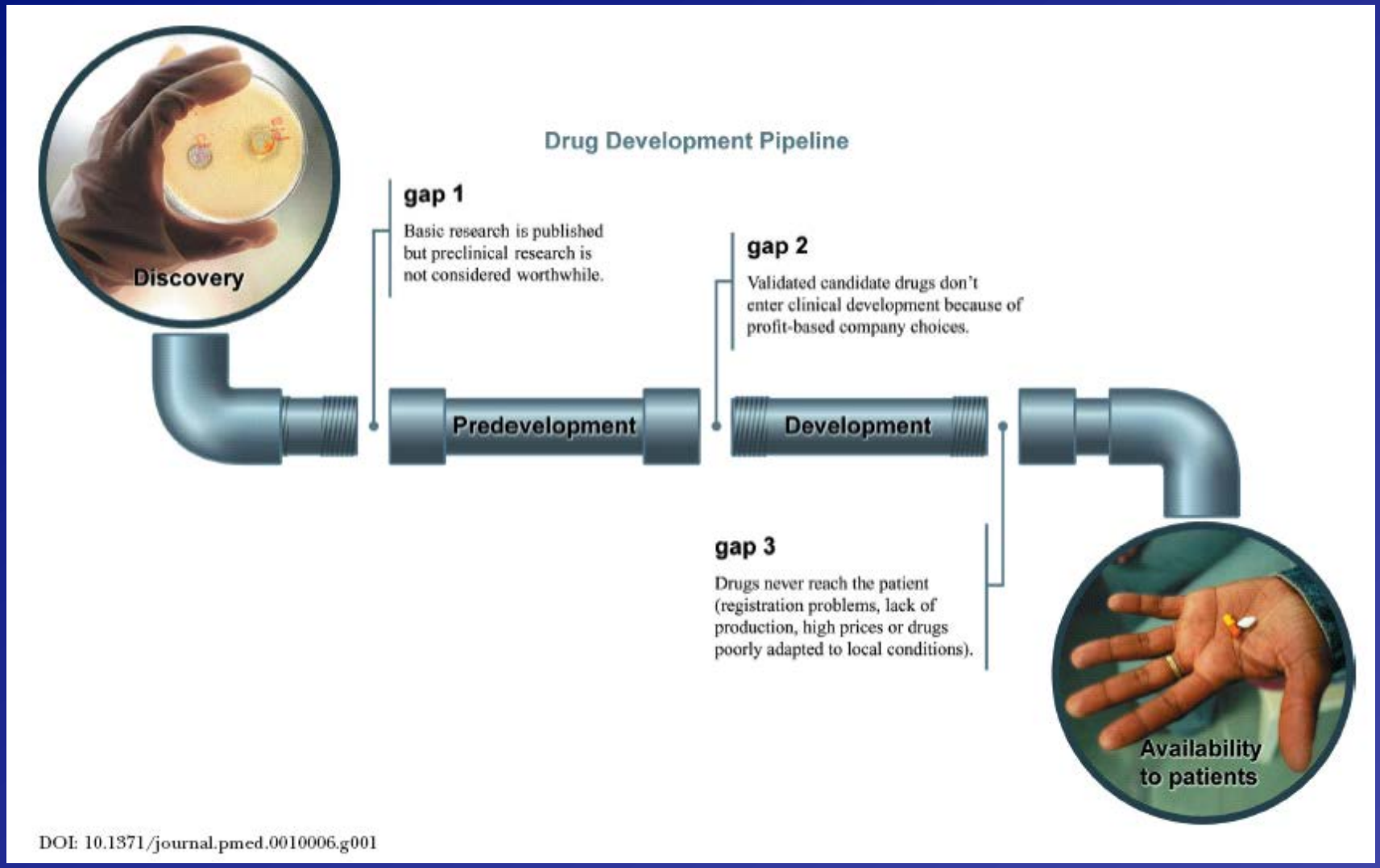



World population arranged by income
Distribution of income
Richest
Poorest
RICHEST
Each horizontal band represents an equal fifth of the world's people
World population
World income
Richest 20% 82.7%
Second 20% 11.7%
Third 20% 2.3%
Fourth 20% 1.9%
Poorest 20% 1.4%
POOREST

The 90/10 gap

- 90% of the diseased people benefit from less than 10% of worldwide biomedical research
- Only **1%** of 1400 new drugs which reached the market during the last 25 years are devoted to treat neglected diseases

The research gap



Pecoul, PLoS Med. 2004

Area	New Drugs 1975-2000
Nervous System	211 (15%)
Cardiovascular	179 (12.8%
Cancer	111 (8%)
Respiratory disease	89 (6.4%)
Infectious disease	224 (16.1%)
HIV/AIDS	26 (1.9%)
Tubercolosis	3 (0.2%)
Tropical diseases	13 (0.9%)
Malaria	4
Other drugs	579 (41.6%)
Totale	1393

Troullier et al, Lancet 2002

R&D of new drugs

R is (relatively) market - independent

D is (to a large extent) market-dependent

D costs > 10 x R costs

Hence the neglected diseases

- No market, No new medicines
- Even when some research is done, development is largely insufficient
- Vaccine are also neglected (3% of the drug market)

The landscape of R&D for neglected diseases

- Push and pull incentives
  - Push: direct funding or facilitation of research and development (grants)
  - Pull: promise downstream rewards by organizing a market for eventual end products (patents)

- Public-private partnerships (PPPs) – key mechanisms for push, provide funding and pipeline management
- Funding vehicles and advance-purchase contracts – important examples of pull

A Breakthrough in R&D for Neglected Diseases

- The landscape of neglected-disease drug development has changed dramatically during the past five years, thanks to the formation since 2000 of new pharmaceutical industry neglected-disease institutes, and the creation of new drug development public-private partnership

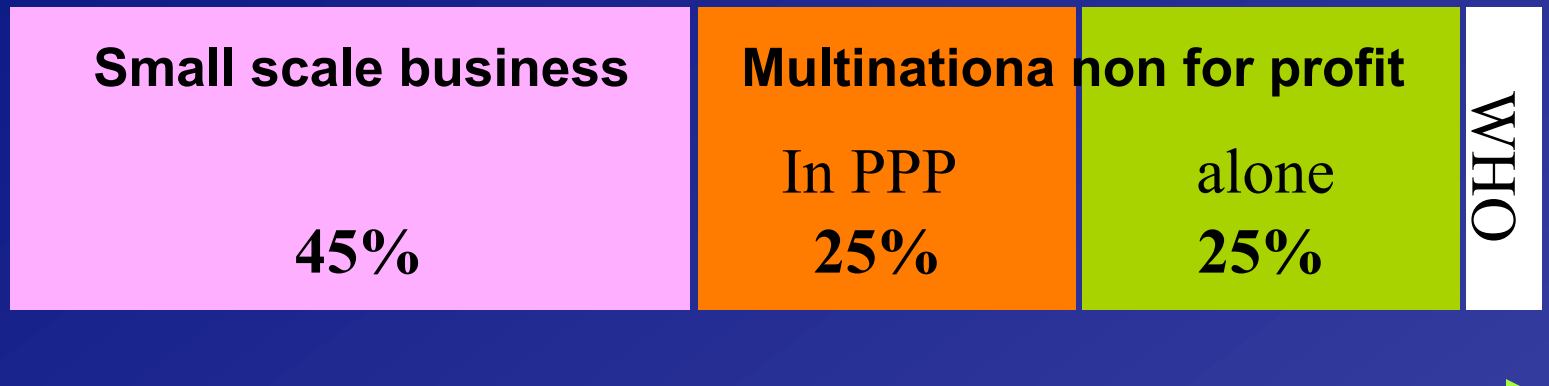
Moran et al. PLOS Sept 8, 2005

A Breakthrough in R&D for Neglected Diseases: New Ways to Get the Drugs We Need

- 63 ND drug projects
- 3 new industry ND institutes
- 18 ND drug projects in clinical trial and 2 in registration
- Translates into around 8-9 new drugs by 2020

Moran et al. PLOS Sept 8, 2005

New Ways to Get the Drugs We Need



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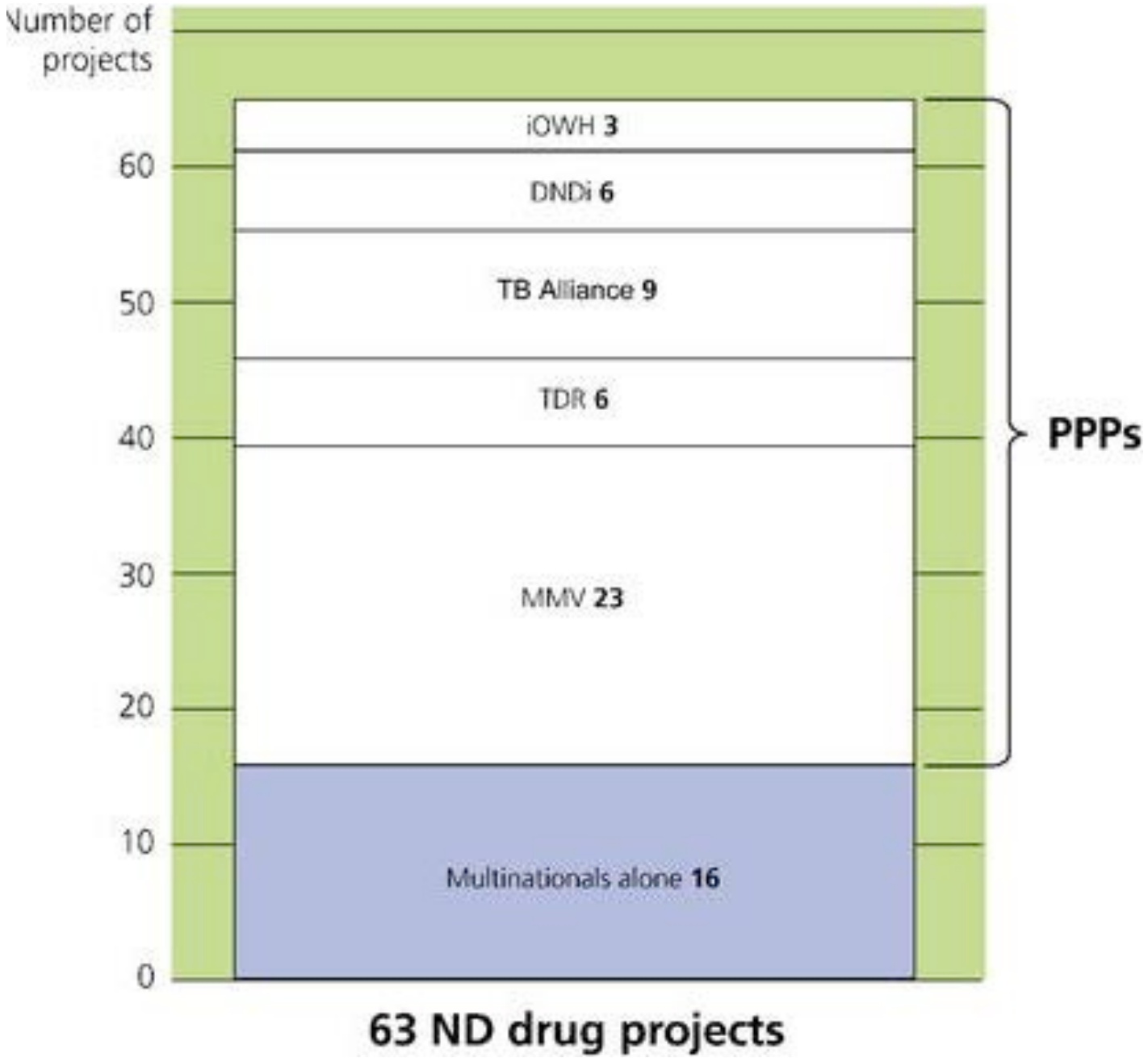

Number of projects
60
50
40
30
20
10
0
iOWH 3
DNDi 6
TB Alliance 9
TDR 6
MMV 23
Multinationals alone 16
PPPs
63 ND drug projects

DNDi

Drugs for Neglected Diseases *initiative*

About DNDI

- In 2003, seven organisations from around the world joined forces to establish DNDi:
  - five public sector institutions (Oswaldo Cruz Foundation from Brazil, Indian Council for Medical Research, Kenya Medical Research Institute, the Ministry of Health of Malaysia and France's Pasteur Institute)
  - A humanitarian organisation, Médecins sans Frontières
  - An international research organisation, the UNDP/World Bank/WHO's Special Programme for Research and Training in Tropical Disease

- DNDi doesn't conduct research and scientific work to develop drugs itself
- Instead, it capitalizes on existing, fragmented R&D capacity, especially in the developing world, and complements it with additional expertise as needed.

The role of multinational pharma companies

- There are currently 32 ND drug project by MPC
- 4 companies have ND divisions
  - GSK, Norvartis, AstraZeneca, Sanofi-Aventis
- They are working on a not-for profit basis

Key factors in the renewed interest of MPC in ND

- Early involvement in R&D
- Involvement of public partners in clinical development phase
- R&D costs subsidised by public parntership
- Distribution of drugs to not-for-profit prices

Longer-term business considerations for MPC being involved in ND drug development

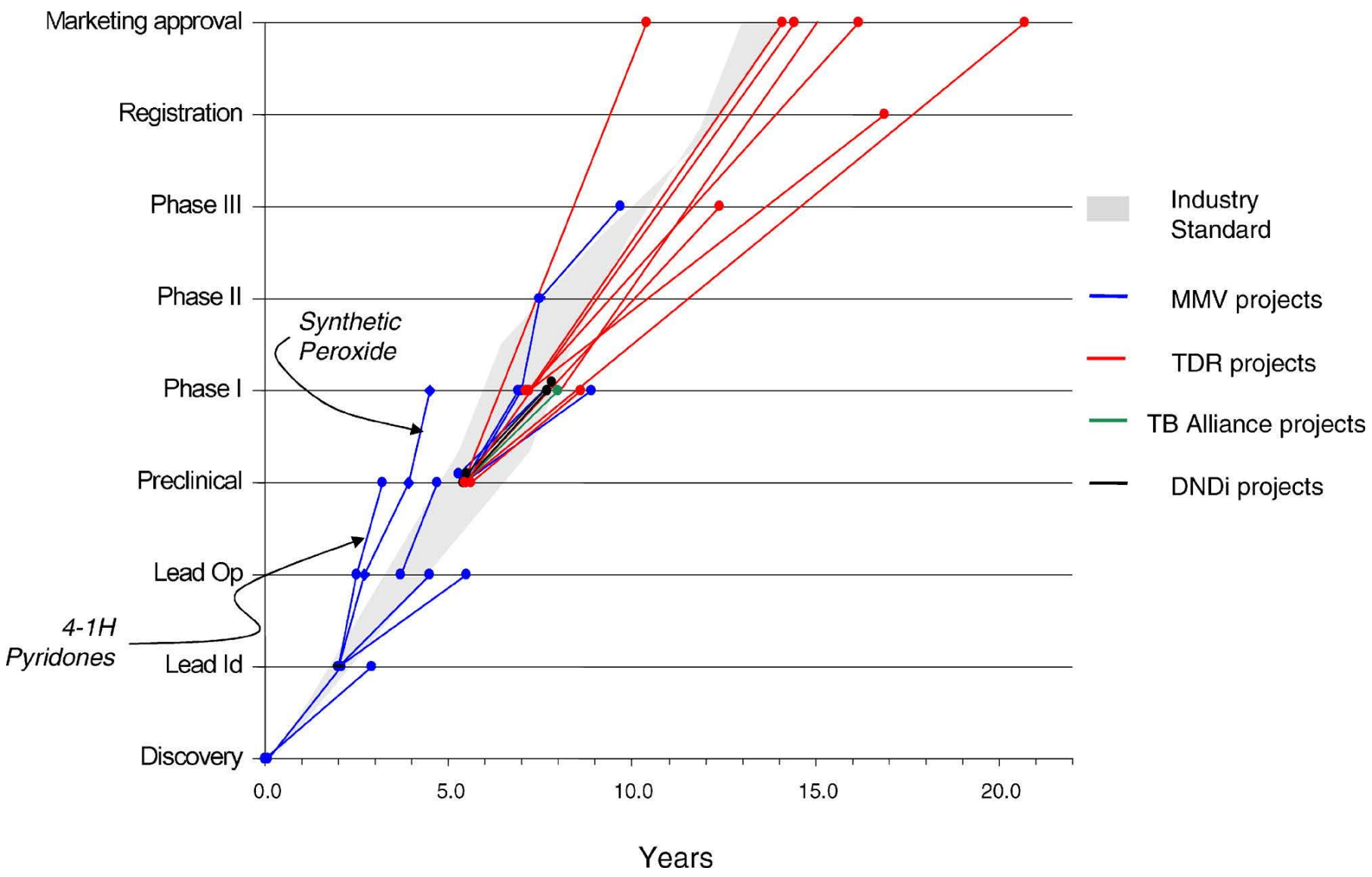
- Minimising the risk to their reputation stemming from growing public pressure on companies over their failure to address developing country needs
- Corporate social responsibility and ethical concerns
- Strategic considerations

- This renewed activity commenced largely in the absence of significant new government incentives and generally without public intervention
- Eighty percent of PPP drug development activity is funded through private philanthropy, while the industry institutes are largely self-funding

Where the money comes from...

Donor	Total funding ($)	% of total
Bill and Melissa Gates F.	158,757,717	58
MSF	29,738,133	11
Rockfeller F.	20,300,000	7.5
Wellcome Trust	2,827,504	1.1
SUBTOTAL	211,623,354	78.5
US Gov.	16,000,000	5.9
UK Gov.	10,909,468	4.1
Netherlands Gov.	10,489,255	3.9
Swiss Gov.	4,422,285	1.6
EU Commission	1,554,150	0.6
SUBTOTAL	43,585,077	16,2

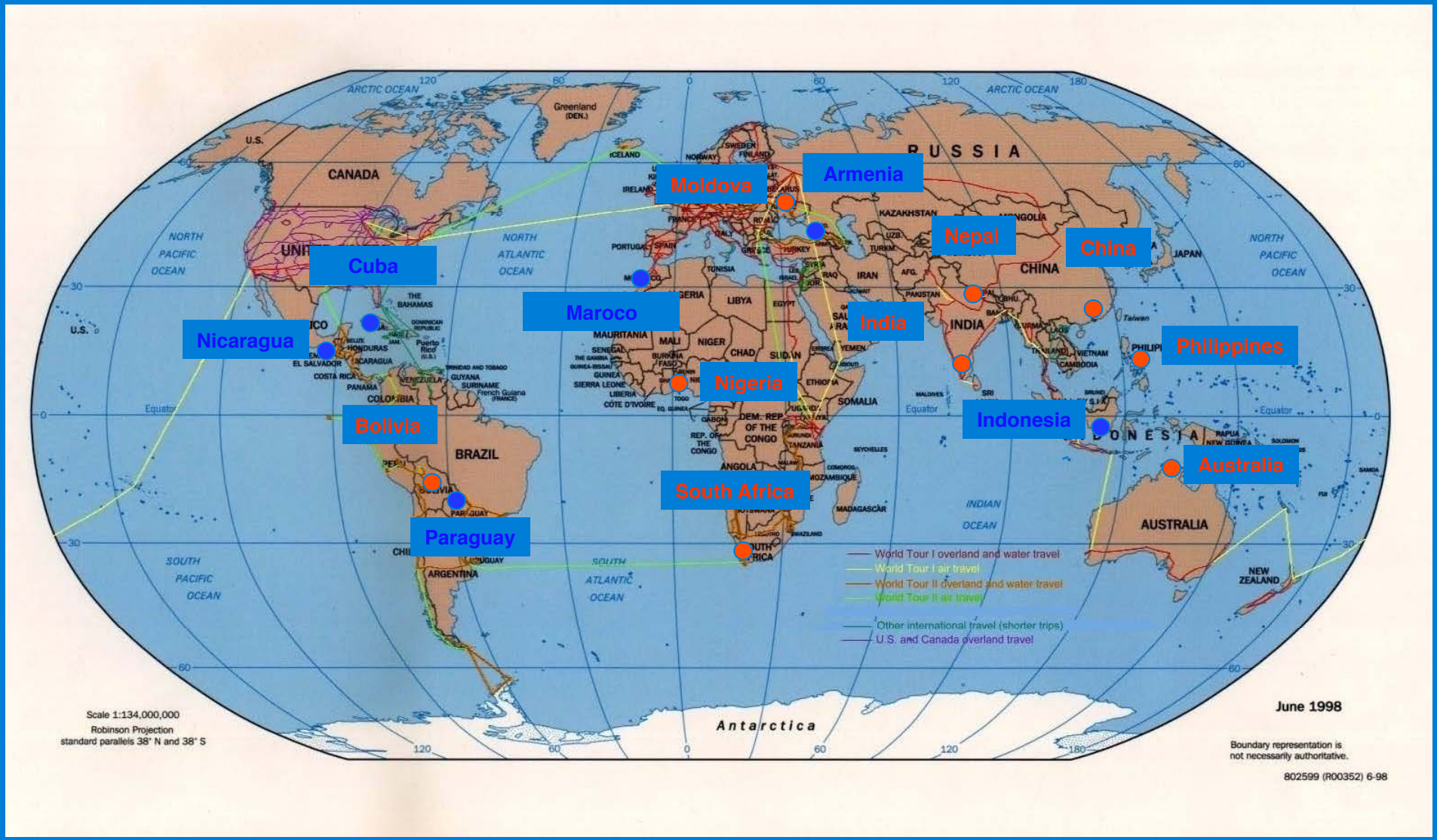
- Nearly half of all PPP projects (49%) and more than half of industry partnering projects (63%) are in the "breakthrough" category, compared to only 8% of drugs developed by industry working alone under the pre-2000 model.


Marketing approval
Registration
Phase III
Phase II
Phase I
Preclinical
Lead Op
Lead Id
Discovery
Synthetic Peroxide
4-1H Pyridones
0.0
5.0
10.0
15.0
20.0
Years
Industry Standard
MMV projects
TDR projects
TB Alliance projects
DNDi projects

Health outcome

- The PPP approach delivered the best health outcomes for developing country patients.
  - Ivermectin: halved the global burden of onchocerciasis between 1990 and 2000
  - Praziquantel: control schistosomiasis in Brazil, the Mahgreb, the Middle East, China, and the Philippines
  - Coartem tablets label extension for paediatric use: first safe, effective, suitable new anti-malarial for many years in Africa

- Government actions are still in the line of bringing big companies back to the field
- Instead, the PPP approach is likely to give better results and should be supported



- Established programs
- Programs in development

Chronic Disease Outreach Program in Australia

‘MARIO NEGRI’ PER L’AMERICA LATINA

El projecto de Enfermedades Renales en Bolivia

Population: 8.328.700
CNS: 2,255,510
Life expectancy: 62 yrs
Income per month: 70 $

ESRD: 650 pt/yr
Dialysis: 30 /yr
Transplant: 8 /yr

- Identify subjects with renal disease and provide the basis for building a regional and nationwide program of prevention of disease progression to ESRD

KIDNEY DISEASE SCREENING PROGRAM IN NEPAL

Screening Team

Community Screening at Dharan: 3218 people

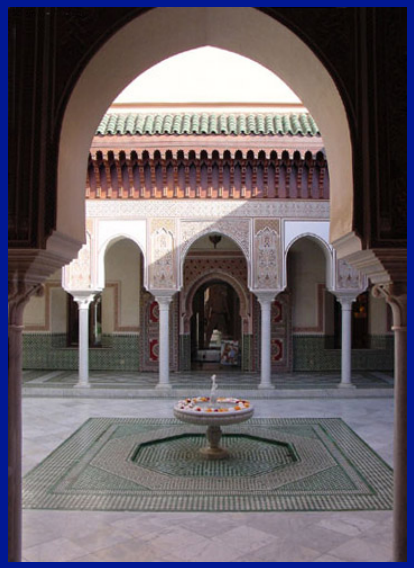
- ≥ 20 years of age
- Demographic profile
- Smoking and life style
- Dipstick proteinuria
- BP measurement
- Random blood Sugar

Follow up:

At Renal Disease Prevention Clinic of Bisheswar Prasad Koirala Institute of Health Sciences (BPKIHS)

THE PILOT EXPERIENCE OF ISN - WHO COOPERATION IN MOROCCO

An epidemiological - intervention study



- ISN-COMGAN Res Com (*M. De Broe*)
- WHO - Morocco (*R. Ben Ammar*)
- Morocco Ministry of Health
- Morocco Nephrology Society (*M. Benghanem Gharbi*)

- Khemisset (*rural*)
- El Jadida (*industrialized*)

25,000 people to be screened