NEGLECTED DISEASES

Luis Alejandro Barrera.
Director
Institute for the Study of Inborn Errors
Bogota, Colombia

Definition

"Diseases that affect almost exclusively poor and powerless people living in rural parts of low income countries". WHO 2002

Orphan diseases

- Orphan diseases comprise both rare diseases and neglected diseases. They are “orphan” with regards to research focus and market interest, as well as of public health policies. Eurordis

List of Neglected Diseases (NTDs)

- There are 14 diseases listed as NTDs: Buruli ulcer, Chagas disease, cholera, dengue/dengue haemorrhagic fever, lepdracunculiasis (guinea-worm), endemic treponematoses, human African trypanosomiasis (sleeping sickness), leishmaniasis, leprosy, lymphatic filariasis, onchocerciais, schistosomiasis, soil-transmitted helminthiasis and trachoma.

Prevalence

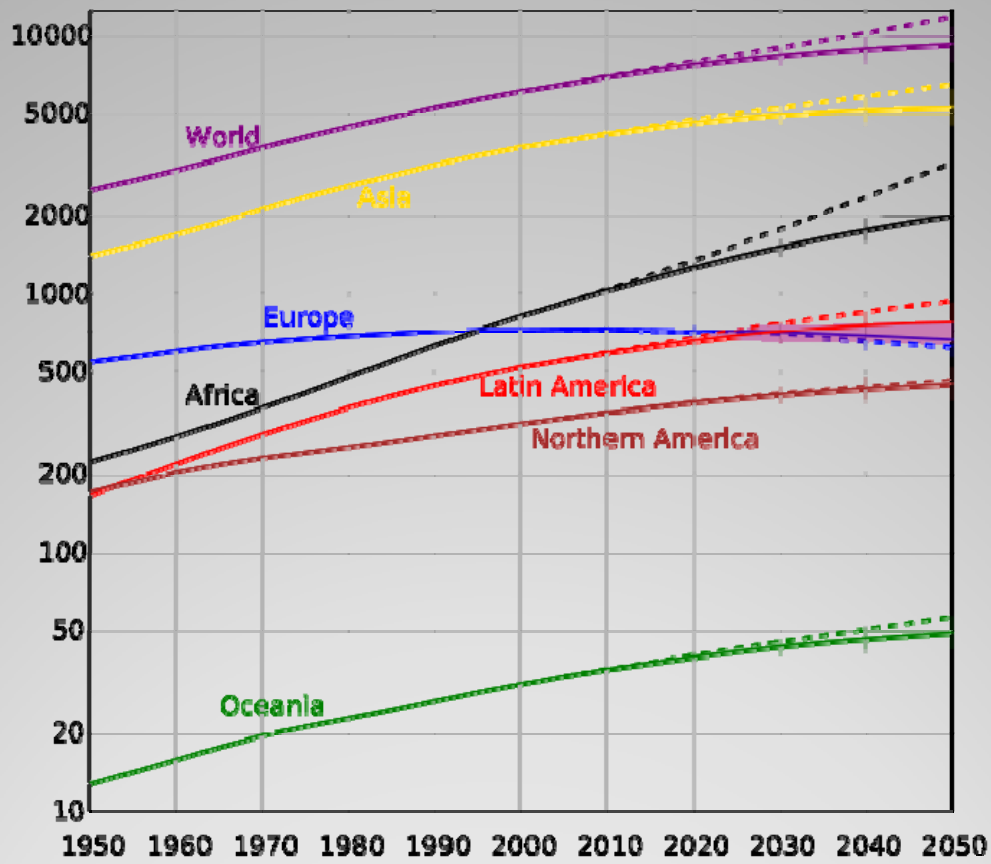
- **Chagas disease**
  From 16 million to 18 million people are infected, mostly in Latin America.
- **Leishmaniasis**
  More than 12 million people are infected. The most severe and rapidly fatal form of the disease, visceral leishmaniasis, is most frequent in India, around 500,000 new cases annually.
- **Schistosomiasis**
  More than 200 million people are infected. Around 20 million show severe consequences.
- **Lymphatic filariasis**
  Around 120 million people are infected.
- **Blinding trachoma**
  Around 80 million people are infected, of which 6 million are blind

- Over 1 billion people suffer from one or more neglected tropical diseases. Aggravated by war ignorance, natural disaster and population growth in those countries. Endemic in more than one hundred of the poorest countries in Africa, Asia and Latin America most often with multiple diseases affecting any given community.
- Over 350 million people already disabled or severely impaired, with many more infected.
- Generally non-fatal, but cause enormous chronic disability and suffering as well as greater susceptibility to other often fatal diseases.
- Tremendous economical loss in poor economies. Over 10 billion anually.

IMPACT

Impact on Development

- Health problems lead to:
  - Poor school performance, loss of productivity, due to dissability. Country´s development slowed down.
  - Treating these will produce more vigorous economies and result in a better quality of life for some of the world's poorest communities.



Continent Population Growth

- The Constitution of the World Health Organisation (WHO) affirms that the highest attainable standard of health is a fundamental right of every human being.

- There is an urgent need to break a vicious correlation between poverty and neglected diseases.

"Conditions of poverty perpetuate these diseases, while the health impact of these diseases perpetuates poverty".

Address to the WHO Global Partners Meeting on Neglected Tropical Diseases

Director-General of the World Health Organization. Geneva, Switzerland
19 April 2007

NTDs Facts

1. Not an immediate threat to wealthier societies. Hidenn diseases affecting people in remote areas.
2. For some NTDs, there are simple and affordable diagnostic tools.
3. Several NTDs are transmitted by insect vectors.
4. Some medicines for NTDs are effective, “not expensive” and easy to administer. Others are toxic and ineffective.
5. Guinea worm is transmitted exclusively by drinking contaminated water and it is now only found in remote rural villages.
6. Buruli ulcer, leismaniasis and lymphatic filariasis all deform and disfigure to such an extent that those affected can be ostracised.

- Because they are not a public health priority in industrialized countries, little research and drug development is performed for these diseases.
- They have been "neglected" by the pharmaceutical industry. They have been neglected by local governments.They have been neglected by world society.

	Drug Market	Population
N. America	40.2	5.1
Europe	26.6	12.1
Japan	15.8	2.1
Africa and Asia	10.6	72.3
Latin America	6.6	8.4

- Only 13 drugs since 1975.
- Strategies. Non- commercial motives, positioning in emerging countries.Non profit no loss model, **private public partnership model (PPP),**
- There are now over 60 drug research projects underway.
- In the four years prior to 2004 Public-Private Partnerships spent £62m ($112m) on a combined portfolio for 46 drug projects.
- According to a report in *The New Landscape of Neglected Disease Drug Development*, a company will have to invest around £220 ($400m) to bring just one commercial drug to the market.

Joint-work Importance

Solutions

- ✓ Effective incentives for the development of new drugs.
- ✓ Improvement of health Systems.
  - ✓ Local actions. Centralized purchasing.
  - ✓ Improvement in medicine delivery to rural communities, through schools.
  - ✓ Early education.
- ✓ Global actions. Funding. International partnership. Civil societies.

- To include the topic of NTDs in the discussion of economic agenda, world development forum bilateral and multilateral trade related treaties, world health agreements and international law.
- To study and promote incentives for the drug development and distribution for NTDs, including exceptions to the patent agreements for these medicines, multilateral collaboration cooperative work among international agencies, corporate partners, academic institutions, faith-based groups, and non-governmental organizations.

- Education. About orphan diseases.
- Public awareness. About impact and solutions. To foster education in developing countries in universities, high and elementary schools, and all massive media.
- Campaigns which favour a world free of, hunger and ignorance without parochialism and territorialism.
- Campaigns in favour of the fundamental right to health for every world citizen.
- Campaigns in favour of adherence to international human-right laws.

ACTIONS TO BE TAKEN BY CIVIL SOCIETY

5.2. Neglected diseases

- Tremendous costs for medical treatments that drain resource-scarce health systems
- Equally high social and economic toll, as physical incapacitation limits school attendance and impairs work productivity, at a cost of over $10 billion annually in very poor economies.

- 'For many years, it was the sad truth that virtually nothing was happening in neglected disease R&D. But we are now seeing some really promising developments that simply did not exist 10 years ago. In reality, the current problem is not that nothing is happening - it is that policy-makers and government donors are still working off this old R&D script. As a result, policies have tended to focus on how to get R&D started but have largely failed to support neglected disease initiatives that are already working on- and in some cases already delivering - new drugs.

- NTDC is composed of individual disease alliances, international agencies, corporate partners, academic institutions, faith-based groups, and non-governmental organizations. NTDC is composed of individual disease alliances, international agencies, corporate partners, academic institutions, faith-based groups, and non-governmental organizations.

- • Generally non-fatal, but base diseases of poverty that cause enormous chronic disability and suffering as well as greater susceptibility to other often fatal diseases.
- • Over 50 million future years of disability-free life lost.
- • Endemic in over 100 of the poorest countries in Africa, Asia and Latin America – most often with multiple diseases affecting any given community.
- • Over 3 billion children, women and men at risk
- • Over 350 million people already disabled or severely impaired, with many more infected-
- • Tremendous costs for medical treatments that drain resource-scarce health systems-
- • Equally high social and economic toll, as physical incapacitation limits school attendance and impairs work productivity, at a cost of over $10 billion annually in very poor economies.

Their Collective Impact

- • Generally non-fatal, but base diseases of poverty that cause enormous chronic disability and suffering as well as greater susceptibility to other often fatal diseases
- • Over 50 million future years of disability-free life lost (or, in comparative terms, over half of the global disease burden from HIV/AIDS)
- • Endemic in over 100 of the poorest countries in Africa, Asia and Latin America – most often with multiple diseases affecting any given community
- • Over 3 billion children, women and men at risk
- • Over 350 million people already disabled or severely impaired, with many more infected
- • Tremendous costs for medical treatments that drain resource-scarce health systems
- • Equally high social and economic toll, as physical incapacitation limits school attendance and impairs work productivity, at a cost of over $10 billion annually in very poor economies.

Their Collective Impact

Gatifloxacin* FDC	TB	WHO/TDR EC OFLOTUB Consortium	Lupin	India	PPP manufacturing partner Possible development partner
Paromomycin*	Leishmaniasis	iOWH/IDA WHO/TDR	Company name not known	India	PPP manufacturing partner
Impavido®	Leishmaniasis	Zentaris WHO/TDR	German Remedies	India	Small company development and distribution partner
Synthetic peroxide*	Malaria	MMV	Ranbaxy	India	Main industry partner: development, trial manufacture, and likely final manufacture and distribution
Pyronaridine-artesunate* FDC	Malaria	MMV	Shin Poong	South Korea	Main industry partner: development, manufacture and distribution
Artesunate-mefloquine FDC	Malaria	DNDi WHO/TDR	Far Manguinhos	Brazil	Main industry partner: development and manufacture

* Clinical trial stage

- Other rare diseases, such as Huntington disease, Spinocerebellar Ataxias, Charcot-Marie-Tooth disease, Amyotrophic Lateral Sclerosis, Kaposi's Sarcoma and thyroid cancer, are specific to adulthood. Whilst many diseases cause symptoms in childhood, these symptoms may not translate into a specific rare diagnosis for years.

- We have included drug development activity only as it relates to the ten neglected diseases listed by the World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO/TDR). These are leishmaniasis, schistosomiasis,
- Human onchocerciasis is a severely disabling filarial disease that is endemic in 28 African countries, six Latin American countries and Yemen. The disease causes a high burden of blindness and visual loss, along with itching and other severe dermal manifestations.
- lymphatic filariasis,
- Chagas disease,
- malaria,
- leprosy,
- African trypanosomiasis,
- tuberculosis
- dengue.

Hookworm, roundworm or diarrhoeal illnesses, are excluded although in many cases our conclusions could equally apply to these.

- It is also to be underlined that **relatively common conditions can hide underlying rare diseases, e.g. autism (in Rett syndrome, Usher syndrome type II, Sotos** Cerebral Gigantism, Fragile X, Angelman, Adult Phenylketonuria, Sanfilippo,...) or Epilepsy (Shokeir syndrome, Feigenbaum Bergeron Richardson syndrome, Kohlschutter Tonz syndrome, Dravet syndrome...). For many conditions described in the past as clinical ones such as mental deficiency, cerebral palsy, autism orpsychosis, a genetic origin is now suspected or has already been described. In fact, a rare disease can be masked by a host of other conditions, which may lead tomisdiagnosis.

- Rare diseases are severe to very severe, chronic, often degenerative and lifethreatening;
- · The onset of the disease occurs in childhood for 50% of rare diseases;
- · Disabling: the quality of life of rare diseases patients is often compromised by the lack or loss of autonomy;
- · Highly painful in terms of psychosocial burden: the suffering of rare disease patients and their families is aggravated by psychological despair, the lack of therapeutic hope, and the absence of practical support for everyday life;
- · Incurable diseases, mostly without effective treatment. In some cases, symptoms can be treated to improve quality of life and life expectancy;
- · Rare diseases are very difficult to manage: families encounter enormous difficulties in finding adequate treatment.

- Firstly, rare diseases are characterized by their low prevalence (less than 1/2,000) and their heterogeneity. They affect both children and adults anywhere in the world.
- Because rare disease patients are a minority, there is a lack of public awareness; these diseases do not represent a public health priority, and little research is performed. The market is so narrow for each disease that the Pharmaceutical industry is reticent to invest in research and to develop treatments for rare diseases.
- There is therefore a need for economic regulation, such as national incentives, as provided for in the EC Orphan Drug Regulation

40% of patients participating in the survey received a wrong diagnosis before
being given the right one. Among them:

- 1 out of 6 underwent surgical treatment based on this wrong diagnosis;
- 1 out of 10 underwent psychological treatment based on this wrong diagnosis.

Lack of access to correct diagnosis: the period between the emergence of the first symptoms and the appropriate diagnosis involves unacceptable and highly risky delays, as well as wrong diagnosis leading to inaccurate treatments: the pre-diagnosis maze;

Lack of information: about both the disease itself and about where to obtain help, including lack of referral to qualified professionals;

· **Lack of scientific knowledge: this results in difficulties in developing** therapeutic tools, in defining the therapeutic strategy and in shortage of therapeutic products, both medicinal products and appropriate medical devices;

· **Social consequences: living with a rare disease has implications in all areas** of life, whether school, choice of future work, leisure time with friends, or affective life. It may lead to stigmatisation, isolation, exclusion from social community, discrimination for insurance subscription (health insurance, travel insurance, mortgage), and often reduced professional opportunities (when at all relevant);

· **Lack of appropriate quality healthcare: combining the different spheres of** expertise needed for rare disease patients, such as physiotherapist, nutritionist, psychologist, etc… Patients can live for several years in precarious situations without competent medical attention, including rehabilitation interventions; they remain excluded from the health care system, even after the diagnosis is made;

· **High cost of the few existing drugs and care: the additional expense of**

coping with the disease, in terms of both human and technical aids, combined with the lack of social benefits and reimbursement, cause an overall pauperisation of the family, and dramatically increases the inequity of access to care for rare disease patients.

· **Inequities in availability of treatment and care: innovative treatments are**

often unevenly available in the EU because of delays in price determination and/or reimbursement decision, lack of experience of the treating physicians (not enough physicians involved in rare diseases clinical trials), and the absence of treatment consensus recommendations.

The consequences of diagnosis delay are tragic:

- Other children born with the same disease;
- Inappropriate behaviour and inadequate support from family members;
- Clinical worsening of the patient's health in terms of intellectual, psychological and physical condition, even leading to the death of the patient;
- · Loss of confidence in the healthcare system.

Up to 50% of patients have suffered from poor or **unacceptable conditions of disclosure. In order to avoid face-to-face disclosure, doctors often give the terrible** diagnosis by phone, in writing - with or even without explanation – or standing in the corridor of a hospital.

Orphan drugs are medicinal products intended for the diagnosis, prevention or treatment of rare diseases. These drugs are called "orphan" because, under normal market conditions, it is not cost-effective for the pharmaceutical industry to develop and market products intended for only a small number of patients suffering from rare conditions. The drugs developed for this unprofitable market would not be financially viable for the patent-holding manufacturer. For drug companies, the cost of bringing an orphan medicinal product to the market would not be recovered by the expected sales of the product. For this reason, governments and rare disease patient organizations have emphasized the need for economic incentives to encourage drug companies to develop and market medicines intended for the "orphaned" rare disease patients.

It is also important to underline that, in a family where a child has a rare disease, most often one of the parents – usually the mother – either completely stops or significantly reduces work remunerated outside home. As a consequence, **while expenses increase dramatically, incomes is considerably reduced.**