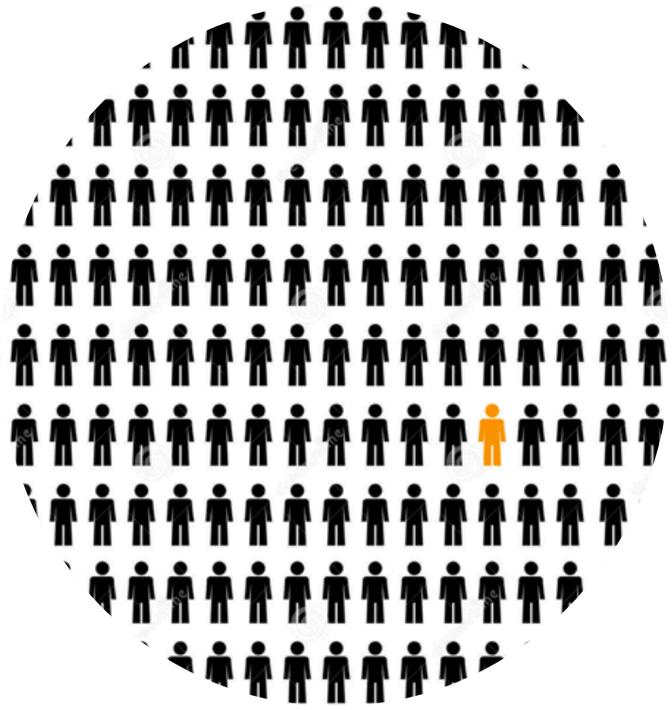
Pharmaceutical Development for Rare & Neglected Diseases



Robert Pipal

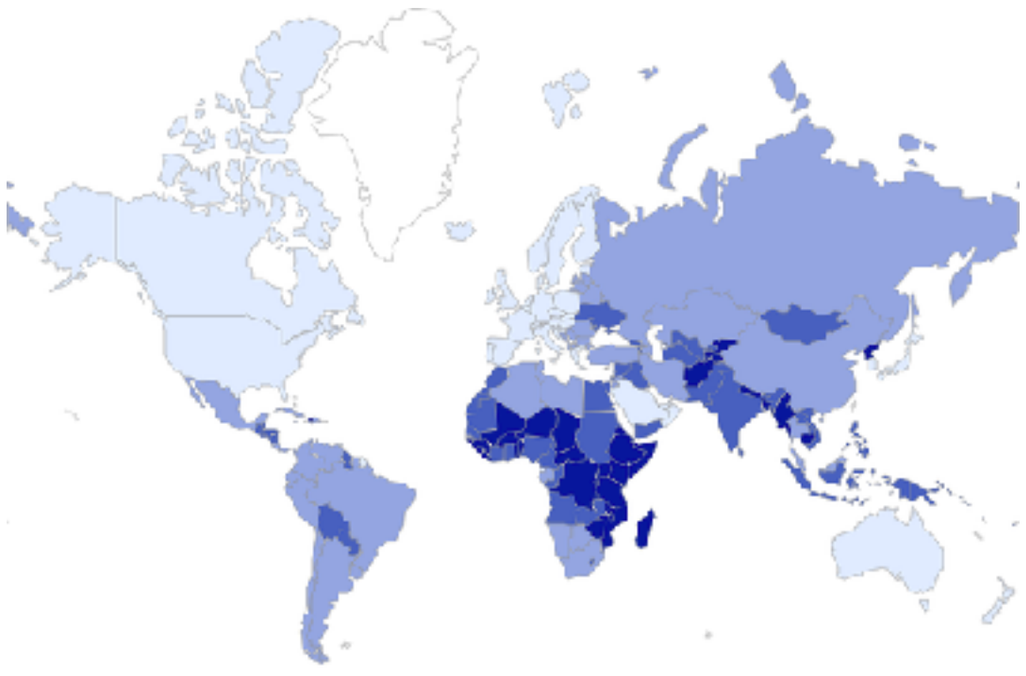
MacMillan Group Meeting

October 7, 2020

Introduction to Rare & Neglected Diseases

How are pharmaceuticals developed for rare & neglected diseases if not economically viable?

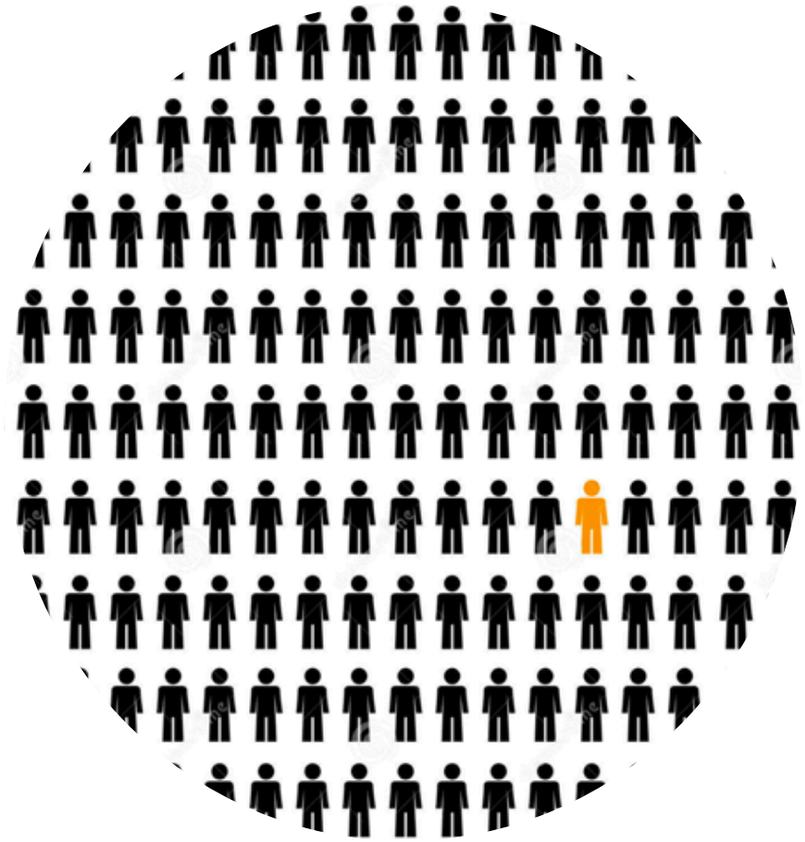
rare diseases *affect less than 200,000 people in the US, or 1 in 1,500 people*



neglected (tropical) diseases *are prevalent, but affect poorer countries*

Pharmaceutical Development for Rare & Neglected Diseases

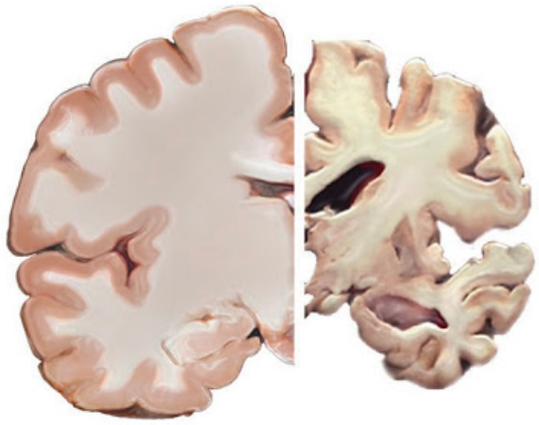
- Introduction
- **Rare Diseases**
  - Impact of Rare Diseases
  - Orphan Drug Act (ODA)
  - Examples of Orphan Drugs
- Neglected Tropical Diseases (NTDs)
  - Global Impact of NTDs
  - Reasons for Neglect
  - World Health Organization Intervention
  - Solutions for NTD Treatment/Prevention
  - Case Studies (3)



Common vs. Rare Diseases

hypertension

1 in 3



Alzheimer's disease

1 in 60

Parkinson's disease

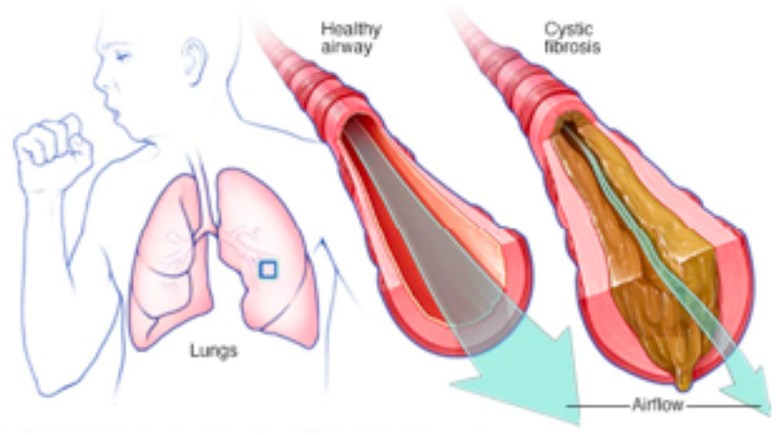
1 in 300

common diseases

rare diseases

sickle cell anemia

1 in 3,500



cystic fibrosis

1 in 11,000

fibrodysplasia ossificans

1 in 2,000,000

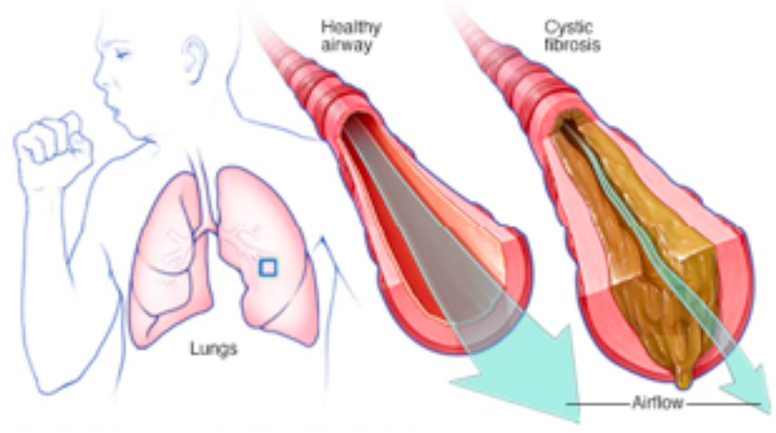
Common vs. Rare Diseases

- 6000–8000 rare diseases exist
- 80% are genetic diseases appearing early in life
- 30% of children with rare diseases die before 5
- affect 6–8% of the global population

drugs which target rare diseases affecting less than 200,000 people in the USA are defined as orphan drugs

rare diseases

sickle cell anemia
1 in 3,500



cystic fibrosis
1 in 11,000

fibrodysplasia ossificans
1 in 2,000,000

Orphan Drug Act (ODA) of 1983

National Organization for Rare Disorders lobbyed for specific legislation encouraging pharmaceutical companies to develop orphan drugs, establishing task force on orphan drugs:

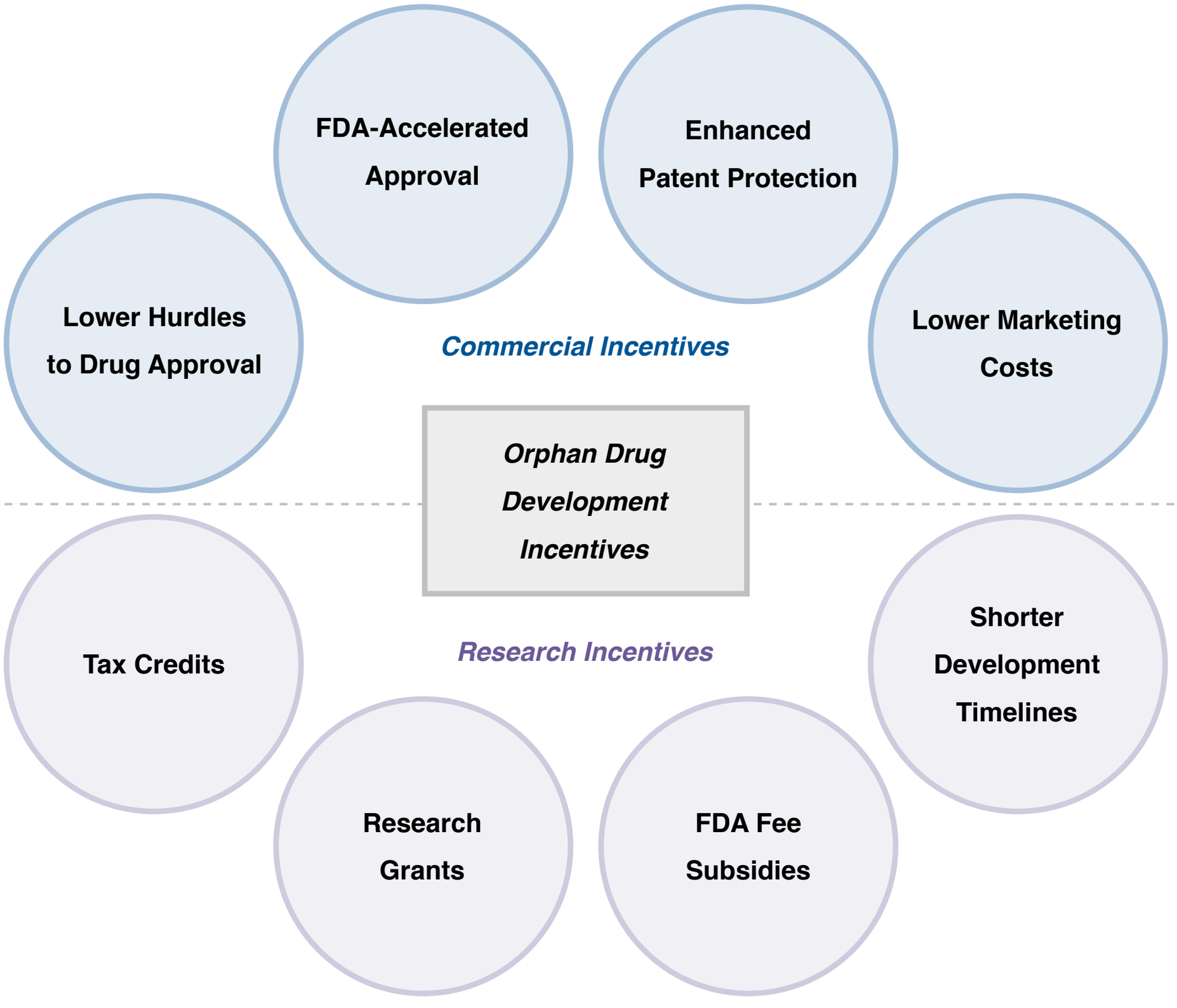
"Whenever a drug has been identified as a potentially life-saving or otherwise of unique major benefit to some patient, it is the obligation of society, as represented by government, to seek and to make that drug available to that patient"

The Orphan Drug Act was passed in 1983 by President Reagan, incentivizing pharmaceutical development for rare diseases

countries including Australia, Singapore, Japan, Canada, Taiwan, and the European Union have passed legislation inspired by the Orphan Drug Act

Melnikova, I. *Nat. Rev. Drug Discov.* **2012**, *11*, 267.

Orphan Drug Act (ODA) of 1983

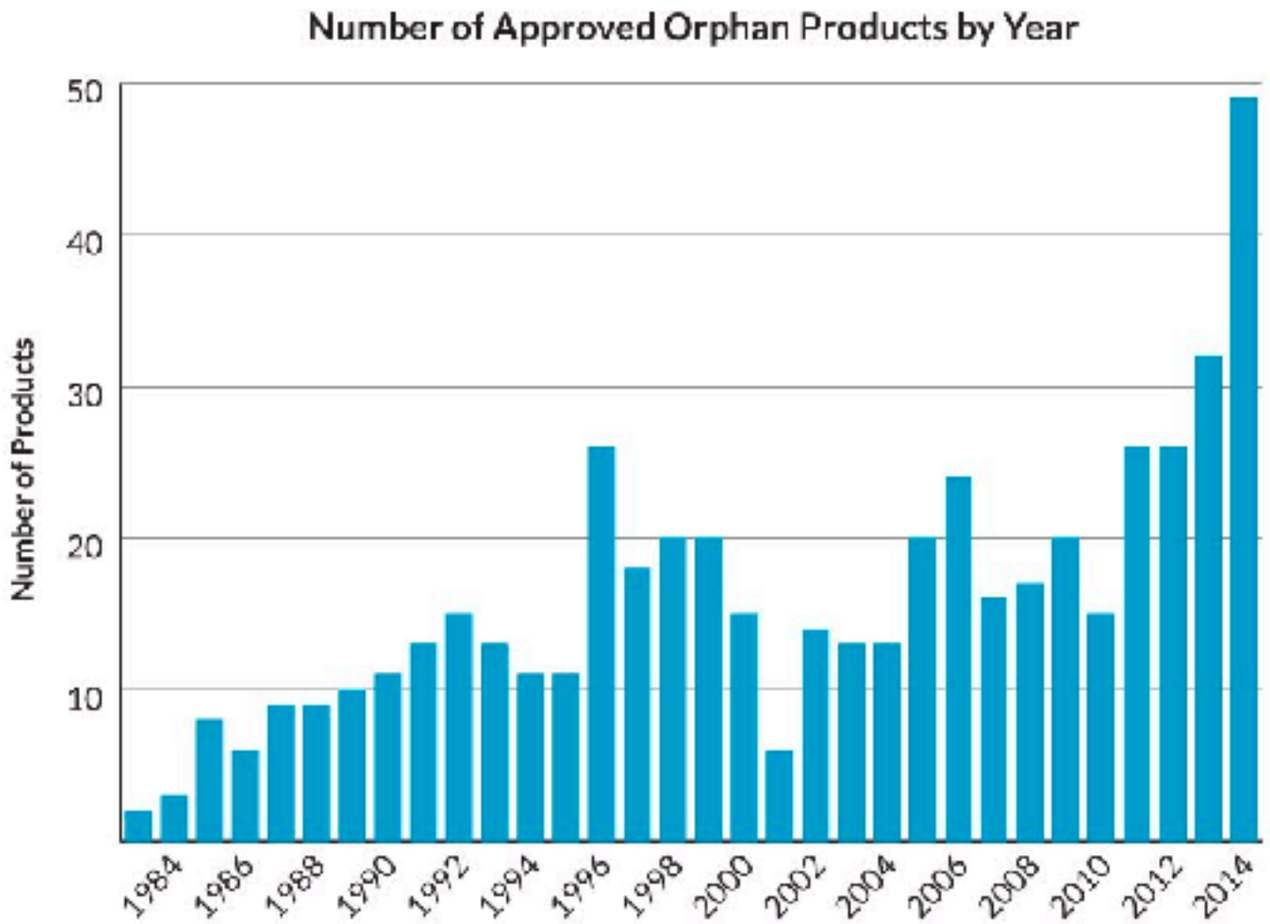


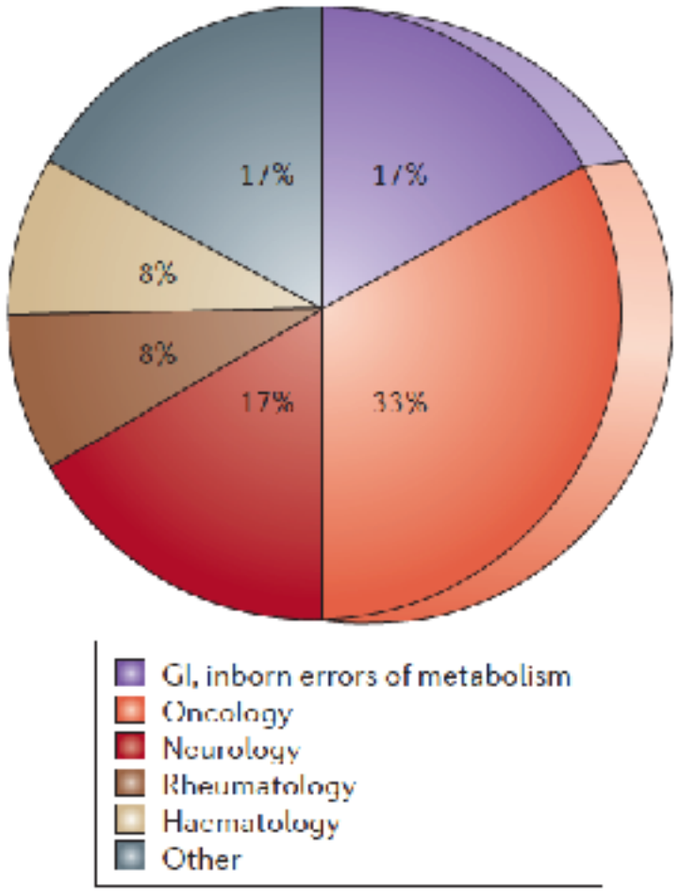
Bhattacharjee, S.; Nandi, S. *Cancers* **2018**, *10*, 298.

Impact of the Orphan Drug Act (ODA)

in the 1970s, only 10 drugs were approved for rare diseases,

since 1983 more than 390 small molecules & biologic orphan drugs have been approved

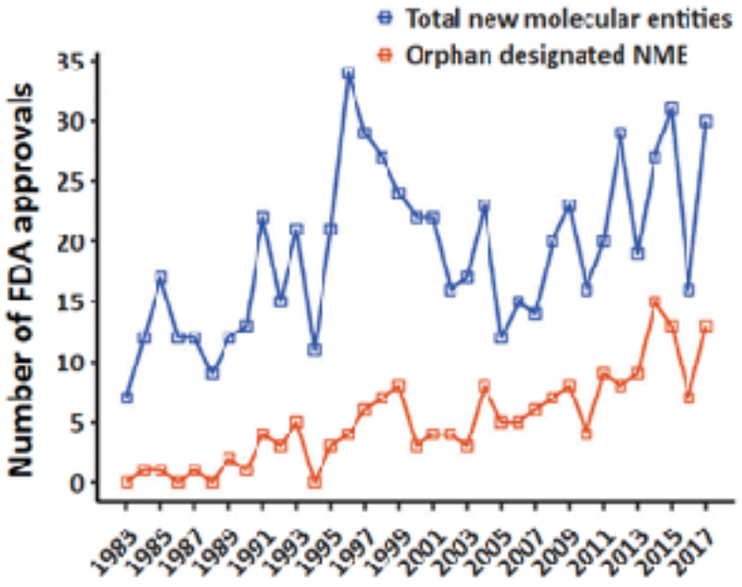


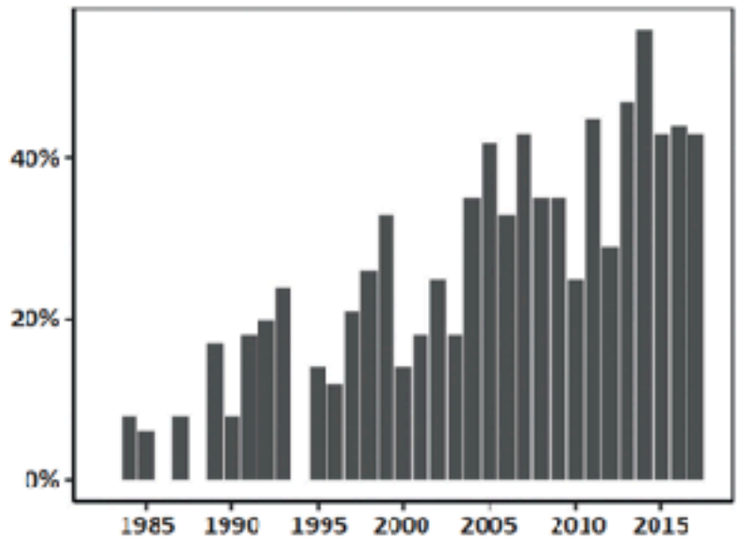


orphan drug approvals by therapeutic area (2006–2011)

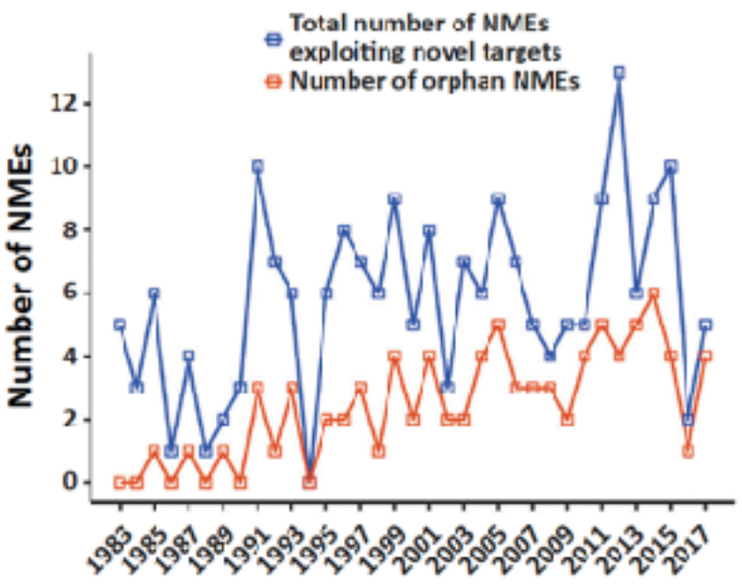
Melnikova, I. *Nat. Rev. Drug Discov.* **2012**, *11*, 267.

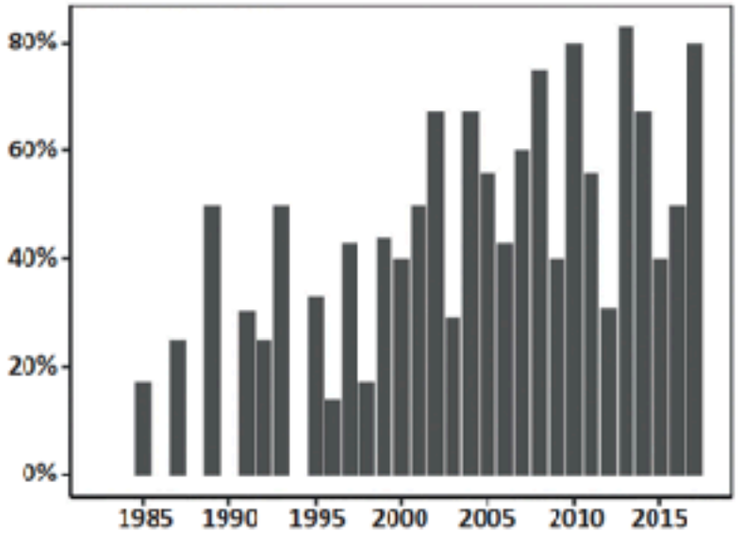
Impact of the Orphan Drug Act (ODA)





proportion of approved orphan-designated NMEs to total approved NMEs





proportion of approved orphan drugs with novel mechanisms to total innovative

over the past three decades,

orphan drugs constitute more than

40% of approved pharmaceuticals

that have expanded the

human drug target landscape

Attwood, M. M.; Rask-Anderson, M.; Schiöth, H. B. *Trends in Pharmacol. Sci.* **2018**, *39*, 525.

Challenges of Pharmaceutical Development for Rare Diseases

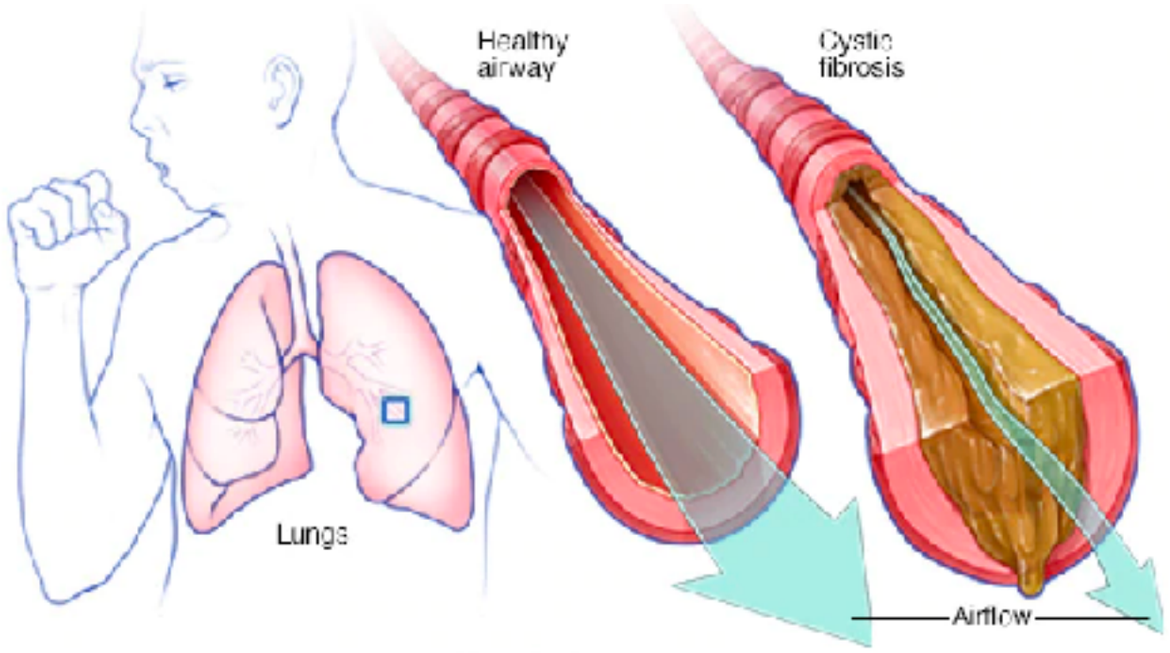
despite recent progress, less than 10% of patients with rare diseases are treated today

Challenges of Orphan Drug Development

- heterogeneity of disease pathology
- poorly understood natural history of disease progression
- limited patients for clinical trials
- lack of biomarkers for predicting outcomes
- heterogeneity in treatment effects
- uncertainties in end points & duration of treatment
- lack of regulatory precedent & harmonization of approval process between different national agencies

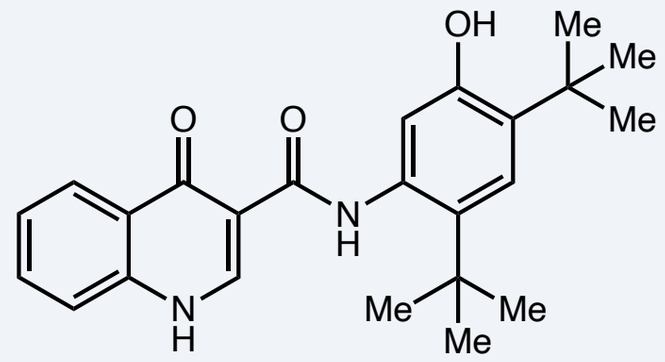
Melnikova, I. *Nat. Rev. Drug Discov.* **2012**, *11*, 267.

Orphan Drug Case Study: Cystic Fibrosis



Cystic Fibrosis

- genetic disorder, mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) protein
- disorder produces thick, sticky mucus which clogs the lungs and obstruct the pancreas
- in 1959, median age of survival in the US was 6 months



ivacaftor

Vertex Pharmaceuticals

costing >$300,000 per year

elexacaftor/ivacaftor/tezacaftor

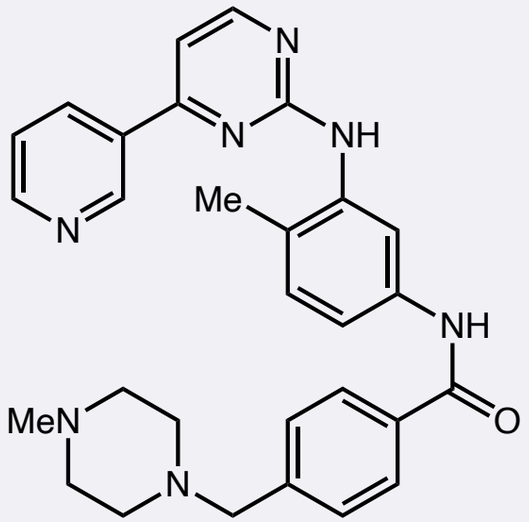
treatment approved in US in 2019

can treat up to 90% of people

with cystic fibrosis

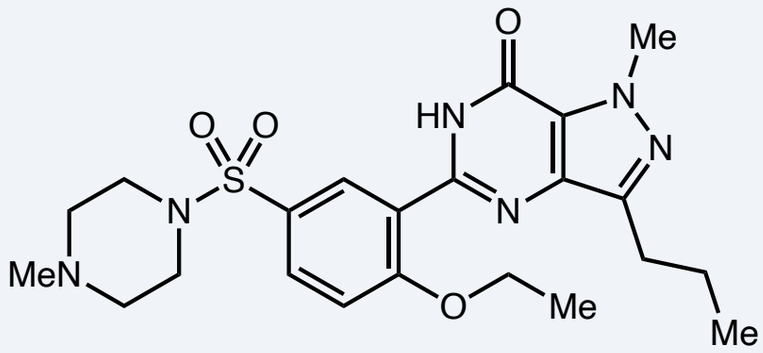
Hollis, A. *Healthc. Policy* **2019**, *15*, 70.

Other Well Known Orphan Drugs



imatinib
Novartis
9 orphan drug designations

drugs can obtain orphan designations for multiple rare diseases



sildenafil
Pfizer
pulmonary arterial hypdertension

existing drugs can be repurposed to obtain orphan status

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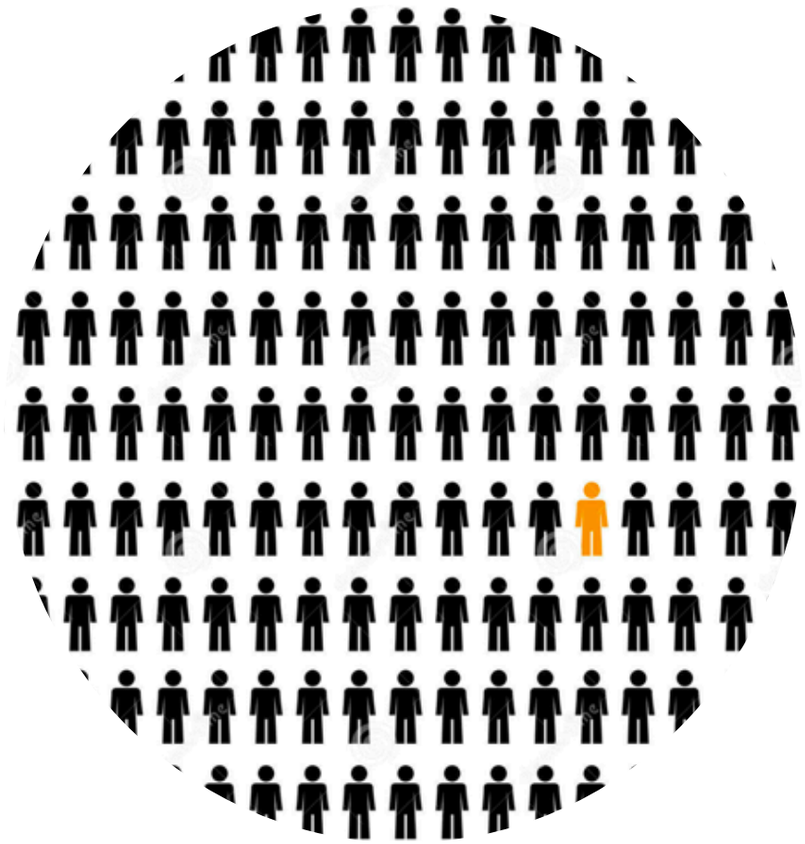


The 20 Neglected Tropical Diseases Defined by WHO

Helminths or Metazoan Worms

Dracunculiasis (guinea worm disease)

Echinococcosis

Foodborne trematodiases

Lymphatic filariasis

Mycetoma & chromoblastomycosis

Onchocerciasis (river blindness)

Schistosomiasis

Soil-transmitted helminthiasis

Taeniasis/cysticercosis

Bacteria

Buruli ulcer

Leprosy

Trachoma

Yaws

Protozoa

Chagas disease

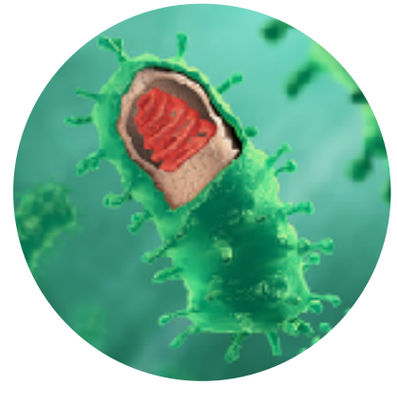
Human African trypanosomiasis (sleeping sickness)

Leishmaniasis

Other

Scabies

Snakebite envenoming

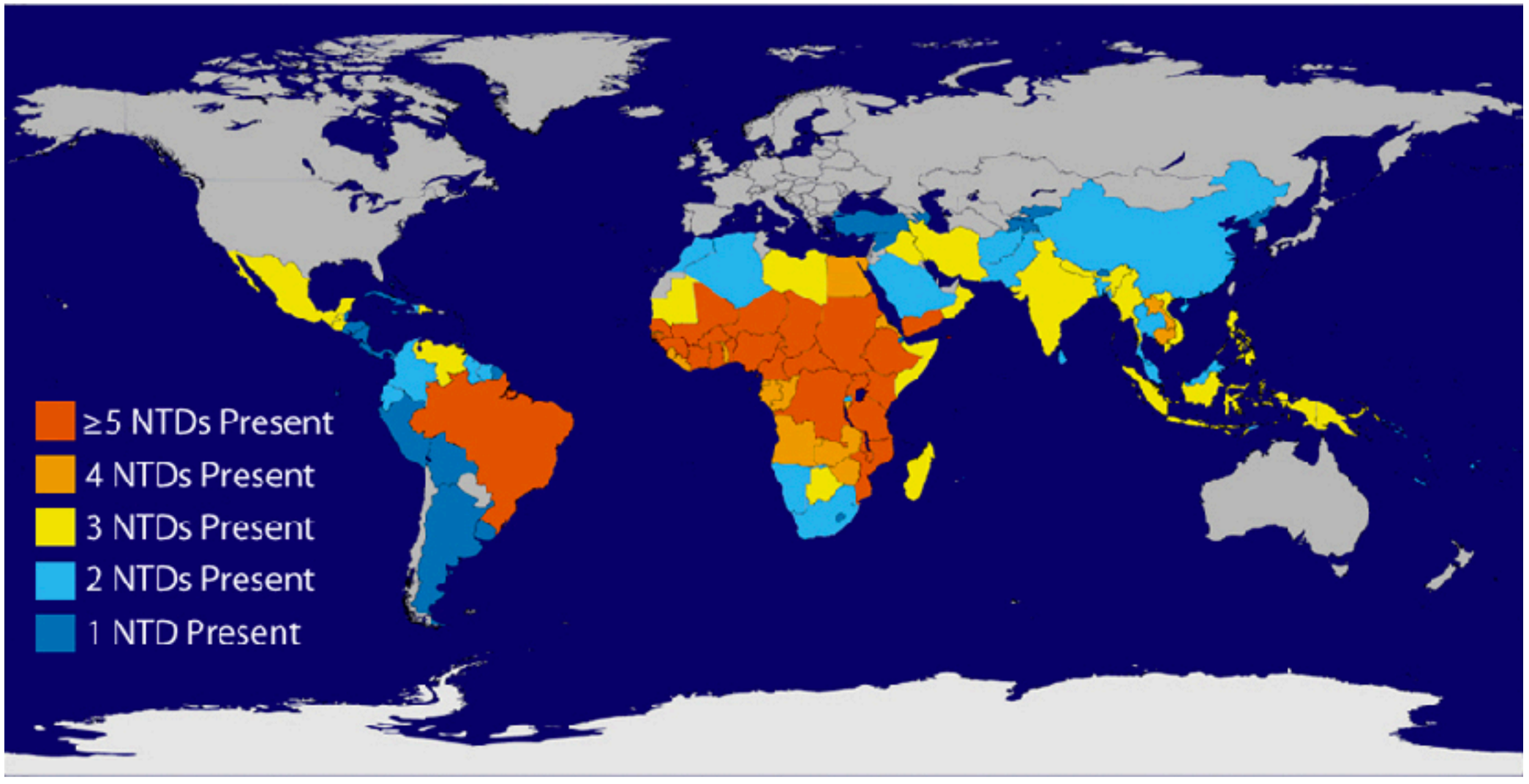


Viruses

Dengue and chikungunya

Rabies

Prevalence of Neglected Tropical Diseases



Neglected tropical diseases are common in 149 countries and affect more than 1.4 billion people (including 500 million children)

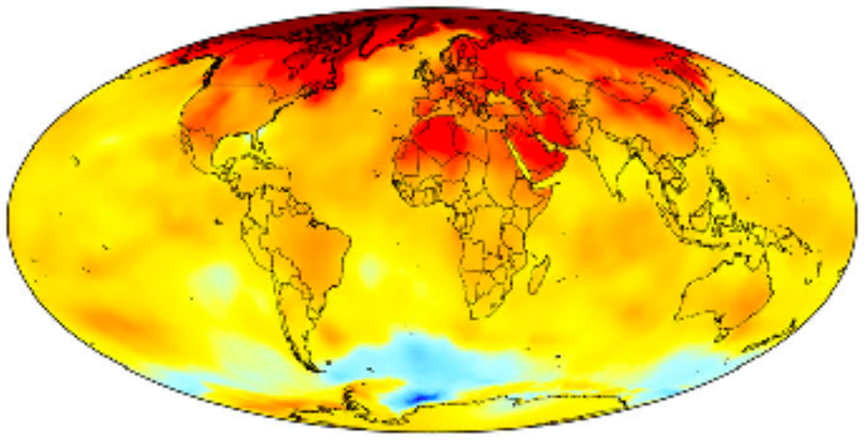
Njoroge, M. et al. *Chem. Rev.* **2014**, *114*, 11138.

Factors Which Exacerbate Neglected Diseases

proximity to disease vectors

lack of sanitation & clean water

lack of adequate healthcare



climate change

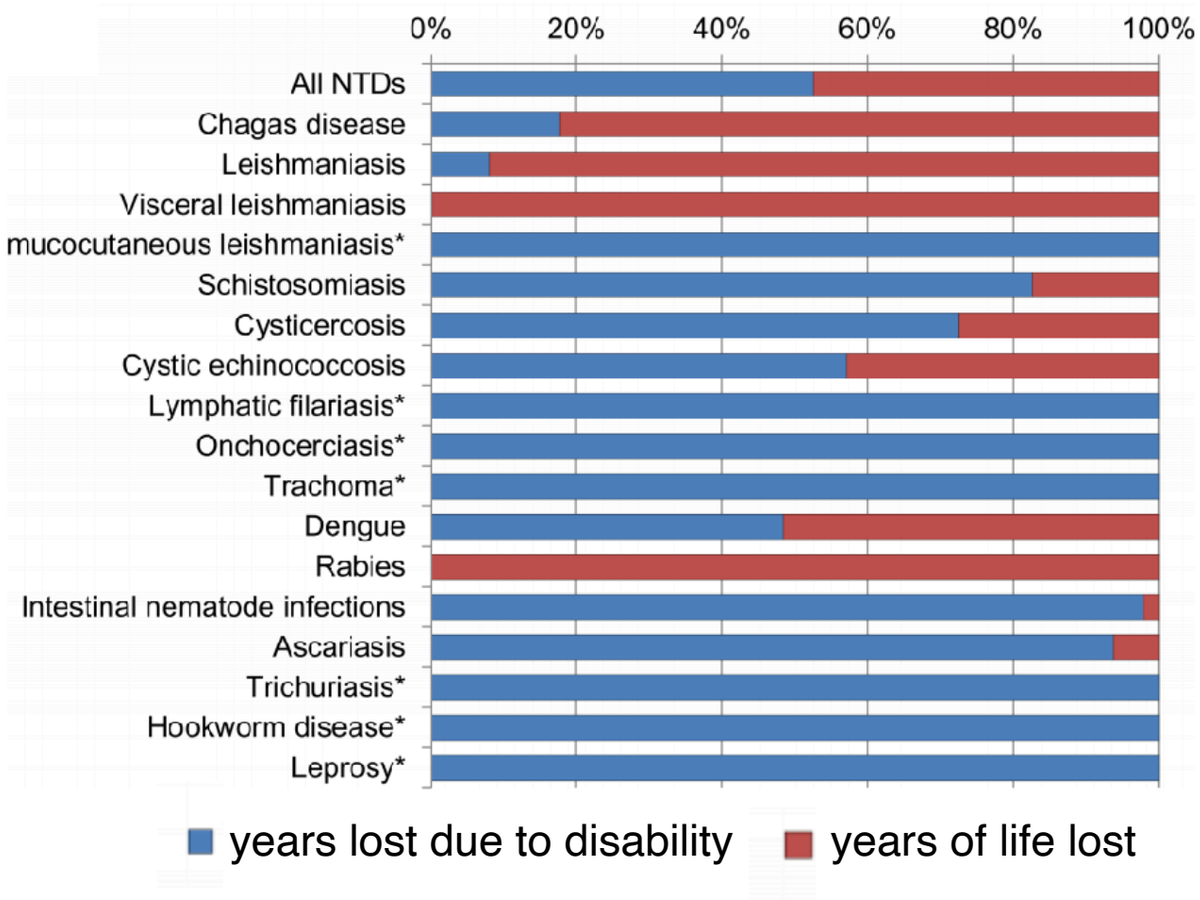
in particular for Dengue fever

Engels, D.; Z, X.-N. *Infect. Dis. Poverty* **2020**, *9*.

Global Impact of Neglected Tropical Diseases

	approx. global prevalence (million)	approx. deaths annually
lymphatic filariasis	120	<500
schistosomiasis	200	15 000–280 000
trachoma	84	<500
onchocerciasis	37	<500
dengue fever	50	19 000
leishmaniasis	12	51 000
Chagas disease	8–9	14 000
human African trypanosomiasis	<0.1	48 000
malaria	207	627 000

additionally, ~1.5 billion people are infected with soil-transmitted helminthiasis worldwide



beyond death and disability, neglected diseases:

- keep children out of schools & adults out of work
- trap communities in endless cycle of poverty
- burden households with costs to seek healthcare
- cost developing economies billions each year

Njoroge, M. et al. *Chem. Rev.* **2014**, *114*, 11138.
Martins-Melo, F. R. et al. *PLOS Negl. Trop. Dis.* **2018**, *12.*

Social Stigma Associated with Many NTDs

lymphatic filariasis

leprosy

yaws

social stigma is not reflected in the global burden through DALYs

deformities can cause denial of marriage, inability to work, social relations and poor mental health

Why are These Diseases Neglected?

several reasons why neglected diseases are “neglected”

- frequently kill, nut not in numbers to the deaths caused by HIV/AIDS, tuberculosis, or malaria
- more common to disable or disfigure than kill
- do not spread to distant countries, rarely affect travellers
- threat only to impoverished settings with low visibility in the rest of the world
- **developing new drugs for these diseases is not economically viable for pharma**

neglected diseases represent 11.4% of global disease burden

***however*… 1.1% of new drugs approved for 1975–1999 specifically for NTDs and 1.2% for 2000–2011**

From: *Working to overcome the global impact of neglected tropical diseases: First WHO report on Neglected Tropical Diseases.* Trouiller, P.; Olliaro, P.; Torreele, E.; Orbinski, J.; Laing, R.; Ford, N. *Lancet.* **2002**, 359*, 2188.*

how are NTDs treated & prevented if drug discovery is not economically viable?

London Declaration on Neglected Tropical Diseases

Excerpt from London Declaration on NTDs

"Inspired by the World Health Organization's 2020 Roadmap on NTDs, we believe there is a tremendous opportunity to control or eliminate at least 10 of these devastating diseases by the end of the decade. But no one company, organization or government can do it alone. With the right commitment, coordination and collaboration, the public and private sectors will work together to enable the more than a billion people suffering from NTDs to lead healthier and more productive lives – helping the world's poorest build self-sufficiency."

Goals of London Declaration

- eliminate or control 10 neglected diseases by 2020
- sustain, expand, and extend drug access programs
- enable adequate funding with endemic countries to implement NTD programs
- advance R&D through partnerships & provision of funding for new treatments

Original Endorsers

Abbott	*GlaxoSmithKline*
AstraZeneca	*Johnson & Johnson*
Bayer	*Lions Clubs International*
Becton Dickinson	*Merck KGaA*
Bill & Melinda Gates Foundation	*MSD*
Bristol-Myers Squibb	*Mundo Sano*
CIFF	*Novartis*
DFID	*Pfizer*
DNDi	*Sanofi*
Eisai	*USAID*
Gilead	*World Bank*

endorsements followed, increasing to 71 organizations

https://www.who.int/neglected_diseases/London_Declaration_NTDs.pdf?ua=1

Impact of London Declaration on Neglected Tropical Diseases

Heading Towards Elimination

Dracunculiasis (guinea worm disease)

Human African trypanosomiasis (sleeping sickness)

Lymphatic filariasis

Trachoma

Yaws

Significant Gains

Leprosy

Onchocerciasis (river blindness)

Rabies

Schistosomiasis

Taeniasis/cysticercosis

Minimal Gains

Echinococcosis

Foodborne trematodiases

Soil-transmitted helminthiasis

Losing the Battle

Chagas disease

Dengue and chikungunya

Leishmaniasis

Hotez, P.; Aksoy, S. *PLOS Negl. Trop. Dis.* **2017**, *11.*

World Health Organization 2021–2030 Road Map

WHO sets new global targets for 2030 to prevent, control, eliminate, & eradicate 20 diseases

Disease	Indicator	2020	2023	2025	2030
TARGETED FOR ERADICATION					
Dracunculiasis	Number of countries certified free of transmission	**187** (96%)	**189** (97%)	**191** (98%)	**194** (100%)
Yaws	Number of countries certified free of transmission	**1** (1%)	**97** (50%)	**136** (70%)	**194** (100%)
TARGETED FOR ELIMINATION (INTERRUPTION OF TRANSMISSION)					
Human African trypanosomiasis (gambiense)	Number of countries verified for interruption of transmission	**0**	**0**	**5** (21%)	**15** (62%)
Leprosy	Number of countries with zero new autochthonous leprosy cases	**50** (26%)	**75** (39%)	**95** (49%)	**120** (62%)
Onchocerciasis	Number of countries verified for interruption of transmission	**4** (12%)	**5** (13%)	**8** (21%)	**12** (31%)

examples from WHO 2021–2030 road map for controlling/eradicating NTDs

From: *Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030.*

Public Health Interventions as Recommended by WHO

lasting cross-sectoral solutions, preventing transmission

veterinary public health

safe drinking water, sanitation, & hygiene (WASH)

integrated vector management

large scale preventative treatment

innovative & intensified disease management

medical solutions

Engels, D.; Z, X.-N. *Infect. Dis. Poverty* **2020**, *9.*

Prevention through Water, Sanitation, & Hygiene (WASH)

as of 2017:

- 2.3 billion (1 in 3) people without sanitation facilities
- 844 million people lack access to safe/clean drinking water

Water Sanitation & Hygiene

WHO Global Strategy for WASH

improve awareness of benefits of WASH in context of NTDs

use WASH & NTDs monitoring to track progress

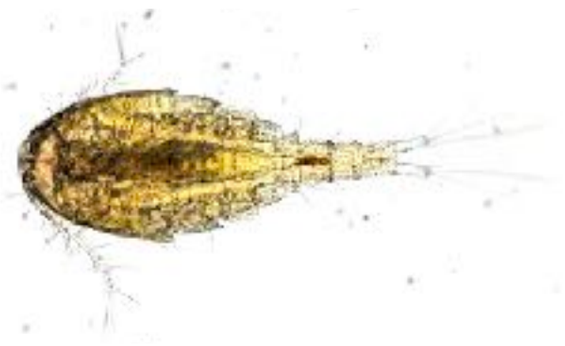
strengthen evidence on how to deliver effective WASH interventions for NTD control

plan, deliver, & evaluate WASH and NTDs programs

Integrated Vector Management for Neglected Disease Prevention

tsetse fly
African trypanosomiasis

mosquito
malaria, Dengue fever, chikungunya, Zika…



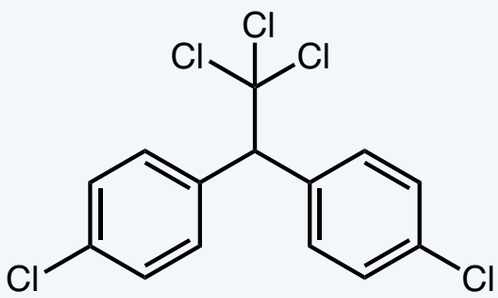
water flea
dracunculiasis

kissing bug
Chagas disease

sandfly
leishmaniasis

snail
schistosomiasis

Vector Management with Insecticides



DDT

first modern insecticide

Paul Müller – 1948 Nobel Laureate

"for his discovery of the high efficiency of DDT as a contact poison against several arthropods."

U.S. soldier sprayed for typhus-carrying lice

DDT broadly employed 1945–1972 for:

- WHO anti-malaria campaign
- Preventing typhus and malaria in WWII

Turusov, V.; Rakitsky, V.; Tomatis, L. *Environ. Health Perspec.* **2002**, *110*, 125–128.

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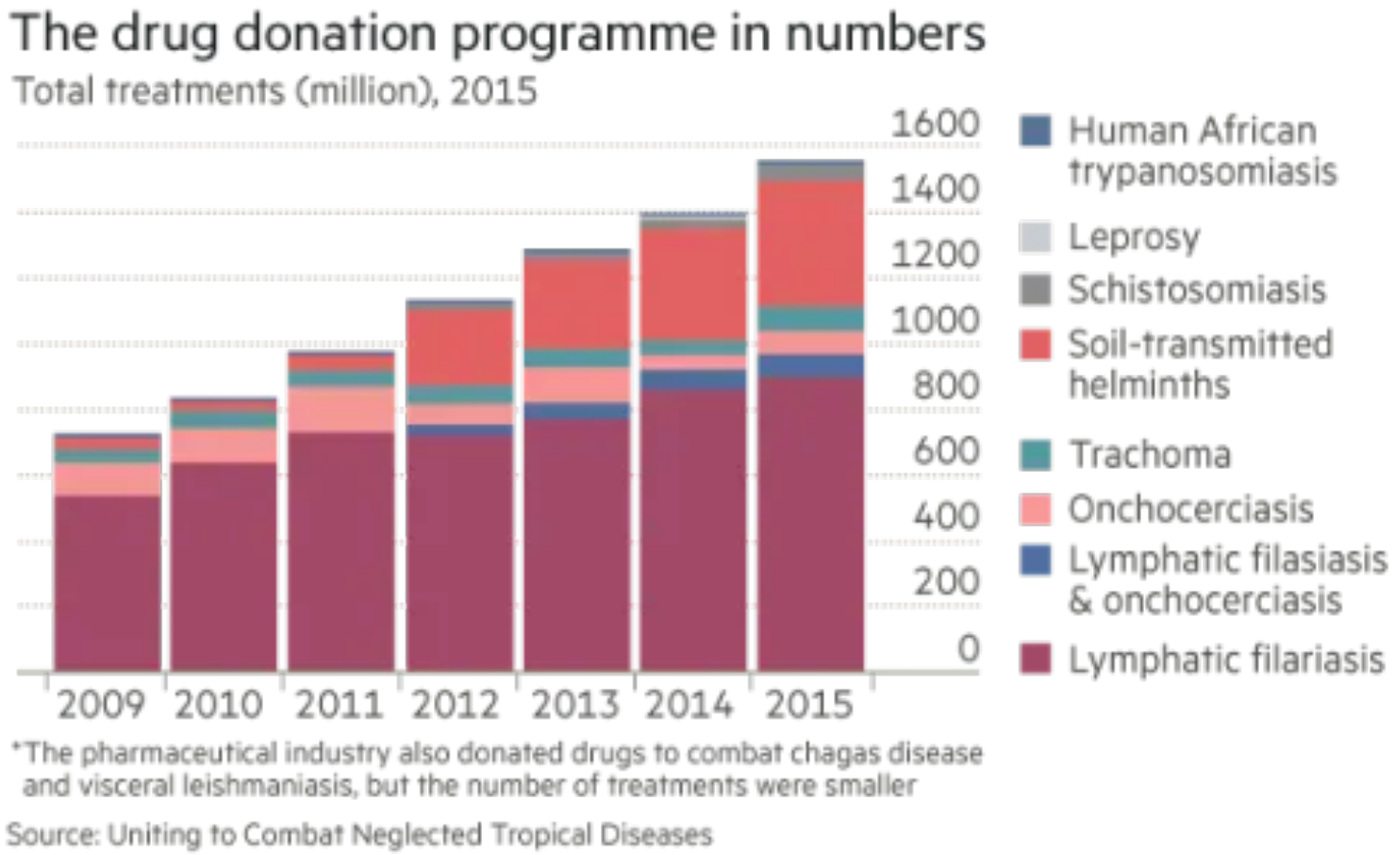
Engels, D.; Z, X.-N. *Infect. Dis. Poverty* **2020**, *9.*

Large Scale Prevention & Treatment with Drugs

Eleven pharmaceutical companies have been donating medicines for NTDs for over a decade:

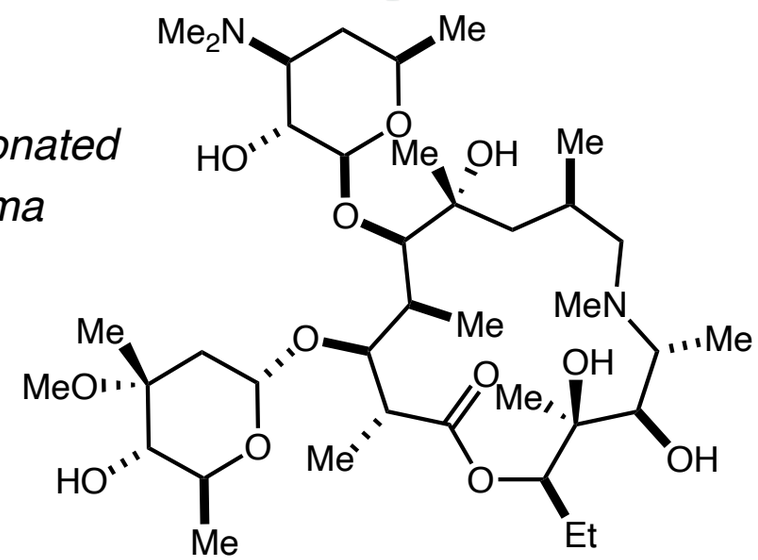
Bayer, Eisai, EMS, Gilead, GSK, J&J, MSD, Merck KGaA, Novartis, Pfizer, Sanofi, etc.



Guinness World Record for the most medication donated in 24 hours (207 million doses)

Large Scale Prevention & Treatment with Drugs

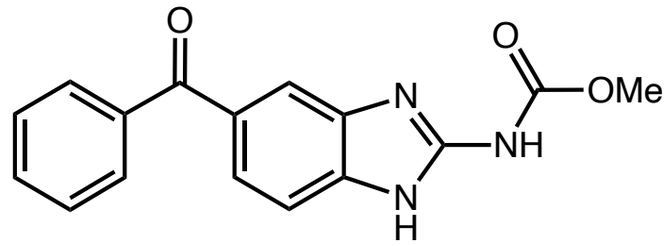
MERCK



azithromycin

>740 million *doses donated for treating trachoma*

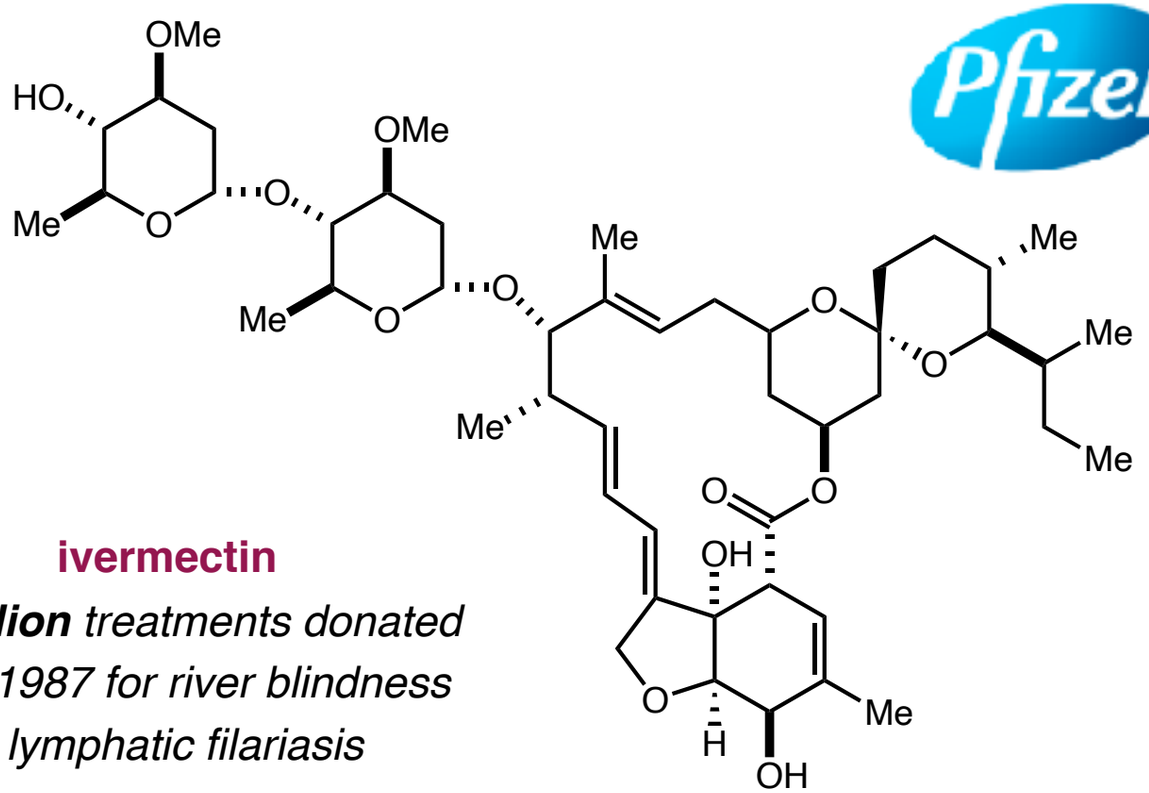
Johnson&Johnson



mebendazole

200 million *tablets donated per year for soil-transmitted helminthiases*

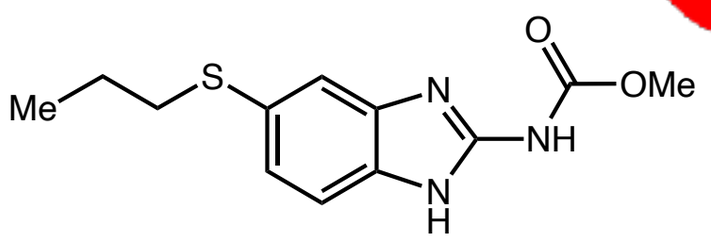
Pfizer



ivermectin

3.4 billion *treatments donated since 1987 for river blindness & lymphatic filariasis*

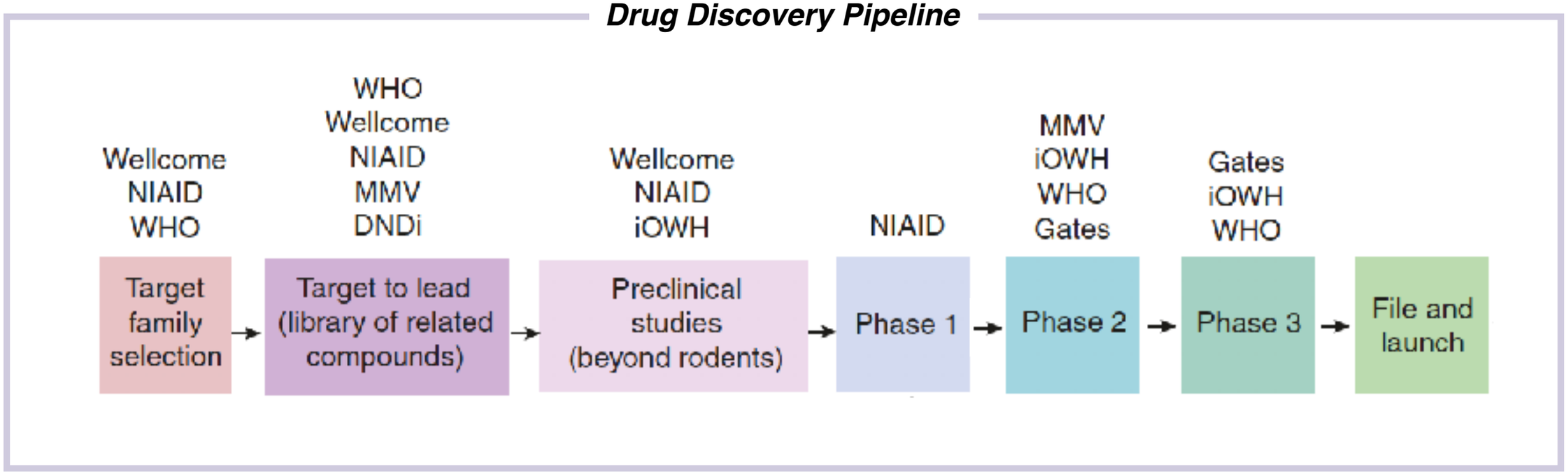
gsk



albendazole

5 billion *tablets donated since 2000 for soil-transmitted helminthiases*

Drug Development for Neglected Tropical Diseases



philanthropic organizations

BILL & MELINDA GATES *foundation*

wellcome trust

The Sandler Family Foundation

non-profit organizations

MMV
Medicines for Malaria Venture

iOWH
Institute for OneWorld Health

global & public organizations

NIH National Institute of Allergy and Infectious Diseases

World Health Organization

Renslo, A. R.; McKerrow, J. H. *Nat. Chem. Biol.* **2020**, *2*, 701.

Drug Development for Neglected Tropical Diseases

DNDi
Drugs for Neglected Diseases *initiative*

Drugs for Neglected Diseases *initiative* (DND*i*)

- founded by doctors without borders, WHO, & 5 international research institutions
- orchestrate drug development with >180 partners (public, private, academic, non-profit, & philanthropic sectors)
- developed eight new treatments for NTPs

World Intellectual Property Organization Re:Search

- established in 2011, works with Merck, MSD, J&J, Novartis Pfizer, GSK, Takeda, Eisai
- orchestrate public-private partnerships (e.g. industrial library collections available to academic labs)
- facilitated over 70 research collaborations as of 2014

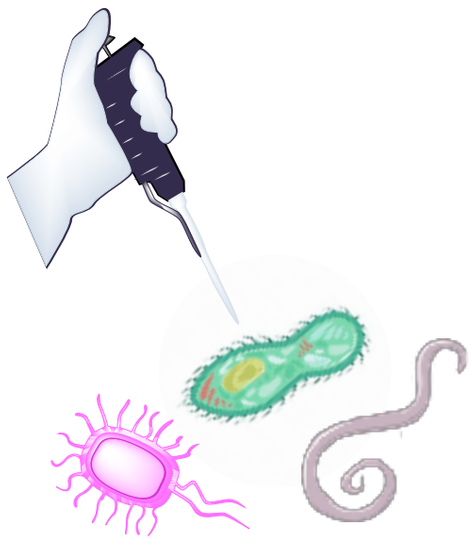
Ramamoorthi, R.; Graef, K. M.; Dent, J. *Int. J. Parasitol. Drugs Drug Resist.* **2014**, *4*, 220.
Renslo, A. R.; McKerrow, J. H. *Nat. Chem. Biol.* **2020**, *2*, 701.

Drug Development for Neglected Tropical Diseases

Unique aspects of drug development against neglected diseases

- Cost of goods must be low (production and distribution)
- Orally available (administered in rural settings)
- Drug combination desirable for rapid cure and minimizing resistance
- Greater tolerance for adverse effects (shorter therapy, seriousness of condition)

target-based



phenotypic screening

drug repurposing

Njoroge, M. et al. *Chem. Rev*. **2014**, *114*, 11138.

Priority Review Vouchers (PRVs) as Incentives

Priority review vouchers (PRVs) are granted as incentives to drug companies to develop drugs which may not be otherwise profitable

- includes NTDs as well as malaria, cholera, tubercuolisis, Ebola, Zika, rare pediatric diseases, etc.

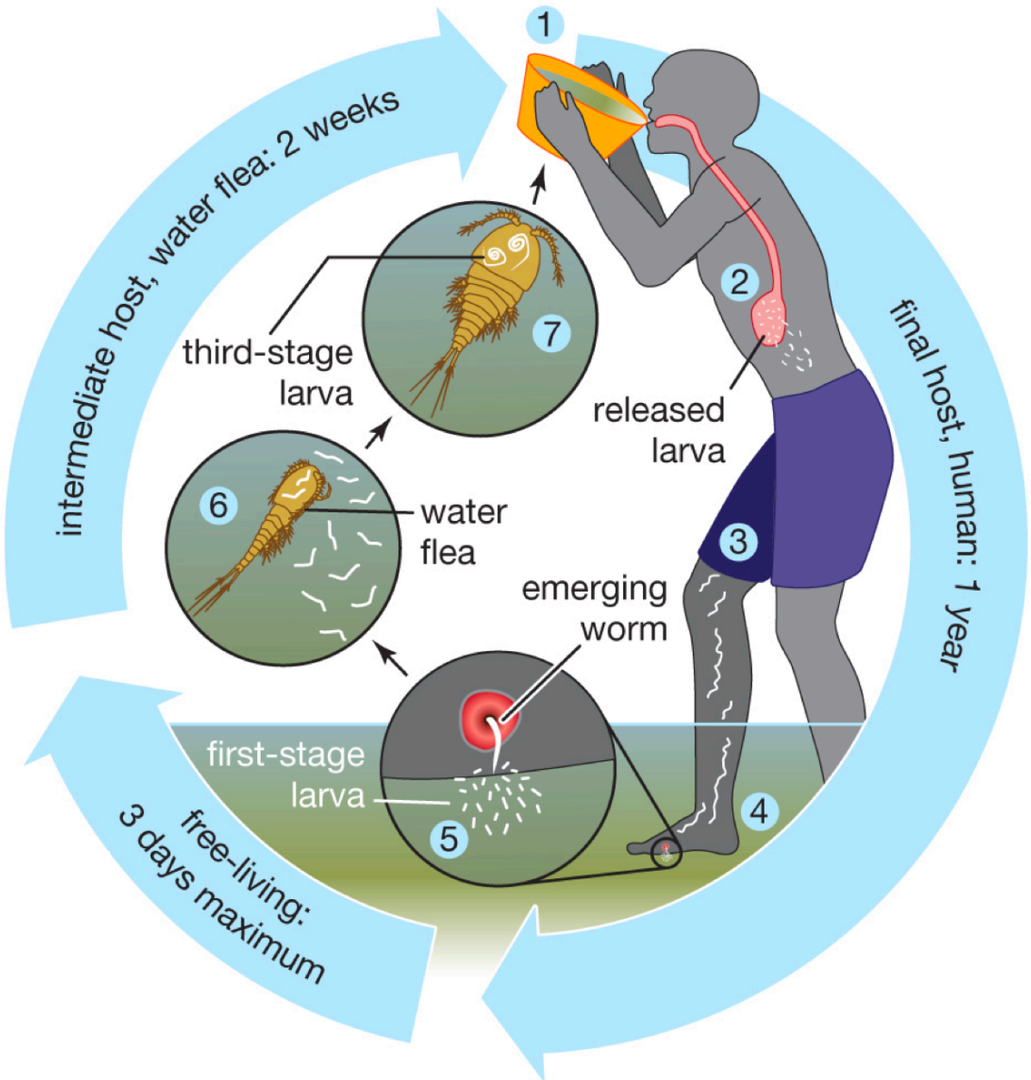
- proposed by David Ridley in 2006, law made in 2007
- PRVs used to expedite the review process for a drug
- valued at $100–500 million, but can also be sold for $50–350 million

Ridley, D. B.; Grabowski, H. G.; Moe, J. L. *Health Aff.* **2006**, *25*, 313.

Case Study I: Dracunculiasis (Guinea Worm Disease)

Guinea Worm Disease (GWD) is caused by the parasite *Dracunculus medinensis.*

GWD affects poor communities in remote parts of Africa, 3.5 million cases in the mid-1980's



Guinea worm life cycle

female Guinea worm

- adult female Guinea worm: 60–100 cm
- characterized by blister, typically on leg
- painfuly, can cause vomitting & dizziness

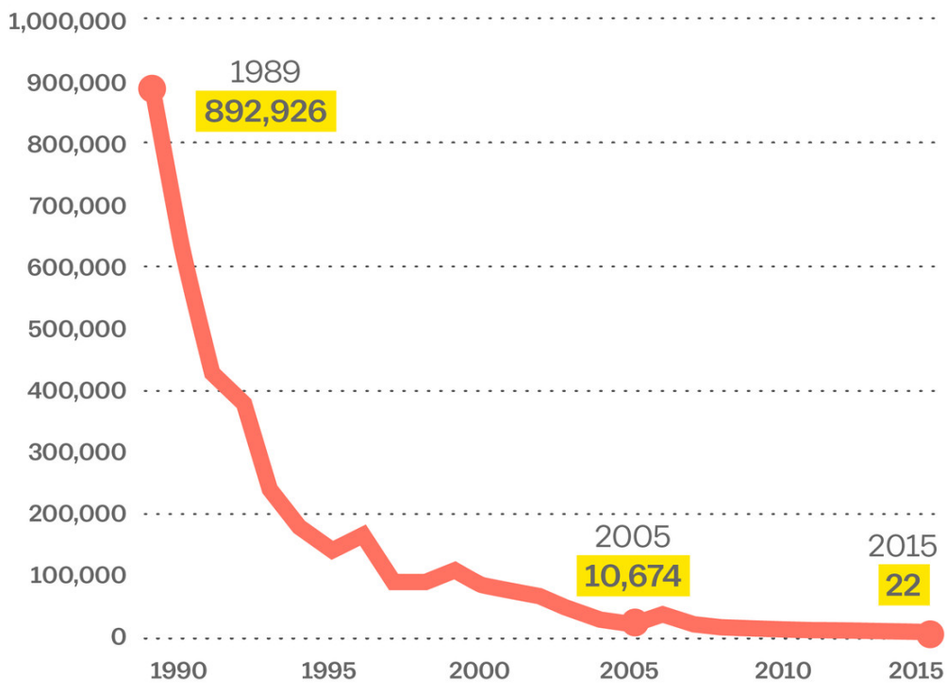
Information obtained from: cartercenter.org

Case Study I: Dracunculiasis (Guinea Worm Disease)

Eradication efforts by the Carter Center

- founded by Jimmy Carter, took lead for Guinea Worm Eradication Program
- funded by donor agencies, foundations, institution, and government
- provides technical & financial assistance, filters, larvicide, medical kits

THE CARTER CENTER



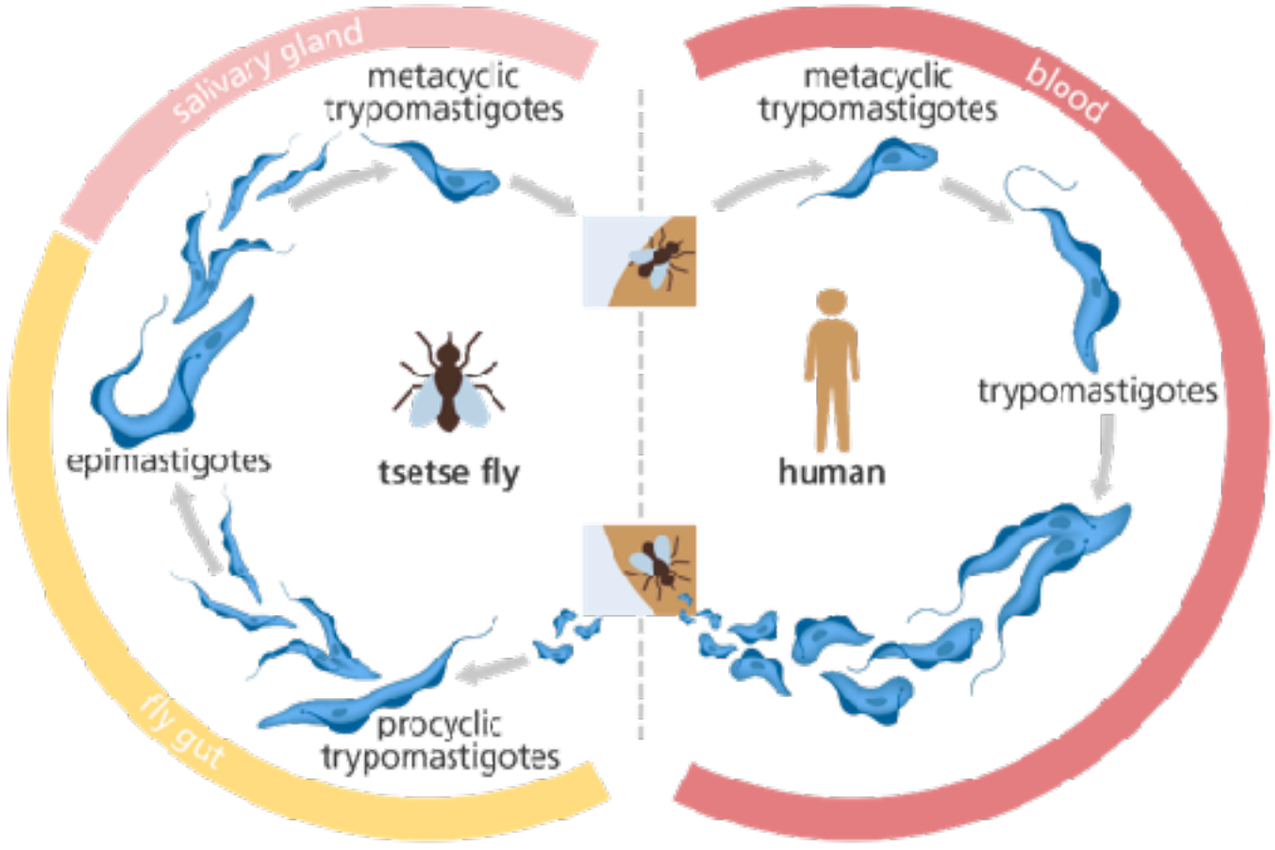
- 53 reported cases in 2019 in 4 countries
- likely to be first parasitic disease globally eradicated
- still likely more than 1,000 cases in dogs

Information obtained from: cartercenter.org

Case Study II: African Trypanosomiasis (Sleeping Sickness)

African trypanosomiasis (sleeping sickness) is caused by the protozoan parasite *Trypanosoma brucei*, which is transmitted by the bite of an infected tsetse fly

- characterized by fevers, headaches, itchiness, & joint pains in first few weeks
- progresses to confusion, poor coordination, numbness, & trouble sleeping months later
- typically causes death without treatment
- caused 34,000 deaths in 1990



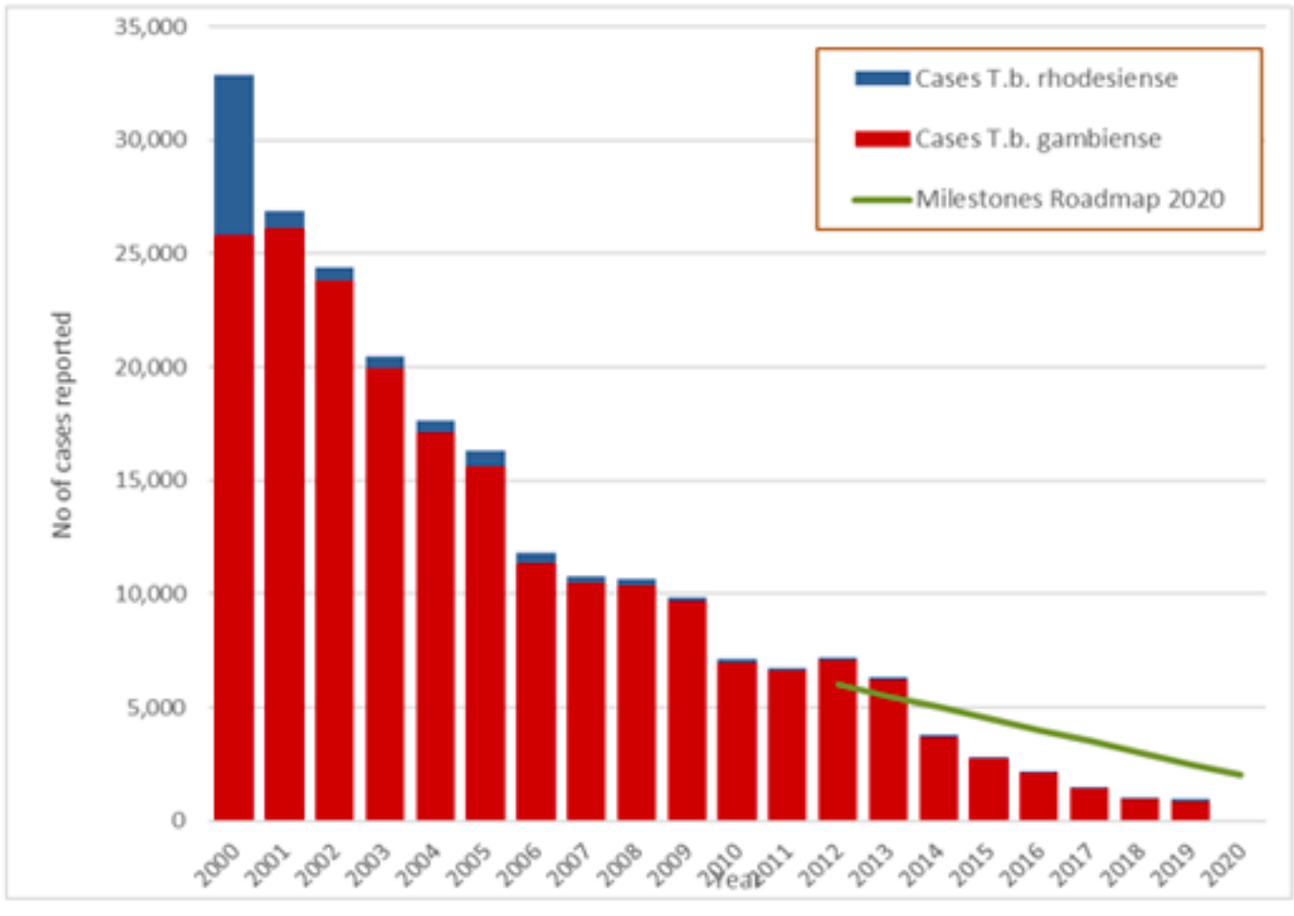
Information obtained from: www.who.int (Trypanosomiasis, human African (sleeping sickness).

Case Study II: African Trypanosomiasis (Sleeping Sickness)

Methods for Disease Prevention

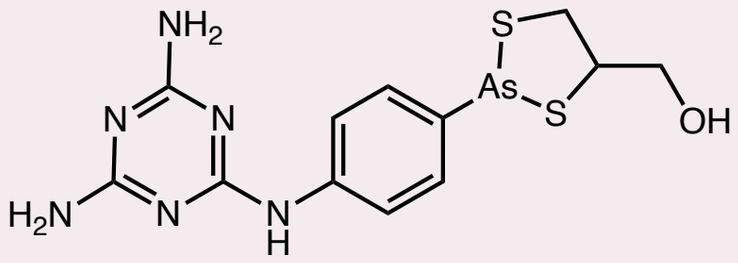
- PATTEC eradication of tsetse vector population levels through use of fly traps and insecticide
- regular active surveillance via blood sampling for early-stage disease detection

Tsetse Fly Trap



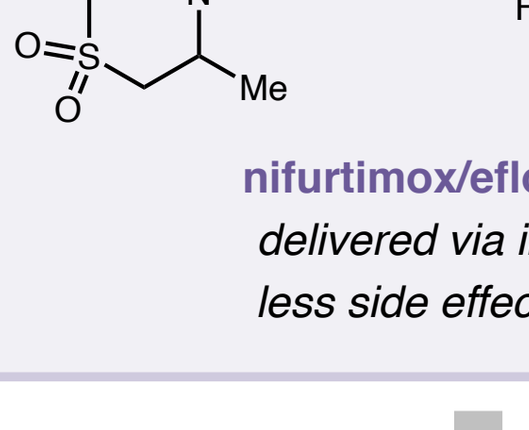
Information obtained from: www.who.int (Trypanosomiasis, human African (sleeping sickness).

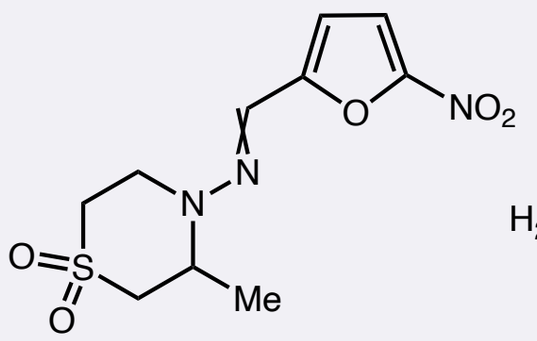
Case Study II: African Trypanosomiasis (Sleeping Sickness)



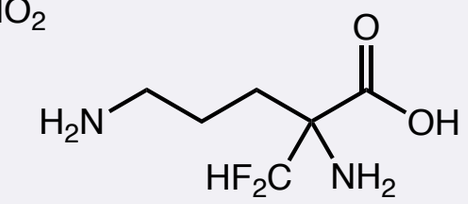
melarsoprol

delivered via injection,
1 in 20 people die during treatment





DNDi
Drugs for Neglected Diseases *initiative*

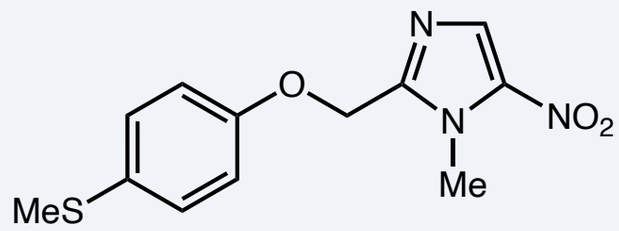


nifurtimox/eflornithine

delivered via injection,
less side effects, safer

SANOFI

DNDi
Drugs for Neglected Diseases *initiative*



fexinidazole

orally administered drug

Information obtained from: dndi.org

Case Study III: Soil-Transmitted Helminthiasis

Ascaris

807–1,121 million

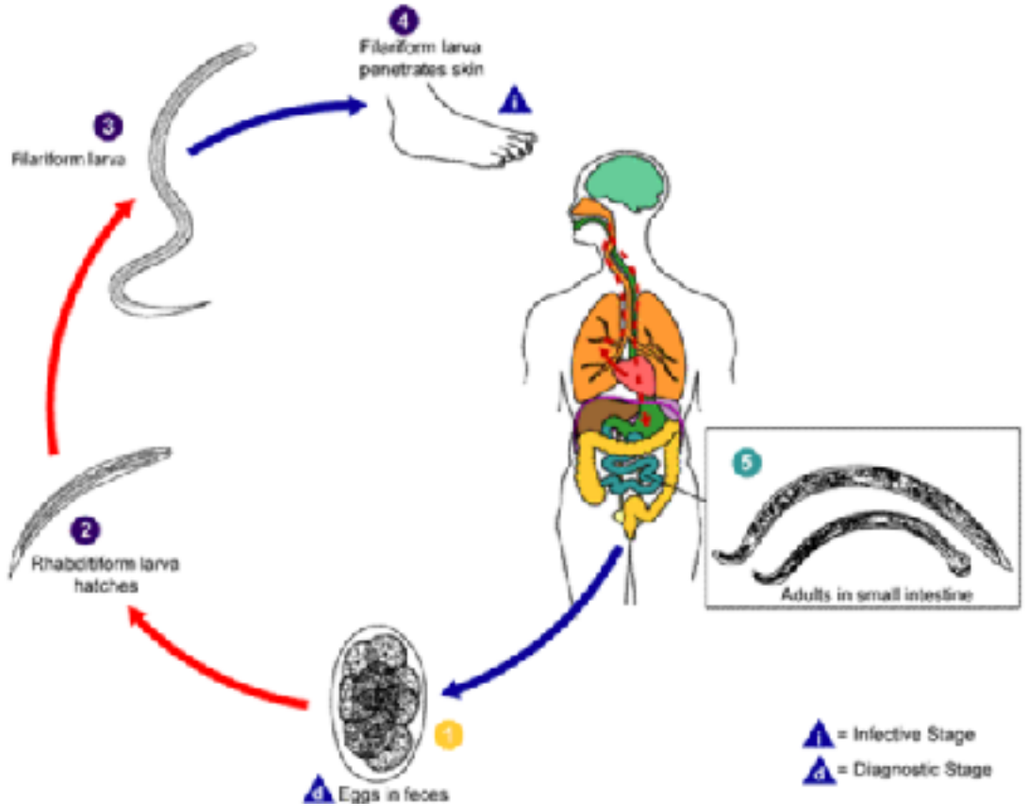
Whipworm

604–795 million

Hookworm

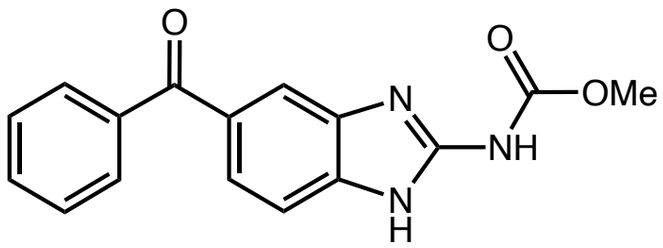
576–740 million

- soil-transmitted helminths live in the intestine
- eating eggs of *Ascaris* & whipworm infect
- hookworm larvae infect via penetrating skin
- causes anaemia, lethargy, pain, malnutrition
  physical & cognitive delay



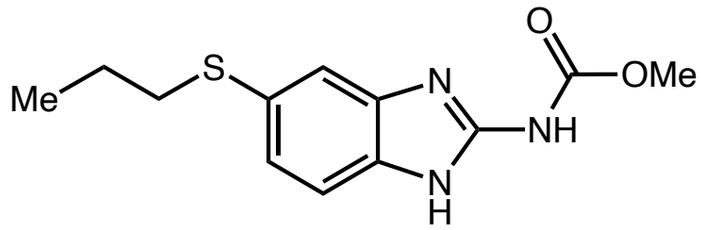
Information obtained from: https://www.cdc.gov/parasites/sth/index.html

Case Study III: Soil-Transmitted Helminthiasis



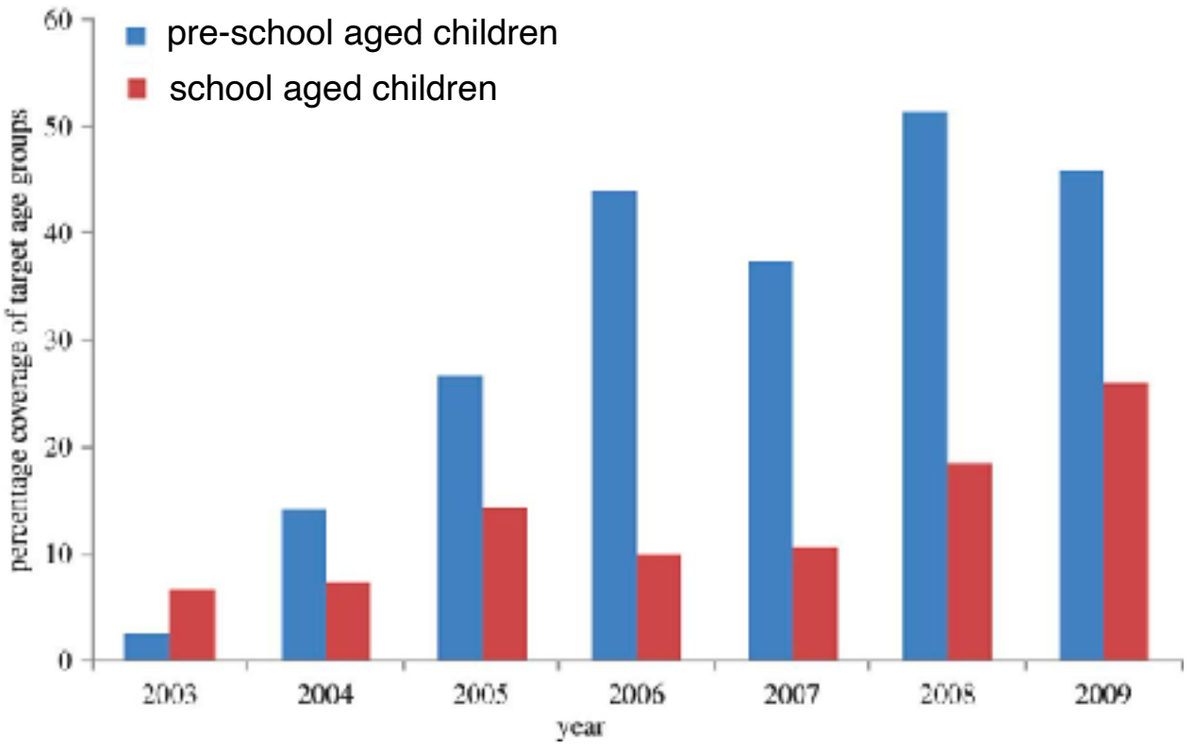
mebendazole

200 million *tablets donated per year for soil-transmitted helminthiases*



albendazole

5 billion *tablets donated since 2000 for soil-transmitted helminthiases*



Water Sanitation & Hygiene

Anderson, R.; Truscott, J.; Hollingsworth, T. D. *Phil. Trans. R. Soc. B* **2014**, *369.*

Pharmaceutical Development for Rare & Neglected Diseases

- **Introduction**
- **Rare Diseases**
  - Impact of Rare Diseases
  - Orphan Drug Act (ODA)
  - Examples of Orphan Drugs
- **Neglected Tropical Diseases (NTDs)**
  - Global Impact of NTDs
  - Reasons for Neglect
  - World Health Organization Intervention
  - Solutions for NTD Treatment/Prevention
  - Case Studies (3)