Pharmaceutical Development for Rare & Neglected Diseases

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MacMillan Group Meeting
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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

**Common Diseases**
- Hypertension
  - 1 in 3
- Alzheimer’s disease
  - 1 in 60
- Parkinson’s disease
  - 1 in 300

**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 lobbied 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.

Orphan Drug Act (ODA) of 1983

**Commercial Incentives**
- FDA-Accelerated Approval
- Enhanced Patent Protection
- Lower Marketing Costs

**Research Incentives**
- Tax Credits
- Research Grants
- FDA Fee Subsidies
- Shorter Development Timelines

Lower Hurdles to Drug Approval

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

Impact of the Orphan Drug Act (ODA)

Over the past three decades, orphan drugs constitute more than 40% of approved pharmaceuticals that have expanded the human drug target landscape.

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

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

Other Well Known Orphan Drugs

Drugs can obtain orphan designations for multiple rare diseases

Imatinib
Novartis
9 orphan drug designations

Sildenafil
Pfizer
Pulmonary arterial hypertension

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

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

Global Impact of Neglected Tropical Diseases

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

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, 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

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

<table>
<thead>
<tr>
<th>Heading Towards Elimination</th>
<th>Significant Gains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dracunculiasis (guinea worm disease)</td>
<td>Leprosy</td>
</tr>
<tr>
<td>Human African trypanosomiasis (sleeping sickness)</td>
<td>Onchocerciasis (river blindness)</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>Rabies</td>
</tr>
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<td>Schistosomiasis</td>
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<td>Taeniasis/cysticercosis</td>
</tr>
<tr>
<td><strong>Minimal Gains</strong>                                                                         <strong>Losing the Battle</strong></td>
<td></td>
</tr>
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<td>Echinococcosis</td>
<td>Chagas disease</td>
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<td>Dengue and chikungunya</td>
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<tr>
<td>Soil-transmitted helminthias</td>
<td>Leishmaniasis</td>
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**World Health Organization 2021–2030 Road Map**

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

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Indicator</th>
<th>2020</th>
<th>2023</th>
<th>2025</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dracunculiasis</td>
<td>Number of countries certified free of transmission</td>
<td>187 (96%)</td>
<td>189 (97%)</td>
<td>191 (98%)</td>
<td>194 (100%)</td>
</tr>
<tr>
<td>Yaws</td>
<td>Number of countries certified free of transmission</td>
<td>1 (1%)</td>
<td>97 (50%)</td>
<td>136 (70%)</td>
<td>194 (100%)</td>
</tr>
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**TARGETED FOR ELIMINATION (INTERRUPTION OF TRANSMISSION)**

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</tr>
</thead>
<tbody>
<tr>
<td>Human African trypanosomiasis (gambiense)</td>
<td>Number of countries verified for interruption of transmission</td>
<td>0</td>
<td>0</td>
<td>5 (21%)</td>
<td>15 (62%)</td>
</tr>
<tr>
<td>Leprosy</td>
<td>Number of countries with zero new autochthonous leprosy cases</td>
<td>50 (26%)</td>
<td>75 (39%)</td>
<td>95 (49%)</td>
<td>120 (62%)</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>Number of countries verified for interruption of transmission</td>
<td>4 (12%)</td>
<td>5 (13%)</td>
<td>8 (21%)</td>
<td>12 (31%)</td>
</tr>
</tbody>
</table>

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

**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

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**WHO Global Strategy for WASH**

- Improve awareness of benefits of WASH in context of NTDs
- Strengthen evidence on how to deliver effective WASH interventions for NTD control
- Use WASH & NTDs monitoring to track progress
- 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**

*Cl* 

**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.”

**DDT broadly employed 1945–1972 for:**

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

U.S. soldier sprayed for typhus-carrying lice

Public Health Interventions as Recommended by WHO

 lasts 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

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

azithromycin
>740 million doses donated for treating trachoma

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

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

albendazole
5 billion tablets donated since 2000 for soil-transmitted helminthiases
Drug Development for Neglected Tropical Diseases

Drug Discovery Pipeline

philanthropic organizations

non-profit organizations

global & public organizations

Drug Development for Neglected Tropical Diseases

Drugs for Neglected Diseases initiative (DNDi)

- 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

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)

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, tuberculosis, 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

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.

- **female Guinea worm**
  - adult female Guinea worm: 60–100 cm
  - characterized by blister, typically on leg
  - painfully, can cause vomiting & 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

Information obtained from: cartercenter.org

- 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
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](http://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

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

- **nifurtimox/eflornithine**
  - delivered via injection,
  - less side effects, safer

- **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](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

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