Neglecting Diseases

Jason Silverstein
Department of Anthropology
Harvard University
“I will give you a talisman. Whenever you are in doubt or when the self becomes too much with you, apply the following test: Recall the face of the poorest and the weakest man whom you may have seen and ask yourself if the step you contemplate is going to be of any use to him.”

Gandhi
In What Follows

1. What are neglected diseases?

1. Why are diseases neglected?

2. When are diseases confronted?
What are Neglected Diseases?

- Chronic
- Disabling
- Cycle with poverty
Cycles of Poverty and Disease

- Poverty
- Disease
- Workers Disabled
- Economic Collapse
- Food Shortage
What are Neglected Diseases?

What are Neglected Diseases?

**Helminth Infections (7)**
- Ascariasis; trichuriasis; hookworm infection; filariasis; onchocerciasis; dracunculiasis; schistosomiasis

**Protozoan infections (3)**
- Leishmaniasis; Chagas disease; human African trypanosomiasis

**Bacterial infections (3)**
- Buruli ulcer; leprosy; trachoma

What are Neglected Diseases?

Where are Neglected Diseases?

<table>
<thead>
<tr>
<th>Region</th>
<th>Population</th>
<th>NTD Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle East</td>
<td>140 Million</td>
<td>8.4 Million</td>
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<tr>
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<tr>
<td>Latin America &amp; Caribbean</td>
<td>174 Million</td>
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Hotez & Thompson, PLoS NTDs, (2009)
Why are Diseases Neglected?

Political Anesthesia

We do not feel we need to know anymore than we already know (Didier Fassin)
Why are Diseases Neglected?

No Market, No Power

Not a 10/90 Gap

A 1/99 Gap
Why are Diseases Neglected?

A Living Crisis

Living with neglected diseases.

A chronic, not lethal, condition.
Why are Diseases Confronted?

National Security Threat

When a disease threaten our homeland, or interests abroad
Yellow Fever Vaccine
NDs in US Diplomatic Hot-Spots

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Gandhi
Strategies for addressing the neglected diseases of the bottom billion

The case of Chagas disease

Jennifer Manne, MSc, ScD/MD candidate
Harvard School of Public Health
Boston University School of Medicine
Outline

1. What is Chagas disease?

2. Prevention of Chagas disease and its challenges

3. Treatment of Chagas disease and its challenges
Agenda

1. What is Chagas disease?

2. Prevention of Chagas disease and its challenges

3. Treatment of Chagas disease and its challenges

Carlos Chagas, discovered Chagas disease in 1909
8 – 10 million people are infected with Chagas disease

- Concentrated in Latin America
- Increasing in other areas due to migration
- US has about 300,000 cases

The parasite and vector

Trypanosoma cruzi parasite

Triatoma vector

Source Image Credits: agsci.oregonstate.edu; cals.ncsu.edu/mercia-maps-quizzes
## Transmission and disease course

<table>
<thead>
<tr>
<th>Disease transmission</th>
<th>Disease course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vector</strong></td>
<td><strong>Acute</strong></td>
</tr>
<tr>
<td></td>
<td>• 4-8 weeks</td>
</tr>
<tr>
<td></td>
<td>• Flu-like</td>
</tr>
<tr>
<td><strong>Mother to child</strong></td>
<td><strong>Intermediate</strong></td>
</tr>
<tr>
<td></td>
<td>• 5 – 20 years</td>
</tr>
<tr>
<td></td>
<td>• Silent</td>
</tr>
<tr>
<td><strong>Blood products</strong></td>
<td><strong>Chronic</strong></td>
</tr>
<tr>
<td></td>
<td>• Lifetime</td>
</tr>
<tr>
<td></td>
<td>• Heart or GI</td>
</tr>
</tbody>
</table>
Agenda

1. What is Chagas disease?
2. Prevention of Chagas disease and its challenges
3. Treatment of Chagas disease and its challenges
Prevention has several approaches

Vector control through house spraying

Education

In addition, some countries screen blood products
Results of prevention efforts

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence Rate (1983)</th>
<th>Incidence Rate (2000)</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>5.8</td>
<td>1.2</td>
<td>80</td>
</tr>
<tr>
<td>Brazil</td>
<td>5</td>
<td>0.28</td>
<td>95</td>
</tr>
<tr>
<td>Chile</td>
<td>5.4</td>
<td>0.38</td>
<td>94</td>
</tr>
<tr>
<td>Paraguay</td>
<td>9.3</td>
<td>3.9</td>
<td>60</td>
</tr>
<tr>
<td>Uruguay</td>
<td>2.5</td>
<td>0.06</td>
<td>99</td>
</tr>
</tbody>
</table>

Source: WHO 2002

Prevention effective in reducing infestation and incidence of disease
Once in place, sustainability is a challenge

Community collaboration to enforce surveillance

Maintaining interest through “Chagas week”

Funding for such programs remains limited
Agenda

1. What is Chagas disease?

2. Prevention of Chagas disease and its challenges

3. Treatment of Chagas disease and its challenges
Diagnosing and treating Chagas Disease?

Diagnosis

Treatment

#1

#2
Who is responsible for ensuring access to treatment?

1. The World Health Organization
2. Country governments
3. Pan American Health Organization
4. Pharmaceutical companies that make the drugs
5. All of the above
6. None of the above
Four challenges to global treatment access

- Case identification
- Technology transfer
- Treatment side effects
- Drug donation

Estimated that less than 1% of infected patients receive treatment
Technology transfer of benznidazole

- Technology transfer from Roche to Lafepe (2003)

- Challenges:
  - Production approval/capacity
  - Drug shortage (2011)
  - Cost to produce

#1 Benznidazole
Drug donation of nifurtimox

• Drug donated from Bayer to WHO (2002 – present)

• Challenges:
  Lack of information
  Market distortion
  Delayed changes to guidelines
  Logistic/coordination problems

#2 Nifurtimox
Progress in treating Chagas disease

- Benznidazole shortage increases awareness of supply chain problems
- Public pressure to restart production in 2012 and identify second producer
- Greater efforts being made to understand supply chain problems
- Posaconazole and ravuconazole – new compounds in clinical trials
Summary of major lessons in Chagas disease

- Prevention through vector control has been successful
- Surveillance and sustainability remain challenges for prevention
- Access to treatment is limited, partly due to problems with drug availability
Life cycle of *T. cruzi*

1. Triatomin e bug takes a blood meal (passes metacyclic trypomastigotes in feces; trypomastigotes enter bite wound or mucosal membranes, such as the conjunctiva).
2. Metacyclic trypomastigotes penetrate various cells at bite wound site. Inside cells they transform into amastigotes.
3. Amastigotes multiply by binary fission in cells of infected tissues. Trypomastigotes can infect other cells and transform into intracellular amastigotes in new infection sites. Clinical manifestations can result from this infective cycle.
4. Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream.
5. Triatomin e bug takes a blood meal (trypomastigotes ingested).
7. Multiply in midgut.
8. Metacyclic trypomastigotes in hindgut.

CDC

http://www.dpd.cdc.gov/dpdx

Safeer・Healthier・People

diagram: [Life cycle of T. cruzi](https://www.cdc.gov/dpdx/trypanosomiasis/trypomastigote.html)
### History of benznidazole and nifurtimox supply chains

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971</td>
<td>Benznidazole registered by Roche.</td>
<td></td>
</tr>
<tr>
<td>1972</td>
<td>Benznidazole registered by Bayer HealthCare.</td>
<td></td>
</tr>
<tr>
<td>1971</td>
<td>Nifurtimox registered in South America by Bayer HealthCare.</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Roche transfers patent and technology for benznidazole to LaFepe.</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Bayer HealthCare-WHO Nifurtimox Donation Program established to provide 2 million Lampit tablets over a five-year period.</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>LaFepe receives benznidazole API and tablets from Roche.</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Benznidazole API and tablets donated by Roche expire; Nortec Quimica technically able to produce benznidazole API but not approved by ANVISA.</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>PAHO passes resolution “Elimination of Neglected Diseases and other Poverty Related Infections” recommending antitypanosomal therapy for CD-infected children and adults.</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>LaFepe informs MSF it will not be able to fulfill orders made for over 800,000 tablets of benznidazole; shortly after promises to restart production.</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>Bayer HealthCare-WHO extend donation program to provide 5 million Lapit tablets over 5 year period + 1.5 million USD for logistics.</td>
<td></td>
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<tr>
<td>2004</td>
<td>LaFepe receives approval for benznidazole production from ANVISA.</td>
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Innovating for (and with) the Bottom Billion

Karolina Maciag
MD/PhD Candidate, Harvard Medical School/MIT
Immunology / Health Sciences and Technology

www.uaem.org
Innovating for (and with) the Bottom Billion

1. **Big Science**: Chagas drug candidate screening at the Broad Institute

2. **Serendipity**: Vancouver and visceral leishmaniasis

3. **An ounce of prevention**: Preventing intestinal worm infections with devices and vaccines
1. Place parasites
2. Place drug candidates
Chagas screen

385,000 chemical compounds

11,550 hits

500 nontoxic to cells

20 kill parasites in cells

Effective and safe in animals and humans
Back to the drawing board
Innovating for (and with) the Bottom Billion

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www.uaem.org
Visceral Leishmaniasis (kala azar)

INFECTED
12 million

YEARLY NEW CASES
1.7 million

AT RISK
350 million

November 2009: “Our intellectual property should not become a barrier to essential health-related technologies needed by patients in developing countries.”

Harvard Among Six Schools Urging Drug Access for Poor (Update1)

By John Lauermann - Nov 09, 2009

Nov. 9 (Bloomberg) -- Harvard University and Yale University are among six schools pledging to encourage companies to give poor countries better access to drugs and medical products stemming from discoveries made on their campuses.

U. of California Agrees to Formally Promote 'Global Access' to Its Inventions

By Goldie Blumenstyk

The University of California system has adopted new guidelines that could help ensure that new medicines and other inventions based on university research are more accessible and affordable in the developing world.

Officials said the change, which would be carried out through university licensing, was partly a response to a years-long campaign by student activists, who have been urging universities to adopt such "global access" licensing policies.
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Intestinal worms

INFECTED
>1.2 billion

YEARLY DEATHS
unknown

AT RISK
>3 billion

http://www.who.int, http://howstuffworks.files.wordpress.com,
$3

$25/3yr

http://www.vestergaard-frandsen.com/
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Universities Allied for Essential Medicines
Leveraging academic research for global health
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Thank you!

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