The changing epidemiology and geographic spread of leishmaniasis and Chagas disease

September 16, 2014
Institute of Medicine
Forum on Microbial Threats

James H. Maguire, MD
Harvard Medical School
Brigham and Women’s Hospital
Boston, Massachusetts
Leishmania and *Trypanosoma cruzi*: Vector-borne flagellate protozoa of order Kinetoplastida

**Leishmania**
- Multiple species
- Phlebotomine sand fly
- Not Australia, Antarctica
- ~12 million cases

**Trypanosoma cruzi**
- Single species (6 DTUs)
- Triatomine bugs
- Americas
- ~8 million infected

Largely diseases of poverty
Leishmaniasis

- Transmission: vectorborne, rarely other routes
- >20 species infect humans, all but 2 zoonotic
- Variation in clinical presentation, drug susceptibility, ecology, and epidemiology even within species
- Subclinical infection often > clinical
- Three major clinical presentations
- Treatment, when needed, effective

Cutaneous
Mucosal
Visceral
Phlebotomine sand flies

- >800 species, 98 known/suspected vectors of leishmaniasis (*Phlebotomus, Lutzomyia*)
- 50°N-40° occupy all types of ecological niches
- Tiny (<3.5mm), weak fliers
- Female take blood meal for egg development;
  - may have preferred host, few hosts, or many
  - *Leishmania* in rodents, hyraxes, marsupials, edentates, canids, humans
- Breeding sites: dark, humid, soil rich in organic material (rarely identified in nature)
- Humid, dark, cool diurnal resting places
Leishmaniasis

- Tremendous diversity of parasites, vectors, mammalian hosts and niches reflect
  - evolution over past 80 million years in response to natural ecological changes
  - more recently, human activity
- Ongoing emergence, re-emergence, and spread
Cutaneous leishmaniasis in the Americas

- Increasing incidence, broadening geographic range
- Complex epidemiology
  - ≥12 species
  - Multiple sand fly species
  - Different reservoirs
  - Different ecology
- *L. braziliensis*
  - Lesions slow- or non-healing
  - Mucosal lesions
Baurité, Ceará State

- >100 cases/yr
- Unknown:
  - species
  - vector
  - reservoir
  - transmission
• Sand fly captures in and around houses, CDC light traps, animal, human landing captures,
• Trap and examine 800 sylvatic animals
• Case control study of infection in children and dogs
Association of canine infection with cutaneous leishmaniasis in children

<table>
<thead>
<tr>
<th></th>
<th>Number of pairs</th>
<th>Exposure</th>
<th>Odds ratio (95% C.L.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases and controls</td>
<td>63</td>
<td>Seroreactive dog</td>
<td>3.2 (1.3-6.1)</td>
</tr>
<tr>
<td>All cases and controls</td>
<td>63</td>
<td>Seroreactive dog with lesion</td>
<td>6.0 (1.8-20.4)</td>
</tr>
<tr>
<td>Cases and controls with</td>
<td>63</td>
<td>Seroreactive dog</td>
<td>9.0 (1.1-71.0)</td>
</tr>
</tbody>
</table>
Cutaneous leishmaniasis in the US

  - Reservoir: woodrats (*Neotoma*)
  - Vector: *Lutzomyia anthopora*
  - Expansion to north and east
- Cutaneous leishmaniasis in travelers
- Cutaneous leishmaniasis in the US military
  - Desert Storm and Desert Shield
  - 2001-2006 1,283 cases

Visceral leishmaniasis in the USA

- Before 1999: sporadic cases
  - imported dogs
  - dogs that never traveled
- 1999: 41% of foxhounds in kennel NY state infected with *L. infantum*
- 2000-2003: 18 states, Canada
- >1000 dogs infected (~12,000 tested)
- *Lu. shannoni*: competent vector
- No human cases
- Transmission:
  - vectorborne not demonstrated
  - dog-to-dog
  - transfusion

Schantz P, Duprey Z. 2006
Visceral leishmaniasis in Brazil

- Agent: \textit{L. chagasi} (=\textit{infantum})
- Vector: \textit{Lutzomyia longipalpis}
- Reservoir: domestic dog, foxes (opossums, rodents)
- Traditionally disease of rural areas, periphery of towns

\begin{figure}
\centering
\includegraphics[width=\textwidth]{distribution_map.png}
\caption{Distribution of Visceral leishmaniasis in South and Central America due to \textit{Leishmania donovani chagasi}}
\end{figure}
Visceral leishmaniasis in Brazil

- Now primarily peri-urban/urban
- Shift followed intense rural to urban migration since 1970s
Leishmaniasis in Brazil

- First epidemic in Teresina
- Epidemics later in other cities in NE, North, SE, Central West
- Increased incidence (>4000 cases/year), cases in 19 states, DF, Rio de Janeiro
- Leishmania/HIV coinfections increasing,
- Public health response (reactive spraying; culling seropositive dogs) unsuccessful
- New strategies (insecticide-inpregnated collars, vaccine)

VISCERAL LEISHMANIASIS in PIAUI, BRAZIL 1983-1994

CHN Costa, Rabello 2003, Gontijo 2004; Werneck 2012
Leishmania/HIV coinfection

- HIV increased risk of clinical VL by 10-1000x
- Infection with zoonotic or new zymodemes
- Atypical presentations; more difficult to treat; frequent relapses
- Similar picture with immunosuppressive therapy
- Coinfected highly infectious to sand flies
Visceral Leishmaniasis in Europe

- *Leishmania*/HIV coinfection:
  - Previously 70% of cases in children
  - HIV: 75% 31-50 years
  - 85% male > 70% IV drug users
  - *Leishmania* acquired by needle in ~10%

- Dramatic decrease in incidence since HAART
- Large outbreak in Madrid (hares)
- Northern spread of vectors, infected dogs
- Concern about introduced parasites, vectors

(Euro Surveill 2013,18(30),pii; Trends Parasitol 2013,29:579).
Visceral leishmaniasis in East Africa

• Sudan: 1983 to mid-1990s
  • Civil war; epidemic ("killing disease")
  • >100,000 deaths/280,000 cases
  • Recent epidemic 25,000 cases, 5% mortality

• Recent spread to non-endemic areas
  • Sudan, Somalia, NE Kenya, Ethiopia
  • Movements of populations
  • Limited access to medical care/drugs
  • Malnutrition
  • Meteorological changes
  • HIV coinfection (especially Ethiopia 2° migration of laborers, sex workers; 20-40% coinfection)

• Treatment with paromomycin and sodium stibogluconate
Visceral leishmaniasis in South Asia

• ~80% of global cases/global mortality
• *Leishmania donovani*; anthroponotic
• 1960s: nearly eliminated by vector control (malaria eradication)
• Since 1970s: resurgence
• Intermittent epidemics, especially Bihar, India
  • 1977: 100,000 cases
  • 1990 – 1992: 250,000 cases
• Resistance to antimonial drugs:
  • > 60% Bihar state
  • Resistance now in Nepal
Leishmaniasis in Bangladesh

- Mymensingh >50% of all cases in Bangladesh
- Rising rates 2000-2003
- Mortality high-18% in women

Cases of kala-azar in a single village, 2000-2001

Map showing kriged values

Para
“BA”

KA density
- 0 -
- 31 -
- 63 -
- 94 -
- 126 -

Map showing kriged values
Visceral leishmaniasis, Mymensingh

• Median time to diagnosis 4 months
• 2000-2004: sodium stibogluconate often not available in government health posts
• Transmission intra-household, near-neighbor
• Families with cases likely to have sold assets to pay for health care
• Families incur heavy debts; care for one case and indirect cost 1.2 times annual per capita income

Trop Med Intern Health 2006;11:757-764
Visceral leishmaniasis control strategy

• Decrease human reservoir of infection
  – Rapid specific diagnostics at local level
  – Earlier care-seeking
  – Improved availability of treatment

• Interrupt human-sand fly contact
  – Insecticide impregnated bed nets
  – Other vector control
Leishmaniasis elimination: health ministers sign memorandum of understanding

The health ministers of India, Nepal and Bangladesh signed a memorandum of understanding on 18 May 2005, pledging to eliminate kala azar from their countries.

Initial target 2015, now 2020
Chagas (American trypanosomiasis)

- Transmission primarily vector-borne, also congenital, transfusion- and transplantation-associated, oral, laboratory accidents
- Acute infection usually not recognized
- Infection lifelong, 20-30% develop chronic Chagas heart disease or GI mega-syndromes
- Treatment (benznidazole, nifurtimox) unsatisfactory
Triatomine vectors of *T. cruzi*

- >130 species, many competent to transmit, small # account for most human infection
- Strictly hematophagous: primarily mammals (>100 species infected with *T. cruzi*), birds
- Wild (sylvatic) habitat:
  - animal refuges, such as burrows, palm trees, tree holes, rock crevices
  - opossums, armadillos, wood rats, raccoons, birds
Domestication of triatomines

- Accelerated following European colonization
- Some triatomines adapted irreversibly to stable host environment, source of blood
- Infection of humans, domestic animals, rodents
- Domesticated species responsible for greatest number of human infections
Castro Alves, Bahia 1974-82 (n=1364)

- *Panstrongylus megistis*: domestic vector
- Stable transmission: 44.3% of population infected
- 60% of adults 20-55 years infected, 14% of infected children with abnormal electrocardiogram

Percent infected with *T. cruzi*

Outbreak of acute Chagas disease, Riacho de Santana, Bahia: 1970s

- Dispersal of *Triatoma infestans* from Cochabamba valley in Bolivia reaching greatest extent in NE Brazil in 1970s
- Passive transport of bugs
  - Increased motor traffic from south
  - Pilgimages to Bom Jesus de Lapa
- Drought

**Rhodnius prolixus** in Central America

- **Rhodnius prolixus**: domesticated vector in Colombia and Venezuela, central America north of Central Costa Rica
- Bugs taken to San Salvador in 1913 for research purposes accidentally released
- Spread widely, initially along Pan American Highway, in Central America, Mexico
- 2010: Rhodnius prolixus eliminated from Central America by spraying

(Parasites & Vectors 2012, 5:45)
Rural → urban migration

- Urban/periurban transmission
- ↑transfusion-associated cases

- Transmission: 10-20% per unit from infected person
- In early 1980s, >20,000 cases/yr

<table>
<thead>
<tr>
<th>Country</th>
<th>Setting</th>
<th>Year</th>
<th>N</th>
<th>% (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>Rural (hi)</td>
<td>1982</td>
<td>1028</td>
<td>20.1</td>
</tr>
<tr>
<td>Argentina</td>
<td>Rural (l-m)</td>
<td>1982</td>
<td>5923</td>
<td>7.9</td>
</tr>
<tr>
<td>Brazil</td>
<td>Brasilia</td>
<td>1984</td>
<td>2413</td>
<td>14.6</td>
</tr>
<tr>
<td>Brazil</td>
<td>Londrina</td>
<td>1981</td>
<td>3000</td>
<td>7.5</td>
</tr>
<tr>
<td>Bolivia</td>
<td>Santa Cruz</td>
<td>1983</td>
<td>268</td>
<td>63.0</td>
</tr>
<tr>
<td>Guatemala</td>
<td>Various</td>
<td>1987</td>
<td>1260</td>
<td>5.0</td>
</tr>
<tr>
<td>Mexico</td>
<td>Puebla</td>
<td>1985</td>
<td>200</td>
<td>16.5</td>
</tr>
</tbody>
</table>

Schmunis 1994; Storino 1994
Southern Cone Initiative - 1991

- 6 million sq miles (Chile, Argentina, Uruguay, Paraguay, Bolivia, Brazil)
- 11 million infected (60% of total)
- Interrupt vectorborne transmission by eliminating *T. infestans* (domesticated vector)
- Interrupt bloodborne transmission by serologic screening and exclusion of infected donors
Southern Cone Initiative

- Cost: $30-50 million/yr
- Argentina < 0.5% of children ≤ 4 yrs infected
- Andean and Central American initiatives
- 2014: 7-8 million persons infected (vs. 16-18 million in 1980s)
Obstacles to elimination of Chagas disease in Southern Cone

• Reinfestation of houses with *T. infestans* after insecticide spraying (sylvatic *T. infestans*, passive transport from other areas, insecticide resistance, operational issues, limited resources)

• Infestation by sylvatic triatomines

• Urbanization of Chagas disease, e.g., Arequipa, Peru: ↑migration from rural areas in 1980s-early ‘90s as result of terrorist movements, changes in land tenure laws

Andean and Central American Initiatives:
1997-98

Major obstacles:

- Reinfestation from peridomestic/ sylvatic populations of vectors with overlapping domestic and sylvatic cycles (*T. dimidiata*).
- Cost of long term sustainability.
- Insecticide resistance.
- Blood donor screening.

Transmission cycles of *T. cruzi*

Domestic

Sylvatic

Overlapping domestic and sylvatic

Miles MA. BMJ 2003;326:1444
Chagas disease in Amazon region

- *T. cruzi* infection in 33 species of wild mammals and 10 species of sylvatic triatomines
- Outbreaks, sporadic cases of acute Chagas disease from ingestion of juices (açaí) contaminated with bug feces, ground bugs or opossum scent gland secretions, or gathering piaçaba (palm tree)
- Concerns about migrations of persons from endemic areas, deforestation leading to domestication of triatomines

Mem Inst Oswaldo Cruz, 107:145, 2012
Oral transmission of *T. cruzi*

- >1000 acute cases, 138 outbreaks (S. America)
- 71% attributed to contaminated food, beverages
  - Açaí juice (Amazon)
  - South of Amazon: sugar cane
  - Caracas school outbreak” guava juice
- Unusual features, severity, mortality
Chagas disease in the United States

- Chagas disease is enzootic in the U. S.
- Number of infected persons in US ≥ the number in 8 of the 21 “endemic” countries
11 potential vector species

> 18 infected reservoir species identified

Species

<table>
<thead>
<tr>
<th>Triatomine bugs</th>
<th>% positive (T. cruzi)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. gerstaeckeri</td>
<td>43.8</td>
</tr>
<tr>
<td>T. neotomae</td>
<td>79.8</td>
</tr>
<tr>
<td>T. protracta</td>
<td>25.2</td>
</tr>
<tr>
<td>T. recurva</td>
<td>20.3</td>
</tr>
<tr>
<td>T. rubida</td>
<td>4.4</td>
</tr>
<tr>
<td>T. sanguisuga</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Mammals

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Opossum</td>
<td>36</td>
</tr>
<tr>
<td>Racoon</td>
<td>67</td>
</tr>
<tr>
<td>Armadillo</td>
<td>29</td>
</tr>
<tr>
<td>Dogs</td>
<td>23</td>
</tr>
</tbody>
</table>

T. protracta
Autochthonous cases of Chagas disease in US (n=23)

- 6 acute cases
- 17 asymptomatic cases
  - 16 identified in study of blood donors (2006-2010)
  - Estimated 1 US autochthonous case per 354,000 donations

J Inf Dis 2000;181,359
Emerg Infect Dis 2007, 13 (4)
International migration and Chagas disease

Source: Schmunis Mem Inst Osw Cruz 2007
Chagas disease in the United States

- 1 confirmed congenital case
- 5 cases: definite transfusion-associated
- 5 cases: transplantation-associated
- 1995 confirmed seropositive donors of blood products since 2007 (reported to AABB Chagas Biovigilance Network)


- 300,000 persons infected
- 30,000-45,000 cases of undiagnosed heart disease
- 63-315 congenital Chagas disease cases/year
• Large numbers of chronic unrecognized infections
• Small risk of vectorborne transmission
• Non-vectorial routes of transmission increasing importance
Chagas disease: challenges for Latin America, USA, other non-endemic countries

- Prevent new infections
  - Latin America: eliminate vectorborne transmission, prevent household reinfestation (surveillance)
  - All: prevent oral/sporadic, congenital, transfusion-associated, transplantation-associated transmission
- Identification of millions of infected persons and provision of adequate medical care