Neglected Tropical Diseases: Best options for control and how to reach the scale required.

Lyle McKinnon
Oct 2011 IID Presentation
Box 2. Common Features of the Neglected Tropical Diseases

- Ancient afflictions that have burdened humanity for centuries
- Poverty-promoting conditions
- Associated with stigma
- Rural areas of low-income countries and fragile states
- No commercial markets for products that target these diseases
- Interventions, when applied, have a history of success

Why are they neglected?

- compete with more visible diseases like HIV/AIDS, tuberculosis, and malaria
- no explosive outbreaks - chronic problems
- do not travel internationally so don’t affect wealthy nations
- affect the poorest of the poor - no incentive for the development of new diagnostic tools, drugs and vaccines
- cause enormous misery but do not kill large numbers of people.
- Endemic countries have limited resources to invest in health and competition for funds is fierce.
- The stigma associated with debilitating and deforming diseases makes the afflicted reluctant to seek care.

Adapted from http://www3.imperial.ac.uk/schisto/whatwedo/whatarentds
Key questions

• What is the public health benefit of treating neglected tropical infections?
• Are new treatment and prevention tools needed, or is it merely a question of delivery of existing tools?
• What is the existing coverage?
• What are barriers to effective delivery and/or development of new drugs/vaccines?
• How best to implement control programs?
NTD Control could have huge Impact

- impair childhood growth, physical fitness, development, and school attendance
- impair worker productivity
- often disfiguring, painful
- major cause of anemia
  - hookworm alone accounts for 35% and 73% of anemia and severe anemia
- 500,000 deaths and 56M DALYs
Overlap of Neglected Tropical Diseases

- geographically,
- same age groups,
- require same drugs
- Can treat 7 NTDs for $0.40/person/year using 4 drugs,
  - Ivermectin [Merck];
  - Azithromycin [Pfizer];
  - Albendazole [GlaxoSmithKline];
  - Praziquantel

Most individuals are ‘polyparasitized’
Focus is often on the Big 3

- HIV, malaria, and TB
- NTDs cause sig. DALYs (below)
- major difference is cost-effectiveness of interventions

Lower respiratory tract infections (91.3M), HIV/AIDS (84.5M), diarrheal diseases (62M), NTDs (56.6M), Malaria (46.5M), Tuberculosis (34.7M), Measles (21.4M)
Minimal cost of interventions

<table>
<thead>
<tr>
<th>Disease</th>
<th>Target Population</th>
<th>Numbers to Be Treated in Target Population</th>
<th>Drug, Source, and Cost If Not Donated</th>
<th>Delivery Strategy</th>
<th>Distribution Costs (Ex Drug)</th>
<th>Annual Cost Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic filariasis</td>
<td>Total eligible population in endemic areas</td>
<td>300 million</td>
<td>Mectizan donated by Merck and albendazole by GlaxoSmithKline</td>
<td>MDA for five years</td>
<td>$0.10 per person treated = $30 million</td>
<td>$30 million + donated drug</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>School-aged children plus other high risk groups</td>
<td>200 million</td>
<td>Praziquantel at $0.25 per treatment = $50 million</td>
<td>MDA in high risk area plus school health programmes</td>
<td>$0.15 per person treated = $30 million</td>
<td>$30 million + $50 million = $80 million</td>
</tr>
<tr>
<td>Intestinal helminths</td>
<td>Pre-school-aged and school-aged children</td>
<td>400 million</td>
<td>Albendazole at $0.02 per treatment = $12 million</td>
<td>MDA via community directed treatment</td>
<td>$0.10 per person treated = $40 million</td>
<td>$40 million + $12 million = $52 million</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>Total eligible population in hyper/mezzo endemic areas</td>
<td>80 million</td>
<td>Mectizan donated by Merck</td>
<td>MDA via community directed treatment</td>
<td>$0.10 per person treated = $8 million</td>
<td>$8 million + donated drug</td>
</tr>
<tr>
<td>Trachoma</td>
<td>Total population in endemic areas</td>
<td>168 million</td>
<td>Zithromax donated by Pfizer</td>
<td>MDA for five years</td>
<td>$0.20 per person treated = $34 million</td>
<td>$34 million + donated drug</td>
</tr>
<tr>
<td>Summary</td>
<td>The population of sub-Saharan Africa is an estimated 700 million</td>
<td>Up to 500 million individuals will receive treatment for one or more of these infections</td>
<td>$62 million + drug donations</td>
<td></td>
<td>= $204 million for five years</td>
<td></td>
</tr>
</tbody>
</table>

Table modified from [23], with permission from Elsevier.
Assumptions for Table 3 are as follows: (1) An estimated 500 million people will be reached and treated as appropriate for five diseases at a total cost of $204 million. (2) The per-person cost will therefore be $408. (3) Cost savings by combining delivery could reach an estimated 25%. (4) After five years’ intervention, it is expected that mass chemotherapy of some of these infections will no longer be necessary, but monitoring will be recommended on a longer-term basis to confirm this hypothesis. (5) Delivery could be combined with vaccinations (polio, measles-mumps-rubella, measles) and vitamin A capsules.

The distribution costs are estimates derived from experience with vertical programmes. Schistosomiasis is very focal and therefore requires more extensive mapping data to determine the target population. Trachoma delivery costs include some allowance for surgical intervention in extreme cases.

MDA, mass drug administration.
DOI: 10.1371/journal.pmed.0020336.t003
**Immunological impact**

- Many NTDs, helminths in particular, are powerful immunogens and chronic infections – suppressive, Th2 -skewing
- Some evidence these can impact childhood vaccines, immunity/susceptibility to HIV, TB, and malaria
- Impetus for ‘Big 3’ programs to include NTDs
**Global coverage of STH deworming**

Good news >160m kids treated. Bad news is >1,2B at risk.

**Issues:**
- poor reporting (only 50% of countries with reliable data)
- poor implementation (26% of SAC-Africa)
- range = 0-144%

2006 Data. **Black** indicates countries with >75% coverage of pre-school children

Global Need

Proportion of children (1-15 years of age) in the country requiring preventive chemotherapy for soil-transmitted helminthiases, worldwide, 2010

Challenges

• Financing
• Reach remote areas
• Research and monitoring questions
  – compliance, drug interactions, resistance, sustainability,
• Target kids the same age,
• Human resources
  – a midwife and nurse to cover 30,000
  – incentive system
• Integrate into existing programs to achieve coverage

Gyapong et al Lancet 2010
Integration: What Why How Who

- Horizontal - vertical debate rages on
- Elimination programs - vertical by definition
- Vertical programmes have a track record, measurable outcomes
- Some nations spend $10/person/year on health
- Can vertical NTD programs be used to build health care system capacity?

Gyapong et al Lancet 2010
Poor market for New Drug and Vaccine development

- Main market is the global, rural poor
- Philanthropy - “creative capitalism”
- Government - particularly of affected countries
- NIH/FDA fast track for development of orphan drugs

- Balance between R&D vs. implementing current, effective strategies
Private - Public Partnerships

Schistosomiasis Control Initiative
Partnership for Parasite Control (STH)
Human Hookworm Vaccine Initiative
International Trachoma Initiative
Global Alliance to Eliminate Lymphatic Filariasis
African Programme for Onchocerciasis Control

Drugs for Neglected Tropical Diseases initiative
WHO Programme to Eliminate Sleeping Sickness

- cover a wide range of NTD
- Some focus more on implementation, others on R&D, some both
### Drugs for Neglected Diseases initiative

#### DNDi Portfolio

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Clinical</th>
<th>Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>LS</td>
<td>LO</td>
<td></td>
</tr>
<tr>
<td><strong>Discovery Activities</strong></td>
<td><strong>HAT LO Consortium</strong></td>
<td><strong>Nitroimidazole backup (HAT)</strong></td>
<td><strong>Fexinidazole (HAT)</strong></td>
</tr>
<tr>
<td></td>
<td>• Scynaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pace Univ.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>VL LO Consortium</strong></td>
<td><strong>Oxaborole SCYX7158 (HAT)</strong></td>
<td><strong>New VL treatments – Bangladesh</strong></td>
</tr>
<tr>
<td></td>
<td>• Advinus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• CDRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chagas LO Consortium</strong></td>
<td><strong>Alternative formulations of Amphotericin B (VL)</strong></td>
<td><strong>New VL treatments – Africa</strong></td>
<td><strong>NECT (Stage 2 HAT)</strong></td>
</tr>
<tr>
<td>• CDCQ</td>
<td></td>
<td></td>
<td>Nitfumizox - Etorrhinione</td>
</tr>
<tr>
<td>• Epilchem</td>
<td><strong>Nitroimidazole (VL)</strong></td>
<td><strong>New VL treatments – Latin America</strong></td>
<td>Co-administration</td>
</tr>
<tr>
<td>• Murdoch Univ.</td>
<td><strong>Drug combination (Chagas)</strong></td>
<td><strong>Benznidazole Paediatric dosage form (Chagas)</strong></td>
<td><strong>SSG &amp; PM (VL in Africa</strong></td>
</tr>
<tr>
<td>• FUOP</td>
<td></td>
<td></td>
<td>co-administration</td>
</tr>
<tr>
<td><strong>Exploratory</strong></td>
<td><strong>K777 (Chagas)</strong></td>
<td><strong>Azoles E1224 &amp; Biomarker (Chagas)</strong></td>
<td><strong>New VL treatments</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Flubendazole Microfilaricide (Helminth)</strong></td>
<td><strong>Paediatric HIV (exploratory)</strong></td>
<td><strong>in Asia</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Exploratory</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Major Collaborators

- **Sources for hit and lead compounds:** GSK, Anacor, Merck, Pfizer, Novartis (GNF, NITD), TB Alliance, ...
- **Screening Resources:** Eaklee, Institut Pasteur Korea, Univ. Scynaxis, Univ. Dundee, ...
- **Reference screening centres:** LSHTM, Swiss Tropical & Public Health Institute, University of Antwerp

**HAT:** Human African Trypanosomiasis  
**VL:** Visceral Leishmaniasis
Schistosomiasis Control Initiative

- created in 2002 at Imperial College London - 20M GBP from Gates Foundation
- by 2007, 40M Schistosome treatments
- further funding from USAID and Geneva Global
- Currently targeting 7 NTDs in an integrated approach
Campaign to eradicate Guinea worm

1980s - 3.5M cases/year

So far there have been 197 confirmed cases in the first quarter of 2011, almost all of which have been in South Sudan.

No drugs - Key is clean drinking water.
Summary points

• Relatively small expenditure for major potential impact
• Way to improve the health of the global poor
• NTDs not in millennium development goals, but their effective control would contribute towards meeting 7 / 8 MDGs
• NTD programs among the most effective development investments in any sector (World Bank)
Maybe one day, they will be known as the ‘diseases formerly known as neglected’...

It is clear that elephantitis is a problem