NEGLECTED TROPICAL DISEASE VACCINES:
THE “ANTIPOVERTY VACCINES”

Human Hookworm, Schistosomiasis,
Leishmaniasis, Chagas Disease

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The Global Burden of Disease Study 2010: Interpretation and Implications for the Neglected Tropical Diseases

Introduction
The publication of the Global Burden of Disease Study 2010 (GBD 2010) and development, specifically from non-communicable diseases (NCDs), and overall economic productivity [1][2][3]. New DALYs account for direct costs of treatment,
### Expected number of cases in 2010 and 95% confidence intervals of the neglected tropical diseases (mean and uncertainty) as extrapolated from the Global Burden of Disease Study 2010.

- **Ascariasis**: 819 million
- **Trichuriasis**: 465 million
- **Hookworm Disease**: 439 million
- **Schistosomiasis**: 252 million
- **Lymphatic Filariasis**: 36 million
- **Onchocerciasis**: 30 million
- **Food-borne Trematodiases**: 16 million
- **Cutaneous Leishmaniasis**: 10 million
- **Chagas disease**: 7.5 million
- **Trachoma**: 4.4 million
- **Cysticercosis**: 1.4 million
- **Echinococcosis**: 1.1 million
- **Dengue**: 179,000
- **Visceral leishmaniasis**: 76,000
- **African Trypanosomiasis**: 37,000
- **Rabies**: 1,100
- **Yellow Fever**: 100

### DALYs vs. Deaths

- **Rabies**
- **African trypanosomiasis**
- **Dengue**
- **Leishmaniasis**
- **Chagas disease**
- **Neglected tropical diseases and malaria**
- **Echinococcosis**
- **Other neglected tropical diseases**
- **Ascariasis**
- **Schistosomiasis**
- **Cysticercosis**
- **Intestinal nematode infections**
- **Lymphatic filariasis**
- **Onchocerciasis**
- **Trachoma**
- **Yellow fever**
- **Trichuriasis**
- **Hookworm disease**
- **Food-borne trematodiases**
Estimated DALYs (in millions) of the NTDs from the Global Burden of Disease Study 2010.

<table>
<thead>
<tr>
<th>Disease</th>
<th>DALYs from GBD 2010</th>
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<tbody>
<tr>
<td>NTDs TOTAL</td>
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<tr>
<td>Leishmaniasis</td>
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<tr>
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<tr>
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<tr>
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<td>0.33 million</td>
</tr>
<tr>
<td>Echinococcosis</td>
<td>0.14 million</td>
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</tbody>
</table>

Vaccines for Discussion in Red

40% of GBD from NTDs

Important New Role for WHO

- WHO can fill an important niche
  - No International Agency has committed to NTD Vaccines
  - GAVI Agenda is focused on under-5 childhood mortality
  - Little interest in vaccinating against DALYs and Poverty?
Important New Role for WHO

– Major activities
  • Fostering partnerships
    – Coordinating PDPs and Developing Country Manufacturers
    – Promoting involvement of multinational companies
  • Shaping elimination strategies for vaccines

– More granular activities
  • Demand Forecasting and Consensus Building
  • Developing endpoints and targets
  • Prequalification
  • Pathways to licensure
    – Registration in disease-endemic countries – WHO prequalification
    – US FDA
    – Article 58 of the European Agency

ANTHELMINTHIC VACCINES
Hookworm and Schistosomiasis
Timeline for elimination and eradication for the NTDs:

**REQUIREMENT FOR NEW TECHNOLOGIES**

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**Human Hookworm Infection**

- Highly prevalent neglected tropical disease – 440 million people
- 3.2 million DALYs
- A leading cause of maternal and childhood anemia in low- and middle-income countries

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Medical Need: Deworming Deficiencies

- Minimal efficacy in Cochrane Analysis
- Single dose mebendazole has low efficacy against *Necator americanus* mean 15% cure rates (0-68% cure rates)
- Outright drug failure in some African communities
- Single dose albendazole variable efficacies and rapid rebound infection

Targeting Blood-feeding in the Hookworm Gut in Phase 1 Trials

>90% reduction *Nippostrongylus* In mice

Na-GST-1 + Na-APR-1 Bivalent Vaccine

Pathogen, disease and unmet medical need: Human Hookworm

Target groups/indications - vaccine:
1. Intended for children under the age of 10 years who are at risk for acquiring moderate and heavy hookworm infections. Administered by intramuscular injection up to two doses.
2. Can be administered concurrently with other childhood vaccines.
3. Efficacy of at least 80% in preventing moderate and heavy hookworm infections caused by *N. americanus*.

A potential elimination strategy

HOOKVAC: A New European-African Consortium
Albert Schweitzer Hospital

“*The purpose of human life is to serve, and to show compassion and the will to help others*”
250 million cases (90% Africa)
3..3 million DALYs and up to 280,000 deaths
WHA 65.19 Resolution for schistosomiasis elimination

A Vaccine for Female Genital Schistosomiasis
“Backdoor HIV/AIDS Prevention Strategy”
Pathogen, disease and unmet medical need: Schistosomiasis

• Existing Treatment:
  – Chemotherapy is the main treatment
  – Reducing contact between at risk populations and contaminated water by the construction of wash houses and safe water supplies

• Unmet public health need:
  – Estimated that the number of people with Schistosomiasis over the past fifty years has not changed, even though distribution of the disease has changed
  – 250 million people who are infected, 120 million of these are symptomatic and 20 million with the severe disease
  – Estimated six hundred million people are at risk for infection
  – Vaccines used in combination with other control strategies, including the use of new drugs, are needed to make elimination of schistosomiasis possible

Pathogen, disease and unmet medical need: Schistosomiasis

• Target groups/indications - vaccine:
  1. Intended for both school aged children and adults
  2. Administered by intramuscular injection up to two doses
  3. Can be administered concurrently with other anti-schistosomiasis drugs as well as other childhood vaccines
  4. Efficacy of at least 40% in reduction of worm burden
Vaccine development: Schistosomiasis Candidates

- History of Vaccine R&D:
  - Vaccine development strategies against schistosomes currently target the prevention of infection or the reduction of parasite reproduction.
  - Most current approaches have focused on using recombinant protective antigens from stage-specific parasites in various formulations.

- African Schistosomiasis:
  - The Institute Pasteur/INSERM have developed a Sh28GST (28-kDa recombinant glutathione-S-transferase) Alum formulation that has completed Phase II and Phase III.
  - The Sabin Vaccine Institute PDP and DMID/NIH are investigating Sm-TSP-2 (9-kDa recombinant tetraspanin) Alhydrogel® ± GLA vaccine that is entering Phase I.
  - The Oswaldo Cruz Foundation (Fiocruz) is investigating an Sm-14 (14-kDa recombinant fatty acid binding protein) with the adjuvant GLA vaccine.

Three Vaccines in Clinical Trials for African Schistosomiasis

<table>
<thead>
<tr>
<th>Candidate Name/Identifier</th>
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<th>Phase II</th>
<th>POC</th>
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Pathogen, disease and unmet medical need: Leishmaniasis

- **Key facts:**
  - Leishmaniasis is a vector borne disease caused by >20 Leishmania species and spread by the bite of sandflies

- **Impact:**
  - Two major forms of the disease
  - Visceral Leishmaniasis (VL)
    - 100,000 annual new cases, fatal if untreated
  - Cutaneous Leishmaniasis (CL)
    - 10 million cases causing disfigurement
Leishmaniasis Control and Prevention

• Rationale
• Current approaches
  – Sandfly control
  – Reservoir control
  – Case detection and management
  – China in the 1950s: mass treatment, killing of dogs, insecticides
• Most CL and VL are zoonoses
• Vaccine needed to prevent human disease
  – Hyperendemic areas
  – Outbreak and conflict settings

Pathogen, disease and unmet medical need: CL

• Existing Treatment:
  – Chemotherapy is the main treatment
  – Controlling one of the main reservoirs of this infection, dogs (presents logistical concerns)
• Unmet public health need:
  – Estimated that if the population within seven countries of Latin America: Bolivia, Brazil, Colombia, Ecuador, Mexico, Peru and Venezuela were vaccinated using a vaccine formulation that would provide at least 10 years of protection that an estimated 41,000-144,000 cases of CL could be averted
    • This would come at a cost that is lower than the cost of current recommended treatments
  – Even a vaccine that provides as little as 50% efficacy, and only 5 years of protection, would still remain cost effective
CL Vaccine in Outbreak Setting

- Chaparral, Colombia
- 2004
- 8,444 CL cases per 100,000 residents
- If Vaccinated
  - 478-1827 out of the 2810 cases averted
  - $13,384-58,464 saved
  - Depending on compliance

CL and Conflict

>100,000 new cases

"Aleppo Evil" : The Ulcer, the Boil, the Sand-fly, and the Conflict
Pathogen, disease and unmet medical need: VL

- **Existing Treatment:**
  - Chemotherapy is the main treatment
  - Controlling one of the main reservoirs of this infection, dogs (presents logistical concerns)

- **Unmet public health need:**
  - Lee et al Am J Trop Med Hyg
  - In Bihar: Results found a potential vaccine to be cost-effective (and in many cases economically dominant, i.e., saving costs and providing health benefits) throughout a wide range of vaccination costs and vaccine efficacies, and VL risks. Overall, our study strongly supports the continued development of a VL vaccine.

Vaccine development: Leishmaniasis

- **History of Vaccine R&D:**
  - Proof of concept = Leishmanization
  - Live parasites vs. Killed parasites + BCG
  - Widely used in Iran Iraq War
  - Inconsistent results

- **Candidates & Approaches:**
  - Infectious Disease Research Institute (IDRI) has brought three different recombinant protein based candidates to the clinic, and have completed multiple Phase I and Phase II studies using novel adjuvant formulations
  - The Sabin PDP is investigating vaccines using salivary proteins of the sand fly vectors known to transmit *Leishmania* parasites. These salivary proteins are being paired with traditional recombinant Leishmania proteins as transmission blocking vaccines, and are in pre-clinical testing

### Development Status of Current Vaccines

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<thead>
<tr>
<th>Candidate Name/Identifier</th>
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Pathogen, disease and unmet medical need: Chagas Disease

• Key facts:
  – Vector borne disease caused by the parasite Trypanosoma cruzi and spread by the triatomine bug, also known as the “kissing bug”
  – Affects almost exclusively the poorest people living in these regions, especially because of the kissing bug vector’s propensity to live in poor-quality dwellings, as well as lack of access to essential medicines and vector control practices

• Impact:
  – Estimated at 7.5 million cases, but possibly at least that number in Mesoamerica (Texas, Mexico and Central America)
  – Most of the disability and deaths result from chronic Chagas cardiomyopathy, a condition that develops in approximately 30% of individuals infected with T. cruzi
  – Maternal-to-child transmission leading to congenital Chagas disease has also emerged as an important route of transmission, especially in Mesoamerica and North America where an estimated 40,000 pregnant women are infected

Pathogen, disease and unmet medical need: Chagas Disease

• Existing Treatment:
  – Benznidazole and nifurtimox are the main treatments
    • Limited efficacy in chronic stage
    • Significant side effects
    • Long treatment duration
    • Contraindicated in pregnancy

• Unmet public health need:
  – A vaccine compared to drug treatment would potentially allow for use in pregnancy and thus prevent congenital transmission and have reduced toxicities compared to the drugs.
  – Vaccine could have a potentially a higher efficacy
  – Vaccine-linked chemotherapy – combining vaccine + benznidazole
**Pathogen, disease and unmet medical need: Chagas Disease**

- **Target groups/indications - vaccine:**
  1. Intended for both children and adults
  2. Administered by intramuscular injection up to two doses
  3. Can be administered concurrently with other trypanocidal drugs as well as other childhood vaccines
  4. Efficacy of at least 80% efficacy at preventing the onset of cardiac complications

**Vaccine development: Chagas Disease**

- **History of Vaccine R&D:**
  - Multiple murine models for acute and chronic *T. cruzi* infection have been developed. Non Human Primates are also being used and can become naturally infected.

- **Candidates & Approaches:**
  - The Sabin PDP is accelerating the development of a bivalent therapeutic vaccine for the treatment of chronic Chagas disease.
  - UTMB is studying the use of the antigens TcG1, TcG2, and TcG4 as possible vaccine candidates in preclinical models – also under evaluation at Sabin
  - University of Georgia is screening *T. cruzi* genes for promising antigens
  - University of Texas at El Paso is pursuing the MASP antigen as a possible vaccine antigen and it is also being tested in murine models
  - Universidade Federal de Santa Catarina as well as the Universidade Federal de Minas Gerais also has active vaccine discovery programs

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(Quijano-Hernandez et al, 2011)
Key Take-Home Messages

- Elimination targets for NTDs set by WHA 65.19 and 66.12
- New vaccines will be needed for NTD elimination
  - Also, backdoor strategy for HIV/AIDS malaria elimination
  - Some NTD vaccines key role in conflict / post-conflict
- NTD vaccines need a WHO as a champion – GAVI emphasizing U5 child mortality vaccines
- WHO Role for shaping control and elimination strategies using vaccines
- Demand forecasting, consensus building, endpoints, prequalification, pathways to licensure
- Fostering partnerships – PDPs, DCVMN, Pharma