

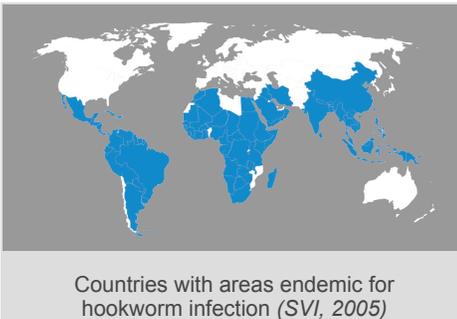
Background

Global Burden | Causative Agent & Transmission | Pathogenesis | Current Control Strategy | Existing Products | Get Involved

What is Hookworm?

Hookworm is a parasitic roundworm of the small intestine that is transmitted through the soil. Although most patients are asymptomatic, heavy worm burdens lead to anemia, diarrhea, abdominal pain, weight loss and loss of appetite. While hookworm is associated with a relatively small number of deaths, chronic anemia caused by the disease is associated with significant morbidity.

Global Burden



Hookworm is found throughout the tropics and subtropics. It is estimated that 600-700 million people are infected worldwide, resulting in the loss of approximately 1.1-22.1 million DALYs annually and 65,000 lives annually.^{1,2}

| WHO Region | DALY (in thousands) ³ |
|-----------------------|----------------------------------|
| Africa | 377 |
| Americas | 20 |
| Eastern Mediterranean | 43 |
| Southeast Asia | 286 |
| Western Pacific | 364 |
| Total: | 1,090 |

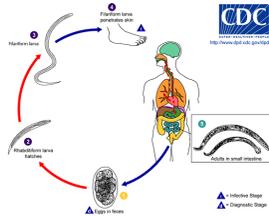
The economic impact of hookworm is difficult to estimate. However, retrospective studies of the effects of hookworm control and treatment in the United States demonstrated that children cured of hookworm were more likely to attend school and on average earned 45% higher incomes as adults as compared to children who grew up with hookworm.¹

Causative Agent and Transmission



A hookworm in its immature, noninfectious stage (photo: CDC)

Hookworm is caused by two organisms, *Necator americanus* and *Ancylostoma duodenale*. *N. americanus* causes 85% of hookworm infections and is found throughout the Americas, sub-Saharan Africa, Southeast Asia, China, and Indonesia. *A. duodenale* is restricted to the Middle East, North Africa, and India.



Hookworm life cycle.

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Humans are infected with hookworm when free-living larval stages of the worm in the soil penetrate the skin. The larvae travel through the blood stream to the lungs where they migrate up the trachea and, through coughing and subsequent swallowing, pass through the stomach to the small intestine. Female hookworms in the small intestine shed eggs into the stool of the host. When latrines or toilets are not available, eggs from the feces of infected hosts contaminate the soil and water. In the soil, the eggs hatch and develop through three larval stages before infecting a new host through penetration of the skin.

Pathogenesis

The adult hookworm when located in the small intestine burrows into the intestinal lining rupturing capillaries to access the host's blood. The worm survives by feeding on this blood. Blood loss through intestinal damage and worm feeding lead to the anemia associated with hookworm. Worms can survive in the intestine for 1-18 years.

Children and pregnant women are particularly susceptible to iron deficiency anemia (IDA) as the result of hookworm infection. In children IDA can lead to impaired neurological development and cognitive function. In pregnant women IDA can lead to low infant birth weight and even infant death.

Current Control Strategy

Current control strategies for hookworm include a combination of mass drug administration (MDA) with benzimidazoles (albendazole or mebendazole) and improvement of sanitation to reduce fecal contamination in the local environment.

Existing Products

▶ Drugs

Mass drug administration programs primarily use albendazole (single dose efficacy approximately 75%) for the treatment of hookworm. Mebendazole and pyrantel pamoate can also be used but are significantly less effective.² Albendazole is also used for MDA to treat lymphatic filariasis and other soil transmitted helminths such as ascariasis and trichuriasis providing crossover treatment for hookworm.

▶ Vaccines

There is currently no vaccine approved for the prevention of hookworm. Vaccines in development are discussed in the next section.

▶ Diagnostics

Diagnosis of hookworm relies on microscopic examination of feces for egg contamination. This has an overall low sensitivity for hookworm diagnosis as eggs in stool are not visible until 8 weeks after infection with *N. americanus* or 38 weeks after infection with *A. duodenale*. Furthermore, hookworm eggs are difficult to distinguish from the eggs of other worm infections.

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References

1. WHO (2010) First WHO report on neglected tropical diseases 2010: working to overcome the global impact of neglected tropical diseases.
2. Hotez PJ et al. (2010) "Developing vaccines to combat hookworm infection and intestinal schistosomiasis." *Nature Reviews Microbiology* **8**: 814-826.
3. Keiser J, Utzinger J (2008) "Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis." *JAMA* **299**: 1937–48

Get Involved

To learn how you can get involved in neglected disease drug, vaccine or diagnostic research and development, or to provide updates, changes, or corrections to the Global Health Primer website, please view our FAQs or contact us at globalhealthprimer@bvgh.org.

Pipeline & Analysis

Drugs | Vaccines | Diagnostics | Get Involved

Drugs

The development of novel drugs for hookworm is not considered an immediate priority. Although drug resistance is possible, it is not yet widespread. At this point in time, resources are focusing more heavily on improving the coverage of mass drug administration among school children and vaccines to prevent hookworm infection.

Future drug discovery programs will most likely focus on the repurposing of veterinary medications for worm infections, new combination therapy programs, or discovery of single products that can target multiple parasitic or neglected diseases in a single dose.

Vaccines

▶ PIPELINE

| Product/Research Program | Developers | Discovery | Pre-clinical | Phase I | Phase II | Phase III |
|--------------------------|---|-----------|--------------|---------|----------|-----------|
| NaGST-1 | Human Hookworm Vaccine Initiative Oswaldo Cruz Foundation Sabin Vaccine Institute | | | | | |
| NaAPR-1 | Human Hookworm Vaccine Initiative Oswaldo Cruz Foundation Sabin Vaccine Institute | | | | | |
| NaASP-2 | Human Hookworm Vaccine Initiative Oswaldo Cruz Foundation Sabin Vaccine Institute | | | | | |

▶ ANALYSIS

There are currently two vaccines in pre-clinical development for hookworm. Neither vaccine has entered clinical development at this point. These vaccines target the parasite blood feeding pathway.

A previous effort for hookworm vaccine development using a larval protein antigen, Na-ASP-2, included an initial phase I clinical trial in 2005 in the U.S. Unfortunately, when a subsequent phase I study was conducted in a population with potential previous hookworm exposure in Brazil, patients experienced allergic reactions immediately after vaccination. Development of ASP-2 as a vaccine candidate was halted in 2007/2008. In order to avoid the risk of negative allergic reactions in the future, the hookworm vaccine community decided to shift its strategy from focusing on protein antigens from larval stage worms to focusing on antigens associated with worm blood feeding.

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Diagnostics

New point of care diagnostics for hookworm are needed for use in parallel with mass drug administration (MDA) programs. A key challenge of MDA is determining when mass treatment should stop. Diagnostics that can be used in extremely rural areas by minimally trained community volunteers (potentially those already involved in the MDA program) are needed to determine when transmission of hookworm has been interrupted in a village. The same diagnostics should be used to monitor communities to insure reintroduction does not occur.

The majority of ongoing diagnostic development is focusing on optimizing microscopic detection of eggs rather than novel tests. Biomarker discovery and immune response profiling associated with vaccine programs may inform novel diagnostic development.

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Tools

Drugs | Vaccines | Diagnostics | Get Involved

The following series of tables describe the availability of tools for research, discovery, and development of novel drugs, vaccines, and diagnostics for hookworm. The tools listed in the following tables are not intended to be an all-inclusive list but rather capture the most common tools used for drug, vaccine, and diagnostic development. The tools available for human hookworm research and development are not extensive.

Drug Development Tools

| Basic Research: Target Identification | Target Validation | Screening: Hit/Lead Identification Optimization | Pre-clinical Validation | Clinical Validation |
|--|---|---|---|--|
| <p>Genome: <i>Necator americanus</i> genome sequencing is in progress</p> <p>Key databases: Nematode.net</p> <p>In vitro culture: Larval stages from eggs isolated from infected people</p> | <p>Gene knock-outs: No</p> <p>Conditional gene knock-outs: No</p> <p>Transposon mutagenesis: No</p> <p>RNAi: No</p> <p>Other antisense technology: No</p> <p>Viability assays: Yes, using adult <i>Ancylostoma caninum</i> (dog hookworm) motility</p> <p>Transcription microarrays: Limited, primarily only for <i>Ancylostoma caninum</i> (dog hookworm)</p> <p>Proteomics: Limited, primarily only for <i>Ancylostoma caninum</i> (dog hookworm)</p> <p>Crystal structures: Limited, available for antigens being pursued for vaccine development</p> | <p>Whole-cell screening assays: No</p> <p>Enzymatic screening assays: Limited</p> | <p>Animal models: Yes</p> <p><i>A. ceylanicum</i> or <i>A. caninum</i> infection of dogs</p> <p><i>A. ceylanicum</i> infection of hamsters</p> <p><i>Ancylostoma</i> spp. and <i>N. americanus</i> in mice but non-physiological due to lack of intestinal blood feeding</p> <p>Hamster adapted <i>N. americanus</i></p> | <p>Monitoring treatment efficacy: Yes, indirectly through egg counts in stool and effects on anemia</p> <p>Availability of endpoints: Indirect measurements of parasite survival including egg counts in stool and anemia</p> <p>Availability of surrogate endpoints: No</p> <p>Access to clinical trial patients / sites: Yes</p> |

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Vaccine Development Tools

| Basic Research: Antigen Identification | Immune Response Characterization | Clinical Validation |
|---|--|--|
| <i>See drug development tools above</i> | Predictive animal models: Several models with limited relevance Detection of endogenous antigen specific response in clinical samples: Yes Natural immunity well characterized: No, studies ongoing but complex | Surrogate markers of protection: Surrogate markers of infection available but not immunity Challenge studies possible: No, although clinical infections were performed in '70s and '80s to study immunology |

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Diagnostic Development Tools

| Basic Research: Biomarker Identification | Biomarker Validation | Clinical Validation |
|--|---|---|
| <i>See drug development tools above</i> | Biomarkers known: Yes Access to clinical samples: Yes Possible sample types: Stool | Access to clinical trial patients/sites: Yes Treatment available if diagnosed: Yes |

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Product Details

NaAPR-1

Synonyms:
NaAPR-1

Disease:
Soil-Transmitted Helminths: Hookworm

Target/Technology:
Recombinant/purified protein vaccines

Specific Indication:
Preventive, N. americanus

Mechanism of Action:

Product Type:
Vaccine

Molecule Class:

PRV Eligible?
Yes

Administration Route:

Notes:

Clinical Trials:

Publications:

20948553

NaASP-2

Synonyms:
NaASP-2

Disease:
Soil-Transmitted Helminths: Hookworm

Target/Technology:
Recombinant/purified protein vaccines

Specific Indication:
Preventive, N. americanus

Mechanism of Action:

Product Type:
Vaccine

Molecule Class:

PRV Eligible?
Yes

Administration Route:

Notes:

Discontinued during Phase I trial in Brazil (2007-2008) due to allergic reaction in patients from endemic areas.

Clinical Trials:

NCT00120081
NCT00473967

Publications:

20948553

NaGST-1

Synonyms:
NaGST-1

Disease:
Soil-Transmitted Helminths: Hookworm

Target/Technology:
Recombinant/purified protein vaccines

Specific Indication:
Preventive, N. americanus

Mechanism of Action:

Product Type:
Vaccine

Molecule Class:

PRV Eligible?
Yes

Administration Route:

Notes:

Clinical Trials:

Publications:

20948553

Developer Details

Sabin Vaccine Institute (United States)

| Type | Disease | Product/Research Program | Current Phase |
|---------|--------------------------------------|--------------------------|---------------|
| Vaccine | Soil-Transmitted Helminths: Hookworm | NaGST-1 | Pre-clinical |

Sabin Vaccine Institute (United States)

| Type | Disease | Product/Research Program | Current Phase |
|---------|--------------------------------------|--------------------------|---------------|
| Vaccine | Soil-Transmitted Helminths: Hookworm | NaAPR-1 | Pre-clinical |

Sabin Vaccine Institute (United States)

| Type | Disease | Product/Research Program | Current Phase |
|---------|--------------------------------------|--------------------------|---------------|
| Vaccine | Soil-Transmitted Helminths: Hookworm | NaASP-2 | Phase I |

Human Hookworm Vaccine Initiative (United States)

| Type | Disease | Product/Research Program | Current Phase |
|---------|--------------------------------------|--------------------------|---------------|
| Vaccine | Soil-Transmitted Helminths: Hookworm | NaGST-1 | Pre-clinical |

Human Hookworm Vaccine Initiative (United States)

| Type | Disease | Product/Research Program | Current Phase |
|---------|--------------------------------------|--------------------------|---------------|
| Vaccine | Soil-Transmitted Helminths: Hookworm | NaAPR-1 | Pre-clinical |

Human Hookworm Vaccine Initiative (United States)

| Type | Disease | Product/Research Program | Current Phase |
|---------|--------------------------------------|--------------------------|---------------|
| Vaccine | Soil-Transmitted Helminths: Hookworm | NaASP-2 | Phase I |

Oswaldo Cruz Foundation (Brazil)

| Type | Disease | Product/Research Program | Current Phase |
|------|---------|--------------------------|---------------|
|------|---------|--------------------------|---------------|

| | | | |
|---------|--------------------------------------|---------|--------------|
| Vaccine | Soil-Transmitted Helminths: Hookworm | NaGST-1 | Pre-clinical |
|---------|--------------------------------------|---------|--------------|

Oswaldo Cruz Foundation (Brazil)

| Type | Disease | Product/Research Program | Current Phase |
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| Vaccine | Soil-Transmitted Helminths: Hookworm | NaAPR-1 | Pre-clinical |

Oswaldo Cruz Foundation (Brazil)

| Type | Disease | Product/Research Program | Current Phase |
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