NEGLECTED TROPICAL DISEASES
Identifying Research Gaps and Opportunities
Neglected Tropical Diseases: Identifying Research Gaps and Opportunities
Report of Workshop Held on September 27, 2007

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Neglected Tropical Diseases: Identifying Research Gaps and Opportunities
Introduction

Tropical diseases have been part of the NIH mission since its founding and are incorporated into the Public Health Service Act as part of the NIH mission. International collaborative efforts as well as public-private partnerships are generating new opportunities for making substantial progress in novel interventions for many infectious diseases of the tropics. Growing public interest in global health could add to this momentum. International efforts in malaria, tuberculosis and HIV are providing an infrastructure that overlaps geographically with endemic areas for many other infectious diseases, creating prospects for shared research capabilities and opportunities. The availability of new methodological approaches such as genomics, proteomics, synthetic chemistry, molecular and genetic epidemiology, as well as increases in information and communication technologies, may further enhance prospects for progress in research on many infectious diseases found in the tropics. Although many such diseases have been historically thought of as resulting from poverty, they have been more recently recognized as a significant cause of poverty that must be addressed in order to break the cycle of poverty.

Neglected tropical diseases (NTDs) are a group of conditions that are among the most common infections in the world’s most impoverished individuals. These diseases are caused by parasitic worms, protozoa, and bacteria, and primarily affect low income countries throughout sub-Saharan Africa, Asia, and Latin America. The majority of these diseases are transmitted by insect vectors, including mosquitoes, black flies, sand flies, and tsetse flies. Others are spread by contaminated water or soil infested with worms. While NTDs can be fatal, most often they result in chronic disabilities leading to disfigurements, impaired development, complications in pregnancy, and ultimately loss of worker productivity. In fact, NTDs rank closely with diarrheal diseases and malaria in the number of years lost to disability and premature death, or disability adjusted life-years (DALYs). Thus, NTDs perpetuate poverty by placing huge burdens on both the health and economic development of low-income countries. While treatments for some NTDs are available, many are not well tolerated by patients and have significant adverse side effects. The need for new interventions to prevent and treat these diseases becomes even more urgent in light of limited access to existing treatments, rapid reinfection following treatment, and drug resistance. (WHO; Global Network for Neglected Tropical Diseases; Hotez, et al. N Engl J Med. 2007 Sep 6; 357(10):1018-27)

Despite the burden of disease, research progress in NTDs lags behind many other infectious diseases. Research progress has been greatly hampered due to a number of obstacles, including:

- complex pathogen life cycles that are laborious and often expensive to maintain in the laboratory
- limited molecular tools for genetic manipulation and analysis on a genome-wide scale
- limited animal models of infection that mimic the human disease

At NIH, the National Institute of Allergy and Infectious Diseases (NIAID) supports basic and applied research to better understand, treat, and ultimately prevent infectious diseases, such as NTDs. In order to better understand current NTD research gaps and opportunities, the Division of Microbiology and Infectious Diseases (DMID) within the NIAID convened a workshop of leading experts in the various fields of NTD research.
Introduction

Meeting participants were charged with addressing the following questions:

- What are the most important current research gaps in NTDs research and how can these best be addressed?
- What are the current barriers to research on NTDs and how might these be overcome?
- Which research areas are most promising in terms of identifying and advancing development of new strategies to combat NTDs?
- Are there overlapping areas of research and synergies that could have an impact on multiple NTDs?

The neglected tropical diseases (NTDs) discussed in this workshop:

- **Protozoa**
  - Trypanosomiasis
  - Leishmaniasis
- **Helminth**
  - Schistosomiasis
  - Filariasis
  - Hookworm
  - Soil-transmitted nematode infections
- **Bacteria**
  - Trachoma
  - Leprosy
  - Buruli ulcer

To address these questions, invited experts first provided disease-focused presentations for each of the NTD pathogens listed in the table above. During these presentations, the experts provided a technical, non-prioritized description of research gaps and resource needs for each parasite. A summary of these presentations are presented in the Pathogen Specific Areas section in the appendix of this report.

Following these disease-focused presentations, the NTDs were separated into three pathogen focus areas for discussion: Protozoa, Helminth and Bacteria. Meeting attendees were divided into discussion groups according to expertise and charged with identifying research priorities in immediate, intermediate and long-term time frames for these pathogen groups and the vectors that transmit them. These priorities as well as general background information on individual diseases are presented in the Research Priorities within Pathogen Groups section of this report.

As these diseases share many common obstacles that have hampered research progress, a number of cross-cutting areas became apparent through presentations and discussions at the meeting. See the Cross Cutting Areas section of this report for a summary.
Research Priorities within Pathogen Groups

Protozoa (Trypanosoma and Leishmania)

Parasitic protozoa are single-celled organisms that cause a variety of debilitating and life-threatening diseases in humans. Species of parasitic protozoa from two genera, *Trypanosoma* and *Leishmania*, are responsible for diseases in the NTD group discussed at this meeting.

Protozoa in the genus *Trypanosoma* cause two types of diseases in humans: African sleeping sickness and Chagas’ disease. African trypanosomiasis (sleeping sickness) is caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* and is transmitted by the tsetse fly (*Glossina* spp.). An estimated 60 million people in 36 countries in sub-Saharan Africa are at risk for African trypanosomiasis, with an estimated 50,000-70,000 people infected (http://www.who.int/mediacentre/factsheets/fs259/en/). Sleeping sickness is invariably fatal if left untreated, and available treatments produce severe side effects in some patients. Major epidemics are a constant threat to the economic development of Central and East Africa.

American trypanosomiasis (Chagas’ disease) is caused by *Trypanosoma cruzi* and is transmitted by insects commonly known as “kissing bugs” of the subfamily *Triatominae* (Family *Reduviidae*). The acute phase of the disease following infection may last for a few weeks or months and often goes undetected. Untreated cases, however, may develop into chronic infections leading to damage to the nervous system, digestive system, and heart. An estimated 100 million people are at risk in 21 countries in Central and South America with 16-18 million people infected. There are 1 million new cases of chronic disease and more than 45,000 deaths annually. (http://www.who.int/tdr/diseases/chagas/direction.htm#burden)

Leishmaniasis is caused by protozoa in the genus *Leishmania* (20 species are pathogenic for humans) and is transmitted by the phlebotomine sandfly. An estimated 350 million people are at risk in 88 countries with 12 million people infected. There are three basic forms of the disease: cutaneous, mucocutaneous, and visceral. Cutaneous leishmaniasis, the most common form of the disease, results in non-healing, scaling lesions of the skin that often ulcerate and become infected secondarily with bacteria. Mucocutaneous leishmaniasis affects mucous membranes and produces destructive and often disfiguring lesions of the face. In visceral leishmaniasis (also known as kala-azar), the most severe form of the disease, the parasite infects internal organs such as the liver, spleen and bone marrow, resulting in death if left untreated. More than 90 percent of the world's cases of visceral leishmaniasis are in India, Bangladesh, Nepal, Sudan, and Brazil. In addition, the incidence of HIV/Leishmania co-infections is increasing, especially in southern Europe. (http://www.who.int/leishmaniasis/burden/en/)

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Immediate Priorities

For specific information on basic science research gaps, please see the Pathogen-Specific Areas section. Identifying new drug targets and developing animal models for drug evaluation (especially for *T. cruzi* and *Leishmania* parasites) are important due to the relatedness of these organisms, and a comprehensive comparison of Trypanosomatid genomes could provide important insights. For example, such comparative efforts could identify genes important for pathogenicity that are common to all three parasites, and functional studies could then be pursued in *T. brucei*, the only parasite for which genetic manipulation is currently feasible. Host immune responses to parasites may contribute either to protection or to pathology, and the molecular correlates of these responses remains unknown. Similarly, interventions that modulate the host’s immune response so as to enhance protection and mitigate pathology may be beneficial. *Leishmania* and *T. cruzi* are intracellular parasites, meaning they spend a significant portion of their life cycles residing inside human cells. A greater understanding of this intracellular phase may provide important insights relevant to evasion of host immune responses and parasite metabolism that in turn could lead to the identification and development of novel antiparasitic interventions.

Insect vectors are responsible for transmission of these protozoan parasites. As such, basic science research on the biology of insect vectors is an important priority, particularly research aimed at identifying vector molecules essential for parasite growth and development in the insect. Additionally, improved methods of vector population management, such as paratransgenesis, are important for disease control. (Paratransgenesis is a technique that modifies symbiotic microbes living within the vector to produce molecules that prevent disease transmission.)

Databases, such as GeneDB, are needed in order to integrate and organize available information (e.g. genomic data) for use by the community. Such databases may increase understanding of parasite gene function leading to the identification of unique targets for drug and diagnostic development. Because the value of such databases is dependent on the extent to which the scientific community utilizes them, community involvement in database development and maintenance will be important.

Intermediate Priorities

Improved molecular tools are important for investigating the function of predicted genes. Such tools may include:

- cloned sets of gene sequences (“open reading frames”) that code for proteins, as well as the means (“shuttle vectors”) to express proteins based on such sequences in various systems; and
- high-throughput studies of gene function using RNA-interference (RNAi) to systematically shut down each parasite gene in order to identify the necessary components of a particular cellular process.

Information obtained from the use of the molecular tools described above may lead to the identification of new biomarkers, molecular indicators of the presence of infection or the extent of disease. Such markers can form the basis for development of new diagnostics to determine the same. Furthermore, biomarkers can be used to monitor insect vector populations in the field for species identification, pathogen presence, and insecticide resistance.

Long Term Priorities

Drug development leading to new treatment options is important as currently available drugs are expensive, limited in number, and often toxic. In addition, parasite resistance to existing drugs in increasingly common. Field sites are essential for research efforts on a number of NTDs. However, more than one disease may be present at the same location. Thus, in the future field site capacity in endemic areas should include expertise in multiple disease areas for treatment, vaccination and vector management. Where co-morbidity exists, coordination to understand the effects of managing multiple diseases is possible. Since these pathogens are transmitted via insect vectors, increased vector research is also important, particularly with respect to vector competence and vector/pathogen interactions. To optimize the impact of these research activities, it will be
important to establish a dialog with disease control programs so that research findings and new interventions can be incorporated into control efforts in a timely fashion.
Helminth Infections (Schistosomiasis, Filariasis, Hookworm, and Related Infections)

Parasitic worms are among the most common causes of chronic human infections worldwide – particularly schistosomiasis, filariasis, onchocerciasis and intestinal roundworm infections. **Schistosomiasis** is caused by trematode flatworms of the genus *Schistosoma*. An estimated 600 million people are at risk in 74 countries with 200 million infected. While mortality remains relatively low, tens of millions have debilitating chronic morbidity. ([http://www.who.int/schistosomiasis/en/](http://www.who.int/schistosomiasis/en/))

**Lymphatic filariasis** (elephantiasis) is caused by the parasitic filarial worms *Wuchereria bancrofti* and *Brugia malayi*. An estimated 1.2 billion people are at risk in 83 countries throughout the tropics and sub-tropics of Asia, Africa, the Western Pacific, and parts of the Caribbean and South America. An estimated 120 million people are infected worldwide with at least 40 million people severely affected with hydrocoele, lymphedema or sub-clinical lymphatic damage. ([http://www.who.int/mediacentre/factsheets/fs102/en/index.html](http://www.who.int/mediacentre/factsheets/fs102/en/index.html))

**Onchocerciasis** (river blindness) is caused by the filarial worm *Onchocerca volvulus* and is transmitted through the bites of infected black flies of the *Simulium* species. The disease is prevalent in 30 countries of Africa, 13 countries in the Americas (including Mexico, Guatemala, Ecuador, Colombia, Venezuela, and Brazil) and in Yemen. Worldwide, there are around 18 million people infected and 270,000 people who have become blind as a consequence of long-term infection. ([http://www.cdc.gov/ncidod/dpd/parasites/onchocerciasis/factsht_onchocerciasis.htm](http://www.cdc.gov/ncidod/dpd/parasites/onchocerciasis/factsht_onchocerciasis.htm))

**Intestinal helminth (roundworm) infections** are among the most common human infections, especially in tropical and sub-tropical countries, and are the leading cause of disease burden in children aged 5 to 14 years. Worldwide, 1.5 billion people are infected with *Ascaris* ([http://www.cdc.gov/ncidod/dpd/parasites/ascaris/factsht_ascaris.htm](http://www.cdc.gov/ncidod/dpd/parasites/ascaris/factsht_ascaris.htm)), 800 million with *Trichuris* ([http://www.dpd.cdc.gov/DPDx/HTML/Trichuriasis.htm](http://www.dpd.cdc.gov/DPDx/HTML/Trichuriasis.htm)) and 1.3 billion with hookworms ([http://www.cdc.gov/ncidod/dpd/parasites/hookworm/factsht_hookworm.htm](http://www.cdc.gov/ncidod/dpd/parasites/hookworm/factsht_hookworm.htm)). Moderate infections are associated with poor physical and mental development, while more intense infections can result in severe anemia (hookworms), intestinal obstruction (ascarisis), and chronic colitis (trichuriasis).

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**Helminth Research Priorities**

*Schistosoma spp.*, Filarial worms, Hookworms, Soil-Transmitted Nematodes

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**Immediate Priorities**

For specific information on **basic science** research gaps, please see the **Pathogen-Specific Areas** section.

Improved **diagnostics** are important for helminth infections because they are essential for assessing epidemiologic aspects of these diseases and enhancing the effectiveness of ongoing global control or elimination programs. Further, vaccine and drug development efforts must detect and quantify active infection at an early stage. To address this need, attention should be directed at the following:

- new target diagnostic molecules (**biomarkers**) that identify the infecting pathogen
- diagnostic markers that will aid in monitoring vector populations and their rates of infection
- increasing the sensitivity of existing assays, particularly through the use of new test platforms

**Drugs** are currently being used in global health programs targeting more than half a billion people each year, yet each of these programs relies on only one or two effective drugs. With the ever present threat of parasitic worms developing resistance to these drugs and with therapeutic profiles (i.e., the combination of efficacy and toxicity) of available drugs being less than ideal, potential new drugs need to be identified. Genomic and proteomic tools offer new opportunities to identify new drug targets and to define mechanisms of action for currently used drugs. Such knowledge could provide a firm scientific rationale for all research efforts to detect resistance and to develop new drugs. Use of both **in vivo** models and high-throughput screens are essential for early-stage studies to screen for new drugs, to establish proof-of-principle, and eventually to advance new leads into pre-clinical drug-development studies.

**Clinical Studies** provide opportunities to define currently unanticipated effects of co-infections on expected therapeutic outcomes or vaccine responses and to define strategies to prevent potential adverse effects. Specifically, there is a dearth of information on the following:

- co-infections, in which one infection has the potential to affect the pathogenesis and clinical outcome of another co-morbid disease
- individualized responses to WHO’s Expanded Program on Immunization (EPI) or other vaccines as a result of helminth co-infections
- multi-drug treatment interventions and their effects on the therapeutic outcomes of coincident infections

Because of the complexity of life cycles, the limited range of animal models, and the restricted opportunities for researchers (particularly those in the U.S. or Europe) to work with patients with helminth NTDs, **reagents and materials resources** including repositories of the relevant parasite, vector and human specimens are important to maintain scientific progress. Indeed, as noted by meeting participants, the availability over the past four decades of NIAID-supported resource repositories has proven essential for much of the successful research in both filariasis and schistosomiasis.

**Databases** that effectively integrate and organize available information (e.g. genomic data, reagents and materials resources) for use by the community could greatly advance research efforts on helminth parasites.

**Intermediate Priorities**

Improved **diagnostics**, such as point-of-care (POC) assays, that require only small amounts of sample material and are suitable for use in field sites would be especially valuable for field research and use in large-scale control programs. New proteomic/genomic approaches can be used to identify diagnostic targets for use in POC assays that would both detect and quantify active infection. Once validated, these new assays could also be used for routine screening of asymptomatic individuals for the presence of these parasites. **Biomarkers**, including the small metabolic products of infecting parasites and infected hosts, can now be studied through techniques such as high-throughput mass spectroscopy and new microarray assays. Studies of host and pathogen biomarkers have the potential to identify states of disease progression, protection afforded by experimental vaccines, and even pre-symptomatic infection.
Increased development of **reagents and materials resources** is important for the storage and distribution of well-characterized field specimens from individuals with different disease stages. Such a resource would greatly facilitate research on infections caused by helminths.

Continued development of lead compounds affecting potential targets identified in earlier studies is a priority. Chemistry resources will be essential for modifying lead candidates through computational and synthetic approaches. For promising candidates, capacity for formulation, production scale-up, and safety and toxicity testing will be useful.

**Clinical studies** offer opportunities to investigate unique and important aspects of these diseases, some of which may have broader implications, such as:

- the interrelation of host responses to helminth infection and environmental allergens as both result in elevated immunoglobulin E (IgE) antibodies, suggesting that immune responses in these conditions share common elements
- the effect of molecules produced or induced by these parasites during the course of infection
  - vasoactive molecules – those capable of dilating or constricting blood vessels
  - anticoagulant molecules – those capable of preventing blood clotting

The maintenance of **databases** should be on-going and, optimally, expanded to allow increasing research opportunities and needs to be addressed in a timely manner.

**Long Term Priorities**

Development of rapid, sensitive, quantitative, and inexpensive point-of-care **diagnostics** (as described above) is important to support clinical studies of new interventions. Long-term support of **drug** development will be critical for advancing drug candidates further into Phase I clinical trials, with the potential of Phase II trials and beyond. In view of the potential for pathogens to develop resistance to widely deployed drugs, it is important to develop and maintain a robust pipeline of new antihelminthic therapeutics. Current mathematical modeling of transmission and disease prevention supports the importance of a schistosomiasis **vaccine** that could ultimately be used in conjunction with drug therapy. In the zoonotic setting of disease caused by *Schistosoma japonicum*, a vaccine for animal use might also be important. A similar rationale exists for the filarial diseases (lymphatic filariasis [LF] or *Onchocerca volvulus* [OV]).
**Bacteria (Trachoma and Mycobacterial Infections)**

**Buruli ulcer** is caused by infection with *Mycobacterium ulcerans* and can result in extensive skin ulcerations, which are typically found on an infected individual’s arms or legs. If not treated early, the ulcerations can cause extensive skin and soft tissue destruction that often leads to the restriction of joint movement, and in time, the patient may require limb amputation. There is evidence that *M. ulcerans* is not transmitted person to person but is an environmental mycobacterium that is likely transmitted to humans from aquatic environments, small aquatic animals and biofilms. Humans appear to have increased risk of infection in areas with stagnant or slow moving water, but the mode of transmission is still under investigation. While disease has been reported in 30 countries, the extent of disease within these countries is not known. ([http://www.who.int/buruli/en/](http://www.who.int/buruli/en/))

**Leprosy (Hansen’s Disease)** is a chronic infectious disease that affects skin, nervous tissue, respiratory tract, and eyes and is caused by infection with *Mycobacterium leprae*. While treatment is available in early stages of the disease, there is no treatment once nerves are damaged. *M. leprae* is capable of causing a wide range of clinical manifestations including peripheral neurological damage (nerve damage in the arms and legs), which causes sensory loss in the skin as well as muscle weakness. People with long-term infection may lose the use of their hands or feet due to repeated traumatic injury resulting from lack of sensation. The stigma long associated with leprosy still exists in many parts of the world and the psychological and social stigma may be more difficult to deal with than the actual physical illness that it causes. Recent trends in Hansen’s Disease epidemiology suggest a decline in the actual number of cases. The number of new cases detected annually has raised questions about the source of infection, transmission, and incubation period of *M. leprae*. ([http://www.who.int/lep/en/](http://www.who.int/lep/en/))

**Trachoma** is an infection of the eye caused by the bacterium *Chlamydia trachomatis* and is the leading cause of preventable blindness in the world. Trachoma presents as a chronic inflammation of the conjunctiva that in turn can cause scarring of the conjunctiva and cornea, leading to blindness. Chronic, repeat infections occur most often in children under 10 years of age. Approximately 11 million cases of infection and 8 million cases of blindness occur annually worldwide. Trachoma is endemic in the poorest regions of Africa, Asia and the Middle East, and in some parts of South America and Australia. ([http://www.who.int/blindness/causes/priority/en/index2.html](http://www.who.int/blindness/causes/priority/en/index2.html))

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Immediate Priorities
For specific information on basic science research gaps, please see the Pathogen-Specific Areas section.

The development of drugs effective against trachoma and mycobacterial infections is important. Possible strategies may include:

- a safe, non-injectable drug therapeutic regimen for \textit{M. ulcerans} using existing antibiotics approved for other infections
- assessment of antibiotic resistance in \textit{M. leprae} by using clinical isolates from multiple regions of the world where leprosy is prevalent
- establishing community-wide antibiotic regimens for trachoma treatment and elimination programs and applying results to develop mathematical models for other community-wide programs

As field sites are critical for NTD research, building and enhancing field site capacity in endemic areas represent important priorities for these bacterial diseases. Improving integration of international research efforts with developing country laboratories would also be helpful. As an example, this could involve developing and maintaining resources to provide critical materials to developing country laboratories (\textit{e.g.}, the armadillo model for growing \textit{M. leprae}). These laboratories could reciprocate by providing certified clinical reagents and other specimens for use in international research efforts.

Increased development of reagents and materials resources is also important, including repositories of the relevant parasite and human specimens, such as those provided by the Leprosy Research Support program (see NIAID Resources section).

Intermediate and Long Term Priorities
Biomarkers are molecular indicators of the presence of infection. Such markers can form the basis for diagnostics development to determine the presence of infection or the extent of disease progression. Development of such diagnostics is important, including point-of-care (POC) assays that are rapid and employ a common platform for use with multiple chemical components and organisms.

Vaccine Development is also a possibility for these bacterial infections. One strategy would be to identify epitopes, or parts of molecules unique to these bacteria that are recognized by the human immune system, that may be useful for vaccine development. The large scale study of bacterial proteins (proteomics), particularly their structures, may aid in identifying these unique epitopes. Further, such epitopes may be identified from biomarkers used in development of diagnostics.
Cross-Cutting Areas

Diagnostics and Biomarkers

Improved diagnostics and biomarkers were identified as important research priorities for a number of NTDs. Diagnostics are needed to identify infected patients for treatment, to conduct surveillance of treatment effectiveness, and for assessing outcomes in drug and vaccine efficacy trials. Diagnostics and biomarkers should be able to identify active infection as well as stage or form of disease. Ideally, assays for related or multiple NTDs might be performed on the same platform so as to simplify infrastructure needs as well as to allow for testing for multiple agents in areas where co-infections commonly occur. Nanotechnology and other new technologies may lead to new platforms at the micro-level and thus allow for maximum usage of limited specimen materials. High-throughput screens may provide an efficient method to identify new diagnostic targets in the pathogens and markers for monitoring vector populations in the field.

Database and Computational Resources

Databases of genomic-related information that are curated and regularly updated as well as tools/software that can be used to access and query them were identified as important research priorities for a number of NTDs. In order to avoid duplication of efforts, databases should contain information on approaches (e.g., drug targets) that have proven unsuccessful as well as those that have succeeded. Databases might also include a list of specimens (parasites, vectors, DNA, etc.) available in repositories that have been well characterized and can be used for a variety of purposes. These resources are anticipated to facilitate progress in developing diagnostics, biomarkers, drugs, and vaccines by identifying host or infectious agent proteins that are upregulated in specific disease states.

Reagent/Materials Resources

Resource centers that can readily distribute and collect materials nationally and internationally are important for research on all NTDs, and continued support for existing resource centers for filariasis, schistosomiasis, and leprosy was identified as a priority by meeting participants. It is also important to maintain well-characterized field specimens (including the range of pathogenic forms of individual diseases) that are made available through resource repositories and are included as part of a database for field studies. Research materials such as whole infectious organisms or organism components (especially for difficult to maintain/prepare organisms) are useful, as are reagents such as monoclonal antibodies, recombinant clones, and microarrays. In addition to parasite-specific microarrays, microarrays that include genes from multiple parasites as well as the human host could prove beneficial for research efforts.

Field Resources

Several groups noted that multi-functional sites that serve as shared field resources could greatly benefit the field. Such sites could be used to gather clinically validated specimens for use in diagnostic and biomarker development. They could be used to study co-morbidity issues and to assess preventive or therapeutic interventions. Field sites are also essential for developing vector management strategies, and personnel at such sites can serve as resources for a variety of intervention studies. Efforts to incorporate research capacity into program intervention sites should be considered as a cost-effective way to both conduct research and assess the effectiveness of public health/program interventions. As appropriate, efforts to interface with large-scale international programs aimed at malaria, TB, and HIV research, should also be considered. For example, informed consent strategies could be developed that anticipate the use of specimens over the long term and as new research issues arise or technologies become available.

Drug Development

For all NTD organisms, development of new or better drugs is a research priority as is an approach based on rational drug design, in which structural information about targets is used as the basis for creating new drugs. For many NTDs, limited drug regimens are available and may be toxic. Without a larger, more diverse arsenal of drug therapies, there is an increased risk for organisms to develop resistance against the few existing drugs.
Genomic information and high-throughput screening are likely to facilitate identification of new drug targets. Studies are ongoing to screen drugs approved for alternative indications for activity against NTDs. This work should continue and, if resources permit, be expanded. Parasitic infections have complex effects on human physiology, thus as an added benefit, parasite products may serve as the basis for drug development for non-parasitic diseases, e.g., as immune modulators, vasculature modulators, or anticoagulants. Further, improved animal models are important for many NTDs in order to facilitate preclinical drug development efforts.

**Vaccine Development**

Prophylactic vaccines may not be viable for NTDs of low incidence or prevalence; however, with the immunopathology associated with many NTDs, these diseases might be appropriate targets for therapeutic vaccines. Additionally, for diseases that are also present in an animal reservoir, there is potential to reduce disease incidence in humans indirectly by vaccinating these animals. Animal hosts could also serve as proof-of-principle for developing human vaccines. When designing such vaccines, scientists should consider characteristics of target populations and possible treatment modalities (preventive versus therapeutic).

**Basic Research Issues**

“Molecular toolboxes” for NTDs were identified as an important research priority by many of the groups. While this may vary by infectious agent, the basic concept involves common methodologies for genetic manipulations (e.g., RNAi, recombinant vectors for gene knockouts). For all the NTDs, it is important to better understand the molecular basis of pathogenesis. For example, determinants of the different clinical forms of Chagas’ disease are not known, and the roles of toxins in bacterial NTDs are not fully understood. Knowledge in these areas would enhance the ability to develop treatment strategies such as drugs and therapeutic vaccines as well as to define diagnostics and biomarkers. As many NTDs are transmitted by invertebrate vectors, a greater understanding of the interaction between vector and parasite is also important. Such research may be useful to identify potential targets for parasite growth and survival within the vector and transmission to the human host.

**Clinical Research Issues**

Defining clinical correlates for protective immune responses and surrogate markers for disease pathogenesis or resolution were identified as research priorities. Furthermore, defining the “infectome”, i.e., the array of genes preferentially expressed during the disease state, for individual stages of disease as well as for the infectious agent and its vector would be useful. The infectome includes correlates of microbial pathogenesis, and changes in the expression of genes in the infectome may provide insights into both host and microbial responses to therapy. This knowledge is important to develop and assess preventive and therapeutic strategies. It may also help to elucidate the role of host genetic factors in susceptibility, resistance, and response to infection, as well as the effects of vector saliva on the pathogenesis of the parasite in the human host. Further, it is important to determine the effects of co-infections and/or multiple treatments on the pathogenesis of an immune response to NTDs. Likewise, the effect of multiple infections on responses to candidate NTD drugs and vaccines should be determined. Clinical trials require research infrastructure and field sites, and there is the potential to coordinate NTD trials with facilities that are participating in studies of malaria, tuberculosis, HIV or other infectious diseases.

**Mathematical Models**

As interventional studies are designed, consideration should be given to collecting data and information that could be used to validate mathematical models of disease intervention strategies. It would be beneficial if extant empiric data could be made available to mathematicians to develop and test models.

**Investigator Base**

A “critical mass” of investigators is essential for progress in any research endeavor. Strategies to attract and retain new investigators for NTD research need to be explored, especially given the high degrees of complexity of carrying out research in these diseases that may deter investigators from entering or staying in the field.
**Funding Opportunities**

Investigators should be made aware of the variety of mechanisms and funding sources that may support their research goals. This is especially true for international collaborative efforts. In order to assure the relevance and appropriateness of proposed research, it would be beneficial if study sections reviewing applications on high priority translational research topics (e.g., diagnostics) included specialized expertise and familiarity with NTDs.

**Collaborative Opportunities**

When possible, research efforts could be coordinated to enhance targeted, cost-effective goals. Better communication between basic researchers and program/intervention investigators may be beneficial in accomplishing this. Control programs and research programs in individual NTDs could benefit from better linkages, and attempts to highlight such benefits and encourage such interactions should be made. Creative, ethical approaches to human subject issues need to be sought to facilitate harmonization between intervention programs and research. Solving complex problems, such as drug development and vector management strategies will require interdisciplinary research approaches, and where possible these should be facilitated.
### NIAID Resources

#### Research Resources Relevant to NTDs

<table>
<thead>
<tr>
<th>Activity</th>
<th>Resource/URL</th>
<th>Contact</th>
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<tbody>
<tr>
<td>Maintenance and supply of schistosome-infected snails and mammals through which investigators can obtain schistosome life stages. Three major schistosome species affecting humans (<em>S. mansoni</em>, <em>S. haematobium</em>, and <em>S. japonicum</em>) obtained either in their specific snail host, or in infected mammals.</td>
<td>NIAID Schistosomiasis Resource Center <a href="http://www.schisto-resource.org/">http://www.schistore.org/</a></td>
<td>D. McGowan <a href="mailto:dmcgowan@niaid.nih.gov">dmcgowan@niaid.nih.gov</a></td>
</tr>
<tr>
<td>The repository offers three filarial parasite species (<em>B. malayi, B. pahangi and D. immitis</em>). These parasites are maintained in the laboratory by alternate passage through mammalian definitive hosts and arthropod vectors. The Filariasis Repository Service includes molecular resources.</td>
<td>NIAID/NIH Filariasis Research Reagent Repository Center <a href="http://www.filariasiscenter.org/">http://www.filariasiscenter.org/</a> <a href="http://www.filariasiscenter.org/mole-center/index.htm">http://www.filariasiscenter.org/mole-center/index.htm</a></td>
<td>D. McGowan <a href="mailto:dmcgowan@niaid.nih.gov">dmcgowan@niaid.nih.gov</a></td>
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A complete listing of NIAID’s research resources may be found at [http://www.niaid.nih.gov/research/resources/](http://www.niaid.nih.gov/research/resources/).
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Appendix: Proceedings from Working Groups on Specific Pathogens

Meeting participants were divided into three discussion groups based on expertise to prioritize research goals for the NTDs discussed. The immediate, intermediate, and long-term goals for each pathogen group (protozoa, helminth, and bacteria) are described in the main body of this report. This appendix contains a more technical, non-prioritized listing of research gaps and resource needs for each pathogen.

Protozoa

Trypanosoma brucei

Basic Science Research Gaps
The genome for *Trypanosoma brucei* has been sequenced and is available electronically (http://www.tigr.org/tdb/e2k1/tba1/intro.shtml). Despite the availability of the genome, a function has not been assigned to the majority of predicted genes, and in cases where the function is known, the genes have been found to be highly divergent or unique. Thus, many challenges remain that would benefit from expanded efforts.

Diagnostics and Biomarkers
With the genetic relationship among Trypanosomatid organisms, there is an opportunity for using common technical approaches and exploiting the knowledge from bioinformatics and genomics to develop biomarkers that can be used to elucidate pathogenesis, to form the basis for point-of-care diagnostics, and to confirm infection for treatment with currently available drugs and/or enrollment of participants in drug trials. These biomarkers encompass pathogen and host, including host immune responses. In conjunction with this effort, validated clinical and field samples (and possibly some experimental samples) for developing and testing diagnostics and biomarkers is important. Access to analytical resources, such as mass spectrometry, protein arrays and immunoassays, is another component required for this work. Developing appropriate platforms is necessary; information on the kinds of platforms available should be provided to the research community. A repository for materials essential for development of diagnostics and biomarkers would be beneficial, especially for materials that are already available and developed in specific research labs, such as cloned gene sequences, monoclonal antibodies, and recombinant vectors. Markers for monitoring vector populations in the field are also crucial, including vector species identification, pathogen presence and insecticide resistance.

Target Identification and Candidate Therapeutics
Drug development requires multiple disciplines and the exploration of multiple drug targets. The unique metabolism of the trypanosomes, the fact that 25 percent of the genome encodes protein enzymes, and the close genetic relationship of the Trypanosomatid protozoa may provide unique opportunities for therapeutics in terms of targets and classes of compounds. As in the genome projects for these organisms, community coordination will be beneficial.

Vaccines
Vaccines are not a priority for *T. brucei*, as antigenic variation makes prophylactic vaccines unlikely. However, there is a remote possibility for the development of therapeutic vaccines, which may alleviate the suffering of infected individuals. Further, transmission blocking vaccines may also be considered including strategies for targeting the insect vector as well as animal reservoirs.

Disease Control
The Trypanosomatid diseases offer an opportunity to study the impact of multiple control measures in disease eradication/reduction including the coordinated use of drugs, insecticides, transmission blocking vaccines, etc. These measures may include management strategies that affect tsetse fly populations and contact with the human host. Knowledge gained from interventions in these diseases may also provide insights useful for other NTDs.
**Trypanosoma cruzi**

**Basic Science Research Gaps**
There are numerous significant gaps in our knowledge of Chagas’ disease. Whether clinical forms are associated with parasite and/or host genetic variation is unknown as are the fundamental molecular and cellular events that lead to organ enlargement and malfunction during the clinical course of infection. Also, little is known about the role of innate immunity in preventing establishment of infection, the mechanisms controlling the host’s initial response to infection, the effect of treatment on the host’s immunological memory and resistance to re-infection, the effect of length of infection on immune control, and the parasite mechanisms of immune evasion.

**Target Identification and Candidate Therapeutics**
The development of less toxic drugs and of drugs effective for treating patients during the chronic stage of *T. cruzi* infection is essential. Drug candidates currently in early stages of testing and development include protease inhibitors and anti-fungal triazoles. Development of new drugs could be enhanced by identifying biochemical pathways unique to the parasite, validating potential drug targets, developing screening assays, and testing libraries of compounds.

The limited arsenal of available drugs could be used more effectively by early disease detection leading to a shortened course of treatment. Such a strategy may decrease the rate of drug resistance. Placebo-controlled trials are key in demonstrating efficacy of chronic disease treatment.

**Diagnostics and Biomarkers**
It is important to determine whether additional specific tests can be developed for diagnosing infections. This is particularly important due to concerns about potential for contamination of the blood supply. Accurate diagnostics could address this problem. Furthermore, surrogate biomarkers for infection are critical for future assessments of vaccine effectiveness in preventing long-term sequelae, determining disease outcomes, and predicting therapeutic outcomes in drug treatment trials.

**Host Response, Immunology, and Vaccines**
A vaccine for humans may decrease the number of circulating organisms and therefore decrease transmission; however, this approach will not address animal reservoirs harboring parasites with human infective potential. Domestic animals living in close proximity to humans serve as parasite reservoirs, thus a vaccine developed for domestic animals would likely reduce transmission to humans indirectly. An acute phase vaccine for Chagas’ disease may also be useful for preventing or controlling infection in children.

**Resources**
With respect to the genomics of American Trypanosomiasis, it is important to sequence, assemble and annotate additional non-hybrid isolates, to expand Expressed Sequence Tag (EST) databanks, to establish curated community-supported databases, and to identify biochemical pathways that are viable drug targets (e.g., transsialidases, phosphokinases, genes involved in DNA replication/repair).

**Vector Biology**
A greater understanding of the molecular interactions that occur between *T. cruzi* parasites and the triatome gut, e.g., the signals for differentiation of epimastigotes into infective trypomastigotes, is a priority. Studies on vector ecology and population structure are also necessary as is a better understanding of vector behavior. For example, it has been demonstrated that triatomines in the peridomestic environment come into contact with infected animals and humans and become involved in the human food chain. The significance of this behavior and its implications was demonstrated by the recent episodes of human *T. cruzi* infections following açai juice consumption in Brazil.


**Leishmania** species

**Basic Science Research Gaps**
Better use of the existing Leishmania genome sequences could accelerate progress in understanding basic processes of these parasites. A more complete understanding of the mechanism(s) of intracellular survival, including amastigote biology and the host’s immunological response, will be crucial to future progress. Furthermore, the molecular basis for chronicity of infections is not known and could be potentially aided by the development of animal models. Studies employing gene deletions in *Leishmania* spp. and RNAi in *L. braziliensis* could facilitate the functional characterization of genes of interest.

**Host Response, Immunology, and Vaccines**
Better understanding of the immunology of *Leishmania* infections, the genetics of human susceptibility and resistance, and the basis for the different disease forms (cutaneous, muco-cutaneous, and visceral) is key in facilitating *Leishmania* vaccine development. Additionally, the affect of sand fly saliva on the pathogenicity of different *Leishmania* species is important to understand.

Since dogs are also susceptible to *Leishmania* infections and serve as reservoirs, a vaccine for dogs may limit transmission as well as inform development of vaccines for human use. For example, Brazilian investigators are pursuing the concept of combining a *Leishmania* vaccine with a rabies vaccine for dogs as a way of controlling both diseases.

*Leishmania* vaccines have been tested internationally, including a heat-killed vaccine in Iran and therapeutic vaccines in Brazil and Sudan. If information can be made available about the specific results from such efforts in a timely manner, they may provide insights and potentially accelerate the further development of human vaccines. Efforts are also underway to develop a vaccine based on sand fly saliva proteins.

**Vector Biology**
As leishmaniasis is transmitted to humans via an insect vector, an increased knowledge of sand fly biology, ecology and behavior is an important priority. In addition, it is important to further define the molecular interactions between vector and parasite. Such research may lead to the development of new vector management strategies, insecticides and transmission blocking vaccines.

**Target Identification and Candidate Therapeutics**
Drug resistance and drug development are areas that would benefit from further investigation. Recent studies on Interleukin-10 and the pathogenesis of human visceral leishmaniasis suggest that future drugs and vaccines need both to target the parasite and manipulate the immune response.

**Resources**
Investigational resources are vital to progress and may include controllable and inducible expression systems that do not break down over time, large-scale knock-out systems that are readily usable for hundreds to thousands of genes, and other genetic tools such as the Cre-lox DNA recombination system and RNAi. Databases, similar to those available for yeast and *C. elegans*, which catalog available information (e.g. genomic data), are key to *Leishmania* research.
**Helminth**

**Schistosoma species**

**Basic Science Research Gaps**

It is important to better understand the immunology and pathology of schistosome infection (in human and in model systems), the effects of schistosome infection on the immune response system, the role of host genetic polymorphisms in resistance to disease and in morbidity, and the effect of drug treatment on the immune responses to disease.

Genomic and post-genomic technologies (including proteomics and glycomics) could be applied to schistosome life-cycle forms, to vector snail species as well as to organisms *in situ* and *ex vivo*. The goals would encompass the sequencing, annotation, and database development for both parasite and vector genomes, which would expedite comparisons of snail and parasite species and strains. It is anticipated that additional *Schistosoma* genomes will be available shortly, and *Biomphalaria glabrata* snail genome sequencing efforts are ongoing.

A better understanding of the basic biology of schistosome life-cycle stages may facilitate their use as a model parasite system. Increased research on schistosome fecundity and egg excretion, schistosome germ cells, host–parasite interactions, and the infected host’s neurobiology and neuromuscular physiology will also provide useful information.

Developing a “molecular tool box” for schistosomes, including knockouts and transgenic lines, to allow and enhance studies of genes, molecules and organism functions through the life cycle stages is a priority. Biochemical and molecular studies, incorporating genomics, glycomics, and proteomics, can help elucidate schistosome membrane biology and metabolism during different life stages. Furthermore, it is important to better characterize functional roles and possible medical uses of molecules produced/released by shistosomes.

**Diagnostics**

It is important to optimize and combine existing diagnostic tools more effectively, including immunological assays that detect infection or assess disease status and ultrasound detection to evaluate pathology. Assays that measure worm burdens in active infection are also important as are diagnostic tools for detection of morbidity or pre-morbidity.

**Transmission**

Increased knowledge of the ecological and biological aspects of the snail vector would likely lead to greater understanding of the snail responses to schistosome infection, how these responses relate to differences in parasite strains and whether there are comparative differences in field *versus* laboratory parasite isolates. The influence of societal components on disease transmission is also an important area that may benefit from increased research. More information on transmission dynamics including mathematical models and the role of humans and natural non-human hosts is important. Geographic Information System and ground verification are important to better understand transmission patterns and predictions, and to understand geo-spatial (micro) determinants of risk.

**Disease Burden and Epidemiology**

In terms of morbidity, it is important to determine the proportion of specific pathology (e.g., liver disease, anemia, etc.) in a study population that is attributable to schistosomiasis as opposed to other causes (e.g., hepatitis, iron deficiency), to adapt standardized tools for Quality-Adjusted Life Years assessment to schistosomiasis, and to obtain accurate disability weights, including recalibration of Disability-Adjusted Life Years.
Certain schistosome infections have been associated with an increased risk of certain cancers (e.g., *S. haematobium* and bladder cancer) and can have an adverse affect on reproductive health and fertility (male and female). It is important to understand the role of host genetics in these effects, as well as the impact that such genetic effects may have on the ability to vaccinate certain populations. A more advanced understanding of the effects of co-morbidities is important, which may include the impact of 1) interactions between schistosomiasis and other infections (*i.e.*, HIV, malaria, hepatitis B and C, soil-transmitted helminths), 2) interactions that occur with dual schistosome infections (*S. mansoni* and *S. haematobium*), and 3) the interactions of schistosomiasis with noninfectious conditions (*e.g.*, malnutrition, alcoholism, autoimmunity).

**Host Response, Immunology, and Vaccines**
As indicated above, host immune responses play significant roles in both protection and pathology in schistosome infections, and further investigation in these areas is necessary to improve our understanding of these aspects. The discovery and evaluation of potential vaccines is an important priority for these diseases.

**Target Identification and Candidate Therapeutics**
Treatment regimens should be optimized and tailored towards different transmission conditions. Proteins or pathways that are potential drug target candidates should be identified, and the mechanism of action needs to be defined for both existing and future drugs. Furthermore, it is important to develop and test newly identified drug targets (*e.g.*, orally active ozonides), and to develop standardized assays and/or markers of resistance to praziquantel in order to more effectively monitor the nature and/or spread of drug resistance.

**Top Three Research Priorities**
The top three priorities for schistosomiasis research are (1) a concerted effort to develop a “molecular tool box” for schistosomes; (2) coordinated field studies of multiple aspects of schistosomiasis in humans (diagnosis, resistance, morbidity, co-morbidity, immunology, genetics of both hosts and parasites); and (3) a focus on drug development, including discovery, defining mechanisms of action, and detecting and monitoring mechanisms of resistance.

In addition to this report, a comprehensive, cohesive agenda was developed as part of a series of meetings and e-mail solicitations involving a broad spectrum of investigators involved in all aspects of schistosomiasis infections from genomics to social sciences. (PLoS Negl Trop Dis. 2007 December; 1(3): e32)

**Filarial Worms**

**Basic Conceptual Research**
The conceptual gaps in our knowledge that may benefit from increased research include the following:

1. The interactions among the (recently sequenced) *Brugia malayi* nuclear genome, the *B. malayi* mitochondrial genome, the *Wolbachia* genome, and human host or mosquito vector genomes are poorly understood.
2. What determines the essence of parasitism (*i.e.*, what distinguishes parasitic from free-living nematodes at the genome level), and the immunological and biological mechanisms by which the parasite evades the host are also poorly defined.
3. The molecules that are essential for critical stages of filarial development need to be identified.
4. The genetic basis of infection and disease susceptibility in humans and mosquitoes needs to be elucidated.
5. The role of the *Wolbachia* bacterial endosymbiont in the biology of filariae and ways to exploit this role for disease prevention or treatment should be determined.
6. The increased use of genomic and proteomic data as research tools needs to be implemented.
Basic Translational Research
Areas of translational research that may benefit from further investigation include the following:

1. How chronic filarial infection affects responses to other infections or to vaccines.
2. The mechanisms that determine the interplay between allergy and host responses to filaria (or other helminth) infections, and how treatment affects these altered responses.
3. The key elements of filarial pathogenesis, including the mechanisms of ‘homing’ to lymphatics, the attractants that direct worms to form nests or nodules and the mechanisms of vascular dilatation.
4. Methods to effectively immunize against filarial infections or against specific parasite stages.
5. Identification of the mechanisms that determine the pathogenesis of lymphatic or onchocercal disease and the clinical expression of these diseases.
6. Identification of filarial secretory products that could be used as leads for drug development for filariasis as well as other, non-parasitic, diseases.

Translational Operational Research
Two critically important priorities for translational operational research are the development of sensitive indicators of drug susceptibility and emerging drug resistance, and new drugs with increased effectiveness against adult-stage parasites.

Operational and Vector Research
There are several research priorities that would effectively support ongoing global programs to eliminate lymphatic filariasis (LF) and to control or eliminate river blindness due to *Onchocerca volvulus* (OV), including overall strategies to protect the effectiveness of drug-based programs. In the area of clinical epidemiology, more sensitive population sampling techniques would aid the detection of infection above threshold levels (below which infection cannot persist) and would enhance surveillance strategies to monitor post-treatment-program populations and potential recurrence of filaria transmission. Diagnostic tests that can specifically determine the absence of filarial transmission or the absence of adult worms in populations are also important as are methods to ensure good clinical and morbidity management. Furthermore, adequate monitoring tools of vector control strategies for both mosquitoes and black flies would be useful, including the means to 1) to monitor black fly infection rates and establish transmission levels, 2) to monitor the development of larvicide resistance in black fly populations, and 3) to determine whether vector control can be a cost-effective adjunct to the current Lymphatic Filariasis or *Onchocerca volvulus* elimination programs based on Mass Drug Administration.

Coordination of Research Efforts
Given the enormous burden of filariasis disease, the extraordinarily cost-effective package of interventions for the helminth NTDs, and the recent global investments in implementing it, it is important to develop global leadership to aid in providing a scientific backstop for this investment to ensure its success. Promotion of a collaborative network of investigators in both endemic and non-endemic countries to address basic research questions and provide tools to facilitate the operational support for the large NTD implementation programs would enhance these efforts. Development of relevant reagent resource centers and appropriate funding opportunities would help in both facilitating and coordinating such international research efforts.

A consensus filariasis research agenda has been developed through a series of meetings and publications including the November 2004 supplement to the *American Journal of Tropical Medicine and Hygiene*.

Hookworm and Soil-Transmitted Nematode
There are numerous challenges facing investigators interested in research on the major soil transmitted nematode (STN) species, which include *Ascaris lumbricoides*, *Trichuris trichiura*, the hookworms (*Ancylostoma duodenale*, *A. ceylanicum*, *Necator americanus*), and *Strongyloides* (*S. stercoralis*, *S. fuelleborni*). Factors that contribute to the persistent research gaps include the following:
1. The pathogenesis of these diseases and mechanism of action of specific virulence factors are poorly defined.
2. It is currently not possible to reliably manipulate STN gene expression.
3. Available animal models are cumbersome and do not always replicate human disease. For some animal hosts, there are few available immunologic reagents.
4. Currently available diagnostics remain labor-intensive and difficult to scale up for population based epidemiologic investigations and control program monitoring.
5. There are limited data correlating laboratory (animal) and field (human) studies.

**Basic Science Research Gaps**
The pathogenesis of most STN infections has remained poorly elucidated, and the number of specific virulence factors identified for each of the major parasite species is few. Moreover, for those specific genes and gene products thought to be important in infection and/or pathogenesis, it has been difficult to demonstrate a definitive role due to the inability to reliably silence gene expression \textit{in vitro} or \textit{in vivo}. The current status of gene silencing using RNAi in STN species is not yet at a point of broad application, although progress is being made. Moreover, the evidence to date suggests that effective techniques for RNAi mediated silencing may need to be optimized for each gene product, STN species and life cycle stage independently. This will require a substantial amount of research to develop these methods in the coming years.

At present, neutralization through vaccination with recombinant proteins is the most commonly utilized method of targeting or inhibiting specific parasite proteins, but this approach has a number of important limitations for evaluating large numbers of targets. Additional work needs to be focused on developing novel molecular targets for drug and vaccine development using high throughput methods.

The animal models available for the study of STN infections are extremely limited, with few exceptions. Mice and rats are not efficient models for the study of hookworm and \textit{Ascaris}, although they can be manipulated in order to characterize certain aspects of the early infectious process, \textit{e.g.}, skin invasion and tissue migration. In the case of \textit{Trichuris}, although mice are susceptible (to \textit{T. muris}), there are significant strain differences in efficiency of infection, making broad generalizations to human disease difficult. By contrast, the animal models that reliably mimic human disease pathogenesis, \textit{e.g.}, dog/hamster (hookworm), pig (\textit{Ascaris}), and even non-human primates, are limited by prohibitive costs and/or a lack of reagents for the sophisticated study of innate and acquired immune responses. As a result, relatively little information exists with regard to host and parasite factors that are necessary and/or sufficient for infection.

The major STN species are also limited in terms of available genome coverage, despite the efforts of the Washington University sequencing project. Clearly more efforts need to be focused on completing the genome coverage of each STN dataset.

**Diagnostics**
There has been little progress in adapting molecular and high-throughput techniques to the study of STN infections. However, recent progress in the development of PCR based techniques that allow for speciation of hookworm in endemic areas is a potentially important advance. Fecal antigen detection assays have also been developed for hookworm, but to date, have not been validated in large scale field settings. Very little has been done to improve upon fecal microscopy for the other STN species, \textit{i.e.} \textit{Ascaris}, \textit{Trichuris}, and \textit{Strongyloides}. More effective diagnostics would substantially improve disease monitoring programs, as well as provide for early detection of anthelminthic drug resistance.

**Gaps in Epidemiology Research**
Due to limitations in animal models for the study of STN infections, it has been difficult to validate observations made in field settings under more controlled laboratory conditions. As a result, much of the work in the field is limited by significant confounding variables, most notably co-infection with multiple STN species and wide variability in host factors (susceptibility, nutrition, etc). In particular, more work is needed on the genetic basis Neglected Tropical Diseases: Identifying Research Gaps and Opportunities
Appendix: Proceedings from Working Groups on Specific Pathogens: Helminth

of susceptibility, as well as other behavioral/social factors that might influence infection within populations. Additional information on the population genetics from both the human host and parasite side would be a great advance.
Bacteria

Mycobacterium leprae

Basic Science Research Gaps
It is anticipated that developments in genomics and proteomics may facilitate advances in the development of epidemiological, diagnostic and immunological tools to provide a better understanding of leprosy with the goal of devising new intervention strategies.

Pathogenesis and Clinical Epidemiology
Because there is confusion at the international level about the prevalence and incidence of leprosy disease, a new perspective on epidemiological measurements is needed as well as approaches involving active, rather than passive, case finding. New approaches should determine the true prevalence of leprosy and the actual disease burden. In addition, it is important to develop new molecular tools that could be applied to study transmission.

It is important to develop the means to detect and treat M. leprae infection prior to the development of clinical symptoms in order to prevent both nerve function impairment (NFI) and nerve damage.

Diagnostics
Within the realm of diagnostic development, the following areas are important: increased epidemiological studies; studies to assess the effect of interventions; development of methods to detect preclinical and latent infection in order to provide early diagnosis, identify individuals at risk and monitor treatment; and creation of specific diagnostic methods based on cell mediated immunity.

Host Response, Immunology, and Vaccines
New molecular tools could be used to identify M. leprae-specific T-cell responses and to predict the risk of disease in affected populations.

As leprosy is also caused by Mycobacterium, progress made in tuberculosis vaccines could stimulate leprosy vaccine research. Furthermore, since many people have natural immunity to leprosy, there is potential for immunotherapy in susceptible individuals.

Target Identification and Candidate Therapeutics
It is important to determine the minimum length of effective multi-drug therapy (MDT) and to develop new molecular tools to detect drug resistance and define its extent. Alternatives to standard MDT therapy are important and new antituberculosis therapeutics in development could have a positive impact on the identification of new leprosy therapeutics.

Resources
Cohorts are important for implementation and testing of potential interventions, including MDT, chemoprophylaxis, and immunotherapy, and for understanding, treating and preventing NFI and leprosy reactions. The assembly of such cohorts requires investment, training, collaboration within and outside the leprosy research community (e.g., TB research community, disability services), cooperation with government health services and with International Federation of Anti-Leprosy Associations (ILEP) and other non-governmental organizations (NGOs), support for established consortia (e.g., Initiative for Diagnostic and Epidemiological Assays for Leprosy (IDEAL)), and maintenance of “core” labs and facilities (e.g., leprosy endemic sites and personnel and resource centers (see above)). Further, the maintenance of laboratories in leprosy endemic sites and multidisciplinary research consortia are important.
Appendix: Proceedings from Working Groups on Specific Pathogens: Bacteria

**Collaborative Needs**
The continued collaboration between clinical sites and research laboratories is important. Multidisciplinary approaches may help to address key areas in leprosy research. In addition to collaborative funding efforts, advocacy will be important for sustaining and expanding research and program efforts in leprosy.

**Mycobacterium ulcerans**

**Research Gaps**
The ecology of *M. ulcerans* is unclear. It is not known where in the environment it is amplified or how transmission occurs. It is also not clear if there are anthropogenic environmental changes that are responsible for the recent spread and increase in disease. In terms of pathogenesis, it is not clear under what conditions production of the toxin mycolactone is favored or the role of the extracellular matrix in pathogenesis.

**Diagnostics**
The development of a simple, rapid diagnostic field test for Buruli Ulcer is an important priority.

**Therapeutics**
It is important to optimize antibiotic therapy and to determine if an antibiotic regimen can cure small Buruli ulcer lesions before they progress to larger lesions requiring surgical intervention.

**Chlamydia trachomatis**

**Basic Science Research Gaps**
Advances in trachoma disease prevention and treatment could be facilitated by the following:

1) a system for genetic transformation,
2) an understanding of the molecular and cellular basis for chlamydia immunity,
3) a determination of whether subtle differences between trachoma strains are clinically important,
4) a determination of whether bacterial variants affect transmission, infectious load, clinical severity, or risk of sequelae, and
5) a determination of whether current strain-typing methods are optimal or if there is a need for more informative typing methods.

**Diagnostics**
The development of point of care diagnostic is needed in order to determine whether individuals need to be retreated with antibiotics.

**Pathogenesis Knowledge Gaps**
Corneal scarring associated with *C. trachomatis* infection is the proximal cause of blindness in trachoma. However, it is not clear why scarring appears so late in the disease process and why scarring only develops in some individuals. It is also not clear if host genetics or specific host responses are involved in this process. A possibility for studying this issue would be developing and/or expanding the non-human primate model for pathogenesis and immunity.

**Vaccines**
It is not evident if a vaccine is still the best approach for true eradication of trachoma, but if so, it is important to identify pathway(s) that are suitable for vaccine development.
**Opportunities from the SAFE Intervention**

There is an opportunity to gain information about a number of aspects of trachoma disease and public health intervention from the SAFE Program. SAFE is a WHO initiative designed to reduce blindness that is associated with long-term infections with *C. trachomatis*. The intervention consists of four aspects: Surgery, Antibiotics, Face washing and Environmental change. The surgical component is a simple procedure that a health-care worker can be trained to do. The antibiotic component consists of a single dose of azithromycin, which Pfizer is committed to providing for every infected person in the world. There are a number of research and practical questions that remain to be answered. It is not clear if the surgical techniques can be improved effectively. With respect to the antibiotic regimen, the questions include: what percent population coverage is required for the intervention to be successful; what is the appropriate time interval to re-treatment (6 months versus 12 months); what is the appropriate age at which children should begin treatment (less than 6 months or less than 12 months); when should treatment of a community stop; and can mass antimicrobial treatment eliminate trachoma at the community level over the long term.

With respect to the face washing and environmental aspects of the SAFE intervention, there are considerable problems with both the indicators and the effectiveness of these interventions. Thus, it is not clear to what extent an 'unclean face' is a cause versus an effect of trachoma transmission, nor is it clear how programs should prioritize the face washing and environmental aspects. Similarly, it is unclear as to whether epidemiological, risk, or disease features are the most important predictor of successful interventions in given communities, or if all three contribute and have an interactive effect.

**Natural History, Mathematical Modeling**

An issue related to the SAFE intervention is how mathematical modeling could facilitate intervention approaches. Too often mathematical transmission models in the literature are not tied with existing data and are not validated. Community-wide treatments for trachoma offer a unique situation to study such models as there is specificity in the time of treatment, the persons treated and the ability to determine infection status. Thus, it is possible that trachoma elimination programs could provide data for infectious disease models and could answer the question as to whether antibiotics can eradicate an infectious disease.

**Intervention Programs**

A potential beneficial effect of integrated NTD programs could be that mass azithromycin treatments may reduce respiratory, diarrheal and skin diseases. Cost-effectiveness could be achieved by coordinating the trachoma programs with other NTD intervention programs.