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TROPICAL DISEASES AND THEIR  
SIMULTANEOUS TREATMENT  
WORLDWIDE

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## DESCRIPTION

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<b>Abstract:</b>  <p>The purpose of this study was to evaluate an oral medication that is used for number of neglected tropical diseases at the same time to find out which treatments can be successful for this type of approach. For the purpose of this study, literature search was carried out and Medline database was searched (1966 through June 2007) for RCTs studying oral drug treatments for neglected tropical diseases. According to the data, around one billion people are affected by one or more neglected tropical diseases (ETD). They are considered "neglected" because they persist exclusively in the poorest and most marginalized. Report further revealed that despite the magnitude of the number of people suffering from neglected tropical diseases, less than 1% of the nearly 1400 drugs registered between 1975 and 1999 were used to treat tropical diseases. The figures and data used in this study revealed that the various factors that are hampering efforts to rescue from oblivion the ETD, as well as progress in the prevention, elimination and eradication of some of these diseases. Results of this study revealed that integration of treatment for tropical diseases can be facilitated by treating 2 or more diseases simultaneously.</p>		
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## 1. INTRODUCTION

The purpose of this study was to evaluate an oral medication that is used for number of neglected tropical diseases at the same time to find out which treatments can be successful for this type of approach. Results of this study revealed that integration of treatment for tropical diseases can be facilitated by treating 2 or more diseases simultaneously.

### 1.1. A Short History of Tropical Diseases

The nosological category of tropical diseases grew out of the colonial expansion of European nations and the United States at the end of the nineteenth century. In less than a hundred years, *tropical medicine* became a term increasingly devoid of meaning, as scientific research, deteriorating public health infrastructures, and rapid, large-scale human displacement (among other reasons) produced the identification of new vector-borne infections in temperate climates and the reemergence of others long gone. In addition, the largest proportion of diseases found today in tropical countries are not due to parasites or vector-borne agents but to globally distributed causes such as tuberculosis, HIV, and smoking, whose prevalence and severity are increased by the conjunction of poverty, hunger, and lack of medical care. (Chirac, 2006 p. 26)

The list of infections with a primary locus of transmission in tropical areas is vast, so this entry will comment only on the most important causes of disability (short- or long-term incapacitation on a mass scale). Those selected by Murray and Lopez in their analysis of the global burden of disease include four diseases transmitted by the bite of a mosquito (malaria, dengue hemorrhagic fever, Japanese encephalitis, and lymphatic filariasis); four transmitted by other arthropods (onchocerciasis, trypanosomiasis, Chagas disease, and leishmaniasis); two acquired by contact with a contaminated environment—soil (intestinal nematode infections) or water with

infected snails (schistosomiasis); one acquired through contact with contaminated secretions or by flies (trachoma); and leprosy, for which close, prolonged personal contact is the suspected mode of transmission. A succinct exposition of the natural history, preventive measures, and drug therapy for these diseases can be found elsewhere. In all of these diseases, treatment (if available) to cure the infection will partially or not at all reverse the long-term disability produced by the disease. In almost all of these diseases, the initial infection usually produces a short, undifferentiated febrile illness or may be asymptomatic. Only malaria, dengue, and Japanese encephalitis are likely to produce life-threatening syndromes on first infection, and the resulting long-term disability (other than the incapacitation due to malarial relapses) mostly depends on the severity of the initial episode and sequelae from shock or respiratory compromise. Among all these diseases, the major producers of days of illness and early death according to Murray and Lopez are malaria (by far the most common), filariasis, leishmaniasis, and intestinal nematodes, so they are considered in the short space allowed by this entry. It must be emphasized, though, that the true illness burden is underestimated because of the lack of local resources, even for data collection (Hotez 2004, p. 24).

Malaria is caused by any of four protozoan *Plasmodium* species (*falciparum*, *malariae*, *ovale*, and *vivax*) and produces fever, chills, sweats, and headache for a week to a month or longer, with relapses at irregular intervals for years thereafter, unless the proper antibiotic is provided. Falciparum malaria may progress to jaundice, shock, renal and liver failure, encephalopathy, and coma, with case-fatality ratios of 10–40 percent if untreated. Cases of cerebral malaria may recover with significant neuromotor deficits (Molyneux 2005, p. 99).

In contrast, the severe manifestations of lymphatic filariasis are usually the result of repeated infections that are active for years. *Wuchereria bancrofti*, *Brugia malayi*, and

*Brugia timori* larvae, transmitted by mosquitoes, lodge in the lymph tissue and the lungs and may produce paroxysmal nocturnal asthma, chronic lung disease, renal disease, arthritis, adenitis, lymphangitis, chyluria, and elephantiasis of the genitalia or limbs. Drug treatment clears most microfilariae from the blood but may not destroy all adult worms, so it must usually be repeated at yearly intervals. The principal goal in the treatment of these patients is to prevent secondary bacterial infections in areas swollen with lymph, which can be accomplished through good hygiene, prevention and cure of skin lesions, exercise, elevation of affected limbs, and wearing of appropriate shoes. Hydrocele (collection of fluid inside the scrotal sac) can be treated with surgery. A very useful guide for management of areas with lymph swelling (lymphedema) has been recently published. (Dreyer et al 2002, p. 52)

Onchocerciasis (river blindness) is also produced by filarial worms (*Onchocerca volvulus*) but transmitted by the bite of infected *Simulium* (black) flies. The microfilariae migrate through the skin and produce a chronic systemic illness with skin edema and atrophy, subcutaneous or periosteal fibrous nodules, and, if they reach the eye, visual disturbances or blindness (Utzinger 2006, p. 44).

The introduction of ivermectin for onchocerciasis in 1987 was a milestone of disease treatment in less developed countries because of the efficacy and safety of the drug and because the manufacturer (Merck) decided to donate it without charge. This gift provided the incentive for establishing community-based distribution networks in affected areas (even if they had no established public health systems), stimulated similar donations by other pharmaceutical companies, and is seen as an example of what could potentially be accomplished for AIDS therapy. Leishmaniasis, caused by a number of species of the protozoan genus *Leishmania*, is transmitted by the bite of sandflies and produces cutaneous and mucosal lesions that may last weeks or months and then heal spontaneously, only to recur even years later with dissemination and

nasopharyngeal tissue destruction. Visceral leishmaniasis (kala-azar), characterized by fever, diarrhea, abdominal pain, hepatosplenomegaly, pancytopenia, and progressive emaciation, is usually fatal within 3–20 months if untreated (Fincham 2003, p. 16). The principal intestinal nematode infections are hookworm disease (uncinariasis, by *Ancylostoma duodenale*, *Ancylostoma ceylanicum*, and *Necator americanus*), roundworm disease (*Ascaris lumbricoides*), and trichuriasis (*Trichuris trichiura*) (Hotez 2006, p. 20).

Hookworm eggs passed with feces hatch in the ground. Larvae penetrate human skin (usually the bare feet) and migrate through lymphatics and blood to the lungs, up the trachea, and then down the esophagus to the small intestine, where they attach to the wall, feed off the patient's blood, and produce thousands of eggs each day. This process may result in pulmonary infiltrates, cough, and tracheitis, but the major cause of disability in heavy infections is iron deficiency, with hypochromic microcytic anemia, hypoproteinemia, and retarded mental and physical development of children. *Ascaris* and *Trichuris* are acquired by the ingestion of eggs through pica or contaminated vegetables. The larvae attach to the mucosa of the intestine, and heavy infections may produce bowel obstruction, bloody stools, diarrhea, nutritional deficiency, and growth retardation in children (Chirac 2006, p. 15).

The principal specialized medical care required by the long-term sequelae of these “tropical” infections can be grouped as follows: neurological and physical rehabilitation for cerebral malaria, encephalitis due to dengue or Japanese encephalitis virus, lymphatic filariasis, and leprosy; skin care and reconstructive surgery for lymphatic filariasis, leprosy, leishmaniasis, and onchocerciasis; ophthalmologic treatment for onchocerciasis, trachoma, and leprosy; gastroenterological expertise in hepatic schistosomiasis and Chagasic megacolon; and cardiological, urological, and pulmonary care for Chagasic cardiomyopathy, urinary schistosomiasis, and filarial



interstitial lung disease, respectively. Unfortunately, these services are required by populations with other highly endemic severe diseases, such as HIV, that have little access to education and medical attention and are also burdened by poverty and malnutrition.(Hotez 2006, p. 60)

## 2.TROPICAL DISEASES IN DEVELOPED COUNTRIES

Still, tropical diseases are more prevalent in developing countries, where conditions all too commonly foster their spread. War refugees migrating to other areas carry infections with them. Economic and social crises stress health systems. And unsanitary conditions due to rapid urbanization and rapid population growth foster an environment in which insects and other animals can transmit disease-producing organisms.

### 2.1.Malaria

Sometimes called the King of Diseases, malaria yearly strikes up to 500 million people, 90% of them in Africa, with up to 2.7 million deaths, mostly young children. Malaria is caused by four species of Plasmodium parasites, transmitted to humans by infected female Anopheles mosquitoes. Symptoms include a spiking fever, shaking chills, and flu-like symptoms. Anemia or liver problems may develop. If treatment is delayed, severe infection may lead to kidney failure, coma, and death.

Malaria kills so many African children because they lack immunity, says tropical disease specialist Lt. Comdr. Alan Magill, M.D., of Walter Reed Army Institute of Research. Americans in Africa--travelers or troops--also are at risk because their immunity to malaria is like a child's, he says. They have more severe malaria than Africans who have survived past age five and developed immunity. "At our study site in Kenya," he says, "if you drew blood from 100 seemingly normal Africans at the

local market, you'd find malaria parasites in most of their blood streams. They're infected, and the transmission cycle goes on, but they don't have obvious ill effects." (Albonico 2003, p. 343-352)

The national Centers for Disease Control and Prevention (CDC) gets about 1,000 reports a year of malaria in the United States. Since 1957, nearly all these cases were acquired in areas of the world where malaria is known to occur.

Domestic malaria, in fact, was declared eradicated in this country in the 1940s. But from 1957 through 1994, the CDC got 76 reports of malaria cases that may have been transmitted locally, including some from suburban New Jersey in 1991 and New York City in 1993. A 1995 report from Michigan was the first that far north since 1972. "In most cases, evidence indicated that locally infected mosquitoes did transmit the disease," says CDC malaria expert Lawrence Barat, M.D. "Anopheles mosquitoes are present throughout the contiguous United States. But we've never found an infected mosquito in the United States. More recently, we've had outbreaks of Plasmodium falciparum malaria, the more severe form. We want to monitor this very closely." (Albonico 2003, p. 343-352)

For several decades after the Second World War, the drug of choice for malaria treatment and prevention was chloroquine (Aralen and generics). "The drug was well tolerated, fast-acting, and cost only 9 cents to cure a child," says Robert Gwadz, Ph.D., assistant chief, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases (NIAID). However, in the 1950s, he says, resistance to chloroquine in falciparum malaria appeared in South America and Southeast Asia and spread throughout both continents and eventually into Africa. "Chloroquine is now useless in most malarious areas." (Albonico 2004, p. 1205-1210)

The FDA has since approved numerous anti-malaria drugs. Many are not marketed here or are used here only for indications other than malaria.

Chloroquine remains the treatment of choice for patients with malaria caused by species still susceptible to the drug. Resistance to chloroquine is becoming more common, however, and alternative drugs are necessary.

In the United States, Barat says, oral quinine given together with either tetracycline or sulfadoxine-pyrimethamine (Fansidar) is the best regimen for treatment of mild to moderate falciparum malaria acquired in areas where resistance to chloroquine has been identified. For patients with complicated malaria who are too ill to take oral medicine, intravenous quinidine is used in the United States. Mefloquine (Lariam) and halofantrine (Halfan) are also used to treat chloroquine-resistant falciparum malaria. Halofantrine is not currently marketed here. Intravenous quinine is used in other countries. (Albonico 1995, p. 538-541)

The incidence of malaria continues to increase, Gwadz says, "in part due to the spread of resistance to chloroquine and several of its substitutes, but also to reduced effectiveness and acceptability of mosquito-killing insecticides." (Balk 2002. p 273-282)

In 1995, the World Health Organization established a system to monitor drug resistance in Southeast Asia and the Western Pacific. The parasite can be difficult to treat because it can change form to escape the human immune system, says Neil Goldman, Ph.D., associate director for research at FDA's Center for Biologics Evaluation and Research. Goldman says scientists at the center's Laboratory of Parasitic Biology and Biochemistry conduct research "to learn how this process takes place and figure out how to interrupt it. If we make a break in the circle, maybe we can stop infection."

NIAID scientists also are conducting the first human trial of a vaccine to block transmission of malaria parasites from infected people.

## 2.2. Other Mosquito-Borne Disease

*Aedes* mosquitoes, mainly *A. aegypti*, an urban-dwelling insect, can transmit four types of dengue viruses, causing about 20 million cases of disease in more than 100 countries each year. *A. aegypti* mosquitoes tend to bite in the daytime, especially just after dawn and just before dark. Dengue fever begins suddenly with high fever, severe frontal headache, joint and muscle pain, and sometimes vomiting and rash. Patients usually recover without complications. More serious, dengue hemorrhagic fever can lead to shock, bleeding, and death. There is no specific treatment. Symptoms can be treated with bed rest, intravenous fluids, and drugs to reduce fever. In 1995, the worst dengue epidemic in 15 years hit Latin America and the Caribbean. Worldwide, the more than 600,000 cases of hemorrhagic fever caused 24,000 deaths. CDC in 1995 diagnosed dengue fever in 86 U.S. travelers, up from 46 during 1993-1994 and 17 in 1992.

*A. aegypti* mosquitoes also spread the yellow fever virus. Peru in 1995 had the biggest yellow fever epidemic in the Americas since 1950. West Africa also experienced an epidemic that year. Mild yellow fever causes flu-like symptoms. Severe cases may involve bleeding and liver problems, sometimes leading to delirium, convulsions, coma, and death. Treatment is symptomatic. Prevention consists of vaccination and personal protection against mosquitoes. Yellow fever vaccine must be approved by WHO and given at approved vaccination centers. The Pan American Health Organization (PAHO) helped in the vaccination campaign that controlled the Peru epidemic. PAHO is the regional WHO office for the Americas. (Albonico 1994 p. 585-589)

### 2.3. Elephantiasis and River Blindness

Worms related to the heartworms that can hurt dogs can give humans lymphatic filariasis, a disease affecting about 120 million people worldwide. Infected female *Aedes*, *Anopheles*, and various other mosquitoes deposit the worm larvae while biting. The adult worm can damage the lymph system, resulting in elephantiasis--disfiguring swelling in the legs, arms, and other areas. The FDA has approved diethylcarbamazine (Hetrazan) for treatment. Surgery may be needed if certain areas, such as the scrotum, are affected.

River blindness (onchocerciasis) is caused by pre-larval and adult stages of *Onchocerca volvulus*, a filarial parasite transmitted by female black flies. Living near rapidly flowing rivers and streams, black flies bite by day. Most of the 17.6 million people who have onchocerciasis are in Africa, though the disease is common in certain areas of Central America as well. Short-term travelers appear to be at low risk for infection, which is usually found in Americans only when they stay in these areas a long time in roles such as missionaries, field scientists, and Peace Corps volunteers. Symptoms include an extremely itchy rash, lumps under the skin, and eye inflammation that can lead to blindness.

Ivermectin kills the parasite at the stage when it causes symptoms. Merck, Sharp & Dohme provides this drug free to countries where river blindness is common. It is available here from the CDC under an agreement with the FDA. According to John Becher, one of two pharmacists who oversee the drug service, "we provide certain drugs and biologics as a public health service. Most are for rare diseases." Ivermectin and other drugs for tropical diseases available through the service are not approved in the United States but are provided under investigational drug exemptions granted by the FDA. (Albonico 1999, p. 591-596)

NIAID's Laboratory of Parasitic Diseases conducts research toward vaccines for elephantiasis and river blindness. While nearly everyone exposed becomes infected, a few individuals are resistant, says Thomas Nutman, M.D., who heads one immunology section. "These resistant individuals have antibodies in their blood that are specific to certain important parasite proteins. We identify the proteins, clone them, manufacture enough so we can study them, and then test them." Testing is in test tubes instead of in animals, which don't take the infection as humans do.

(Barry 2007, p. 2561-2564).

#### 2.4.Flatworms, Snails, and Schistosomiasis

Flatworms cause schistosomiasis. First-stage larvae infect freshwater snails, then evolve into cercariae larvae, which exit the snails and swim along to find a human host. Penetrating the skin, male and female cercariae move in the bloodstream to the intestines or bladder and mate. Eggs excreted in human waste end up in the water supply, restarting the cycle. About 200 million people worldwide are infected. Severe disease leads to about 200,000 deaths each year.

Most symptoms are due not to the worms, but to eggs trapped in tissue. Short-term infection may be symptomless or cause such symptoms as fever, itchy rash, headache, joint and muscle pain, diarrhea, and nausea. Chronic infection can damage the liver, kidneys, and bladder, or intestines. The FDA has approved praziquantel (Biltricide) as treatment.

Places where schistosomiasis is most prevalent include Brazil, Puerto Rico, and St. Lucia (an island in the East West Indies); Egypt and most of sub-Saharan Africa; and Southern China, the Philippines, and Southeast Asia, according to CDC. At greatest risk are people who wade, swim, or bathe in fresh water in rural areas where sanitation is poor and snail hosts are present.

Travelers to such areas should not swim in fresh water; salt water, like the ocean and chlorinated pools, is considered low risk. Bathing water should be heated to 122 degreesF or treated with iodine or chlorine, as for drinking. Filtering water with paper coffee filters may remove the parasites. If these methods are impossible, CDC recommends that travelers let bathing water stand three days; cercariae rarely live longer than 48 hours. (Bartoloni 1993, p. 114-116)

### 2.5. Trypanosoma Diseases

The parasites *Trypanosoma brucei gambiense* and *T. brucei rhodesiense* cause African sleeping sickness. About 20,000 cases worldwide are reported yearly. Infected tsetse flies, which bite during the day, transmit this extremely serious disease.

East Africa's sleeping sickness, due to *T. brucei rhodesiense* infection, causes symptoms within days to weeks. West Africa's chronic gambiense variety may not cause the "sleeping" part of the illness until months to years after exposure. Symptoms include fever, headache, lethargy, and confusion, which may progress to convulsions, coma, and death.

Suramin, available from the CDC, is for the early stages of both gambiense and rhodesiense sleeping sickness. Melarsoprol, an arsenic derivative, is also available from the CDC to treat final stages of both varieties. If the patient is known to have gambiense, however, the drug eflornithine (Ornidyl), approved by the FDA, is more effective and safe because melarsoprol can cause serious, even fatal, nervous system problems in some patients. Eflornithine is useful for both early and late stages of gambiense sleeping sickness; it is not effective for rhodesiense sickness.

*Trypanosoma cruzi* causes Chagas' disease, which affects at least 16 million people in Central and South America. The parasite infects reduviid bugs. When the bugs defecate, they deposit the parasite, which can enter a human through a break in the

skin or through a mucous membrane, such as that which lines the nose, mouth, or eyes. The best prevention is to avoid potential reduviid habitats--mud, adobe, and thatch buildings, especially those with cracks or crevices. If this isn't feasible, spraying infested areas and using bed nets can help prevent infection.

In its short-term stage, Chagas' disease may cause no symptoms or may cause fever, swollen lymph nodes, and inflammation of the heart or, rarely, the brain. Deaths occur, mainly in children, but most patients survive, their symptoms usually disappearing after four to six weeks. Many years later, about a fourth of patients develop serious, sometimes fatal, heart infection or damaged digestive organs, such as an enlarged esophagus or colon for the long term. Nifurtimox is available from CDC for the treatment of short-term Chagas' disease. There is no accepted anti-parasitic treatment for chronic illness.

About 70% of cases occur in Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay. In 1991, the health ministers of those six countries began a program to eliminate Chagas' disease by the end of this century. Since then, house infestation has declined 75% to 98% in some areas, PAHO reports. (Beach 1999, p. 479-486)

Twelve cases were reported between 3 and 27 November 2008, all Finnish travellers returning from Gambia (Valve et al., 2008 p. 15). Five of these patients were female, seven were male. Age distribution was between 27 and 66 years. Their travel destinations were tourist resorts near Banjul. Nine travellers did not take any chemoprophylaxis, three used chloroquine prophylaxis. Ten of the 12 patients had received information about the malaria risk and recommended chemoprophylaxis. The duration of their stay in Gambia was between one and two weeks except for one patient who stayed four weeks. Three had complications that required treatment in intensive care, but all three recovered. For nine patients, the diagnosis was made



within three days of onset of symptoms. The three patients with complications had been diagnosed with a delay of up to eight days.

## 2.6. More Tropical Diseases

The tropics are usually defined as that part of the equatorial world bounded by the tropics of Cancer and Capricorn. Defining a tropical infectious disease is not as straightforward. Almost all infectious diseases can be found in the tropics; there are a great number that occur predominantly in the tropics; and there are a few, such as sleeping sickness, that are only found in the tropics. Before discussing some of the more prevalent tropical infections of today, it is worth taking a brief look at the history of a few of these infections.

Tropical sprue, one of infectious diseases causing generalized malabsorption, is a progressive and chronic malabsorptive disease occurring in people living in certain tropical countries. This disease characterized by abnormalities in intestinal structure and function, symptoms related to malabsorption, and get respon to treatment with folic acid, tetracycline, or both. Tropical sprue is different with subclinical malabsorption, an endemic condition in tropical countries that may produce similar structural changes, but that does not produce symptoms. Tropical sprue occurs both in the native population and in foreigners who live in tropical places for long periods.

(Bill 2009, p.5)

The incidence of tropical sprue is declining or not, is not clear. It is unknown that with improve nutrition, good sanitation, or prompt treatment with antibiotics of acute diarrhea is useful for this disease. The most important hypothesis about the cause of tropical sprue is that it describes a form of small bowel bacterial overgrowth. Most individuals with tropical sprue have evidence of aerobic gram-negative bacterial overgrowth and at least some of these strains appear to secrete enterotoxins. It is

unclear what distinguishes individuals with tropical sprue from other patients with bacterial overgrowth (other than the obvious epidemiology).

Typical clinical manifestation of tropical sprue begins as an acute diarrheal disorder that then more advanced into a chronic persistent diarrhea. Over the course of several months, evidence of more substantial malabsorption develops that associated with progressive weight loss. Tropical sprue also can cause megaloblastic anemia and also there is variable evidence for other deficiency states. It can be fatal if tropical sprue is not treated. (Hotez 2006, p.467–482)

Dysfunction of the mucosa considered as the basis for malabsorption. Histologically, the villi are shortened and thickened (partial villous atrophy); the flat mucosa of celiac sprue is unusually observed. There are disruption of microvilli and reduced brush border enzyme levels of enterocytes. In tropical sprue can present chronic inflammatory infiltrate in the submucosa and megaloblastic changes may be presented in the crypt epithelium.

Tropical sprue is diagnosed depend on recognition of malabsorption in patient complaining of diarrhea who was a resident of one of the endemic countries. The diagnosis should suggest where there are finding of B12 or folate deficiency and typical biopsy changes. Other infectious problems must be excluded, such as giardiasis or cryptosporidiosis.

Treatment of tropical sprue includes pharmacologic doses of folic acid (5 mg daily), injection of B12 (if deficient), and antibiotic. The treatment of choice is Tetracycline (250 mg four times a day) or sulfonamide. Antibiotic therapy should be continued for 1–6 months. Optimal therapy includes both folate and an antibiotic; therapy with folic acid alone does not allow resolution of all of the structural changes in the intestine and therapy with antibiotic alone delays correction of the vitamin deficiencies until

structural integrity is restored. With optimal therapy, improvement should be seen over the course of a few weeks. (Zu 1992, p.95–99)

Around the Rio Dulce area, the occurrence of tropical diseases is quite rare but isolated cases of intestinal problems, malaria and dengue fever will occasionally crop up. Some years ago there was a minor outbreak of cholera in the Fronteras area. The solution is simply this: 1) Under no circumstances should you drink the river water. 2) Don't bathe in the river near or downstream of heavily populated areas, ie. Fronteras. Some have expressed a general interest in tropical diseases and have complained of the lack of information about such diseases. To satisfy this need the following general overview of tropical diseases worldwide is included here. Some of the diseases covered below do not occur in Central America but are included to satisfy the curious. Readers with a taste for the macabre may be especially interested in the news-clip about the Ebola virus.

Tropical diseases are illnesses that either occur uniquely in tropical and subtropical regions (which is rare) or, more commonly, are either more widespread in the tropics or more difficult to prevent or control. The tropics are more problematic for certain diseases for two reasons:

- 1) Tropical climates are more conducive to certain diseases.
- 2) Areas of poverty and primitive sanitation conditions are more common in the tropics. (Verhagen 2001, p.54)

The most important diseases in the tropical regions of Southeast Asia, Africa, and South America are malaria, schistosomiasis, leprosy, filariasis, trypanosomiasis, and leishmaniasis. Although effective chemotherapy and insecticides have reduced or eliminated malaria in most of the western hemisphere, these measures have been less successful in Asia. Both the infecting parasite and its mosquito carrier have become resistant to current drugs and 200 million persons are estimated to have malaria in

tropical areas. In sub-Saharan Africa some 1 million children under five die of the disease each year.

Schistosomiasis has never been common in temperate climates, but it affects 125 million persons worldwide, of whom approximately 20 percent are at least partly disabled by the disease. Praziquantel, a highly effective new drug, is now available for treatment of schistosomiasis. Leprosy has also always been more common in tropical than in moderate climates, and about 11 million persons in the world have this illness. In endemic areas many severe cases of leprosy are now resistant to the drug first used against it, and newer, more expensive therapy must be employed. Filariasis is a common tropical debilitating illness caused by infection with roundworm larvae. Trypanosomiasis, which results from infection with a protozoan parasite, has caused 10 million cases of human sickness in Africa alone. A related protozoan in South America causes a less deadly form of trypanosomiasis called Chagas' disease. Leishmaniasis is also a result of worm infection, and in its Asian and African forms the disease can damage the internal organs.

Although tuberculosis is largely under control in developed countries, it is still a considerable public health problem in much of the world and is responsible for about half a million deaths annually, 75 percent of them in Asia. Other diseases for which treatment is available but which are still common in developing countries include cholera, yellow fever, yaws, and amoebic dysentery.

Two forms of cancer, Burkitt's lymphoma and liver cancer, are very common in Africa and Asia, respectively, although rare in temperate zones. Burkitt's lymphoma is thought to be due to a combination of massive infection with a virus early in life and malaria in adulthood. Liver cancer may be caused by infection with the hepatitis B virus. (Jüni 2002, p.2407–2408)

As many as 25 million persons have become blind from preventable diseases in tropical countries. These diseases include xerophthalmia, due to lack of vitamin A in the diet; onchocerciasis, or river blindness, an infection of the skin by filarial larvae that may also affect the conjunctiva of the eye; and trachoma, a chronic conjunctival infection caused by the parasitic bacterium *Chlamydia trachomatis*, which is transmitted by flies or through close personal contact. (Bundy 1992 , p.168–179)

Finally, a number of severe virus-caused fevers that were identified during the 1970s are found predominantly in tropical regions. These diseases include Lassa, Ebola, Marburg, Bunya, and Chikungunya fevers, some of which cause death by hemorrhage (hemorrhagic fever). One member of this family, dengue virus, was known for many years but has recently spread to the Caribbean and Mexico. All these diseases are rare.

### 3.THEORETICAL FRAMEWORK

The number of cases of malaria diagnoses in Finland last year was a new record for this decade. More than 40 people were treated for the disease. In addition, over 30 people sought treatment for Dengue fever infections. Until last year the annual number of cases of Dengue fever has been around 20. The number is increasing which is a worldwide tendency also.

According to National Institute for Health and Welfare, many Finns have perhaps forgotten that various travel destinations require different health precautions. People travel on tourist holidays to the tropics and don't necessarily remember that a holiday in Africa is quite a different thing than a trip to Europe or even to Asia," says Pekkanen. (Belizario 2003, p. 35-42)

Although many package tour organizers provide information on their web sites about health risks, not all do, and Pekkanen urges travellers to speak with a doctor before holidaying in the tropics. The neglected tropical diseases are a group of 13 infections

that affect more than 1 billion people worldwide, who live in extreme poverty.

Although inexpensive oral drug therapies exist to treat these conditions, they are often not accessible to the affected populations, people who live in remote areas on less than US \$2 a day and without access to health care. The perpetuation of neglected tropical diseases results in part from unsafe water, poor sanitation, and substandard housing conditions. Infection with neglected tropical diseases can trigger life-long disabilities, disfigurement, and social stigma, and the stigma in turn makes people, particularly women, reluctant to seek care. Left untreated, these conditions result in severe morbidity that could be prevented.

Seven of the 13 neglected tropical diseases are caused by worms (elephantiasis, guinea worm, hookworm, river blindness, roundworm, schistosomiasis, and whipworm), 3 are protozoal (African sleeping sickness, Chagas disease, and leishmaniasis) and the rest are bacterial (Buruli ulcer, leprosy, and trachoma).

Trachoma is the leading cause of preventable blindness in the world, elephantiasis is the second-leading cause of permanent disability in the world (by causing disfigurement of legs and genitalia), and hookworm causes severe anemia and is consequently one of the most important maternal-child problems.

(Behnke 1994, p. 187-195)

#### 4.HYPOTESIS

Neglected tropical diseases contribute to 500 000 deaths per year worldwide.

Additionally, these conditions result in 57 million disability-adjusted life-years lost annually, a number almost as high as that associated with human immunodeficiency virus (HIV)/AIDS, tuberculosis, or malaria. Infection with a neglected tropical disease may increase susceptibility to HIV/AIDS and worsen outcomes in those with HIV/AIDS, tuberculosis, or malaria. Neglected tropical diseases primarily affect

younger individuals and can result in slowed growth and poor school performance in children and decreased work productivity in adults, thereby perpetuating poverty.

## 5.THE PROBLEM TO BE SOLVED

Despite the huge impact of neglected tropical diseases worldwide, the ability to treat them is largely unknown in the general medical community, and there is little public awareness of and response to this problem. In part, this is the result of a skewed distribution of studies published in the general medical literature in which clinical trials generally have little relevance to the 10 leading causes of the global burden of disease. Furthermore, less than 1% of new drug development over the last 30 years has been aimed at advancing drug treatments for tropical diseases.

There is a substantial geographic overlap of neglected tropical diseases, with up to 6 diseases occurring in a single region. A large proportion of people are infected with more than 1. Additionally, neglected tropical diseases often augment the deleterious effects of one another. Therefore, the World Health Organization (WHO) and others have advocated the implementation of an integrated approach to neglected tropical disease management that could use drug therapies that simultaneously target 2 or more neglected tropical diseases. By delivering treatments using the same health sector infrastructure (eg, population-based, annual mass drug distribution), an intervention could be more effective than if each disease was targeted separately. Control of these diseases could lead to poverty decline. (Bill 2009, p. 25)

I have systematically reviewed the evidence from randomized controlled trials (RCTs) evaluating oral medications that treat multiple neglected tropical diseases simultaneously to determine which treatments could be effective for such an integrated approach.

## 6.LITERATURE REVIEW

This chapter will discuss the review of the literature regarding the tropical diseases.

Tropical infectious diseases are models of inflammation in which various mediators and cytokines have important pathogenic roles. Changes in hemodynamics, fluid compartmentalization, endocrine function and membrane transport can occur and can exert systemic effects on organ function. Nitrogen wasting is a well-recognized feature of infectious illness, accompanied by deficits of potassium, magnesium, phosphate and trace elements. Artificially induced hyperthermia produces catabolic changes that are similar to those observed during infection. Hyperventilation due to pyrexia can cause respiratory alkalosis, leading to hypokalemia and hypophosphatemia. Diarrhea can deplete salt and water reserves. Severe infection can be associated with shock, renal dysfunction and multiple organ failure.

The clinical spectrum of severe tropical diseases encompasses a wide range of pathophysiological changes that are comparable to those seen in patients with severe sepsis. Malaria, leptospirosis, dengue hemorrhagic fever and febrile conditions are good tropical disease models. Fluid and electrolyte alterations are features of tropical diseases. Hyponatremia, hypokalemia, hypocalcemia and hypophosphatemia are often associated with tropical diseases, especially severe cases. Polyuria is occasionally observed. As these changes are usually transient and do not cause symptoms, they tend to be overlooked by clinicians; nevertheless, they are of pathophysiological interest. Some even reflect the severity of disease and can be therapeutically relevant. Malaria and leptospirosis are common and acute, and these are therefore the most frequently studied tropical diseases. This review of fluid, electrolyte and mineral perturbations in tropical diseases focuses on these two conditions.

At first sight, no institution better illustrates the departure in imperial policy than the Tropical Diseases Research Fund. Colonial Secretary Joseph Chamberlain (1895-



1902), a leading champion of constructive imperialism, initiated the Fund in order to encourage the understanding and prevention of disease in the empire. (Albonico 2002, p. 685–690)

Subsidised by the annual contributions of crown colonies and the Government of India, the advisory committee of the Fund would play an instrumental role in institutionalising the study of tropical diseases in Britain. From 1903 until the outbreak of World War I, the advisory committee promoted the study of tropical diseases, chiefly by subsidising research science at Cambridge University, the Liverpool and London Schools of Tropical Medicine, and London University. These beneficiaries of the Fund were not only the location of some of the earliest studentships, positions and laboratories in helminthology, parasitology, protozoology and entomology but also collectively represented the centre of tropical disease research for the British Empire in the twentieth century. Undoubtedly, the domestication of tropical disease research referred to the exigencies of the late nineteenth century British Empire. In stressing change in imperial policy, however, historians have too often overlooked how the social power of the imperial state as a metropolitan employer of doctors and source of funding for the scientific community shaped the response to the problem of disease in the empire.' (World Health Organization. Trachoma 2009, p. 52-85)

Two forms of cancer, Burkitt's lymphoma and liver cancer, are very common in Africa and Asia, respectively, although rare in temperate zones. Burkitt's lymphoma is thought to be due to a combination of massive infection with a virus early in life and malaria in adulthood. Liver cancer may be caused by infection with the hepatitis B virus.

As many as 25 million persons have become blind from preventable diseases in tropical countries. These diseases include xerophthalmia, due to lack of vitamin A in

the diet; onchocerciasis, or river blindness, an infection of the skin by filarial larvae that may also affect the conjunctiva of the eye; and trachoma, a chronic conjunctival infection caused by the parasitic bacterium *Chlamydia trachomatis*, which is transmitted by flies or through close personal contact.

Preserving the health of imperial servants and, when resources permitted, indigenous inhabitants, defined the minimum and maximum of the colonial medical services. But the oversupply of practitioners in Britain made the delivery of primary care in the empire a practical possibility. The Colonial Office routinely filled vacancies in the far-flung dependent empire without having to offer special incentives beyond a modest base salary. Colonial governments, in turn, maximised the labour of imperial doctors by linking their remuneration to the discretion of the colonial administration or governor and performance-based incentives.

Wherever the Union Jack flew in the British Empire, there was sure to be colonial medical personnel nearby. No matter the cause of expansion, the underlying viability of the empire ultimately depended on the survival of its colonial personnel. This imperative, together with Victorian fiscal economy, determined the mission of the colonial medical services: the cost-efficient delivery of health care to European servants and, when resources permitted, colonial subjects. Whatever the success the services realised were largely due to the role of the imperial state as an employer of metropolitan medical professionals.

The Colonial Office was one of the largest employer of full-time civilian medical professionals. By the end of the century, it filled well over 300 positions. In a medical market that suffered from a chronic surplus of qualified medical professionals, the leverage that came with being a large civilian employer enabled the Colonial Office to satisfy the personnel needs of a far-flung empire on its own terms. Unlike the entry requirements of the Army and the Indian and Naval Medical Services, the Colonial

Office neither set a competitive examination nor required the completion of post-graduate training. At most, it expected applicants to be from 23 to 30 years of age, preferably single and possess two qualifications (medical and surgical). Beyond these formal requirements, the applicant had to pass a health assessment and submit to an interview with a private secretary and/or staff member of the Colonial Office. These minimal requirements did more than simply ensure the largest pool of potential applicants. They also provided maximum flexibility in meeting the personnel needs of the empire. Forecasting vacancies was virtually possible for an empire whose staffing heterogeneity was matched only by its geographical diversity. Nor were imperial officials, who were ever conscious of economy, prepared to be burdened with a large supply of underemployed imperial doctors as was the case with the state services (Simeon 1995, p. 1875–1883). Instead, the Colonial Office staggered the appointment process to accommodate the personnel needs and fiscal imperatives of the empire. Prospective candidates submitted their applications in April. Those who were approved were then placed on the Secretary of State's appointment list. From this list, candidates were matched as vacancies opened during the year. Placement on this list did not guarantee an appointment. No promise is given that any appointment will be eventually made,' prospective applicants were warned, 'and it is not possible to forecast either the number or the nature of the vacancies which will arise in the course of any given year. Moreover, the duties of imperial medical personnel did not require specialised professional training. Of course, the needs varied from colony to colony, but in general imperial doctors were expected to serve the needs of European personnel and their families at no charge as well as colonial subjects as resources allowed. Most appointments were at the district level. Within these districts, which could be quite extensive, officers were charged with varied responsibilities. 1° These included attending the local hospital, poor-house or asylum, overseeing the sanitation

of the district, and performing public vaccinations. Once a practitioner accepted an appointment, he quickly became the financial captive of the colonial service. Even before being dispatched to a colony, imperial doctors were expected to purchase costly outfits, including clothing, camp cutlery and medical kits. Although the base salary varied from colony to colony, it was consistently low in comparison with average salaries at home. They ranged from a low of £100 to 300 for probationers, some district medical officers and colonial surgeons to £400 to 700 for most district officers and up to £800 for the chief medical officer of the Gold Coast colony. To be sure, housing and travel supplements diminished the high cost of living in the empire. Imperial doctors still lost ground since salary increases were not automatic. Usually, they were awarded at the discretion of the colonial administrator or governor after the completion of a probationary period-lasting from two to three years-or after a fixed number years of service, and capped at a maximum salary level.

(Hotez 2006, p. 467–482 )

Colonial governments used the discretionary nature of salary increases and conditions attached to private practice to ensure that imperial doctors made the execution of their duties a priority. They also took steps to make duty one with self-interest through performance based financial incentives. In the Leeward Islands and British Honduras, for example, medical personnel received fees for successful vaccinations, post-mortem examinations, courtroom appearances, and executing lunacy and burial certificates. In Fiji, they received capitation fees for treating indentured labourers. Stipends were awarded to medical personnel for assuming additional duties, such as taking charge of public institutions such as the civil prison or the lunatic asylum in Gibraltar; or serving as the officer of health in Lagos; or as ex officio inspector or resident surgeon of the Lock Hospital, superintendent of the civil medical hospital or health inspector of emigrants in Hong Kong. These and other administrative tools

certainly enabled colonial governments to deliver health care in a cost-efficient manner. Yet, the emphasis on addressing a narrow range of primary health care problems ultimately circumscribed the role of imperial doctors as agents of preventive medicine or, for that matter, investigators. This did not necessarily mean that colonial governments were indifferent to the health of the colonised. On the contrary, colonial governments authorised a wide spectrum of ordinances that dealt with general health. (Zu 1992, p. 95–99)

These ranged from financing public works projects, from establishing and maintaining water systems, improving the collection and removal of sewage, hospital and cemetery construction, to preventing the spread of rabies by regulating dog ownership to imposing quarantine measures against cholera and plague. These and other measures did not depend on the authority of imperial doctors as experts per se, but rather on a host of variables. These ranged from the advice of sanitary engineers, previous encounters with infectious or contagious diseases, the commitment of the colonial governor or administrator, the availability of local financial resources, and the cooperation of property-owners and other interest groups. The politically constructed nature of public health therefore shaped the local response to the problem of disease. Predictably, neither imperial doctors nor colonial officials present a flattering picture when faced with endemic or epidemic disease. Spasms of concentrated-and, not infrequently, counter-productive-activity punctuate long periods of seeming indifference. (Jongsuksuntigul 1993, p. 724–729)

Until the last decade of the nineteenth century, imperial officials in London took little notice of infectious disease crises in the periphery. Even in the age of the telegraph, distance, together with economy, conspired against ameliorative action directed from the centre. This posture changed as the strategic value of Britain's empire, especially in Africa, rose in the face of colonial and imperial challenges. Zululand, where tsetse

fly disease surfaced in 1894, represented a critical region in the consolidation of British hegemony in southern Africa against the expansionistic Boer nation.(Goodfellow 1966, p. 3) Uganda, the epicentre of the 1901 sleeping sickness epidemic, was no less important. This region not only formed the heart of the British East African protectorate, but also insulated the higher reaches of Britain's most important imperial trading conduit to the East-the Nile River Canal-from French and German encroachment.(Galbright 1972, p. 5) With stakes so high and local resources constantly stretched and quickly overwhelmed, it is not surprising that imperial officials looked elsewhere for assistance. In 1894 and 1901, the Colonial Office and Foreign Office respectively consulted the Royal Society concerning the tsetse fly and sleeping sickness epidemics. In 1899, the Colonial Office again solicited the advice of the Royal Society regarding the relationship of blackwater fever to malaria. These consultations led to the formation of an advisory committee for tsetse fly investigations in Zululand in 1896, two sleeping sickness research expeditions to East Africa, and a malaria commission in 1899. (Verhagen 2001, p. 54)

No satisfactory explanation has yet been given as to why the imperial state consulted with Royal Society. To be sure, the Society was the leading scientific institution in Britain and the empire. The tug of imperial duty does not explain why the Society supplemented the costs of these metropolitan initiatives. Rather, as a recipient of a government subsidy since 1850, the Royal Society was neither in a position to say no to the solicitations of the state, nor could it resist contributing to the costs of research in the empire. As the next section will show, this relationship mediated the conduct of imperial science and helped foster the formation of the Tropical Diseases Research Fund.

These funding decisions did not operate in a vacuum. On the contrary, they replicated the uneven power relationship between the imperial metropole and the colonial

periphery. No different from other forms of economic extraction, these allocations represented a net diversion of scarce resources from the periphery to the metropole. This diversion had real consequences for the social production of knowledge about disease in the empire. The very growth of scientific specialities and specialist knowledge in Britain remained enmeshed in the continued occupational subordination of medical personnel in the empire as primary care-givers. (Yangco 1981, p. 285–290)

Schistosomiasis has never been common in temperate climates, but it affects 125 million persons worldwide, of whom approximately 20 percent are at least partly disabled by the disease. Praziquantel, a highly effective new drug, is now available for treatment of schistosomiasis. Leprosy has also always been more common in tropical than in moderate climates, and about 11 million persons in the world have this illness. In endemic areas many severe cases of leprosy are now resistant to the drug first used against it, and newer, more expensive therapy must be employed. Filariasis is a common tropical debilitating illness caused by infection with roundworm larvae. Trypanosomiasis, which results from infection with a protozoan parasite, has caused 10 million cases of human sickness in Africa alone. A related protozoan in South America causes a less deadly form of trypanosomiasis called Chagas' disease. Leishmaniasis is also a result of worm infection, and in its Asian and African forms the disease can damage the internal organs. (Jüni 2002, p. 2407–2408)

## 7. REVIEW OF FLUID, ELECTROLYTE AND MINERAL PERTURBATIONS IN TROPICAL DISEASES

Tropical infectious diseases are models of inflammation in which various mediators and cytokines have important pathogenic roles. Changes in hemodynamics, fluid compartmentalization, endocrine function and membrane transport can occur and can exert systemic effects on organ function. Nitrogen wasting is a well-recognized

feature of infectious illness, accompanied by deficits of potassium, magnesium, phosphate and trace elements. Artificially induced hyperthermia produces catabolic changes that are similar to those observed during infection. Hyperventilation due to pyrexia can cause respiratory alkalosis, leading to hypokalemia and hypophosphatemia. Diarrhea can deplete salt and water reserves. Severe infection can be associated with shock, renal dysfunction and multiple organ failure.

The clinical spectrum of severe tropical diseases encompasses a wide range of pathophysiological changes that are comparable to those seen in patients with severe sepsis. Malaria, leptospirosis, dengue hemorrhagic fever and febrile conditions are good tropical disease models. Fluid and electrolyte alterations are features of tropical diseases. Hyponatremia, hypokalemia, hypocalcemia and hypophosphatemia are often associated with tropical diseases, especially severe cases. Polyuria is occasionally observed. As these changes are usually transient and do not cause symptoms, they tend to be overlooked by clinicians; nevertheless, they are of pathophysiological interest. Some even reflect the severity of disease and can be therapeutically relevant. Malaria and leptospirosis are common and acute, and these are therefore the most frequently studied tropical diseases. This review of fluid, electrolyte and mineral perturbations in tropical diseases focuses on these two conditions.

This research report is very important for me in order to understand the basic purposes of tropical disease and their simultaneous treatment worldwide. Beginning the tropical disease section with a detailed consideration of tropical microvascular dynamics allows a smooth transition from cardiovascular-related topics to kidney-related topics. In addition, reductions in Tropical disease and glomerular filtration rate (GFR) are often associated with many pathophysiological conditions including hypertension, malaria, heart failure, and diabetes, and it is essential for the student to obtain a solid



foundation regarding the principal mechanisms regulating tropical hemodynamics.  
(Knowler, 2008, p. 25-32).

The following objectives provide a clear guide for factors regulating tropical disease dynamics:

- 1) To be able to define and calculate the influence of tropical disease.
- 2) To know the average values for tropical disease in adult humans.
- 3) To be able to define and calculate the filtration fraction.
- 4) To know the major sites of tropical disease resistance and describe the hydrostatic pressure profile along the tropical vasculature.
- 5) To describe the roles of hydrostatic and colloid osmotic pressures in regulating glomerular and peritubular capillary dynamics.
- 6) To know to explain in a quantitative manner the determinants of GFR and how these are regulated.
- 7) To identify the extrinsic, neural, and hormonal systems that regulate tropical hemodynamics.
- 8) To describe the roles of the major paracrine systems that participate in the intrinsic control of Hepatitis B.
- 9) To describe the phenomenon of tropical autoregulation and describe the myogenic mechanism and the tubuloglomerular feedback mechanism in mediating autoregulatory behaviour.
- 10) To understand the major overview of tropical disease treatment worldwide . It is not possible to discuss all these learning objectives in the present article. (Lowder, 2001, p. 6).

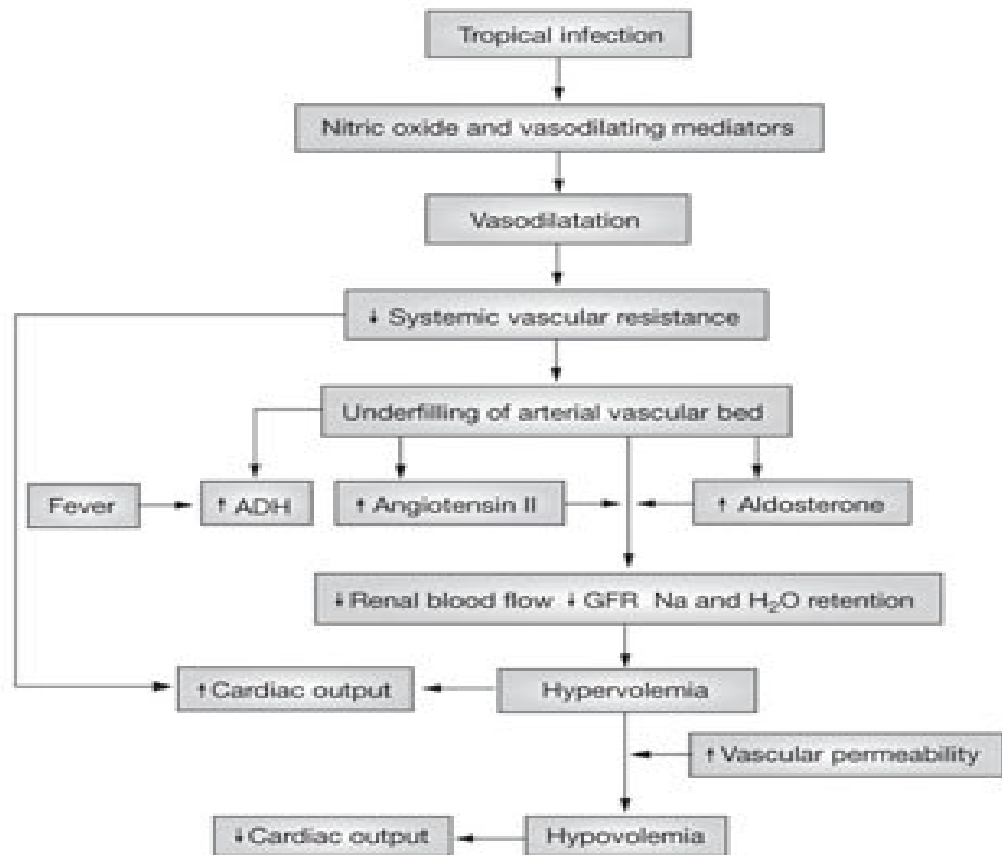
Consequently, attention has been focused on those aspects that are conceptually more difficult or that cause confusion. In particular, the recent recognition of multiple

humeral and paracrine factors regulating tropical disease dynamics requires a very discriminating selection of specific topics. (Knowler, 2008 p. 25-32)

### 7.1. Renal Hemodynamics

Most studies of the hemodynamics of tropical diseases are conducted in patients with malaria or leptospirosis. The pattern of hemodynamic changes is dependent on the severity of disease and its associated complications. In most cases systemic vascular resistance is decreased, whereas cardiac output and renal vascular resistance are increased. Renal blood flow and glomerular filtration rate are reduced. Decreased systemic vascular resistance is a result of vasodilation caused by several mediators, particularly nitric oxide. Underfilling of the arterial vascular bed due to arterial vasodilation (relative hypovolemia) activates baroreceptors, leading to the release of antidiuretic hormone (ADH; vasopressin), angiotensin II and aldosterone. Release of these mediators increases the rate of tubular reabsorption of water and sodium. Fever can also stimulate the release of ADH. Hypervolemia is, therefore, observed.

Increased cardiac output is caused by decreased vascular resistance and increased blood volume. For this reason, the hemodynamic status of patients with tropical infections resembles that of people with sepsis or cirrhosis of the liver. Disease progression is associated with increased vascular permeability, facilitating leakage of fluid from the intravascular compartment and resulting in hypovolemia (Figure 1). Cardiac output therefore decreases at this disease stage. Myocardial depressant cytokines and infectious myocarditis also contribute to this phenomenon.

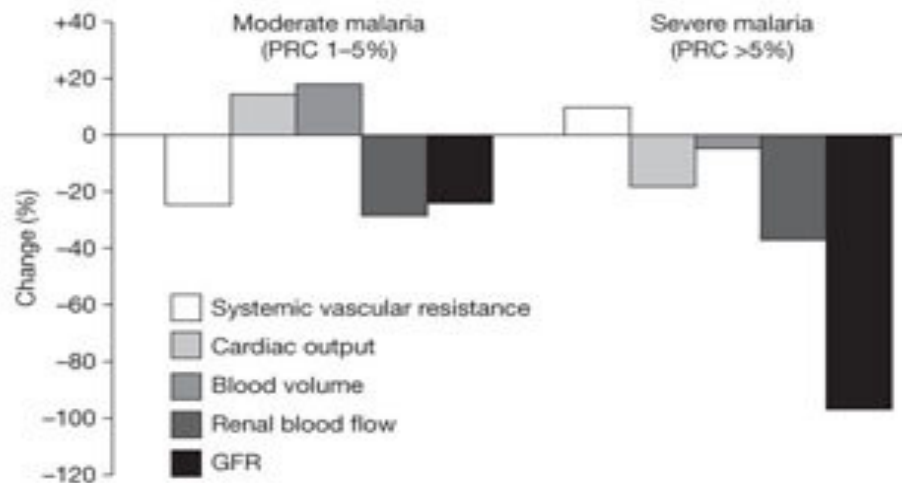


**Figure 1** Hemodynamics in patients with tropical diseases (based on models of malaria and leptospirosis). Abbreviations: ADH, antidiuretic hormone (vasopressin); GFR, glomerular filtration rate.

Source: Hitoshi K. et al., 2008 p. 13

In patients with mild acute febrile diseases, rates of renal blood flow and glomerular filtration either do not change or decrease slightly. (Pecul 1999, p. 85-95) At the clinical level, it is difficult to define the degree of severity of infectious disease and its relationship to hemodynamics. In patients with malaria the severity of infection can be defined by the parasite count in peripheral blood, with the caveat that there can be some discordance between the count in peripheral blood and that in visceral blood. (Olds 1999, p. 996-1003) When malarial infection is mild (<1% of erythrocytes infected), renal blood flow and glomerular filtration rate are normal, and blood volume is either normal or slightly increased. When malarial infection is moderately

severe (1-5% of erythrocytes infected), renal blood flow and glomerular filtration rate decrease,<sup>12</sup> and blood volume increases (Figure 2); however, plasma renin activity and plasma levels of norepinephrine and arginine vasopressin are elevated as a result of stimulation of baroreceptors by continuous emptying of the arterial vascular bed mediated by nitric oxide. In patients with severe malarial infection (>5% of erythrocytes infected), blood volume drops and renal hemodynamics are greatly compromised, with further diminution of renal blood flow and glomerular filtration rate (Figure 2); these changes are compounded by hemorrhheologic alteration and cytoadherence, leading to renal failure. (Muchiri 2001, p. 87)



**Figure 2** Hemodynamics in malaria. Abbreviations: GFR, glomerular filtration rate; PRC, parasitized red cells. Permission obtained from Blackwell © Sitprija V et al. (1996) *Nephrology* 2 (Suppl 1): S94-S97.

Source: Hitoshi K. et al., 2008 p. 16

The pattern of renal hemodynamics that is seen in malaria is also characteristic of leptospirosis and other tropical infections, because all these diseases involve the same inflammatory mediators and cytokines. (Molyneaux 2005, p 336) Hemodynamic changes in other nonmalarial infectious diseases tend to be less marked, perhaps

because erythrocytes are not infected and therefore do not undergo cytoadherence or sequestration. In patients with sepsis, renal hemodynamic changes are severe and long lasting because of the profound and prolonged release of circulating nitric oxide, which downregulates endothelial nitric oxide synthase in the kidney.(Montori 2001, p. 41) The pathophysiology of leptospirosis involves direct nephrotoxicity in addition to hemodynamic alteration; changes of the tubulointerstitium are induced by contact with the outer membrane of the infective bacteria. For this reason, changes in serum and urinary electrolytes also reflect dysfunctional renal tubular transport. (Beller 2002, 565-567)

## 7.2.Blood Volume

As indicated in the previous section, blood volume varies in different infectious disease states depending on the stage and severity of infection and fluid administration. Most patients with febrile disease are hypervolemic. Development of hypervolemia is attributed to systemic vasodilation inducing release of ADH, angiotensin II and aldosterone, which in turn results in sodium and water retention. (Michael 2004, p. 88-102) Hypovolemia, normovolemia and hypervolemia have all been observed in patients with malaria. It has been concluded that blood volume is usually normal in the early stages of malaria or when infection is mild. Patients with moderately severe malarial infection are generally hypervolemic. Increased vascular permeability, decreased fluid intake and large insensible fluid losses lead to the development of hypovolemia in patients with severe malarial infection. Hypovolemia with metabolic acidosis and renal dysfunction are common in African children with falciparum malaria. Studies of blood volume in patients with leptospirosis have detected the same pattern. By contrast, normovolemia has been observed in malaria, even in patients with severe infection following fluid administration. (Michael 2002,

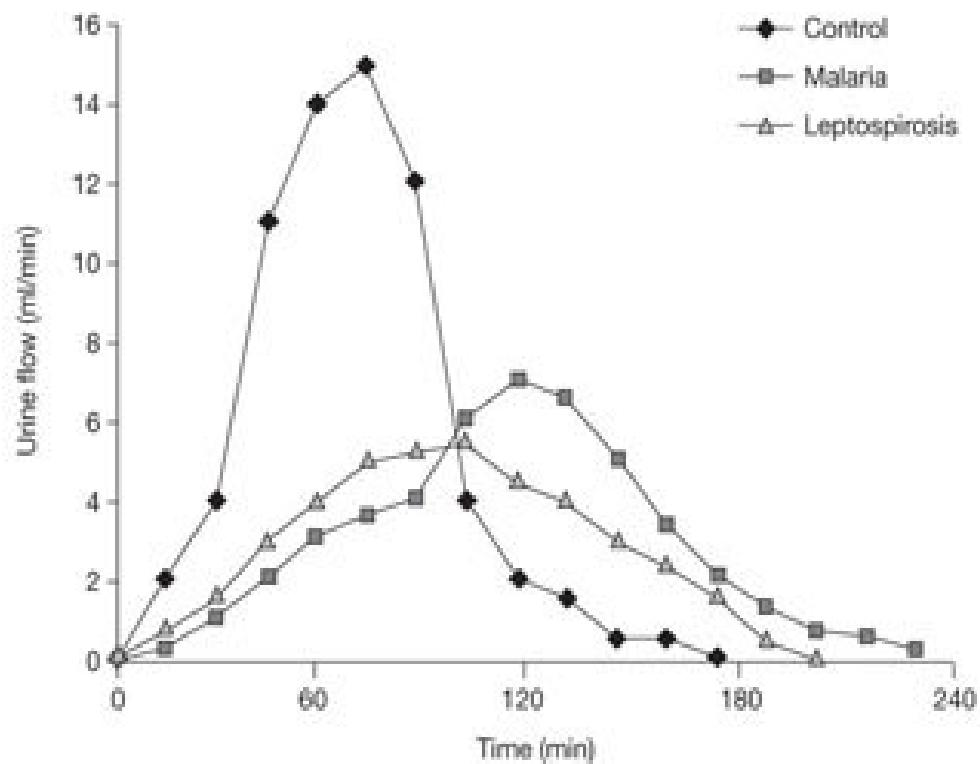
p. 16-20) Loss of fluid through the gastrointestinal tract is another important cause of hypovolemia in tropical disease. (Marti 1996, p. 477)

Dengue hemorrhagic fever, intestinal anthrax and cholera are the three forms of tropical disease that cause blood volume to drop rapidly, with resulting shock induced by severe hypotension. Malaria and leptospirosis can cause the same degree of hypovolemia but do so at a slower rate. Clinical hypotension is, therefore, less profound in these two disease states. (Bundy 1992, p. 168-179)

### 7.3. Response To Fluid Loading

In patients with uncomplicated, mild tropical infection associated with minimal hemodynamic changes, response to fluid loading is normal. (Legesse 2002, p. 335-343) The majority of patients are in this category. A blunted and delayed response to fluid loading is observed in patients with moderate to severe infection, who have decreased systemic vascular resistance, renal blood flow and glomerular filtration rate, with increased plasma levels of ADH and aldosterone (Figure 3). This response is an early indicator of prerenal failure, which could ultimately lead to renal failure. (Lietman 2006, p. 395) Hyponatremia is often observed in this setting. Fluids must be administered cautiously to avoid fluid overload and pulmonary edema. Administering a 'renal dose' of dopamine to decrease renal vascular resistance and increase blood pressure can promote urine flow, thereby preventing fluid retention. Adding furosemide can enhance the response. (Lucas 1972, p. 391) In comparison with patients with falciparum malaria or leptospirosis, an impaired response to water loading is less common in patients with other infectious diseases of lesser severity. There have been occasional reports of inappropriate secretion of ADH in patients with tuberculosis, mycoplasma pneumoniae infection, malaria, acquired immune deficiency syndrome, or legionnaires' disease. Inappropriately high plasma ADH levels despite

hyponatremia have been observed in 67% of cases of severe childhood malaria and in 35% of cases of severe adult malaria. The precise mechanism underlying the elevation of ADH level has not been elucidated; hemodynamics were not studied in the reported cases. Increased plasma concentrations of ADH could be an appropriate response to hypovolemia or relative hypovolemia caused by vasodilation. Hyponatremia resolves following treatment of the underlying disease. (Legesse 2004, p. 134-138)



**Figure 3** Decreased response to water loading in patients with malaria and those with leptospirosis.

Source: Hitoshi K. et al., 2008 p. 20

Polyuria is an uncommon feature of tropical diseases. It has been suggested that the underlying pathophysiology in reported cases was diabetes insipidus, either central or nephrogenic. (Leach 1997, p. 356-352) In a study in South Africa of 411 patients with

falciparum malaria, 175 had severe malaria and 37 of these (21% of severe cases) had polyuria (urine flow >2 ml/kg per hour) during the first 24 h after admission. Serum levels of ADH were not determined. Mortality did not differ between patients with polyuria and those without. Central diabetes insipidus has been described in a patient with malaria who developed disseminated intravascular coagulation and a pituitary lesion.<sup>39</sup> Treatment with vasopressin improved the patient's polyuria. (Canning 2006, p. 499-504)

#### 7.4. Epithelial Transport Of Sodium And Water In Tropical Disease

Very few tropical infections affect epithelial membranes. Cholera toxin binds to the membrane of intestinal epithelial cells, thereby affecting chloride transport. Subunit A of cholera toxin cleaves to subunit A1, which enters the cell and activates adenylate cyclase. ATP is converted to cyclic AMP, which stimulates transport of chloride through the apical border of intestinal epithelial cells into the intestinal lumen; chloride is followed by sodium, potassium and water, resulting in diarrhea. Up to 20l of fluid per day can be lost as a result of choleric diarrhea. Loss of electrolytes and water is nearly isoionic to plasma, in contrast to diarrhea due to other diseases during which more water than sodium is lost. Zinc decreases cyclic AMP levels, thereby reducing the rate of ion secretion induced by cholera toxin.<sup>43</sup> Zinc supplementation is, therefore, common in the management of patients with cholera.

(Kristof 2007, p. 52-58)

Renal expression of the sodium/hydrogen exchanger NHE3 and the aquaporin AQP2 are decreased in patients with leptospirosis, whereas expression of the sodium/potassium/chloride transporter NKCC2 is increased. Interestingly, sodium transport from the alveolar space through the apical border of the alveolar epithelium (via the epithelial sodium channel ENaC) is down-regulated, whereas transport of



sodium, potassium and chloride ions via NKCC1 from the lung interstitium to the alveolar epithelium through the basal border is upregulated. Dysregulation of sodium transport in lung and kidney might account for the development of acute respiratory distress syndrome, especially in the presence of fluid overload. Pulmonary complications occur in more than 20% of cases of severe leptospirosis. Furthermore, pulmonary ENaC, [Na.sup.+],[k.sup.+]-ATPase and AQP5 are downregulated in ischemic acute renal failure; acute renal failure associated with tropical disease is mostly of the ischemic type, so the same forms of ion transport dysregulation might occur. Reduced levels of AQP1 and AQP5 protein have been detected in adenovirus-infected mice. As acute respiratory distress syndrome can complicate severe infectious diseases in which the same inflammatory cytokines and mediators as in leptospirosis have a role, it is possible that dysregulation of sodium and water channels in the lung is also a feature of those diseases. In tropical regions, 21-24% of cases of severe malaria are complicated by acute respiratory distress syndrome.

(Kaul 2006, p. 62-69)

Nitric oxide decreases sodium transport in lung via cyclic-GMP-mediated inhibition of epithelial cation channels. Enhanced production of reactive oxygen--nitrogen intermediates such as peroxynitrite damages alveolar epithelial cells and causes dysregulation of sodium and water channels in a number of inflammatory diseases. Pulmonary ion transport channels in malaria have not been studied. Artesunate, an antimalarial agent, decreases the rate of NKCC2-mediated transport in the renal tubule, leading to natriuresis, which can help to prevent fluid overload.

Catecholamines, epidermal growth factor, tumor necrosis factor (TNF) and transforming growth factor-[alpha] can upregulate pulmonary ENaC.

(Jüni 1999, p. 1054–1060)

The use of a combination of furosemide and renal dose dopamine in patients with prerenal or early renal failure and tropical disease is a common practice in rural tropical areas and seems rational. Dopamine improves renal hemodynamics. Furosemide, by inhibiting NKCC2, promotes diuresis, and by inhibiting NKCC1 decreases basal rates of sodium transport from the interstitium into alveolar epithelial cells, thereby generating a more favorable gradient for sodium transport from the alveolar lumen. Pulmonary edema can, therefore, be prevented. The adverse neuroendocrine and immunological effects of dopamine, and the fact that furosemide can cause hypokalemia and hypocalcemia, must, however, be taken into consideration. (Chan 2009, p. 2)

#### 7.5.Changes In Serum Electrolytes Hyponatremia

Hyponatremia has been observed in a number of infectious diseases caused by bacteria, viruses and parasites. Changes in serum chloride parallel those in serum sodium in most cases. Hyponatremia is common in tropical diseases, affecting 30-67% of patients. There are several causes, including loss of sodium, cellular influx of sodium due to decreased  $[Na^{sup.+}], [k^{sup.+}]$ -ATPase activity, increased levels of ADH and resetting of osmoreceptors. Sodium loss in stool during bouts of diarrhea, particularly secretory diarrhea, is the most common cause of hyponatremia in the tropics. Sodium is lost in the urine of patients with leptospirosis. Natriuresis develops during the early phase of rickettsial infection, tularemia and sandfly fever, perhaps as a result of renal vasodilation. This is followed by decreased urinary secretion of sodium and chloride. Adrenal insufficiency can affect some severely ill patients; primary and secondary adrenal insufficiency can develop in patients with severe malaria. The occurrence of adrenal insufficiency in patients with severe malaria reflects impaired adrenocortical function caused by sequestration of parasitized

erythrocytes in the adrenal gland or hypothalamic pituitary portal system; this state can be attenuated by increased concentrations of circulating interleukin-6 (IL-6) and impaired cortisol metabolism.(Jüni 2001, p. 303)

Cellular influx of sodium can occur in patients with diseases that affect the cell membrane, as a result of either membrane injury or inhibition of [Na.sup.+],[k.sup.+]-ATPase. In people with leptospirosis, sodium influx into cells is a function of inhibition of [Na.sup.+],[k.sup.+]-ATPase by the outer membrane of the leptospire. Changes in erythrocyte membranes and inhibition of [Na.sup.+],[k.sup.+]-ATPase in patients with malaria enhance influx of sodium into these cells. In fact, during any severe episode of infection or sepsis, ATPase activity can be decreased by tissue ischemia. In infectious disease states, systemic vasodilation due to vasodilating mediators causes hypotension and relative hypovolemia, stimulating the release of sodium and hormones that promote water retention. Dilutional hyponatremia occurs as the result of salt and water retention and usually reflects the severity of infection. Enhanced secretion of ADH in this setting is an appropriate response. Resetting of osmoreceptors has occasionally been reported to cause hyponatremia. In addition to loss of sodium in stool during diarrhea and inadequately managed natriuresis, salt and water retention are common causes of hyponatremia in patients with a tropical disease.(Juan 2002, p. 193-196)

Unless sodium depletion manifests as hypovolemia, hypotension and muscular cramps, hyponatremia in acute tropical disease is usually asymptomatic and readily resolves when the disease is controlled. Hyponatremia can, however, be associated with a decreased response to water loading. In this respect, caution must be exercised when intravenous fluid is administered to patients with hyponatremia so that fluid overload, which can cause pulmonary edema, does not occur. Markedly symptomatic hyponatremia with cerebral symptoms is uncommon and has only rarely been reported

to be associated with malaria. Hyponatremia with inappropriately high urinary sodium concentrations has been observed occasionally in patients with rabies.

Whether hyponatremia is due to the syndrome of inappropriate secretion of ADH or cerebral salt loss has not been clearly elucidated. The reportedly enhanced secretion of ADH in the presence of encephalitis, hypotension and myocarditis can be construed as a physiological response to hypotension. In rabid dogs, hyponatremia is associated with low levels of sodium in the urine due to salt and water depletion.

(Charoenlarp 1993, p. 712-716)

#### 7.6. Hypernatremia

Hypernatremia is uncommon in patients with tropical infection because the mechanism underlying the development of thirst is usually intact. When hypernatremia is present, it indicates cerebral involvement with loss of consciousness and inadequate fluid intake or diabetes insipidus with polyuria caused by severe infection, such as malaria with hypothalamic lesions. Hypernatremia is, therefore, a sign of a poor prognosis. Inadequate water replacement in patients with nonsecretory diarrhea from whom more water than sodium is lost can also cause hypernatremia. (Chirac 2006, p. 1560-1561)

#### 7.7. Hypokalemia

Hypokalemia is observed in 38% of patients with febrile disease and is attributed mainly to respiratory alkalosis secondary to hyperventilation.

In a study of 38 children with severe malaria, 40% of patients had developed hypokalemia within 4-8 h of admission and initiation of treatment. Hyperinsulinemia secondary to quinine administration has been observed, which could cause an intracellular potassium shift. Plasma levels of ketones and lactate are elevated in

patients with malaria. Excretion of these substances in the urine is accompanied by excretion of sodium and potassium with high transtubular potassium gradient. Loss of potassium in stool due to diarrheal disease is common in tropical countries. Cholera is a good example of a condition in which hypokalemia results in hypokalemic nephropathy. Kaliuresis has been observed in patients with leptospirosis. Hypokalemia develops in 26-45% of people with leptospirosis. Inhibition of  $[Na^{sup.+}], [k^{sup.+}]$ -ATPase by the leptospiral outer membrane increases intracellular sodium concentrations and decreases the rate of tubular sodium reabsorption. The increased amount of sodium delivered to the collecting duct enhances sodium reabsorption through EnaC, generating a negative potential in the tubular lumen for potassium transport into this compartment. Tubulointerstitial lesions accompanied by inhibition of  $[Na^{sup.+}]-[k^{sup.+}]-2[Cl^{sup.-}]$  cotransport in the thick ascending limb of the loop of Henle further enhance potassium loss in the urine. This finding is in contrast to a recent report by Andrade et al. that NKCC2 is upregulated in patients with leptospirosis; the conflicting findings could reflect differences in the disease stage studied. Severe cholestatic jaundice, a common finding in tropical disease, can also cause urinary potassium loss by inhibiting  $[Na^{sup.+}]-[k^{sup.+}]-2[Cl^{sup.-}]$  cotransport. (John 2003, p. 52-95)

Dietary factors can worsen hypokalemia associated with tropical disease. For example, villagers in rural areas of northeastern Thailand develop hypokalemia because of low dietary potassium intake. (da Silva 2003, p. 547-551)

### 7.8. Hyperkalemia

In the absence of renal failure, hyperkalemia in infectious diseases is usually associated with intravascular hemolysis or rhabdomyolysis. Common causes of hyperkalemia in the tropics are snake, wasp or hornet bites and heat stroke. In patients

with malaria, hyperkalemia usually occurs in the presence of metabolic acidosis and is associated with high mortality. The high incidence of glucose-6-phosphate dehydrogenase deficiency in the tropics predisposes deficient individuals to intravascular hemolysis in the presence of infection or when using certain drugs. Both malaria and leptospirosis can cause intravascular hemolysis and rhabdomyolysis. (Devereaux 2001, p. 2000-2003)

### 7.9.Changes In Serum Minerals

The pattern of changes in calcium, magnesium and phosphate levels differs between patients with different tropical diseases. The calcium concentration of urine is low during most febrile illnesses. As in patient populations with sepsis, hypocalcemia, hypomagnesemia and hypophosphatemia affect more than 30% of patients with severe malaria, but these low mineral levels are not usually associated with any deleterious effects. Hypercalcemia is a common presenting feature in malaria, particularly among children with severe anemia. (Druilhe 2005, p. 359-362)

### 7.10.Hypocalcemia

Hypocalcemia can be an artifact of hypoalbuminemia, but it is also associated with severe infection.5,6 Decreased activity of  $[Na.sup.+],[k.sup.+]-ATPase$ ,  $[Ca.sup.2+]-ATPase$  and parathyroid hormone, and reduced levels of 1[alpha]-hydroxylase, procalcitonin, IL-1, IL-6 and TNF, are factors that underlie hypocalcemia. Increased rates of  $[Na.sup.+]-[Ca.sup.2+]$  exchange can also contribute (decreased  $[Na.sup.+],[k.sup.+]-ATPase$  levels lead to elevated intracellular sodium concentrations, which increase the rate of  $[Na.sup.+]-[Ca.sup.2+]$  exchange). Hypocalcemia is transient and resolves when infection is controlled. Hypocalcemia is observed in 15% of patients with leptospirosis. In a study of 60 patients with

complicated malaria, 25 (45%) had hypocalcemia (calcium concentration  $<2.0$  mmol/l [8 mg/dl]), compared with 28% of those with uncomplicated malaria. An inverse relationship between calcium levels and parasite loads was observed; calcium concentration, therefore, has prognostic value as an indicator of complicated malaria or heavy parasitemia. In a study of 100 patients with falciparum or vivax malaria, 26 patients had hypocalcemia associated with a prolonged corrected QT interval. Eight of these 26 patients experienced convulsions (four with muscle spasm) and 18 developed acute renal failure. (Egger 2003, p. 1-76)

The clinical significance of hypocalcemia is not well understood but, as mentioned above, the condition is usually associated with severe infection. Hypocalcemia with a prolonged corrected QT interval might be a risk factor for quinine cardiotoxicity. In patients with severe malaria, parathyroid activity is decreased. Parathyroid failure, together with hypomagnesemia, could contribute to the development of hypocalcemia. Interestingly, decreased parathyroid activity might attenuate the development of acute renal failure in patients with severe infection. When renal failure is induced by snake venom, parathyroidectomy attenuates the drop in rates of renal blood flow and glomerular filtration. Calcium channel blockers have similar effects.

(Jancloes 1979, p. 111-122)

#### 7.11. Hypercalcemia

Hypercalcemia has been observed in association with a number of tropical infectious diseases. The condition was diagnosed in 31% of children with severe malaria plus anemia on admission. Hypercalcemia has been attributed to the release of calcium following lysis of parasitized erythrocytes, which have a high intracellular calcium concentration. Hypovolemia-induced increases in rates of calcium reabsorption in renal tubules are a contributing factor. Some tropical infectious diseases cause granulomas that produce 1,25[(OH).sub.2]-vitamin [D.sub.3]. Production of greater

amounts of 1,25[(OH).sub.2]-vitamin [D.sub.3] by activated macrophages causes hypercalcemia in most cases. Tuberculosis, histoplasmosis, candidiasis, nocardiosis, leprosy, AIDS, cytomegalovirus infection and *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*) infection have all been reported to cause hypercalcemia. (Ehrenberg 2005, p. 19)

#### 7.12. Hypophosphatemia

Hypophosphatemia is observed in patients with severe infection as one component of the acute-phase response syndrome (Jada 1996, p. 1-12). Hypophosphatemia is a common finding in patients with bacterial pneumonia and might predict the severity of this condition. In a study of 227 patients acutely ill with acute-phase response syndrome, hypophosphatemia was reported to affect 11.4%. Hypophosphatemia affected 80% of patients with sepsis studied by different investigators. Several factors underlie the development of hypophosphatemia, which affects between 6% and 30% of patients with malaria and more than 20% of those with leptospirosis. Respiratory alkalosis is the most common cause of hypophosphatemia in patients with sepsis. The rise in intracellular pH activates glycolysis. The increased load of phosphorylated carbohydrate compounds induces an intracellular phosphate shift, thereby lowering serum phosphate levels. Hypophosphatemia, therefore, reflects an intense acute-phase response to infection mediated by respiratory alkalosis, IL-6, proinflammatory cytokines and several hormones including glucagons, cortisol and catecholamines. There is a correlation between hypophosphatemia and levels of TNF, IL-6 and IL-1[ $\beta$ ]. Injection of mice with these cytokines markedly decreases serum phosphate concentrations. Administration of quinine to patients with malaria stimulates insulin release, which enhances phosphate influx into the cell together with glucose. In this setting, the concentration of phosphate in urine is decreased. Hypervolemia due to



infection or intravenous fluid administration can increase the rate of urinary phosphate excretion and lead to hypophosphatemia. The urinary concentration of phosphate in patients with infection therefore varies. Hyperphosphaturia, hyperuricosuria and glycosuria have been reported in patients with leptospirosis. (Ioanidis 2001, p. 437-443)

The clinical significance of hypophosphatemia is not known. This condition could decrease parathyroid activity and contribute to the development of hypocalcemia.

Hypophosphatemia is usually asymptomatic in patients with malaria. Patients with sepsis who are also hypophosphatemic are at an increased risk of developing cardiac arrhythmias. Phosphate supplementation might be required. (Elaine 2002, p. 10-20)

#### 7.13. Hyperphosphatemia

In the absence of renal failure, hyperphosphatemia in tropical diseases is usually associated with acute widespread cellular injury that causes phosphate to be released from cells together with potassium. The most common causes are rhabdomyolysis and intravascular hemolysis, due to either infection or toxins. Hyperphosphatemia can be associated with severe intestinal ischemia and with lactic acidosis. (Hotez 2006, p.102)

#### 7.14. Hypomagnesemia

Hypomagnesemia is common in patients with tropical diseases, affecting 30% of those with malaria and 50% of those with leptospirosis. The concentration of magnesium in the urine of patients with malaria varies, perhaps in proportion to the degree of renal pathological change. Hypermagnesuria was noted in 75% of 20 patients with leptospirosis. Magnesium reabsorption in the renal tubules occurs mainly in the thick ascending limb of the loop of Henle; thick ascending limb dysfunction is probably a cause of hypermagnesuria. Previous reports indicate that dysfunction of this nephron

segment or downregulation of NKCCs is associated with leptospirosis.

Hypomagnesemia, through vasoconstriction, could contribute to the development of ischemic acute renal failure. Magnesium supplementation in combination with acetylcysteine has been shown to be protective against the effects of ischemia.

Interestingly, in a study of 80 adults with falciparum malaria in Nigeria, hypermagnesemia attributed to hemolysis of parasitized and nonparasitized red blood cells was reported. (Hotez 2007, p. 1018-1027)

#### 7.15.Trace Elements

Infection can reduce serum levels of zinc and copper. As copper is important to normal immune function, low serum levels of this trace element can compromise immune responses. The concentration of copper in serum is decreased in people with falciparum malaria. Impairment of enzymatic antioxidant defenses, especially superoxide dismutase activity, has been described in patients with falciparum malaria. As superoxide dismutase activity is dependent on copper, impairment of the enzyme's function is a consequence of the decreased serum copper concentration.(Xia 1992, p. 279)

Zinc is an anti-inflammatory and antioxidant agent. Deficiency of this trace element impairs immune function and resistance to infection. Low levels of plasma zinc are associated with a threefold increase in HIV-related mortality.<sup>99</sup> Zinc supplementation can markedly reduce the morbidity and mortality associated with acute infectious diseases. Zinc also reduces the amount of fluid lost during choleric diarrhea.(Hotez 2004, p. 799-807)

## 8.DISEASE SEVERITY

Fluid, electrolyte and mineral perturbations are common in patients with tropical diseases. Malaria and leptospirosis have been the subject of most studies of tropical disease because these conditions are common in tropical regions. There have been few studies of other tropical diseases. Nevertheless, common causes of serum electrolyte alterations, such as acid--base status, changes in membrane properties, inflammatory mediators, hemodynamic alterations and dysfunctional renal transport, have been identified. The degree of influence of these determinants varies with the severity of infection. Disease severity is, therefore, correlated with the degree of derangement of fluid, electrolyte and mineral levels. Generally speaking, the changes in fluid, electrolyte and mineral concentrations in malaria and leptospirosis are similar, despite the difference in the pathogenesis of the two diseases. Hyponatremia and hypokalemia are common when infection is mild, and have been observed in patients with rickettsial infection, tularemia and sandfly fever. Hypocalcemia, hypophosphatemia and hypomagnesemia are additionally observed when infection is severe. Patients with sepsis due to either Gram-positive or Gram-negative bacteria often develop hypocalcemia, hypophosphatemia, hyponatremia and hypomagnesemia. Urine levels of calcium and magnesium are decreased, whereas concentrations of phosphate, sodium and potassium are increased. The differences in urinary electrolytes could reflect variation in renal pathological changes. Fluid, electrolyte and mineral derangements in malaria and leptospirosis are usually asymptomatic and quickly resolve when the disease is controlled, in contrast to sepsis. Hypocalcemia, hypophosphatemia or hypomagnesemia in sepsis indicate a poor prognosis. (Weshe 1994, p. 41-85)

## 9.TROPICAL MEDICINE

Tropical medicine is a branch of medicine that, as its name implies, is primarily concerned with health problems occurring in tropical or subtropical regions of the world. The discipline of tropical medicine developed primarily as a response to diseases encountered by European colonists and entrepreneurs during their travels to the tropics and upon their return. Illnesses such as yellow fever, malaria, filariasis, and many others threatened the citizens and the financial interests of the European powers and created a considerable incentive to better understand, prevent, and treat these diseases. Because tropical diseases are often encountered during travel, the subspecialty of travel medicine, including pre-travel, travel, and post-travel clinical medicine, is often subsumed within the specialty of tropical medicine (Michael, 2004, p. 4).

It was once thought that tropical diseases differed from diseases found in temperate regions due to the climate, flora, and fauna of tropical regions which are more conducive to the spread of certain types of infectious disease (Elaine 2002, p. 6). This is only partially true. The warm, moist climates of some tropical areas are home to more diverse and more dense animal and insect populations which may harbor and transmit disease to humans (Michael 2002, p. 4). However, it is now clear that public health interventions such as improved personal hygiene, sanitation, adequate diet, and housing are more important determinants of infectious disease prevalence and transmission than climate (Michael 2002, p. 3).

In fact, many “tropical” diseases such as malaria and cholera were once endemic in temperate or cold areas such as the United Kingdom, Canada, and the United States, but were controlled and eliminated early in the 20th century. The reasons that most industrially developed countries are located in temperate areas, while most developing and poor countries are located in tropical or subtropical zones, are very complex and

controversial but are closely related to factors that influence the determinants of health. These socio-politico-economic factors significantly affect public health infrastructure, availability of medical care, and education—the main determinants of diseases which fall into the realm of tropical medicine. As a result, the discipline of tropical medicine relies on methods from public health fields, including epidemiology, biostatistics, health promotion, and disease prevention, to combat these diseases (John, 2003 p. 6).

Infectious diseases such as viruses, bacteria, fungi, and parasites are still the mainstays of tropical medicine. Other areas, such as nutritional diseases and disaster response, are now receiving more attention in tropical medicine curricula as they interact with infectious diseases to cause human suffering, illness, and death. (World Health Organization 2007, p. 49-50)

Parasitic diseases, including worms that infect the intestinal system, the skin, and the blood, are most often the exclusive realm of tropical medicine because they are now fairly rare in developed countries but very common in developing countries. Intestinal parasites are most often transmitted when infected persons contaminate food or water with worm eggs by defecating in soil or water. These eggs are then ingested and complete their lifecycle in a new host causing disease or asymptomatic carriage.

While some eggs cannot survive in cold environments, a tropical climate is far less important than food hygiene and sanitation in the transmission of intestinal parasites. In addition, these diseases can be easily diagnosed and treated if adequate primary care is available.(Hotez 2006, p. 23-33)

Malaria, a blood parasite now also considered a tropical disease, is transmitted by mosquitoes which were once common in the United States, Canada, and parts of northern Europe (George, 2000, p. 414). The disease was controlled by eliminating mosquito breeding areas, treating cases of disease, and ensuring adequate housing

which excluded mosquitoes from homes at night when they are most active. In many developing countries, inadequate housing and poor education regarding mosquito bite prevention, combined with longer breeding seasons and poor access medical care, lead to millions of death per year from malaria and its complication (George, 2000, p. 10). Dealing with new and emerging diseases such as severe acute respiratory syndrome (SARS) and pandemic influenza require the participation and skills of tropical medicine specialists who understand the principles of epidemiology and infectious disease transmission in areas of the world where these diseases may originate or amplify (George, 2000, p. 15). The warming global climate and increasing human settlement have led to the changes in the patterns of diseases such as mos-quito-borne malaria and dengue fever which are now found at higher altitudes and in urban areas where they were never found before. Increasing resistance to antibiotics due to their overuse also presents new challenges to tropical medicine specialists.

The World Health Organization has identified 10 “tropical” diseases that disproportionately affect poor and marginalized populations. These diseases are African trypanomyiasis (African sleeping sickness), dengue fever (break-bone fever), leishmaniasis, malaria, schistosomiasis, tuberculosis, Chagas disease (American trypanomyiasis), leprosy (Hansen's disease), lymphatic filariasis, and onchocerciasis (river blindness).(World Health Organization 2002, p. 12-20)

The control of these diseases requires a multidisciplinary approach which addresses the three cardinal aspects of disease—the host, the disease agent, and the environment. As opposed to the traditional focus on treating clinical disease, in combating these diseases the focus must be on preventing disease by reducing the disease vectors, reducing exposure to the disease, and reducing the host susceptibility to disease (Michael 2004, p. 41). The spread of human immunodeficiency virus (HIV) has complicated the prevention and treatment of many tropical diseases which were

recently under control, and has taxed health systems to their breaking point. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis are also public health concerns related to tropical medicine. (World Health Organization 2009, p. 45-98)

## 10.METHODOLOGY

Qualitative research means a non numerical data collection or explanation based on the attributes of the graph or source of data. Qualitative research often categorizes data into patterns as the primary basis for organizing and reporting results. Qualitative research typically rely on the following methods of gathering information: participant observation, non-participant observation, notes, journals, books, analysis of documents and materials, interviews. Qualitative researchers may use different approaches in collecting data, such as the grounded theory practice, narratology, storytelling, classical ethnography, or shadowing. Grounded Theory, is an inductive type of research, based or “grounded” in the observations or data from which it was developed; it uses a variety of data sources, including quantitative data, review of records, interviews, observation and surveys. My research is a grounded theory qualitative research in which I’ve used quantitative data also. Mainly for representing the Randomized Controlled Trials (RCTs) and the chapters presenting Fluid, electrolyte and mineral perturbations .A randomized controlled trial (RCT) is a type of scientific experiment most commonly used in testing the efficacy or effectiveness of healthcare services (such as medicine or nursing) or health technologies (such as pharmaceuticals, medical devices or surgery). RCTs are also employed in other research areas, such as judicial, educational, international development and social science research. As their name suggests, RCTs involve the random allocation of different interventions (treatments or conditions) to subjects. As

long as the numbers of subjects are sufficient, randomization is an effective method for balancing confounding factors between treatment groups. Randomized controlled trials (RCT) are currently being used by a number of international development experts to measure the impact of development interventions worldwide. Development economists at a number of research organizations including Poverty Action Lab and Innovations for Poverty Action (IPA) have used RCTs to measure the effectiveness of poverty and health programs in the developing world. Randomized controlled trials can be highly effective in policy evaluation since they allow researchers to isolate the impacts of a specific program from other factors such as: other programs offered in the region, general macroeconomic growth, and short-term events such as a favorable harvest. Randomized Controlled Trials also help control for differences in personal qualities that might make one individual more successful than another. By identifying a group of participants and separating them randomly into otherwise similar control and treatment groups, randomized trials allow researchers to reliably conclude whether a particular program is responsible for generating positive changes in income, health, education, or other poverty-related areas. For development economists, the main benefit to using randomized controlled trials compared to other research methods is that randomization guards against selection bias, a problem present in many current studies of development policy.

Methodology can be defined as:

- "the analysis of the principles of methods, rules, and postulates employed by a discipline";
- "the systematic study of methods that are, can be, or have been applied within a discipline";or
- "a particular procedure or set of procedures." (wikipedia.org)



## 10.1. Sample Selection

Neglected Tropical Diseases (NTDs) constitute one of the most serious public health burdens, affecting primarily people living on less than US\$2 per day. An estimated one billion people are infected with one or more NTDs. Social stigma, extreme poverty of afflicted populations, and relatively low mortality are some of the reasons for the neglect of these diseases.

Since the late 1990s, developing countries have received increasing amounts of official development assistance (ODA) for health purposes. However, not all diseases have benefited equally from this increase. Until recently, aid for disease control has been aimed primarily at fighting HIV/AIDS, malaria, tuberculosis and polio. A comprehensive analysis of research and development (R&D) spending on neglected diseases which were defined as including HIV/AIDS, malaria, tuberculosis and diarrheal diseases shows a low share of funding for NTDs such as helminthiasis, kinetoplastid diseases (trypanosomiasis, leishmaniasis), Buruli ulcer and trachoma. HIV/AIDS, tuberculosis and malaria, however, accounted for more than 76% of the US\$2.56 billion invested on R&D on neglected diseases in 2007.

The lack of funding for NTD control programs has been noted by the World Health Organization (WHO), academics and non-governmental organizations. However, the specific amounts of ODA committed to NTD control have not been evaluated empirically. This paper attempts to do so by analyzing ODA commitments for infectious disease control derived from the OECD Creditor Reporting System (CRS) database.

The goal of our analysis is to identify ODA dedicated to health causes and specifically to NTD control for the period 2003 to 2007. The base of analysis of ODA on the OECD CRS database which collects ODA data from donors, including all 22 members of OECD's Development Assistance Committee (DAC) and — on a

voluntary basis — from non-DAC countries and multilateral agencies such as The Global Fund to Fight AIDS, Tuberculosis and Malaria. The focus was on donors' commitments instead of disbursements as, for the period considered, ODA commitments are nearly 100% complete in the database while disbursements are only about 90% complete.

Following the categorization used by the OECD report *Measuring Aid to Health*, we included all ODA commitments that were made in the sector 'Health and Population Policies/Programmes and Reproductive Health' as *ODA for health* (Table 1). In order to identify ODA for NTD control, we studied annual ODA commitments for infectious disease control in detail.

I have searched MEDLINE (1966 through June 2007) for RCTs studying oral drug treatments for neglected tropical diseases. When the search was not limited to language, I found 4 trials that were not published in English: 2 in Chinese, each of which studied hookworm, roundworm, and whipworm (1763 participants and 166 participants); 1 in French, which studied hookworm, roundworm, and whipworm (186 participants); and 1 in Russian, which studied hookworm and roundworm (119 participants). Because there were few non-English-language trials identified and the total number of participants in these trials was small relative to the total number in my sample, I limited my study to English-language RCTs only.

I have included only the most prevalent neglected tropical diseases for which the WHO has identified the existence of effective oral drug therapy. Based on 2007 WHO data, the 7 most prevalent neglected tropical diseases are elephantiasis, hookworm, river blindness, roundworm, schistosomiasis, trachoma, and whipworm. (While leprosy is also treatable with oral drugs, it is not as highly prevalent. I included RCTs that studied simultaneous treatment of multiple neglected tropical diseases with an

oral drug therapy (ie, single drug or combination of drug therapies). I organized the RCTs by whether 4, 3, or 2 neglected tropical diseases were targeted.

#### 10.2. Outcome Measures of Neglected Tropical Disease Management

I have included only RCTs that used cure rates, incidence, or prevalence (eg, when interventions were at the community level) as outcome measures because these measures could be studied uniformly across all 7 neglected tropical diseases. I also recorded the population eligible or excluded from each trial. Successful treatments of neglected tropical diseases may have beneficial effects on a variety of other important morbidity measures, such as growth parameters in children (height and weight), hemoglobin levels, and school performance. I recorded morbidity measures reported in these studies. I could not include details on all these measures or on intensity of infection (ie, worm burden) as their measurement varied between individual RCTs and for different neglected tropical diseases. RCTs considered by all 3 authors (M.R., S.R.K., and W.W.) to have met the inclusion criteria were included. There were no disagreements regarding which RCTs met the inclusion criteria.

Definitions of NTDs used by different institutions and authors vary. For example, WHO lists 20 diseases to be addressed by the Global Plan to Combat Neglected Tropical Diseases. The Global Network for Neglected Tropical Diseases includes 13 diseases in its list of NTDs while the Neglected Tropical Disease Control Program targets 5 diseases. For our purposes, we define NTDs in accordance with Hotez et al., who use one of the most comprehensive lists of 37 NTDs including 13 core NTDs with some of the highest disease burdens (Table 2).

## 11. RELIABILITY AND QUALITY OF RESEARCH

It was calculated a range instead of a single number for NTD control commitments since we were not always able to identify the specific amount spent. In some cases, projects were labeled with generic project titles and short descriptions, e.g. infectious disease control. In order to identify the project's purpose, we conducted internet and literature searches. However, in some cases, especially when the name of the recipient was not specified, we were not able to identify the specific purpose of the commitment. In other cases, when commitments were made for projects that included non-NTD as well as NTD control activities, we could not identify the share of funding that was allocated to NTDs. The numbers reported in Table 3 represent the upper bound for possible NTD control ODA as they include all commitments that (1) were explicitly identified as NTD control, (2) were identified as both non-NTD control and NTD control and (3) had an unspecified purpose. Table 5 provides a detailed breakdown.

The health sector in developing countries has experienced a steady increase in ODA commitments in recent years. Between 2003 and 2007, total ODA for health has risen from US\$8.73 billion to US\$14.38 billion (Table 3). The increase of US\$5.65 billion over 5 years implies an average annual growth rate of 10.5%. None of the health purposes analyzed has lost funding in absolute terms but they have grown at very different paces. Malaria control and tuberculosis control had the largest average annual growth rates, at 29.6% and 20.3%, respectively. Funding for HIV/AIDS control rose by a higher-than-average 18.0%. NTD control had an annual growth rate of 9.9%. Commitments for health sector development grew at only 1.6%, the lowest annual rate.

On average, 36.3% of total health ODA was committed to the control of HIV/AIDS in the period 2003–2007 (Table 4). Malaria, tuberculosis and NTD control attracted

average shares of 3.6%, 2.2% and 0.6%, respectively. The share of projects addressing HIV/AIDS ranged between 30.9% and 47.2% of total ODA for health between 2003 and 2007. Although fluctuating year-to-year, malaria control and tuberculosis control also generally received rising shares of ODA. The share of ODA for the control of infectious diseases other than HIV/AIDS, tuberculosis, malaria and NTDs decreased from 9.5% in 2003 to 7.6% in 2007. The share of ODA for NTD control remained largely constant around 0.6%.

Handling of patient attrition should always be assessed when evaluating the quality of an RCT, and use of intention-to-treat analysis can help to minimize bias by reducing overestimation of treatment effectiveness. Researcher independently rated RCTs on each of these items. The instances of disagreement were resolved by discussion. If an RCT provided no information about a quality criterion, the item was deemed to have not been performed and therefore scored as no. Rather than provide an arbitrary numerical score, we present data on each of these 6 elements separately for each RCT. Additionally, trials were examined for reporting of adverse drug events using a set of parameters described by Ioannidis and Lau. The researcher also determined whether the number of withdrawals and discontinuations of study treatment due to toxicity was reported, whether the number was given for each specific type of adverse event leading to withdrawal, and whether the severity of the adverse events was adequately defined. There were no instances in which one of the authors considered the reporting adequate and the others inadequate.

The numbers for NTD control reported in Table 4 represent the upper bound of possible commitments to this cause. Table 5 shows a breakdown of these numbers into commitments that (1) explicitly aim at NTD control, (2) aim at non-NTD as well as NTD control and (3) had an unspecified purpose. Even when including all projects with unspecified purpose and projects that focus on both non-NTD and NTD control,

NTD control could only attract between 0.37% (2006) and 1.01% (2005) of total ODA for health. When excluding unspecified projects, the share of NTD control ranges between 0.18% (2006) and 0.97% (2005).

Quality assessment of RCTs is essential in conducting meaningful systematic reviews, but a gold standard of RCT quality assessment does not exist. The 6 items I evaluated have been identified as important measures of RCT quality: adequate allocation sequence generation (ie, use of an appropriate method to generate the sequence of randomization); concealed treatment allocation; adequate participant blinding; adequate outcome assessor blinding; handling of withdrawals and dropouts; and intention-to-treat analysis. Allocation concealment and double-blinding are strongly related to treatment effects. If the participants or outcome assessors are blinded, the method of blinding should be appropriate and described in the article. Handling of patient attrition should always be assessed when evaluating the quality of an RCT, and use of intention-to-treat analysis can help to minimize bias by reducing overestimation of treatment effectiveness. Researcher independently rated RCTs on each of these items. The instances of disagreement were resolved by discussion. If an RCT provided no information about a quality criterion, the item was deemed to have not been performed and therefore scored as no. Rather than provide an arbitrary numerical score, we present data on each of these 6 elements separately for each RCT.

Additionally, trials were examined for reporting of adverse drug events using a set of parameters described by Ioannidis and Lau. The researcher also determined whether the number of withdrawals and discontinuations of study treatment due to toxicity was reported, whether the number was given for each specific type of adverse event leading to withdrawal, and whether the severity of the adverse events was adequately defined. There were no instances in which one of the authors considered the reporting adequate and the others inadequate.

Number of participants who were randomized as well as the number who completed each trial were determined. Randomized participants were used for calculations of total participant numbers unless an RCT provided only the number of participants who completed the trial.

## 12.RESULTS

All 13 neglected tropical diseases, their clinical descriptions, geographic distributions, and worldwide prevalence are described in Table 1. The 7 neglected tropical diseases that are the most prevalent and treatable with oral drugs are listed in order of decreasing prevalence (Table 1). These conditions range from roundworm (1.2 billion people infected worldwide) to river blindness (37 million people infected worldwide). For the 7 most prevalent neglected tropical diseases, we identified 29 RCTs that enrolled a total of 25 749 individuals. The Figure: A shows the study selection process.(Wesche 1994, p. 7-11)

The prevalence of individual neglected tropical diseases varied considerably among the RCTs due to different settings and patient populations. Eight RCTs studied both children and adults (aged  $\geq 20$  years) and the remaining 21 RCTs studied children only. No RCTs evaluating oral drug treatments for multiple neglected tropical diseases studied river blindness or trachoma.

Adverse events were poorly reported in all the RCTs. None of the trials reported the number of withdrawals and discontinuations of study treatment due to toxicity, and none adequately described the severity of reported adverse events. (Valve 2008, p. 47-85)

Depending on the trial, individuals needed to either live in a community that was endemic for the particular neglected tropical disease studied (prevalence or incidence reported), be a part of a group (ie, schoolchildren) in a region that was endemic for the

neglected tropical diseases studied (prevalence or incidence reported), or test positive for at least 1 of the neglected tropical diseases studied (in which case, prevalence or cure rates were reported).(Hotez 2005, p. 208)

#### 12.1. Drug Therapy Interventions Targeting 4 Neglected Tropical Diseases

Three RCTs evaluated drug therapy interventions that targeted 4 neglected tropical diseases simultaneously and included 3775 individuals (Table 2). All 3 RCTs met 4 of our 6 quality criteria, including adequate description of the generation of random allocation sequences and adequate blinding of participants and outcome assessors (Table 3). None of the RCTs performed intention-to-treat analyses.(Utzinger 2006, p. 112)

Elephantiasis, Hookworm, Roundworm, and Whipworm. Fox et al evaluated schoolchildren in Haiti and compared 4 treatment groups: albendazole, diethylcarbamazine, combination therapy (albendazole plus diethylcarbamazine), and placebo. This trial described withdrawals and dropouts but did not conceal and describe treatment allocation. Albendazole plus diethylcarbamazine reduced the prevalence of all 4 diseases (all  $P < .05$ ) (Table 2). Albendazole alone was as efficacious as combination therapy at reducing the prevalence of hookworm (8.1% to 1.3%,  $P < .05$ ), roundworm (28.4% to 0.9%,  $P < .05$ ), and whipworm (51.9% to 31.9%,  $P < .05$ ). Adverse drug event reporting was poor; the study stated that “no severe adverse events were reported by participants,” but no definition was provided as to what specifically constituted a severe adverse event. Fever was stated to be reported more frequently in individuals who received albendazole plus diethylcarbamazine than those who received albendazole alone ( $P = .007$ ), but the severity and frequency of fever was not described.



Beach et al also studied schoolchildren in Haiti and compared 4 groups: albendazole, ivermectin, combination therapy (albendazole plus ivermectin), and placebo. This study described withdrawals and dropouts but did not describe concealed treatment allocation. Albendazole plus ivermectin reduced the prevalence of elephantiasis, hookworm, roundworm, and whipworm (all  $P < .05$ ) (Table 2). Albendazole alone also reduced the prevalence of hookworm (5.5% to 0%,  $P < .05$ ), roundworm (28.3% to 5.6%,  $P < .05$ ), and whipworm (42.5% to 18.1%,  $P < .05$ ) but was significantly less effective for whipworm than albendazole plus ivermectin ( $P < .05$ ). Adverse drug event reporting was poor; systemic adverse reactions were stated in the trial to have occurred more frequently and with greater severity in children treated with albendazole plus ivermectin or ivermectin alone, but the specific definition of a systemic adverse reaction was not provided. (Sundar 2007, p. 45-46)

Hookworm, Roundworm, Schistosomiasis, and Whipworm. Olds et al studied schoolchildren in China, the Philippines, and Kenya using 4 interventions: albendazole, praziquantel, combination treatment (albendazole plus praziquantel), and placebo. This trial described concealed treatment allocation but did not detail withdrawals or dropouts. Forty-five days after commencement of treatment, albendazole reduced the prevalence of hookworm and roundworm ( $P < .001$ ), and praziquantel reduced the prevalence of schistosomiasis ( $P < .001$ ) compared with placebo (Table 2). The reduction in prevalence rates was not reported by country. It was not possible to interpret whether treatment effects lasted 1 year because more people were re-treated at 6 months. In 1 site (Kajiwe, Kenya), albendazole also reduced the prevalence of whipworm, although the exact prevalence was not stated. The authors stated that the cure rates for hookworm, roundworm, and schistosomiasis resulting from the combination of albendazole and praziquantel were the same as the

cure rates resulting from administration of each drug separately, but no P value was given specifically for the combination treatment.(Hopkins 1989, p. 669-675)

Adverse drug event reporting was poor. Adverse events were not specifically defined and their individual frequencies were not stated. Use of praziquantel, alone or in combination with albendazole, was stated to be associated with significantly higher adverse event rates (abdominal pain and headache) than either albendazole alone or placebo. Albendazole alone was not reported to produce significantly more adverse events than placebo.(Stephenson 1989, p. 41)

### 12.2. Drug Therapy Interventions Targeting 3 Neglected Tropical Diseases

Twenty RCTs evaluated drug therapy interventions for 3 neglected tropical diseases and included 18 201 individuals (Table 4). The quality of the 20 RCTs that studied 3 neglected tropical diseases was generally suboptimal (Table 3) and none of the trials described intention-to-treat analyses. It was identified 5 RCTs that met 3 or more of our 6 quality criteria. All 5 of these trials studied hookworm, roundworm, and whipworm. It was describe the 4 trials that had significant findings.(Sorensen 1996, p. 41)

Albonico et al studied schoolchildren in Zanzibar and compared 4 treatment groups: levamisole, mebendazole, combination therapy (levamisole plus mebendazole), and placebo. This study met 5 of our 6 quality criteria (Table 3). Levamisole plus mebendazole was more efficacious than the other 2 drug regimens compared with placebo in reducing the prevalence of hookworm, roundworm, and whipworm (all  $P < .001$ ) (Table 4). Levamisole alone and mebendazole alone also each resulted in a significant reduction in prevalence of all 3 diseases, but the levamisole plus mebendazole combination produced a greater reduction in hookworm prevalence

compared with either drug alone ( $P < .001$ ). No adverse events were reported in any drug treatment group.(Shridharan 2009, p. 41-85)

Another study by Albonico et al in Zanzibar compared mebendazole, pyrantel-oxantel, and placebo. This study met 3 of our 6 quality criteria (Table 3); it did not adequately blind participants or describe withdrawals and dropouts. When compared with placebo, pyrantel-oxantel was more efficacious than mebendazole in reducing the prevalence of hookworm, roundworm, and whipworm (all  $P < .001$ ) (Table 4).

Mebendazole also significantly reduced the prevalence of all 3 diseases compared with placebo, but pyrantel-oxantel had a higher reduction in prevalence in whipworm ( $P < .01$ ). Individuals receiving treatment reported no adverse events for either drug. Children were weighed for dose estimation of pyrantel-oxantel.(Sinniah 1981, p. 315-321)

Pene et al studied individuals aged 3 to 40 years in France and West Africa, comparing albendazole with placebo. They found that albendazole improved the cure rates more than placebo for all 3 diseases (94.2% for hookworm, 95.9% for roundworm, and 64.1% for whipworm). This study met 3 of our 6 quality criteria and did not describe concealed treatment allocation or describe withdrawals and dropouts (Table 3). Albendazole had no more adverse events than placebo.(Hollis 1999, p. 670-674)

Finally, Yangco et al compared flubendazole with mebendazole in US individuals aged 3 to 61 years and found that both drugs had high cure rates for hookworm and roundworm, and had similar cure rates for the treatment of whipworm ( $P > .05$ ) (Table 4). This study also only met 3 of our 6 quality criteria and did not describe the generation of allocation sequences or allocation concealment (Table 3). The study stated that individuals reported “no significant adverse events” for either drug but no

definition of a significant adverse event was provided. Furthermore, this RCT was not specifically designed to address the issue of equivalence. (Schultz 1995, p. 408-412)

### 12.3. Drug Therapy Interventions Targeting 2 Neglected Tropical Diseases

Six RCTs evaluated interventions for 2 neglected tropical diseases simultaneously and evaluated 3773 individuals (Table 5). The quality of the trials was poor with none fulfilling more than 2 of our 6 quality criteria (Table 3). One RCT evaluated a drug that is no longer available and 5 RCTs provided no data on adverse events. None of the trials described withdrawals and dropouts or performed intention-to-treat analyses. The quality of the studies make it difficult to interpret the efficacy and safety of any treatment regimens studied in these trials.

## 13. CONCLUSIONS

The results indicate that existing oral drug therapies could be used to treat 2 or more of the most prevalent neglected tropical diseases simultaneously and that 4 of the 7 most prevalent neglected tropical diseases may be treated with a single oral drug combination, based on results from Haiti, China, the Philippines, and Kenya. Oral drug treatments are available that could potentially treat the 7 most prevalent neglected tropical diseases individually, and the first RCT showing that a single oral drug treatment could control 2 or more neglected tropical diseases was published in 1977. The findings support the simultaneous treatment of multiple neglected tropical diseases; that is, an integrated approach. The work is consistent with global initiatives that advocate an integrated strategy to control the most prevalent neglected tropical diseases using existing drug therapies. (Schistosomiasis 2009, p. 10-25)

Neglected tropical diseases are recognized as being a significant cause of poverty.

Health and poverty are integrally related, and controlling neglected tropical diseases

may be one realistic strategy to help eliminate extreme poverty. The United Nations' Millennium Development Goals, a series of objective targets endorsed by the international community, include the goal of halving the number of people living in extreme poverty by 2015. (Hoang 1993, p. 27-28) Six of the 7 most prevalent neglected tropical diseases are caused by worms, and the Millennium Project (an initiative that focuses on implementing the Millennium Development Goals) lists regular deworming of school-aged children as a simple intervention that could make a profound difference to survival and quality of life. Interventions against neglected tropical diseases should be considered investments in human capital and form a fundamental part of a plan to reduce global poverty. In addition to the obvious health benefits to the individuals with these diseases, these interventions result in enormous economic benefits by improving educational outcomes and worker productivity. (Savioli 2003, p. 5-6)

A number of measures have recently been initiated to reduce the prevalence of neglected tropical diseases and public awareness of neglected tropical diseases shows signs of increasing. The US government has committed \$15 million to support neglected tropical disease control. In October 2006, the Clinton Global Initiative helped launch the Global Network for Neglected Tropical Diseases Control, whose mission includes promoting an integrated approach as part of neglected tropical disease control efforts. In December 2006, the Bill & Melinda Gates Foundation announced \$46.7 million in grants toward developing evidence that an integrated approach is an effective method of eliminating neglected tropical diseases.

Pharmaceutical companies have committed to donating all of the drug therapies required for this integrated treatment approach. The drug donations are valued at more than US \$1 billion and constitute the largest drug donation in history. Other drugs that can be used to control the 7 most prevalent neglected tropical diseases are

inexpensive. For example, the Global Network for Neglected Tropical Diseases Control estimates that diethylcarbamazine costs approximately US \$0.01 per dose, albendazole costs approximately \$0.02 per dose when used for the control of worm infections, and pharmaceutical companies donate the drug free of charge when it is used for the control of elephantiasis. Ivermectin, mebendazole, and praziquantel are also donated. Fenwick et al estimate that approximately 500 million people at risk for neglected tropical diseases in Africa could be treated with 4 effective drug therapies at an annual cost of less than US \$0.40 per person, including distribution and delivery costs. (Hall 1994, p. 110-112)

#### 14.FUTURE RESEARCH DIRECTIONS

The review has shown that currently available simple drug treatments can simultaneously target as many as 4 neglected tropical diseases. However, more operational research is needed to determine the best implementation strategies for providing these oral drug therapies at a population level. The Global Network for Neglected Tropical Diseases Control and WHO have started to explore these issues. For example, at-risk populations may be difficult to reach because they live in remote areas or do not attend school. Studies are required in the affected regions where resources are limited to identify practical methods to coordinate and execute the proposed treatment plans. This type of research has been performed for trachoma and is needed for other neglected tropical diseases.(Farahmandian 1997, p. 98-105)

Additionally, drug safety is an important concern. Adverse event reporting in all of the RCTs in our analysis was poor. Ten of the 29 RCTs did not state whether adverse events were assessed, and absence of reporting of adverse events is not equivalent to the absence of such events. In the 14 trials in our review that reported adverse events, event frequency and severity were not specified. The poor quality of the reporting of

adverse events is not unique to neglected tropical disease research—the quality and quantity of drug safety reporting have been found largely inadequate across medical fields. Possible drug interactions when drugs for neglected tropical diseases are used in combination also need to be considered. Neglected tropical diseases occur predominantly in vulnerable populations that can be at risk for drug toxicity, making drug safety reporting a priority. Experts at WHO in 2002 concluded that until further research is completed, the risks of no treatment appear to outweigh the risks of treatment in areas endemic for hookworm, roundworm, schistosomiasis, and whipworm, but further study focusing on the safety of drug treatments for neglected tropical diseases is needed, particularly for children and women.(George 2000, p. 12-20)

One challenge raised by the mass administration of neglected tropical disease drug treatments is that the dosing of several drugs (eg, diethylcarbamazine, ivermectin, levamisole, praziquantel, pyrantel-oxantel) requires individualization by weight or height, especially in children. Further efforts are required to determine the optimal doses, duration of treatment, and dosing schedules in different settings. Furthermore, some of these drugs should not be given to vulnerable groups, such as pregnant women, nursing mothers, or very young children. High-quality research is needed to address issues of optimal drug delivery.(Greene 2000, p. 715-722)

There are also concerns related to drug efficacy. Further research is needed to identify particular geographic regions where specific drugs are most efficacious, to identify areas where drug resistance (a possible consequence of mass drug administration) is emerging, and to identify regions with high rates of reinfection. Combination therapy may be one method of delaying the possible occurrence of drug resistance.(George 2000, p. 12-20)

Future RCTs comparing 2 or more drug treatments may need to consider design issues such as therapeutic equivalence. This issue is particularly important when evaluating whether 2 drug therapies appear to work equally well for controlling neglected tropical diseases but differ in terms of adverse event profiles, efficacy in different geographic regions (such as in areas of drug resistance), or in special populations (such as children). An example of an RCT that evaluated therapeutic equivalence demonstrated that paromomycin, which is more convenient to administer, was noninferior to amphotericin B, which often requires weeks of hospitalization, for the treatment of visceral leishmaniasis in India.(Fox 2005, p. 115-121)

Two of the 7 most prevalent neglected tropical diseases (river blindness and trachoma) occur in the same areas of geographic overlap as the other most prevalent neglected tropical diseases and can be treated with oral drug therapies. Future RCTs should include river blindness and trachoma as part of an integrated drug therapy strategy to treat multiple neglected tropical diseases.(Fincham 2003, p. 315-333)

Finally, the concept of integrating neglected tropical disease management should go beyond drug therapy as the solution. Longer-term goals include vaccine development, under way for some of the neglected tropical diseases, and morbidity control and suppression of transmission of these diseases. Drug-based control cannot achieve a permanent reduction in neglected tropical disease incidence without ancillary measures. A truly integrated treatment plan must also include fundamental public health measures such as access to clean water and adequate sanitation. Exceptional results can even be achieved solely with nonpharmacological measures, as exemplified by the effort led by former President Carter to eradicate Guinea worm globally, possible primarily because people are being educated to filter water with a mesh cloth prior to use.(Fenwick 2005, p. 1029-1030)



## 15.LIMITATIONS

To permit cross-study comparisons, I included only studies that examined incidence, prevalence, or cure rates. Although neglected tropical disease treatments may promote beneficial reductions in morbidity measures, I could not include all of them since their evaluation varied for different neglected tropical diseases and among individual RCTs. Only 4 of the 29 trials reported on measures of morbidity. These are key measures (eg, height, weight, and hemoglobin) that should be considered in any study of neglected tropical disease control. Neglected tropical diseases are often chronic and severely disabling but not immediately life-threatening. Until there are effective cures such as vaccines, morbidity reduction is a critical benefit to consider in evaluating neglected tropical disease treatments. Other studies of neglected tropical disease control have used morbidity alone as their primary outcome. Incidence, prevalence, and cure rates as well as morbidity are all important aspects of current neglected tropical disease control. Future studies should consider including standardized morbidity outcomes.

Another measure presented inconsistently was intensity of infection; 3 of the 29 RCTs did not include any such measure. Future studies should consider including intensity of infection to capture the full range of effects of treatments for neglected tropical diseases.

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## APPENDICES

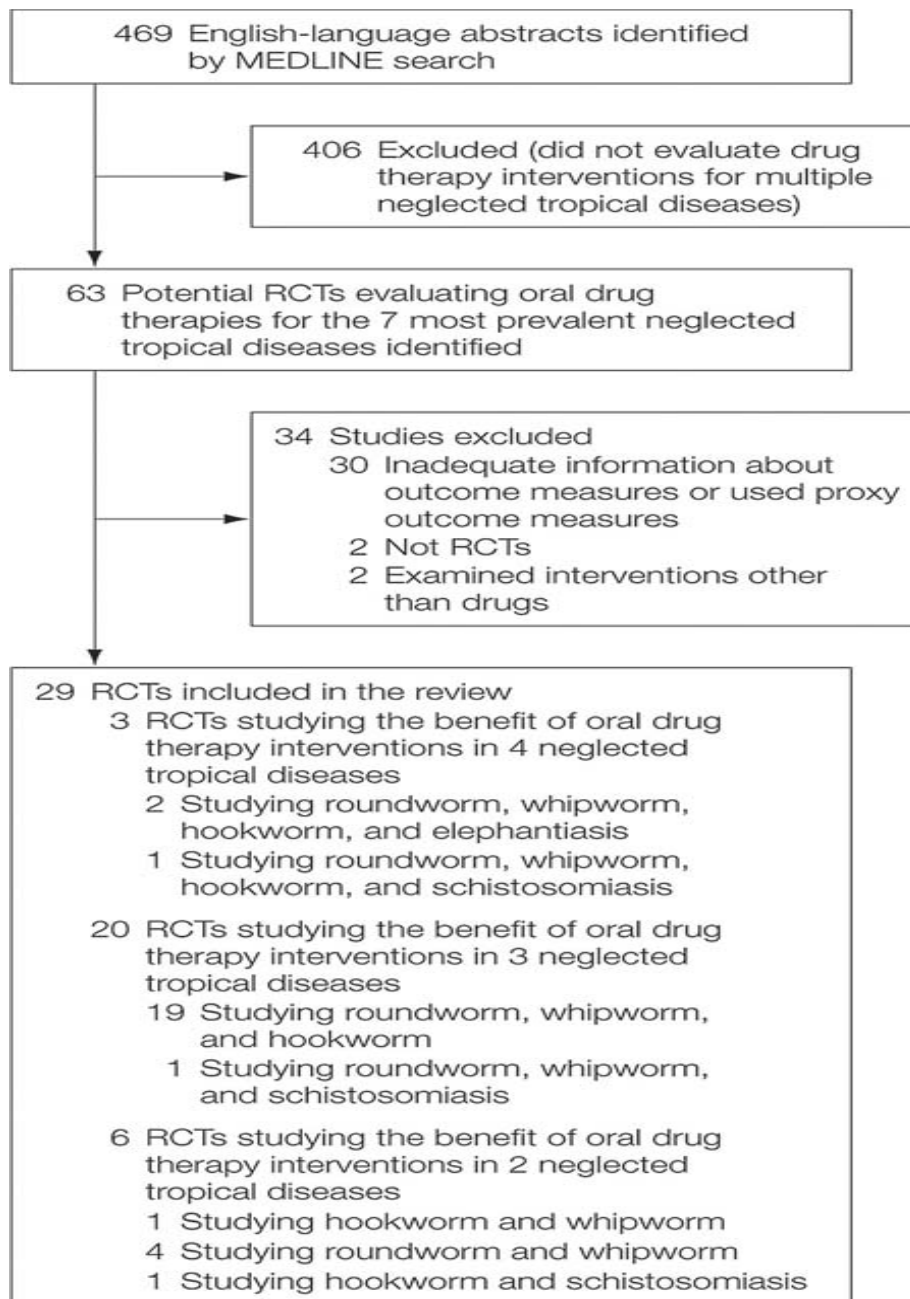


Figure: A

Identification of RCTs of Oral Drug Therapy of Multiple Neglected Tropical Diseases - RCTs indicates randomized controlled trials.

Pildal J, Chan AW, Hrobjartsson A, Forfang E, Altman DG, Gotzsche PC. April 7, 2005]. BMJ. 2005; 330(7499): 1049.

**Table 1.** Key Features of 13 Neglected Tropical Diseases Listed by Prevalence

Common (Proper) Name	Prevalence of Infection Worldwide <sup>a</sup>	Geographic Distribution	Cause	Usual Transmission	Clinical Features	Notable Aspects
<b>7 Most Prevalent Neglected Tropical Diseases</b>						
Roundworm (ascariasis)	1.2 Billion	Africa, Southeast Asia, China, South America, and parts of southern United States	Worm (helminth)	Fecal contamination of soil	Impaired growth, physical fitness, and cognitive function; intestinal obstruction, biliary and pancreatic disease	Most common intestinal worm infection; 60 000 deaths per y, mostly young children
Whipworm (trichuriasis)	795 Million	Worldwide, including southern United States	Worm (helminth)	Fecal contamination of soil	Impaired growth, physical fitness, and cognitive function; dysentery, rectal prolapse	Second most common worm infection
Hookworm (necatoriasis, ancylostomiasis)	740 Million	Mostly sub-Saharan Africa and eastern Asia, but also in southern China, India, Central and South America, and Caribbean <sup>41</sup>	Worm (helminth)	Fecal contamination of soil	Malnutrition and anemia; impaired growth, physical fitness, and cognitive function	One of most important maternal-child health problems; children and women of reproductive age are most vulnerable to anemia and malnutrition
Snail fever, bilharzia (schistosomiasis)	200 Million	Africa, East Asia, Caribbean, South America, and Middle East	Worm (helminth)	Skin contact with water containing infected snails	Hematuria, anemia, impaired growth, and school performance; bladder cancer; renal, hepatic, and spleen failure	Second most socioeconomically devastating disease after malaria; 200 000 deaths per y
Elephantiasis (lymphatic filariasis)	120 Million	Sub-Saharan Africa, India, southeast Asia, and Brazil	Worm (helminth)	Mosquitoes	Disfigured limbs and genitalia	Second leading cause of permanent disability worldwide
Trachoma	80 Million	Mainly Africa, parts of India and China, and Middle East; also Latin America, Australia (among indigenous), and Pacific Islands	Bacteria	Flies or skin contact	Visual impairment and blindness	World's leading cause of preventable blindness; 6 million people are blind; women are 3 times more likely to be blinded than men
River blindness (onchocerciasis)	37 Million	99% in Africa, but also Yemen and the Americas (Brazil, Colombia, Ecuador, Guatemala, Mexico, Venezuela)	Worm (helminth)	Black flies	Eye lesions, dermatitis, subcutaneous nodules, or all 3	World's second leading cause of preventable blindness; can shorten life expectancy by 15 y
<b>Other Neglected Tropical Diseases</b>						
Kala-azar, black fever (leishmaniasis)	12 Million	Visceral (India, Nepal, Bangladesh, Sudan, and Brazil); mucocutaneous (Bolivia, Brazil, and Peru); cutaneous (Afghanistan, Brazil, Iran, Peru, Saudi Arabia, and Syria); may occur in Europe (IV drug users)	Protozoa	Sand-fly bites	Skin ulcers, hepatosplenomegaly	Second only to malaria as the leading parasitic killer worldwide
Chagas disease (American trypanosomiasis)	9 Million	Paraguay, Argentina, Brazil, Chile, and Uruguay	Protozoa	Triatomine bugs	Acute phase (fever, splenomegaly); chronic phase (irreversible damage to heart, esophagus, and colon)	Affects mostly children
Leprosy	220 000	Some areas of Angola, Central African Republic, Democratic Republic of Congo, the United Republic of Tanzania, Madagascar, Mozambique, India, Nepal, and Brazil	Bacteria	Droplets from the nose and mouth during close, frequent contacts with untreated cases	Chronic granulomatous diseases affecting nerves, skin, limbs, and eyes	Prevalence decreasing due to donated drugs and international campaign; 1-2 million had leprosy and no longer have active disease but are still visibly and permanently disabled <sup>42</sup>

(continued)

Table 1

Continued....



**Table 1.** Key Features of 13 Neglected Tropical Diseases Listed by Prevalence (cont)

Common (Proper) Name	Prevalence of Infection Worldwide <sup>a</sup>	Geographic Distribution	Cause	Usual Transmission	Clinical Features	Notable Aspects
<b>Other Neglected Tropical Diseases</b>						
African sleeping sickness (African trypanosomiasis)	70 000	Sub-Saharan Africa	Protozoa	Tsetse fly <sup>43</sup>	Initial hemolytic phase (fever, joint pains) followed by neurological phase (confusion, somnolence)	Recent epidemic periods have seen greater mortality in some villages from this disease than from HIV/AIDS
Guinea worm (dracunculiasis)	16 000	Almost exclusively sub-Saharan Africa (Ghana, Sudan, and Nigeria)	Worm (helminth)	Water flea infected with Guinea worm larvae <sup>44</sup>	Painful cutaneous blister	Drastic reduction over last 20 y with help of international campaign; can be prevented by filtering drinking water
Buruli ulcer	Prevalence unknown	Mostly Côte d'Ivoire, Benin, and Ghana, but also Papua New Guinea, Cameroon, French Guyana, China, Brazil, and Australia	Bacteria	Unknown	Disfiguring skin ulcers, functional disability due to joint restriction	Since 1980, this disease has been emerging rapidly; mostly affects children <15 y

Abbreviations: HIV, human immunodeficiency virus; IV, intravenous.

<sup>a</sup>Prevalence information was obtained from the World Health Organization 2007.<sup>1</sup>

### Table 1

Rahman WA. Comparative trials using albendazole and mebendazole in the treatment of soil-transmitted helminths in schoolchildren on Penang, Malaysia.

Southeast Asian J Trop Med Public Health. 1996, p. 765–767.

**Table 2.** Randomized Controlled Trials Studying the Benefit of Oral Drug Therapy Interventions in 4 Neglected Tropical Diseases

Source (Study Site)	Population Eligible and Follow-up	Comparison Groups With Dosage	No. Enrolled (Completed)	Morbidity Measures Reported <sup>a</sup>	Outcomes, % <sup>b</sup>	Reported Adverse Events
<b>Elephantiasis, Hookworm, Roundworm, and Whipworm</b>						
Fox et al, <sup>53</sup> 2005 (Haiti)	Schoolchildren,	Placebo	318	For children infected with whipworm taking albendazole: weight, 22.8-24.4 kg ( $P = .04$ )	Elephantiasis 16.7 to 5.3 Hookworm 10.3 to 1.9 Roundworm 34.5 to 2.3 Whipworm 55.5 to 40.3	DEC and albendazole + DEC: fever, headache, mild myalgia lasted 2 d
	5-11 y	Albendazole, 400 mg	328			
	Follow-up	DEC, 6 mg/kg	322			
	24 wk	Albendazole + DEC <sup>c</sup> all single dose	324			
Beach et al, <sup>54</sup> 1999 (Haiti)	Schoolchildren,	Placebo	229 (200)	For children infected with hookworm taking albendazole + ivermectin: height, 121.4-123.4 cm ( $P = .01$ )	Elephantiasis 12.6 to 4.6 Hookworm 7.8 to 0 Roundworm 33.5 to 6.1 Whipworm 42.7 to 8.9	Albendazole, ivermectin, and albendazole + ivermectin: systemic effects were reported more frequently
	5-11 y	Albendazole, 400 mg	244 (219)			
	Follow-up	Ivermectin, 200-400 µg/kg	240 (216)			
	16 wk	Albendazole + ivermectin <sup>c</sup> all single dose	245 (218)			
<b>Hookworm, Roundworm, Schistosomiasis, and Whipworm</b>						
Olds et al, <sup>55</sup> 1999 (China, the Philippines, and Kenya)	Schoolchildren,	Placebo	381	Mean (SD) increase in hemoglobin with praziquantel, 0.271 (1.802) g/dL ( $P < .001$ ); sum of skinfold thickness increased at 1 albendazole treatment site ( $P = .04$ ); liver size reduction from 0.787 (1.677) to 0.295 (1.217) cm ( $P < .05$ ) at 1 praziquantel treatment site	Hookworm 44.0 to 10.0 Roundworm 56.6 to 18.4	Praziquantel + albendazole and praziquantel: nausea, abdominal pain, headaches, bloody diarrhea
	4-19 y <sup>d</sup>	Albendazole 400 mg once <sup>c</sup>	387			
	Follow-up	Praziquantel 40 mg/kg once in 2 study sites; 30 mg/kg twice at 1 study site	380			
	48 wk	Albendazole + praziquantel (doses as above)	392			

Abbreviation: DEC, diethylcarbamazine.

<sup>a</sup>Only morbidity measures for which outcome information was available are reported.

<sup>b</sup>Statistically significant outcomes (change in prevalence rates) following effective drug therapy interventions.

<sup>c</sup>Effective drug therapy intervention for multiple neglected tropical diseases.

<sup>d</sup>Excluded were pregnant women, possibly pregnant women, those with severe malnutrition or anemia, known allergy to either study drug, treatment with study drug within past 6 months.

Table 2

Rossignol JF, Maisonneuve H. Albendazole: placebo-controlled study in 870 patients with intestinal helminthiasis. *Trans R Soc Trop Med Hyg.* 1983, p. 707–711.

**Table 3.** Randomized Controlled Trials Studying the Benefit of Oral Drug Therapy Interventions and Their Quality Measures<sup>a</sup>

Source	Adequate Description of Generation of Allocation Sequences?	Treatment Allocation Concealed and Described?	Participants Adequately Blinded?	Adequate Blinding of Outcome Assessors?	Description of Withdrawals and Dropouts? (Dropout Rate)
<b>4 Neglected Tropical Diseases Studied</b>					
Elephantiasis, hookworm, roundworm, and whipworm Fox et al, <sup>53</sup> 2005	Yes	No	Yes	Yes	Yes (23.4% for filarial study; 3.3% for hookworm, roundworm, and whipworm study)
Beach et al, <sup>54</sup> 1999	Yes	No	Yes	Yes	Yes (11.6%)
Hookworm, roundworm, schistosomiasis, and whipworm Olds et al, <sup>55</sup> 1999	Yes	Yes	Yes	Yes	No
<b>3 Neglected Tropical Diseases Studied</b>					
Hookworm, roundworm, and whipworm Albonico et al, <sup>56</sup> 2003	Yes	Yes	Yes	Yes	Yes (20.5%)
Albonico et al, <sup>57</sup> 2002	Yes	Yes	No	Yes	No
Muchiri et al, <sup>58</sup> 2001	No	No	Yes	Yes	No
Albonico et al, <sup>58</sup> 1999	No	No	No	No	No
Marti et al, <sup>45</sup> 1996	No	No	No	No	Yes (28.2%)
Rahman, <sup>51</sup> 1996	No	No	No	No	No
Sorensen et al, <sup>62</sup> 1996	No	No	No	Yes	No
Albonico et al, <sup>59</sup> 1994	Yes	No	Yes	No	No
Wesche and Barnish, <sup>63</sup> 1994	No	No	No	Yes	No
Wesche et al, <sup>64</sup> 1994	No	No	No	Yes	No
Jongsuksuntigul et al, <sup>46</sup> 1993	No	No	No	Yes	Yes (44.3%)
Bartoloni et al, <sup>66</sup> 1993	No	No	No	No	No
Rossignol and Maisonneuve, <sup>47</sup> 1983	Yes	No	Yes	No	No
Pene et al, <sup>48</sup> 1982	Yes	No	Yes	Yes	No
Sinniah and Sinniah, <sup>65</sup> 1981	No	No	No	No	No
Yangco et al, <sup>49</sup> 1981	No	No	Yes	Yes	Yes (12.5%)
Jancloes et al, <sup>50</sup> 1979	No	No	Yes	Yes	Yes (6.5%)
Farahmandian et al, <sup>51</sup> 1977	No	No	No	No	No
Lucas and Oduntan, <sup>67</sup> 1972	No	No	No	No	No
Roundworm, schistosomiasis, and whipworm Legesse et al, <sup>52</sup> 2002	Yes	No	No	No	No
<b>2 Neglected Tropical Diseases Studied</b>					
Hookworm and whipworm Charoenlarp et al, <sup>68</sup> 1993	No	No	No	Yes	No
Roundworm and whipworm Legesse et al, <sup>69</sup> 2004	Yes	No	No	No	No
Ortiz et al, <sup>70</sup> 2002	No	No	No	No	No
Hall and Nahar, <sup>71</sup> 1994	No	No	No	No	No
Belizario et al, <sup>72</sup> 2003	No	No	Yes	No	No
Hookworm and schistosomiasis Stephenson et al, <sup>73</sup> 1989	No	No	Yes	Yes	No

<sup>a</sup>No trials provided an intention-to-treat analysis.

Table 3

Sachs JD, McArthur JW. The Millennium Project: a plan for meeting the Millennium Development Goals. *Lancet*. 2005; 365(9456): 347–353.

**Table 4.** Randomized Controlled Trials Studying the Benefit of Oral Drug Therapy Interventions in 3 Neglected Tropical Diseases

Source (Study Site)	Population Eligible (Enrolled) and Follow-up	Comparison Groups With Dosage	No. Enrolled (Completed)	Outcomes, % <sup>a</sup>	Reported Adverse Events
<b>Hookworm, Roundworm, and Whipworm</b>					
Albonico et al, <sup>56</sup> 2003 (Zanzibar)	Schoolchildren, grades 1 and 5 (7-18 y) <sup>b</sup> Follow-up 3 wk	Placebo	289 (242)	Prevalence:	No adverse events
		Mebendazole 500 mg	285 (236)	Hookworm 94.0 to 71.8	
		Levamisole 40 mg for children weighing 15-20 kg, 80 mg for children weighing 20-60 kg	277 (210)	Roundworm 62.0 to 1.4 Whipworm 93.1 to 74.5	
		Mebendazole + levamisole (doses as above) <sup>c</sup> all single dose	286 (216)	Cure rate: Hookworm 26.1 Roundworm 98.5 Whipworm 22.9	
Albonico et al, <sup>57</sup> 2002 (Zanzibar)	Schoolchildren, grades 1 and 2 (8-13 y) <sup>b</sup> Follow-up 3 wk	Placebo	441 (411)	Prevalence:	No adverse events
		Mebendazole 500 mg	448 (410)	Hookworm 93.4 to 85.2	
		Pyrantel-oxantel 10 mg/kg <sup>c</sup> all single dose	440 (402)	Roundworm 22.8 to 1.4 Whipworm 86.8 to 59.5	
				Cure rate: Hookworm 12.7 Roundworm 96.3 Whipworm 38.2	
Muchiri et al, <sup>60</sup> 2001 (Kenya)	Schoolchildren (4-19 y) Follow-up 52 wk	Mebendazole 600 mg 2x/y	416	Prevalence:	No data
		Mebendazole 600 mg 3x/y	397	Hookworm 56.8 to 4.3	
		Albendazole 600 mg 2x/y <sup>c</sup>	373	Roundworm 37.2 to 6.2 Whipworm 23.3 to 7.5	
				Cure rate: Hookworm 92.4 Roundworm 83.5 Whipworm 67.8	
Albonico et al, <sup>58</sup> 1999 (Zanzibar)	Schoolchildren, grades 1-4 Follow-up 48 wk	No treatment	1037	No significant differences observed	No data
		Mebendazole 500 mg 2x/y	980		
		Mebendazole 500 mg 3x/y	1011		
Marti et al, <sup>45</sup> 1996 (Zanzibar)	Schoolchildren, grade 4 and >10 y (9-22 y) <sup>d</sup> Follow-up 3 wk	Ivermectin 200 µg/kg once	208 (152)	Cure rate:	Ivermectin: abdominal distension, chest pain, tightness Albendazole and ivermectin: loose stools, headache, cough without cold, fever, nausea, dizziness, itching, watery diarrhea
		Albendazole 400 mg/d for 3 d <sup>c</sup>	209 (149)	Hookworm 88.3 Roundworm 99.0 Whipworm 42.6	
Rahman, <sup>61</sup> 1996 (Malaysia)	Schoolchildren (7-12 y) Follow-up 4 wk	Mebendazole 400 mg once	96	Cure rate:	Mebendazole and albendazole: few cases of headache and abdominal discomfort
		Albendazole 400 mg once <sup>c</sup>	96	Hookworm 89.1 Roundworm 87.3 Whipworm 83.4	
Sorensen et al, <sup>62</sup> 1996 (Sri Lanka)	Children 3-15 y Follow-up 3 wk	Mebendazole (local) 500 mg	145	Prevalence:	No data
		Mebendazole (standard) 500 mg	136	Hookworm 50.0 to 11.0	
		Albendazole 400 mg <sup>c</sup> all single dose	118	Roundworm 60.2 to 1.7 Whipworm 71.2 to 55.5	
				Cure rate: Hookworm 77.9 Roundworm 97.2 Whipworm 26.2	
Albonico et al, <sup>59</sup> 1994 (Zanzibar)	Schoolchildren, 6-12 y Follow-up mean 3 wk	Mebendazole (formula 1) 500 mg	1120	Cure rate:	All groups: headache, abdominal discomfort, diarrhea, nausea, itching Albendazole: rash Mebendazole: fever and vomiting
		Albendazole 400 mg <sup>c</sup>	1174	Hookworm 56.8	
		Mebendazole (formula 2) 500 mg	208	Roundworm 98.9	
		Mebendazole (formula 3) 500 mg all single dose	194	Whipworm 10.5	
Wesche and Barnish, <sup>53</sup> 1994 (Papua New Guinea)	Schoolchildren, grades 1-3, 8-13 y Follow-up 3 wk	No treatment	20	Cure rate:	No data
		Mebendazole (formula 1) 100 mg twice daily for 3 d	21	Hookworm 91	
		Mebendazole (formula 2) 100 mg twice daily for 3 d <sup>c</sup>	22	Roundworm 95	
		Mebendazole (formula 3) 400 mg once	16	Whipworm 65	

(continued)

Table 4

Continued...

**Table 4.** Randomized Controlled Trials Studying the Benefit of Oral Drug Therapy Interventions in 3 Neglected Tropical Diseases (cont)

Source (Study Site)	Population Eligible (Enrolled) and Follow-up	Comparison Groups With Dosage	No. Enrolled (Completed)	Outcomes, % <sup>a</sup>	Reported Adverse Events
<b>Hookworm, Roundworm, and Whipworm</b>					
Wesche et al. <sup>64</sup> 1994 (Papua New Guinea)	Schoolchildren, 8-13 y Follow-up 3 wk	Pyrantel pamoate 10 mg/kg (swallow)	30 (20)	Prevalence: Hookworm 100 to 86.4 Roundworm 100 to 27.3 Whipworm 85.4 to 81.8 Cure rate: Hookworm 14 Roundworm 73 Whipworm 5	No data
		Pyrantel pamoate 10 mg/kg (chew)	30 (23)		
		Pyrantel pamoate 10 mg/kg (pulverized) <sup>c</sup> all single dose	29 (22)		
Jongsuksuntigul et al. <sup>46</sup> 1993 (Thailand)	3-80 y <sup>e</sup> Follow-up 2 wk	Mebendazole generic 300 mg	43	Prevalence: Hookworm 100 to 15.7 Roundworm 25.5 to 0 Whipworm 84.3 to 27.5 Cure rate: Hookworm 84.3 Roundworm 100 Whipworm 67.4	No adverse events
		Mebendazole standard 300 mg	44		
		Mebendazole standard 500 mg	56		
		Albendazole standard 400 mg <sup>c</sup> all single dose	53		
Bartoloni et al. <sup>65</sup> 1993 (Bolivia)	2-9 y Follow-up 3-4 wk	Mebendazole 400 mg	62	Cure rate: Hookworm 81.8 Roundworm 100 Whipworm 33.3	No adverse events
		Albendazole 400 mg <sup>c</sup> all single dose	117		
Rossignol and Maisonneuve, <sup>47</sup> 1983 <sup>1</sup>	3-79 y <sup>g</sup> Follow-up 3 wk	Placebo	413	Cure rate: Hookworm 94.9 Roundworm 93.7 Whipworm 66.2	Placebo and albendazole: epigastric pain, dizziness, headache, diarrhea, itching, vomiting
		Albendazole 200 mg for adults and 100 mg for children <12 y <sup>c</sup> both 2 doses for 1 d	457		
Pene et al. <sup>48</sup> 1982 (France, West Africa)	3-40 y <sup>g</sup> Follow-up 3 wk	Placebo	190	No significant differences observed	Placebo and albendazole: epigastric pain, headache, dizziness, itching with both groups Diarrhea and vomiting in albendazole group (37 individuals)
		Albendazole 200 mg for adults and 100 mg for children <12 y both 2 doses for 1 d	202		
Sinniah and Sinniah, <sup>66</sup> 1981 (Malaysia)	Schoolchildren, 6-12 y <sup>h</sup> Follow-up 3 wk	Pyrantel pamoate 10 mg/kg once	Unclear	Cure rate (for mebendazole 6 d): Hookworm 80.6 Roundworm 95.5 Whipworm 85.7 Cure rate (for oxantel-pyrantel pamoate 3 d): Hookworm 82.0 Roundworm 97.7 Whipworm 79.2	Mebendazole and levamisole groups: abdominal discomfort (3 or 4 individuals) 1 of the levamisole groups: mild epileptic symptoms (1 individual) Diarrhea
		Oxantel-pyrantel pamoate 10 mg/kg once			
		Levamisole 100 mg once			
		Mebendazole 100 mg twice daily for 3 d			
		Pyrantel pamoate 10 mg/kg once for 3 d			
Yangco et al. <sup>49</sup> 1981 (US)	(3-61 y) <sup>l</sup> Follow-up 3 wk	Mebendazole 100 mg <sup>c</sup>	19 (16)	Cure rate: Whipworm, 89 for flubendazole and 94 for mebendazole	Flubendazole: brief mild headache (1 individual), intermittent abdominal cramps (1 individual)
		Flubendazole 100 mg <sup>c</sup> both 2x/d for 3 d	21 (19)		
Jancloes et al. <sup>50</sup> 1979 (Zaire)	(0 to >45 y) Follow-up 36 wk	Placebo	669	No significant differences	No adverse events
		Levamisole 2.5 mg/kg once	1061		
Farahmandian et al. <sup>51</sup> 1977 (Iran)	(0 to >41 y) Follow-up 3 wk	No treatment	48	Cure rate: Hookworm 100 Roundworm 96 Whipworm 98	Vomiting, nausea, headache, abdominal pain reported more in thiabendazole and bephenium-hydroxynaphthoate vs levamisole
		Pyrantel pamoate 10 mg/kg	48		
		Levamisole 25 mg/kg <sup>c</sup>	54		
		Mebendazole 100 mg 2x/d for 3 d	54		
		Thiabendazole 50 mg/kg	47		
		Bephenium-hydroxynaphthoate 5 g all once unless otherwise indicated	53		

(continued)

Table 4

Sachs JD, McArthur JW. The Millennium Project: a plan for meeting the Millennium Development Goals. *Lancet*. 2005; 365(9456): 347–353.



**Table 5.** Randomized Controlled Trials Studying the Benefit of Oral Drug Therapy Interventions in 2 Neglected Tropical Diseases

Source (Study Site)	Population Eligible and Follow-up	Comparison Groups With Dosage	No. Enrolled	Outcomes, % <sup>a</sup>	Reported Adverse Events
<b>Hookworm and Whipworm</b>					
Charoenlarp et al, <sup>68</sup> 1993 (Thailand)	Schoolchildren, 6-14 y Follow-up 4 wk	Placebo	133	Cure rate:	No data
		Mebendazole A (treatment 1) 300 mg once	134	Hookworm 63.4	
		Mebendazole A (treatment 2) 300 mg once	133	Whipworm 85.5	
		Mebendazole C (treatment 3) 300 mg once	135		
		Mebendazole C (treatment 4) 300 mg once	135		
		Mebendazole C (treatment 5) 500 mg once	133		
		Mebendazole C (treatment 6) 100 mg 2x/d for 3 d <sup>b</sup>	131		
<b>Roundworm and Whipworm</b>					
Legesse et al, <sup>69</sup> 2004 (Ethiopia)	Schoolchildren, 6-19 y Follow-up 3 wk	Mebendazole (formula 1) 100 mg twice daily for 3 d <sup>b</sup>	166	Prevalence:	No data
		Mebendazole (formula 2) 100 mg twice daily for 3 d	144	Roundworm 81.9 to 2.9	
		Mebendazole (formula 3) 100 mg twice daily for 3 d	154	Whipworm 85.5 to 10.1	
		Albendazole 400 mg once	197	Cure rate:	
				Roundworm 96.5	
				Whipworm 89.8	
Ortiz et al, <sup>70</sup> 2002 (Peru)	2-11 y Follow-up 3-4 wk	Nitazoxanide 100 mg 2x/d for 3 d (age 2-3 y) or 200 mg 2x/d for 3 d (age 4-11 y) <sup>b</sup> vs albendazole 400 mg once	70	Cure rate:	All groups: abdominal pain and nausea Albendazole: vomiting (1 individual) Nitazoxanide or praziquantel: diarrhea Nitazoxanide: headache (1 individual)
		Nitazoxanide 100 mg 2x/d for 3 d (age 2-3 y) or 200 mg 2x/d 3 d (age 4-11 y) <sup>b</sup> vs albendazole 400 mg once	40	Roundworm 89	
		Nitazoxanide 100 mg 2x/d for 3 d (age 2-3 y) or 200 mg 2x/d for 3 d (age 4-11 y) <sup>b</sup> vs praziquantel 25 mg/kg once	100	Whipworm 89	
Hall and Nahar, <sup>71</sup> 1994 (Bangladesh)	5-10 y Follow-up 5 wk	Albendazole 600 mg once	No data	Cure rate:	No data
		Albendazole 800 mg once		Roundworm 92	
		Albendazole 400 mg/d for 3 d <sup>b</sup>		Whipworm 80	
		Albendazole 400 mg/d for 5 d			
Belizario et al, <sup>72</sup> 2003 (the Philippines)	Schoolchildren, 6-12 y <sup>c</sup> Follow-up 51 wk	Albendazole 400 mg and placebo once	149	Prevalence:	No data
		Ivermectin 200 µg/kg and placebo once	146	Roundworm 66.7 to 23.8	
		DEC 150 mg and placebo once	147	Whipworm 95.9 to 43.5	
		Albendazole 400 mg and ivermectin 200 µg/kg once <sup>b</sup>	147		
		Albendazole 400 mg and DEC 150 mg once	147		
<b>Hookworm and Schistosomiasis</b>					
Stephenson et al, <sup>73</sup> 1989 (Kenya)	Schoolchildren, grades 1-7 <sup>d</sup> Follow-up 32 wk	Placebo	104	Prevalence <sup>f</sup> :	No data
		Metrifonate 10 mg/kg once <sup>b,e</sup>	103	Hookworm 94 to 88	
		Praziquantel 40 mg/kg once	105	Schistosomiasis 100 to 62	

Abbreviation: DEC, diethylcarbamazine.

<sup>a</sup>Statistically significant outcomes (change in prevalence or cure rates) following effective drug therapy interventions.

<sup>b</sup>Effective drug therapy intervention for multiple neglected diseases.

<sup>c</sup>Excluded were those receiving anthelmintic therapy within 30 days of the study; those with diarrheal disease, concomitant infection, or underlying disease; previous hypersensitivity to benzimidazole, ivermectin, DEC, or any related compound; or receipt of anthelmintic treatment within 14 days of the study.

<sup>d</sup>Excluded were children with severe anemia (hemoglobin <8.0 g/dL) and heavy schistosomiasis hematobium infection.

<sup>e</sup>Drug is no longer available.

<sup>f</sup>Morbidity measure: hemoglobin increase 0.14 g/dL with metrifonate was higher than with praziquantel ( $P < .05$ ).

## Table 5

Sachs JD, McArthur JW. The Millennium Project: a plan for meeting the Millennium Development Goals. *Lancet*. 2005; 365(9456): 347–353.