

United Nations  
Department of Economic and Social Affairs

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Population Division

Expert Paper  
No. 2011/1

**The development impact of the  
neglected tropical diseases (NTDs)**

*Peter J. Hotez*

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neglected tropical diseases (NTDs)**

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United Nations New York, 2011

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This publication has been issued without formal editing.

## PREFACE

In November 2009, the Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat convened an *Expert Group Meeting on Health, Mortality and Development* at the United Nations Headquarters in New York. The purpose of the meeting was twofold. First, in preparation for the forty-third session of the Commission on Population and Development, the meeting brought together experts and officials of inter-governmental organizations to discuss the challenges in combating the major causes of death and improving health, including consideration of how to strengthen health systems. Second, building upon earlier United Nations Coordination Meetings on the Estimation of Adult Mortality held in 2006 and 2008, the meeting focused on methodological issues in the estimation of adult mortality and initiated a comparison and review of adult mortality estimates for selected countries as produced by different institutions.

The meeting took place from 10 to 12 November 2009. Its agenda and list of participants can be found at <http://www.un.org/esa/population/meetings/EGM-healthmortality/agenda-participantslist.pdf>. A selection of the papers prepared by experts participating in the first part of the meeting is being issued under the Expert Paper Series published on the website of the Population Division ([www.unpopulation.org](http://www.unpopulation.org)).

Since 2000, the Millennium Development Goals (MDGs) have focused international attention on the reduction of major communicable diseases, especially those covered under MDG 6—HIV/AIDS, malaria and tuberculosis. As a result, great strides have been made toward combating those diseases. Yet the burden of disease associated with other infectious and parasitic diseases remains high. In 2009, an estimated 1.2 billion people were suffering from a range of neglected tropical diseases (NTDs), including parasitic diseases caused by worms (e.g., ascariasis, trichuriasis, hookworm and lymphatic filariasis) which are the most common type of infection. Newly available evidence confirms that NTDs contribute to undernutrition, which in turn delays cognitive development in children and, by compromising the health of adults, has a negative impact on economic development in the heavily affected communities. The Population Division is grateful to Dr. Peter J. Hotez, Distinguished Research Professor in the Department of Microbiology, Immunology and Tropical Medicine of the George Washington University and President of the Sabin Vaccine Institute, for having participated in the meeting and having prepared this paper on the prevalence and development impact of the neglected tropical diseases.

The *Expert Paper Series* aims at providing access to government officials, the research community, non-governmental organizations, international organizations and the general public to overviews by experts on key demographic issues. The papers included in the series will mainly be those presented at Expert Group Meetings organized by the Population Division on the different areas of its competence, including fertility, mortality, migration, urbanization and population distribution, population estimates and projections, population and development, and population policy. The views and opinions expressed in the papers that are part of the series are those of their authors and do not necessarily reflect those of the United Nations. The papers in the series are released without undergoing formal editing.

For further information concerning this series, please contact the office of Hania Zlotnik, Director, Population Division, Department of Economic and Social Affairs, United Nations, New York, 10017, USA, telephone (212) 963-3179, fax (212) 963-2147.

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## A. OVERVIEW

The concept of the neglected tropical diseases (NTDs) was established partly in response to the Millennium Development Goals (MDGs) for sustainable poverty reduction (Hotez, 2006; Hotez, 2008a; Molyneux, 2008). Launched in 2000, the sixth MDG, to combat HIV/AIDS, malaria and other diseases, stimulated large-scale initiatives for the control of HIV/AIDS and malaria through two massive stimulus packages from the United States Government—the President’s Emergency Plan for AIDS Relief (PEPFAR) and the President’s Malaria Initiative (PMI)—as well as a third stimulus provided by the Group of Eight (G8) countries through the Geneva-based Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). Through such initiatives, tens of billions of dollars were committed to provide millions of people living in low- and middle-income countries with antiretroviral therapy for AIDS, directly observed treatment for tuberculosis, and drugs and bed nets for malaria.

At the same time, scientists, physicians, public health experts, and global health policymakers concerned about the “other diseases” mentioned in MDG 6 noted a dearth of resources. Of particular concern was a group of tropical infections known as the NTDs, which were prevalent in low-income countries and were increasingly recognized to cause disease burdens comparable to AIDS or malaria. Moreover, there were opportunities to control the NTDs at costs far lower than those required for AIDS, tuberculosis or malaria. Despite the opportunity afforded by targeting the NTDs, none of these conditions was prioritized either by the United States Government or the G8 nations during the first few years of the new millennium.

The absence of global commitment to the NTDs prompted the drafting of a series of policy papers. The first two peer-reviewed papers to use the term NTDs were published in 2005 (Molyneux and others, 2005) and 2006 (Hotez and others, 2006a), respectively. These policy papers as well as subsequent ones in 2006 and 2007 (Brady and others, 2006; Lammie and others, 2006; WHO, 2006; Hotez and others, 2007a; 2007b), highlighted the NTDs as the most common infections in low- and middle-income countries. An estimated 1.4 billion people live below the World Bank poverty level of US\$1.25 per day (a group sometimes referred to as “the bottom billion,”), almost all of whom are adversely affected by one or more of the NTDs (Hotez and others, 2006a; 2007a; 2009a; Musgrove and Hotez, 2010). The major NTDs afflicting the bottom billion are shown in tables 1 and 2, ranked according to their prevalence. The three soil-transmitted helminth (STH) infections (ascariasis, trichuriasis, and hookworm infection) are the most common NTDs, each affecting approximately 600-800 million people worldwide. In order of prevalence, STH infections are followed by schistosomiasis (200 million infected), lymphatic filariasis (LF; 120 million infected), trachoma (60 million to 80 million infected), onchocerciasis (37 million infected), the food-borne trematode infections (>20 million infected), leishmaniasis (12 million infected), and Chagas disease (8 million to 9 million infected) (Hotez and others, 2007a; 2009a).

In spite of their substantial health impact, the NTDs have been ignored relative to the “big three diseases” in part because they cause far fewer deaths, on the order of half a million deaths annually due to the NTDs compared to two million or more deaths each year from AIDS, malaria, or tuberculosis (Hotez and others, 2006a). In 2006, the publication of a revised estimate of the global disability resulting from the NTDs marked a key revelation in global health (Hotez and others, 2006a). Using disability adjusted life years (DALYs) as a metric, it determined that the NTDs result in almost 57 million DALYs lost annually, a burden that is greater than that caused by malaria or tuberculosis and almost as great as the burden of disability resulting from HIV/AIDS (Hotez and others, 2006a; Hotez and others, 2007a). However, such estimates are not universally accepted by the global health community. A new initiative led by the Institute of Health Metrics at

the University of Washington, together with the Sabin Vaccine Institute is working to resolve controversies surrounding disability estimates for the NTDs.

Many of the NTDs share a number of common features. Most of the highest prevalence NTDs are parasitic helminth infections, with the exception of the bacterial infection, trachoma, and the protozoan infections, leishmaniasis and Chagas disease. There are several common protozoan infections including amebiasis, toxoplasmosis, and giardiasis for which there are no global prevalence estimates. Among their major common features, the NTDs shown in tables 1 and 2 are mostly chronic infections lasting years or decades<sup>1</sup> (Hotez and Daar, 2008; Hotez and others, 2007a). During the time when the NTDs cause long-lasting disabilities, they exert their greatest adverse impact on children, women, and adult agricultural workers (Hotez and others 2009a; Perera and others, 2007).

The major NTDs affecting children, including STH infections and schistosomiasis, damage the gastrointestinal tract, liver, and genitourinary tract. In addition, they impair children's growth, nutrition, and physical fitness (Hotez, 2005; King and others, 2005; Hotez and others, 2006a). Furthermore, the NTDs impair intellectual and cognitive development such that infected children are less able to learn in school (Sakti and others, 1999; Jukes and others, 2002; Miguel and Kremer, 2004). Thus the NTDs affect not only the long-term health and development of children, but education as well. While the biomedical mechanisms responsible for these effects require further investigation, iron deficiency anaemia (IDA) and other nutritional deficiencies are believed to be key elements associated with hookworm and schistosomiasis (Hotez, 2005; Hotez and others, 2006a). Chronic inflammation may also represent another underlying mechanism linking the NTDs to adverse health and education effects in children (King and others, 2005).

Girls and young women, especially pregnant women, suffer severe health deficits as a result of the chronic anaemia and inflammation caused by hookworm or schistosomiasis infection (Hotez and others, 2006a). These conditions place pregnant women at increased risk of maternal morbidity and poor pregnancy outcomes (Brooker and others, 2008). In addition, these NTDs cause infertility and may enhance women's susceptibility to malaria and HIV/AIDS. Women are also adversely affected by the stigma of severe disfigurement caused by several of the high-prevalence NTDs, which sometimes causes them to be ostracized by their spouses and community (Hotez and others, 2006b).

Agricultural workers are also severely affected by the NTDs, with the anaemia and chronic inflammation from hookworm and schistosomiasis, respectively, as well as the blindness resulting from either trachoma or onchocerciasis, or the disfigurement from LF, preventing their activities (Gyapong and others, 1996; Hotez and others, 2009a).

In addition to their health and disability effects, Hotez and others (2009a) have summarized the economic impact resulting from NTD-related impairments in child development, pregnancy and worker productivity. For example, chronic hookworm infection in childhood is estimated to reduce future wage-earning by 40 per cent. Moreover, NTD-associated reductions in agricultural activities have been estimated to result in billions of dollars of economic losses annually. Thus, the NTDs represent a cause of economic underdevelopment and an important but largely ignored reason that the bottom billion cannot escape poverty and destitution (Hotez and others, 2009a).

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<sup>1</sup> Dengue fever is an exception.



TABLE 1. HIGH-PREVALENCE AND NTDs WORLDWIDE

	Approximate global prevalence	Disability-adjusted life years	Deaths (annually)	Cause	Transmission	Effects	Endemic Areas	Approaches to control
High prevalence NTD	1.0 to 1.2 billion	14.9 million to 52.1 million	30,000 to 421,000					MDA with rapid impact package
Roundworm (Ascariasis)	800 million	1.2 to 10.5 million	3,000 to 60,000	5- to 14-inch-long <i>Ascaris</i> worms that live in the small intestine	Soil	- Malnutrition and intestinal obstruction in young children - Child stunting - Impaired cognition	Asia, Africa, Americas	MDA with rapid impact package or albendazole or mebendazole
Hookworm	600 million	1.8 to 22.1 million	3,000 to 65,000	0.5 inch-long <i>Necator</i> worms that live in the small intestine	Soil	- Severe iron deficiency anemia and protein malnutrition - “Yellow disease” (anemia) - Child stunting and impaired intellectual and cognitive development - Maternal morbidity and mortality in pregnancy	Asia, Africa, Americas	MDA with rapid impact package or albendazole
Whipworm (Trichuriasis)	600 million	1.6 to 6.4 million	3,000 to 10,000	1- to 2-inch-long <i>Trichuris</i> worms that live in the colon (large intestine)	Soil	- Colitis and inflammatory bowel disease - Child stunting and impaired cognition	Asia, Africa, Americas	MDA with rapid impact package or albendazole or mebendazole
Schistosomiasis	200 million	1.7 to 4.5 million	15,000 to 280,000	0.5- to 1-inch-long blood flukes that live in veins of the bladder or intestines	Fresh water	- Spiny eggs that damage the bladder, intestine or liver and cause inflammation	Mostly in Africa; remainder in Brazil, East Asia, Middle East	MDA with rapid impact package or praziquantel

TABLE 1. HIGH-PREVALENCE AND NTDs WORLDWIDE

	Approximate global prevalence	Disability-adjusted life years	Deaths (annually)	Cause	Transmission	Effects	Endemic Areas	Approaches to control
Schistosomiasis (continued)						<ul style="list-style-type: none"> <li>- Chronic pain, anemia, malnutrition and stunting</li> <li>- Liver and intestinal fibrosis (for <i>Schistosoma mansoni</i> and <i>S. japonicum</i>)</li> <li>- Blood in urine, kidney disease, female genital schistosomiasis (for <i>S. haematobium</i>)</li> </ul>		
Lymphatic filariasis (LF) (elephantiasis)	120 million	5.8 million	<500	2- to 4-inch-long <i>Wuchereria</i> worms that live in the limbs, breasts and genitals	Mosquitoes	<ul style="list-style-type: none"> <li>- Leg swelling</li> <li>- Scrotum enlargement</li> <li>- Disfigurement</li> </ul>	Asia, Africa, Americas	MDA with rapid impact package or diethylcarbamazine + ivermectin + albendazole
Trachoma	60 to 80 million	2.3 million	<500	<i>Chlamydia</i> intracellular bacteria	Poor hygiene, house flies	Blindness	Africa, Asia, Americas	SAFE strategy with azithromycin
Onchocerciasis	30 to 40 million	0.5 million	<500	1- to 20-inch-long <i>Onchocerca</i> worms living in nodules under the skin	Black flies	<ul style="list-style-type: none"> <li>- Microfilariae (larvae) in the skin and eyes</li> <li>- <i>Onchocerca</i> skin disease</li> <li>- Blindness</li> </ul>	Mostly in Africa, some in Latin America	MDA with rapid impact package or ivermectin
Oisthorchiasis and Clonorchiasis	20 million	Not determined	6,000 from cholangio carcinoma					MDA with rapid impact package or praziquantel

Source: Hotez and others (2009a), modified from table 1; and Hotez (2010f). MDA = mass drug administration; SAFE = surgery, antibiotics, face cleanliness, and environmental improvement

TABLE 2. VECTOR-BORNE NTDs WORLDWIDE

	<i>Approximate global prevalence</i>	<i>Disability-adjusted life years</i>	<i>Deaths (annually)</i>	<i>Approaches to control</i>
<b>Vector-borne protozoan and viral diseases</b>	<b>70 million</b>	<b>5.0 million</b>	<b>132,000</b>	<b>Integrated vector management or case detection and management of both</b>
Dengue fever	50 million	0.7 million	19,000	Integrated vector management
Leishmaniasis	12 million	2.1 million	51,000	Case detection and management, and integrated vector management
Chagas disease	8 to 9 million	0.7 million	14,000	Integrated vector management
Human African Trypanosomiasis	<0.1 million	1.5 million	48,000	Case detection and management, and tsetse control

*Source:* Hotez and others (2009a). Modified from table 1. MDA = mass drug administration; SAFE = surgery, antibiotics, face cleanliness, and environmental improvement.

While the NTDs are nearly ubiquitous throughout the impoverished areas of the low- and middle-income countries of sub-Saharan Africa, Asia and the Americas, there are key regional differences in the prevalence, epidemiology, and ecology of these infections. The NTDs are best understood by examining their unique features in separate clusters of low- and middle-income countries. Beyond their large burden in low- and middle-income countries, the NTDs and infections that closely resemble them, sometimes referred to as the neglected infections of poverty, also affect poor people residing in wealthy countries and disproportionately affect certain vulnerable populations, such as people of African descent, aboriginal or indigenous populations, and girls and women.

The geography of the major NTDs in the world's low- and middle-income countries was summarized recently (Bethony et al, 2011), but this information greatly expanded here.

## B. BURDEN OF NTDs IN SUB-SAHARAN AFRICA

Given the high percentage of people living in poverty in sub-Saharan Africa, it is not surprising that this region accounts for a significant percentage of the global disease burden from the NTDs. Approximately one half of the the population living in sub-Saharan Africa lives below the World Bank poverty level, and it is believed that a high percentage of these individuals lives in extreme poverty. Another 150 million people in sub-Saharan Africa live above the World Bank poverty line but on less than US\$2 per day (Hotez and Kamath, 2009). Overall, between one quarter and one third of the world's poor live in sub-Saharan Africa.

The prevalence, distribution, and disease burden from the NTDs in sub-Saharan Africa was reviewed recently (Hotez and Kamath, 2009). A summary of the major NTDs in sub-Saharan Africa ranked according to prevalence is shown in table 3. Helminth infections are the most common NTDs in sub-Saharan Africa, comprising the top six NTDs in the region (Hotez and Kamath, 2009). These conditions account for most of the estimated disease burden from NTDs,

possibly as much as 80-90 per cent. The three major STH infections, also known as intestinal nematode or intestinal helminth infections, are the most common helminthiases, with between one quarter and one third of sub-Saharan Africa's population infected (De Silva and others, 2003). Certain population sub-groups are at particularly high risk of acquiring STH: an estimated one half of the 180 million school-aged children is infected, as is a high percentage of preschool-aged children. Hookworm is the most common NTD in sub-Saharan Africa, with almost 200 million cases in the region.

TABLE 3. THE NTDs OF SUB-SAHARAN AFRICA

<i>Neglected Tropical Disease</i>	<i>Estimated number of cases</i>	<i>Estimated percentage of the global disease burden occurring in sub-Saharan Africa</i>	<i>Sub-Saharan African countries with the highest prevalence</i>
Total NTDs in Africa	500 million	Up to 100	Nigeria, Democratic Republic of the Congo
Hookworm	198 million	34	Nigeria, Democratic Republic of the Congo, Angola, Ethiopia, Côte d'Ivoire
Schistosomiasis	192 million	93	Nigeria, Tanzania, Democratic Republic of the Congo, Ghana, Mozambique
Ascariasis	173 million	21	Nigeria, Ethiopia, Democratic Republic of the Congo, South Africa
Trichuriasis	162 million	27	Nigeria, Democratic Republic of the Congo, South Africa, Ethiopia
Lymphatic filariasis	46 to 51 million	37 to 44	Nigeria, Democratic Republic of the Congo, Tanzania, Ethiopia, Kenya
Onchocerciasis	37 million	>99	
Trachoma	30 million	48	Ethiopia, Sudan, Tanzania, Kenya, Niger
Loiasis	<13 million	100	
Yellow fever	180,000	90	Côte d'Ivoire, Mali, Cameroon, Central African Republic, Ghana, Guinea
Human African trypanosomiasis	50,000 to 70,000 (17,000 new cases annually)	100	Democratic Republic of the Congo, Angola, Sudan, Congo
Leprosy	30,055 (registered prevalence)	14	Democratic Republic of the Congo, Nigeria, Ethiopia, Mozambique
Leishmaniasis (visceral)	19,000 to 24,000 new cases annually	Not determined	Sudan, Ethiopia, Kenya, Uganda
Dracunculiasis	9,585	100	Sudan, Ghana, Mali
Buruli ulcer	>4,000	47	Côte d'Ivoire, Benin, Ghana

Source: Hotez and Kamath (2009), modified from tables 2, 3 and 5.

STH are found in most regions of sub-Saharan Africa, with the exception of the southernmost areas of South Africa where the temperate climate is not favourable for disease transmission. In sub-Saharan Africa most of the cases are caused by the hookworm *Necator americanus*; with the greatest number of cases occurring in Nigeria and the Democratic Republic of the Congo. Overall, hookworm is especially common in countries along the African coast, such as Angola, Côte d'Ivoire, Kenya and Nigeria where the sandy soils are particularly favourable for larval transmission. Unlike other STH, hookworm also occurs in Sahelian countries such as Cameroon, Chad and Mali (Brooker and others, 2002).

In sub-Saharan Africa, hookworm ranks at the top of major causes of disease burden because of the anaemia that results from the blood feedings of the adult parasite (Brooker and others, 2002). Rebecca Stoltzfus and colleagues at Cornell University found that up to 73 per cent of the severe anaemia among school-aged children in Zanzibar may be attributable to hookworm (Stoltzfus and others, 1997a; 1997b). Hookworm is not exclusively a paediatric disease in sub-Saharan Africa; up to one third of pregnant women in the region are infected. Hookworm accounts for a significant percentage of anaemia during pregnancy (Brooker and others 2008).

In addition to hookworm, ascariasis and trichuriasis are important STH infections in sub-Saharan Africa, especially in Nigeria and the Democratic Republic of the Congo, like hookworm, but also in Ethiopia and in South Africa, as well as in some urban environments.

In addition to STH, lymphatic filariasis (LF), onchocerciasis (river blindness), loiasis and dracunculiasis (guinea worm) are important nematode infections in sub-Saharan Africa. More than 40 percent of the world's cases of LF worldwide occurs in sub-Saharan Africa, with a substantial number of cases occurring in Nigeria, the Democratic Republic of the Congo, Tanzania, Ethiopia, Kenya, and Ghana. In these countries, the etiologic agent of LF is *Wuchereria bancrofti*. High rates of swelling of the scrotum (hydrocele) or limbs (lymphoedema) occur and are responsible for significant economic losses due to impaired agricultural worker productivity (Gyapong and others, 1996). Greater than 99% of the onchocerciasis cases in the world occur in sub-Saharan Africa (small foci still exist in six Latin American countries). In Western Africa, a savannah form of onchocerciasis is associated with high rates of blindness, while in Central and Eastern Africa, onchocerca skin disease is an important cause of disabling and often highly disfiguring "troublesome itching" (Amazigo and others, 2006). Loiasis is common in Central Africa where its presence interferes with mass drug administration for onchocerciasis. Great strides have been made in nearly eliminating dracunculiasis except for fewer than 10,000 cases in the Sudan, Ghana, Mali and Niger (WHO, 2008c; 2008d).

Schistosomiasis vies with hookworm as the most important NTD in sub-Saharan Africa. More than 90 per cent of the estimated 200 million cases globally occurs in sub-Saharan Africa (Steinmann and others, 2006; Hotez and Kamath, 2009), and it is estimated that more than three quarters of the population is at risk for infection because they live near fresh water contaminated by disease-transmitting snails. The largest number of cases occurs in Nigeria, Tanzania, Ghana, and the Democratic Republic of the Congo. Schistosomiasis is also a major killer in Africa, accounting for two thirds of the deaths from all high-prevalence NTDs globally. Three forms of schistosomiasis are present in sub-Saharan Africa, each of which results in childhood growth stunting and cognitive effects (Hotez and Kamath, 2009). Urinary tract schistosomiasis caused by *Schistosoma haematobium* accounts for two thirds of cases and more than one half of deaths. Substantial morbidity and mortality result from bladder wall pathology, hydronephrosis, and renal failure. *S. haematobium* infection is also a leading cause of bladder cancer, while in women it causes female genital schistosomiasis (FGS) (Hotez and others, 2009). Both *S. mansoni* and *S. intercalatum* cause intestinal schistosomiasis, while *S. mansoni* is also a significant cause of liver disease, and responsible for most of the remaining one third of African cases not caused by *S. haematobium*. Another platyhelminth infection, cysticercosis, is believed to be common in Burundi and elsewhere in Africa, although prevalence data for this condition are generally not available.

The protozoan NTDs are of great importance in sub-Saharan Africa, including approximately 50,000-70,000 cases of human African trypanosomiasis (HAT) (WHO, 2006b) and outbreaks of visceral leishmaniasis (Reithinger and others, 2007), both vector-borne NTDs transmitted by

tsetse and sandflies, respectively. In the absence of specific treatment, these conditions are considered highly-lethal NTDs. Most of the HAT cases are the chronic form of the disease caused by West African or Gambian HAT and occur in areas where public health breakdown has resulted from conflict or inadequate health systems, such as in the Democratic Republic of the Congo, Angola, the Sudan, the Congo and the Central African Republic. East African or Rhodesian HAT is a zoonosis, which still occurs in Malawi, Uganda and Tanzania. Important outbreaks of visceral leishmaniasis have occurred in the East African countries of the Sudan, Eritrea, Ethiopia, Kenya and Somalia, commonly referred to as the Horn of Africa (Hotez and Kamath, 2009). Many of these outbreaks occur in migratory and refugee populations fleeing conflict zones and are related to increased exposure to sandflies. Because they often occur in remote areas where health systems may be non-existent, the actual number of cases of visceral leishmaniasis in sub-Saharan Africa has not been well established.

Trachoma is still widespread in the savannah regions of Eastern and Central Africa (i.e., Ethiopia, Sudan, Tanzania, and Kenya or in the Sahelian countries). Active trachoma is a significant cause of blindness in the region, and the leading cause of infectious blindness in Africa. Like visceral leishmaniasis, trachoma also has occurred in conflict zones in these regions. Buruli ulcer is an important regional problem in the West African countries of Côte d'Ivoire, Benin and Ghana, while a significant number of the world's leprosy cases occur in the Democratic Republic of the Congo, Nigeria, Ethiopia, and Mozambique. There are several other bacterial NTDs, which are believed to be important, but for which there are almost no prevalence or disease burden data available, including bovine tuberculosis, tick-borne zoonoses, typhoid and non-typhoidal salmonellosis, and yaws. Similarly, there are inadequate data on the major arboviral infections in Africa, including yellow fever, dengue fever, chikungunya fever and rift valley fever. Sub-Saharan Africa has the greatest number of rabies cases outside of India (Hotez and Kamath, 2009).

Among the major recommendations following a recent review of NTDs in sub-Saharan Africa are: 1) the urgency for additional and improved disease burden data, especially for the non-helminthic NTDs, for which there are few efforts at surveillance in the region; and 2) to focus particular attention on the two highest NTD disease burden countries, Nigeria and the Democratic Republic of the Congo, which together account for one third of the helminth infections, as well as a significant amount of the HAT and leprosy. In addition, to understand the situation in the Horn of Africa countries, which have suffered a re-emergence of many NTDs in association with conflict and post-conflict is equally urgent (Hotez and Kamath, 2009). Details of efforts to control the leading NTDs in sub-Saharan Africa through mass drug administration are outlined in Sections G and H.

### C. BURDEN OF NTDs IN LATIN AMERICA AND THE CARIBBEAN

Today, just under 50 million people in Latin America and the Caribbean live below the World Bank poverty line (less than US\$1.25 per day), and approximately 120 million people live below US\$2 per day (Hotez and others 2008a). In Latin America and the Caribbean a large proportion of the poorest people are of African descent so that the NTDs are sometimes thought of as historical legacies of slavery (Lammie and others, 2007). The region exhibits the highest income disparities in the world and, while rural poverty is widespread, there are also significant foci of urban poverty in the *favelas* of Brazil and other slums of major cities.

The American NTDs are listed in table 4 in order of prevalence (Hotez and others, 2008a). As in sub-Saharan Africa, the three major STH infections are the most common NTDs, especially ascariasis and trichuriasis. The greatest number of cases of these two STH infections occurs in

Mesoamerica (including Guatemala and Mexico), as well as on the Pacific coast of South America where STH are linked to malnutrition and growth stunting (Hotez and others, 2008a). Approximately two thirds of Latin America’s hookworm cases, practically all of which are caused by *N. americanus*, occurs in Brazil, as does almost all of Latin America’s cases of schistosomiasis. Schistosomiasis in the Americas is caused by *S. mansoni*. In the Brazilian states of Minas Gerais and Bahia, co-infections with *N. americanus* and *S. mansoni* are common and produce severe anaemia that results in severe physical and cognitive deficits for children and women (Hotez and others, 2008a). With both the largest population in Latin America and the highest rates of NTD infection, Brazil accounts for the lion’s share of the NTDs in the Americas. With the exception of Chagas disease, Brazil accounts for more than one half of the cases of each major NTD in the region (Hotez, 2008a). Outside of Brazil, hookworm occurs frequently in Paraguay, Peru, Central America and the Caribbean region, while intestinal schistosomiasis is found in parts of the Caribbean region, Venezuela and Suriname (Hotez and others, 2008a).

TABLE 4. THE NEGLECTED TROPICAL DISEASES OF LATIN AMERICA AND THE CARIBBEAN

<i>Neglected Tropical Disease</i>	<i>Estimated number of cases</i>	<i>Estimated percentage of the global disease burden occurring in Latin America and the Caribbean</i>	<i>Latin America and the Caribbean countries with the highest prevalence</i>
Total NTDs in LAC	200 million	10 except for Chagas disease	Brazil
Trichuriasis	100 million	17	Brazil, Mexico, Colombia, Guatemala, Venezuela
Ascariasis	84 million	10	Brazil, Mexico, Guatemala, Argentina
Hookworm	50 million	9	Brazil, Paraguay, Guatemala, Colombia
Chagas disease	8 to 9 million	>99	Bolivia,
Schistosomiasis	2 to 7 million	1 to 3	Brazil, Venezuela, Dominican Republic, Guadeloupe, Suriname
Trachoma	1 million	1 to 2	Brazil, Guatemala, Mexico
Lymphatic filariasis	0.7 million	<1	Haiti, Brazil, Dominican Republic, Guyana
Dengue fever	550,000 cases reported in 2006	Not determined	Brazil, Venezuela, Colombia, Mexico
Cysticercosis	400,000	Not determined	Not determined
Leishmaniasis	62,000 CL; 5,000 VL	Not determined	Brazil, Colombia, Peru, Nicaragua, Bolivia
Leprosy	47,612 new cases	11	Brazil, Venezuela, Paraguay, Colombia
Onchocerciasis	64 new cases in 2004	<1	Guatemala, Mexico, Venezuela, Ecuador
Jungle yellow fever	86 new cases in 2004	<1	Brazil, Paraguay

Source: Hotez and others (2008a), modified from tables 1, 2 and 4 to 7.

Four countries of Latin America and the Caribbean—namely, Brazil, the Dominican Republic, Guyana and Haiti—report active transmission of LF, with Haiti ranked number one in terms of total number of cases. Onchocerciasis is close to being eliminated in Latin America with cases

remaining in six endemic countries: Guatemala, Mexico, Venezuela, Brazil, Colombia, and Ecuador. Cysticercosis, fascioliasis, and echinococcosis are also important platyhelminth NTDs occurring in focal areas of the Americas.

Chagas disease (American trypanosomiasis) may be the most widespread protozoan NTD and according to some it is the leading cause of NTD disease burden as measured in deaths and DALYs (Franco-Paredes and others, 2007). However, others have made the case that hookworm and other helminth infections are associated with the highest disease burden in Latin America (Hotez et al, 2008a). Up to 9 million cases of Chagas disease exist in the Latin America and Caribbean region, with 50,000 new cases annually, primarily in regions of intense poverty (Yamagata and Nakagawa, 2006; Franco-Paredes and others, 2007). As a result of Chagas disease, millions of Latin Americans living in poverty develop heart problems (e.g., cardiomyopathy) and hundreds of thousands suffer damage to the digestive system (e.g., megaesophagus and megacolon) (Franco-Paredes and others, 2007; Hotez and others, 2008a).

The epidemiology and ecology of Chagas disease is extremely complex because a multitude of assassin bug species are vectors for infection. In Argentina, Chile, Uruguay and most of Brazil, Chagas disease has been eliminated through intensive vector control efforts targeting *Triatoma infestans*. However, there are concerns that *T. infestans* is now being replaced by another *Triatoma* species, while several different vector species have thwarted control efforts in other parts of the region (Yamagata and Nakagawa, 2006; Franco-Paredes and others, 2007).

Both visceral and cutaneous forms of leishmaniasis occur in Latin America and the Caribbean, where they are primarily zoonoses transmitted from either dogs (especially for visceral leishmaniasis) or wild animals (Hotez and others, 2008a). More than 60,000 new cases of cutaneous leishmaniasis occur annually in Brazil, Colombia, Ecuador, Panama, Paraguay, Peru, and Venezuela. Important factors in the emergence of this disease include urbanization in close proximity to sandfly breeding areas. Visceral leishmaniasis has emerged in Brazil's *favelas* as sandflies breed in areas of poor sanitation.

Trachoma, remains endemic in the Amazonian region of Brazil, and is a common bacterial NTD, while bartonellosis is an important sandfly-transmitted bacterial zoonosis that is still endemic in the Andean region. Leprosy occurs in Brazil, the only Latin American nation that has not yet been able to reduce the prevalence of the disease below the target of one case per 10,000 people. Almost 20 percent of the world's registered leprosy cases occur in the region and Brazil has the second largest number of cases behind China (World Health Organization 2010). In addition, leptospirosis is an important NTD in the *favelas*.

Dengue has emerged as one of the most important arboviral infections in the Americas. Only a small fraction of cases are reported, but the incidence is believed to be on the rise because of an increasing distribution of two *Aedes* vector species, possibly in association with climate change and increasing vector migrations. Urban transmission of yellow fever was noted in Latin America for the first time in 50 years when it was reported in Paraguay in 2008. Rabies is on the decline in the region.

In Latin America and the Caribbean, the NTDs are characterized by two major patterns of disease distribution: 1) the pervasive endemic NTDs such as STH infections, Chagas disease, and possibly dengue, which are widespread, and 2) focally endemic NTDs that occur under circumstances of unique ecologies and human conditions, such as LF and schistosomiasis in the Caribbean, and onchocerciasis in Mesoamerica (Hotez and others, 2008a). Great progress has been made in combating the focally endemic NTDs, and with adequate funding and organization, the



prospect of eliminating LF and onchocerciasis appears attainable over the coming decade. Similarly, both trachoma and leprosy are continuing to decline. Among the current challenges are to complete elimination for the diseases mentioned above and to eliminate schistosomiasis in the Caribbean. At this point, the STH infections are too widespread to be considered for elimination, especially in Brazil where the greatest number of cases exists. Schistosomiasis is also too entrenched in Brazil for purposes of elimination. Outside of the Southern cone, Chagas disease has thwarted elimination efforts, either because elimination of *T. infestans* vectors has not been achieved, or because of sylvatic *Triatoma* species, especially in Mexico, Central America, and the northern areas of South America, which have been shown to re-invade dwellings following the use of insecticide (Hotez and others, 2008a). Dengue control remains a priority, although no elimination efforts are in place.

#### D. BURDEN OF NTDs IN ASIA

With the exception of schistosomiasis, the highest burden of the seven most common NTDs occurs in Asia (Hotez, 2010b). In addition, a large disease burden in Eastern Asia results from food-borne trematode infections. Because of its huge and diverse population, the diseases in Eastern Asia (referring to Southeast Asia and China) are discussed separately from Southern Asia (referring to the Indian subcontinent).

##### 1. Southeast Asia and China

The prevalence, distribution, and disease burden from the NTDs in Eastern Asia was reviewed recently (Hotez, 2010b). The eleven countries of Southeast Asia include Brunei, Cambodia, Indonesia, the Lao People's Democratic Republic, Malaysia, Myanmar, the Philippines, Singapore, Thailand, Timor-Leste and Viet Nam. Poverty is particularly widespread in Cambodia, the Lao People's Democratic Republic and the Philippines where 10 per cent to 30 per cent of the population lives below the World Bank poverty level. A large percentage of Myanmar's population is likely also impoverished, although specific data are unavailable. Even countries such as Indonesia and Viet Nam have more than 40 per cent of their populations living on less than US\$2 per day. More than 100 million Chinese (approximately 10 per cent of China's population) also live below the World Bank poverty level, with 38 per cent living on less than US \$2 per day. Much of China's poverty is concentrated in its western and south-western provinces, especially Guizhou, Sichuan and Yunnan. Practically speaking, the information presented above indicates that hundreds of millions of people in Southeast Asia and China live in poverty and are at risk for acquiring NTDs (Hotez, 2010b).

STH infections are the most common NTDs in Southeast Asia and China (table 5). Today, East Asia accounts for up to one-half of the world's cases of ascariasis, especially in Indonesia and China. Approximately 90 million cases of *Ascaris* infection are found in each country and together these two countries alone represent almost 20 per cent of the world's cases. Tens of millions of people are also infected with ascariasis in the Philippines and Myanmar. Indonesia leads the region in the number of cases of trichuriasis and hookworm, although millions of cases also occur in the Philippines, Myanmar, and the Mekong countries. Together Southeast Asia and China account for almost 40 per cent of the world's cases of trichuriasis and 33 per cent of the cases of hookworm infection (Hotez, 2010b).

Two promising trends have been noted with respect to reductions in the prevalence of STH infections over the last decade. First, in association with economic growth in China's eastern provinces there has been a dramatic reduction in each of the three major STH infections in China

(Hotez, 2002; Hotez, 2010b). These reductions are well documented through two nationwide surveys of parasitic diseases conducted by the Chinese Ministry of Health in 1988-1992 and 2005, respectively. Second, the Mekong countries have aggressively pursued a policy of deworming school-aged children, and countries such as the Lao People's Democratic Republic, Cambodia and Viet Nam are achieving coverage rates that exceed 90 per cent of the population. In contrast, several large Southeast Asian nations such as Indonesia, the Philippines and Myanmar are deworming at low coverage rates and in some cases children in these countries receive albendazole only as part of combined DEC/albendazole coverage for LF.

For LF, the largest number of cases occurs in Indonesia and Myanmar. Whereas *W. bancrofti* is the exclusive human etiology of LF in sub-Saharan Africa and Latin America and the Caribbean, in Indonesia, the Philippines and Malaysia, *Brugia malayi* infection also occurs, while *B. timori* infection is found in Timor-Leste. High coverage rates with diethylcarbamazine and albendazole have been noted for much of Southeast Asia, while China has eliminated LF as a public health problem. In contrast, LF prevalence remains high in eastern Myanmar and along the border with Thailand.

TABLE 5. THE NEGLECTED TROPICAL DISEASES OF EAST ASIA (SOUTHEAST ASIA AND CHINA)

<i>Neglected Tropical Disease</i>	<i>Estimated number of cases</i>	<i>Estimated percentage of the global disease burden occurring in Southeast Asia and China</i>	<i>East Asian countries with the highest prevalence</i>
Total NTDs in East Asia	400 million	30 to 40	Indonesia, China, Philippines, Myanmar
Ascariasis	313 million	39	Indonesia, China, Philippines, Myanmar
Trichuriasis	229 million	38	Indonesia, Philippines, China, Myanmar
Hookworm	178 million	33	Indonesia, China, Thailand
Trachoma	29 million	46	China, Indonesia, Cambodia, Vietnam
Opisthorchiasis/Clonorchiasis	22 million	>90	Thailand, Laos, China
Lymphatic Filariasis	<15 million	<14	Indonesia, Myanmar
Paragonomiasis	14 million	66	China
Schistosomiasis	1 million	0.5	China, Philippines
Taeniasis	>0.5 million	Not determined	China
Echinococcosis	>0.4 million	Not determined	China
Leprosy	0.03 million	14	Indonesia, China, Myanmar

Source: Hotez, J. P. (2010b), modified from tables 2 and 3.

Somewhat unique to Southeast Asia and China are the large number of cases of food-borne trematode infections. Of particular concern are liver fluke and lung fluke infections. For the former, clonorchiasis is endemic in north-eastern China and in southern China, as well as in Taiwan. More than 12 million cases of clonorchiasis are found in China and these numbers have been increasing over the past few years. A second important focus of liver fluke infection is opisthorchiasis, found in northern Thailand and Laos, where roughly 10 million cases occur, and in Cambodia. In addition

to chronic fibrosis and malnutrition, both *Clonorchis sinensis* and *Opisthorchis viverrini* are recognized carcinogens, and approximately 5 per cent of long-standing liver fluke infections lead to a fatal condition known as cholangiocarcinoma (bile duct cancer).

Fewer than one million cases of intestinal schistosomiasis caused by *S. japonicum* occur in China, mostly in the lake regions of Yangtze River provinces in the East and in mountainous areas of Sichuan and Yunnan provinces in the West (Wang and others, 2008; 2009). Because *S. japonicum* infection is a zoonosis transmitted primarily from water buffalo, mass treatment with praziquantel has been less effective than replacing the animal reservoirs with tractors or preventing water buffalo from grazing near snail-infested marshland (Wang and others, 2008; 2009). After China, the Philippines has the largest number of cases of *S. japonicum* infection. A second schistosome species, *S. mekongi*, is also found in Cambodia. Both cysticercosis and echinococcosis are common in north-western China, with the former exhibiting a high prevalence among Uighur minority populations. Overall, approximately half a million cases of taeniasis occur in China. No prevalence estimates are available for South East Asia.

Estimates of the protozoan infections, such as amebiasis and toxoplasmosis, are lacking for Asia. Among the bacterial infections, the most important is trachoma. Almost one half of the world's trachoma cases occurs in China and Southeast Asia, with China accounting for the greatest number of cases by far (Hotez, 2010b). Indonesia and Cambodia are also endemic for trachoma, while Viet Nam has launched major control efforts. Melioidosis (*Burholderia pseudomallei*) has been linked to sepsis in the region, but especially Thailand and , Malaysia. Indonesia accounts for almost 10 per cent of the world's registered cases of leprosy.

Two arbovirus infections are of great health and economic importance to the region. Up to 50,000 new cases (and 15,000 deaths) of Japanese encephalitis occur in Southeast Asia and China annually, mostly as a result of transmission from water birds and pigs by *Culex* mosquitoes. Dengue fever, together with dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) is believed to have emerged from Southeast Asia about 50 years ago and today tens of millions of cases of dengue and half a million cases of DHF/DSS occur annually. Unlike Japanese encephalitis, dengue is transmitted by *Aedes* mosquitoes, with *Aedes aegypti* the preferred vector in urban areas and *A. albopictus* in rural areas. China may be second only to India in terms of the number of canine rabies cases.

## 2. South Asia (Indian subcontinent)

Because of its enormous population living in poverty, India has the largest number of cases of each of the major STH infections of almost any country, although the overall prevalence (i.e. percentage of people infected) is lower than in many other countries in South Asia, such as Bangladesh and Nepal (Bethony and others, 2006). Together, approximately one quarter of the world's cases of ascariasis, trichuriasis and hookworm occurs in India, Bangladesh, Nepal and Sri Lanka. Both *Ancylostoma duodenale* and *N. americanus* are common in India and Nepal, with the former responsible for greater intestinal blood loss (Hotez and others, 2005). Ancylostomiasis has been shown to be a particular problem among pregnant women in Nepal (Stoltzfus and others 1997a). This region also accounts for about one-half the global disease burden from LF (World Health Organization 2008b). A huge socioeconomic impact is associated with LF as a result of impaired worker productivity because of hydrocele and lymphoedema as well as the social stigma associated with this infection (Hotez and others, 2009).

Both visceral leishmaniasis and amebiasis are important protozoan NTDs. In India, visceral leishmaniasis is an important opportunistic infection of HIV/AIDS. Together, Bangladesh, India

and Nepal (in addition to Sudan) contribute approximately most of the global burden of disease resulting from visceral leishmaniasis, with the largest number of cases believed to be concentrated in Bihar State.. South Asia may also have the world's highest disease burden of amebiasis, but there is minimal surveillance for this infection, which make disease burden assessments problematic.

Approximately one million cases of trachoma occur in India and another 300,000-400,000 in Nepal. Worldwide, India has the greatest number of new cases of leprosy, accounting for about one-half of the world's registered cases (World Health Organization, 2010). Only Nepal has reached its elimination target of one case per 10,000 individuals. As noted below, strong programmes for the elimination of leprosy in South Asia are in progress (World Health Organization, 2010). Leptospirosis is an important bacterial NTD, but like amebiasis, there is almost no surveillance data for the region.

Canine rabies is an important viral NTD in South Asia: India alone accounts for roughly one half of the 50,000 deaths from rabies that occur globally each year. Japanese encephalitis is now endemic in India and Nepal.

#### E. BURDEN OF NEGLECTED INFECTIONS IN WEALTHY COUNTRIES

The NTDs do not occur exclusively in low- and middle-income countries. Instead, some important NTDs can be found in the poorest regions of the United States of America, Europe and Japan as well. An important example is Chagas disease (American trypanosomiasis caused by *Trypanosoma cruzi*). Up to one million Hispanic Americans living in the United States are estimated to be infected with *T. cruzi* (Hotez, 2008b), although the actual number is probably closer to 300,000, and there are also several thousand infected immigrants living in Spain (Hotez, 2010a; 2010c). However, to focus only on immigration as a source of NTDs in wealthy countries would be to ignore a health disparity of much greater proportions.

Wealth is not distributed evenly in the United States and Europe. In the United States up to 40 million Americans live below an established poverty level. Demographic studies indicate that people living in poverty in the United States are concentrated in specific geographic regions, especially in the southern part of the country. These regions include the Mississippi Delta (which also includes post-Katrina Louisiana), the Appalachian region, what used to be known as the "cotton belt" and today is comprised of impoverished areas of Alabama and Georgia, and the Mexico border region. The inner cities of the northeast (including the Bronx, New York; Camden, New Jersey; North Philadelphia, Pennsylvania; Baltimore, Maryland; and northeast and southeast Washington, DC) and the Midwest (including Gary, Indiana; Detroit, Michigan; and Chicago, Illinois) also contain areas of intense poverty. African American and Hispanic American minority populations are disproportionately affected by poverty in the above-mentioned areas.

Although neglected infections in wealthy countries would not be considered "tropical," they are nonetheless appropriate to mention here because they closely resemble NTDs in terms of their ability to adversely affect child development and education, maternal health and worker productivity (Hotez, 2008b). For example, among African Americans the major neglected infections of poverty include: toxocariasis, a larval zoonotic helminth infection that may cause asthma and developmental delays in children and is transmitted to humans from dogs (approximately 3 million people infected); trichomoniasis, a sexually transmitted protozoan infection (almost one million infected); and congenital cytomegalovirus infection, a cause of mental disability and deafness (Hotez, 2008b). In some areas of wealthy countries the rates of these

infections are as high as in Nigeria (Hotez, 2009a). Similarly, among Hispanic Americans, Chagas disease is a major neglected infection of poverty, as is cysticercosis, which may be the leading cause of epilepsy among this population (Hotez, 2008b). While the prevalence rates of these two conditions are not as high in the United States as in Mexico and Central America, they are nonetheless worthy of comparison (Hotez, 2009a). There is now evidence for autochthonous transmission of both Chagas disease and cutaneous leishmaniasis in the United States. In Appalachia, strongyloidiasis and other STH infections are still prevalent.

In Europe, poverty is most concentrated in Eastern Europe, especially in the Balkans and in south-eastern Europe (Hotez, 2010c). The post-conflict situation following the war in the Balkans, the break-up of the Soviet Union and the recession of 2008 and 2009 are important social forces influencing health and disease transmission in these regions. STH infections, (ascariasis, trichuriasis, and enterobiasis) remain prevalent in Albania, Armenia, Poland and Turkey and toxocariasis is common throughout Eastern Europe (Hotez, 2010c).

In addition to STH, Eastern Europe (including the former Soviet-block countries) is severely affected by several food-borne helminthiases, including trichinellosis, taeniasis, and opisthochiasis, as well as cystic echinococcosis. High rates of several non-helminthic neglected infections are also present, such as giardiasis and other intestinal protozoan infections, trichomoniasis, toxoplasmosis, brucellosis, leptospirosis and congenital syphilis.

In southern Europe (France, Greece, Italy, Portugal and Spain), several important vector borne neglected infections have been found commonly, such as Chagas disease, as well as visceral leishmaniasis, which is also an opportunistic infection of HIV/AIDS, strongyloidiasis, and a number of important arboviral infections, including chikungunya, sandfly fever and Crimean-Congo hemorrhagic fever.

Specific and detailed data on the neglected infections of the United States and Europe are severely lacking because many of these infections are not reportable either to the United States Centers for Disease Control and Prevention (CDC) or the European CDC and there is no programme for active surveillance of these conditions. In addition, there is a dearth of information on the mechanisms of transmission of infection in the United States and Europe. Few if any programmes for treatment and prevention for the neglected infections of poverty are in place in these populations.

## F. NTDs AND SPECIAL VULNERABLE POPULATIONS

Three major population groups are considered especially vulnerable to the adverse health effects of the NTDs and the related neglected infections of poverty: girls and women; people of African descent; and indigenous peoples.

### 1. *Girls and Women*

Girls and women, especially women of reproductive age, suffer disproportionately from the NTDs. There are multiple mechanisms by which NTDs affect the health of women (Hotez, 2010d). In terms of reproductive health, several high-prevalence NTDs greatly exacerbate the iron deficiency and IDA that results during pregnancy as a result of the high iron demands of the foetus. Studies by Brooker and colleagues (2008) reveal that up to one third of pregnant women in sub-Saharan Africa are infected with hookworm. Throughout sub-Saharan Africa and in some parts of Latin America and Asia a large proportion of anaemia in pregnancy attributed to hookworm

infection. IDA from hookworm infection during pregnancy is linked to increased maternal morbidity and low birth weights. Schistosomiasis is another high prevalence NTD in sub-Saharan Africa that causes anaemia as well as inflammation in the placenta. Both hookworm and schistosomiasis adversely affect fertility.

Certain NTDs in women also increase susceptibility to several sexually transmitted infections (Hotez, 2010d). In both developing and developed countries, trichomoniasis is a common protozoan infection that is sexually transmitted. While there are few estimates for trichomoniasis, its prevalence is believed to be widespread and some studies link it to increased susceptibility to HIV/AIDS (Hotez, 2010d). Of equal concern is that up to 75 per cent of women with urinary tract schistosomiasis from *S. haematobium* infection experience parasite egg deposition and granuloma formation in their upper and lower genital tracts and, as a result, suffer from female genital schistosomiasis (FGS) (Hotez and others, 2009b). FGS is associated with friable and ulcerative lesions that bleed easily and cause inflammation and pain on sexual intercourse. FGS is associated with an increased risk of acquiring HIV/AIDS in Zimbabwe and presumably other areas of high *S. haematobium* transmission as well (Hotez and others, 2009b). Therefore, there is a high level of interest in looking at mass drug administration with praziquantel as a low-cost (US\$0.32 per person annually) approach towards HIV/AIDS prevention in sub-Saharan Africa.

NTDs are an important cause of stigma and social isolation for women in low-income countries (Hotez, 2010d). A key reason for stigma is the extreme disfigurement associated with several high-prevalence NTDs, including LF (breast, limb, and genital lymphoedema), onchocerciasis (Onchocerca skin disease), leishmaniasis (facial lesions of cutaneous disease), and Buruli ulcer and leprosy. Social research studies have shown how women are ostracized for the disfigurement, prevented from marrying or holding their children, and vulnerable to spousal abandonment.

Several NTDs are transmitted to the unborn foetus and result in congenital infections, including Chagas disease, leishmaniasis, and toxoplasmosis. In addition there is some evidence for lactogenic transmission of hookworm infection and strongyloidiasis (Hotez, 2010d).

## 2. People of African descent

The high prevalence of NTDs in sub-Saharan Africa is described above and summarized in table 3. Approximately one half of the population living below the World Bank poverty level is infected with either hookworm or schistosomiasis (Hotez and Kamath, 2009), and it is possible that all of Africa's 400 million poor are afflicted with at least one NTD (Molyneux and others, 2005). During the 500 years of the Middle Passage between the fifteenth and nineteenth centuries, an estimated 11 million captives were abducted from the West African coast and brought to the Americas, with most brought to Brazil or the sugar plantations of the Caribbean (Lammie and others, 2007; Hotez, 2010a). The Atlantic slave trade was responsible for introducing some of the highest prevalence NTDs to the Americas, including hookworm infection (*N. americanus* infection), intestinal schistosomiasis (*S. mansoni*), lymphatic filariasis (*W. bancrofti*), onchocerciasis, amebiasis, leprosy and yellow fever.

Today in the Americas, but especially in the Caribbean and north-eastern Brazil, Guyana, French Guiana, Suriname and Venezuela, the NTDs still disproportionately affect people of African descent (Hotez and others, 2008a; Hotez, 2010a). In the Caribbean, the most affected areas include several populous island nations, such as Haiti, the Dominican Republic, Guadeloupe, Jamaica and Barbados, while in Brazil the urban *favelas* of Fortaleza, Recife, and Salvador and

suburban areas of the Pernambuco, Bahia, and Minas Gerais states are important foci of infection (Hotez and others, 2008a). Because of the disproportionate impact on people of African descent who still live in poverty, the NTDs of Latin America and the Caribbean can be considered legacies of the Atlantic slave trade (Lammie and others, 2007). Similarly, the major high-prevalence neglected infections of poverty in post-Katrina Louisiana and elsewhere in the American South represent some of the greatest health disparities in the United States (Hotez, 2008b).

### *3. Indigenous peoples*

Because they continue to live in poverty and conditions of stress, the world's indigenous peoples suffer disproportionately from NTDs. The full impact of NTDs among the world's indigenous peoples is still largely unexplored, although preliminary studies indicate that this would be an important avenue of research. In Asia for example, China's indigenous peoples exhibit some of the highest rates of STH infections and zoonotic NTDs (echinococcosis, leishmaniasis and trichinellosis) (Hotez, 2010b). In Latin America, rural poverty is especially high among indigenous people in Bolivia, Colombia, Ecuador, Guatemala, Mexico and Peru, where they suffer from extremely high rates of STH infections, as well as onchocerciasis and Chagas disease (Hotez and others, 2008a). High rates of STH infections, onchocerciasis and trachoma occur among Brazil's indigenous peoples, while in Bolivia and Peru they are also afflicted by fascioliasis and cysticercosis in addition to the diseases outlined above. In the North American Arctic region, the Inuit and Alaskan natives are at high risk for several food-borne zoonotic NTDs, including trichinellosis and toxoplasmosis (Hotez, 2010e).

## G. OPPORTUNITIES FOR CONTROL AND ELIMINATION OF THE HIGH-PREVALENCE NTDs

The highest prevalence NTDs are ranked in table 6 and include ascariasis, trichuriasis, hookworm infection, schistosomiasis, LF, onchocerciasis, and the two major liver fluke infections, opisthorchiasis and clonorchiasis. With the exception of trachoma, each of these NTDs is a helminth infection (Hotez and others, 2008b).

### *1. Annual Mass Drug Administration*

In the poorest countries where the high-prevalence NTDs are found, it is possible to treat these conditions through simple and low-cost drugs, which can be provided through highly cost-efficient yearly mass drug administration programmes (Hotez, 2009b). In some cases these programmes have been in place for twenty years or more.

TABLE 6. NEGLECTED TROPICAL DISEASES TREATMENTS THROUGH MASS DRUG ADMINISTRATION

<i>NTD and Major Public Private Partnership (PPP)</i>	<i>Drug(s)</i>	<i>Cost in US dollars</i>	<i>People Treated/Year Treated</i>	<i>People at risk for infection</i>	<i>Percentage Treated</i>
Intestinal helminth infections Ascariasis Trichuriasis Hookworm No specifically dedicated PPP. Both SCI and GPELF treat intestinal helminth infections (see below) <a href="http://www.who.int/">www.who.int/</a> worm control	Albendazole or Mebendazole	0.02 to 0.03	>82 million preschool aged children in 2006	386 million preschool aged children	21
Schistosomiasis	Praziquantel	0.08	13 million in 2005		
Schistosomiasis Control Initiative (SCI) <a href="http://www.schisto.org">www.schisto.org</a>			9 million in 2006 8 million in 2007	779 million	1 to 2 <sup>a</sup>
Lymphatic Filariasis Global Programme to Eliminate Lymphatic Filariasis (GPELF) <a href="http://www.filaria.org">www.filaria.org</a>	Diethyl-carbamazine or Ivermectin + Albendazole	Diethyl-carbamazine is 4.00 for a box of 1,000 tablets  Ivermectin and Albendazole are donated	546 million in 2007	1,303 million	42
Onchocerciasis African Programme for Onchocerciasis Control (APOC) <a href="http://www.who.int/apoc/">www.who.int/apoc/</a>	Ivermectin	Free Donation	32 million in 2003 40 million in 2005	87 million	37 to 46
Trachoma International Trachoma Initiative (ITI) <a href="http://www.trachoma.org">www.trachoma.org</a>	Azithromycin	Free Donation	23 million in 2007	460 million	5 <sup>b</sup>

Source: Hotez, P. J. (2009b).

<sup>a</sup> SCI supports national control programmes in Uganda, Burkina Faso, Niger, Mali, Tanzania, and Zambia. The percentage coverage is based on the total population worldwide at risk for schistosomiasis.

<sup>b</sup> ITI supports national control programmes in 15 countries, Burkina Faso, Ethiopia, Gambia, Ghana, Guinea-Bissau, Kenya, Mali, Mauritania, Morocco, Nepal, Niger, Senegal, Sudan, Tanzania, Uganda. The percentage coverage is based on the total population worldwide at risk for trachoma.



In 2001 the 54<sup>th</sup> World Health Assembly (WHA) resolved to treat at least 75 per cent of school-aged children at risk for STH infections by the year 2010 (WHA resolution 54.19). Treatments are provided at yearly or twice-yearly intervals, depending on the prevalence and intensity levels in the community, and typically without performing pre-treatment diagnostic tests on each child. Treatment yields dramatic reductions in paediatric morbidity and improvements in growth and physical fitness, cognition, memory, school performance and school attendance (Bethony and others, 2006), making both drugs extremely cost-effective health and educational interventions. Despite the WHA resolution, only about 10 per cent of school-aged children who should be dewormed regularly are actually receiving yearly treatments (WHO, 2008a). The percentage of preschool-aged children who receive benzimidazoles is higher because treatment is delivered together with a package of other interventions, including micronutrients and immunizations. However, for school-aged or preschool-aged children living in resource poor settings to receive twice-yearly treatments remains uncommon.

In addition, benzimidazole deworming is widely recommended for pregnant women in their second and third trimesters, especially in hookworm-endemic areas of sub-Saharan Africa, Southeast Asia, and parts of Latin America. However, with the exception of the Mekong countries only a small percentage of women are receiving routine benzimidazoles during pregnancy (Hotez, 2010b).

*Schistosomiasis and liver fluke infections.* The drug praziquantel is effective in treating both schistosomiasis and liver fluke infections. In mass drug administration programmes where schistosomiasis is present, the drug is provided as multiple tablets, with the number administered gauged according to a height pole that serves as a surrogate for weight. Globally, the drug is only partially donated by Merck KGaA and, because each tablet costs US\$0.08 and three tablets are often required for effective treatment of school-aged children, this drug is the most expensive one used for mass drug administration. In sub-Saharan Africa, praziquantel is often not readily available (Hotez and Fenwick, 2009).

In addition to STH, WHA Resolution 54.19 called for regular treatments for schistosomiasis in endemic areas, especially sub-Saharan Africa where more than 90 per cent of the cases occur. However, costs and poor availability lead some investigators to believe that fewer than 2 per cent of eligible children receive the drug (Hotez, 2009b; Hotez and Fenwick, 2009). Indeed, except in the countries where the public-private partnership known as the Schistosomiasis Control Initiative is operating, the actual number of children who receive praziquantel (often together with albendazole) is meagre. An attractive possibility being considered is the elimination of intestinal schistosomiasis in the Caribbean through targeted mass drug administration (Hotez and others, 2008a). The treatment coverage for liver fluke infections in Southeast Asia and China is unknown.

*Onchocerciasis and LF.* Ivermectin is effective in treating both onchocerciasis and LF. The drug is donated by Merck & Co., Inc. through the Mectizan® Donation Program. For both filarial infections, the drug targets the microfilarial stages of the causative organism. In the case of onchocerciasis, where the microfilariae cause both severe pruritus (“troublesome itching”) and blindness, the drug effectively treats both the symptoms and the disease. In Africa, it is administered at yearly intervals in areas where the prevalence of this infection exceeds 40 per cent (Boatin and Richard, 2006). For LF, targeting the microfilariae can interrupt transmission when it is administered yearly for two to six rounds. Outside of the onchocerciasis-endemic areas of Africa and in Asia and the Americas the drug diethylcarbamazine is used for mass drug administration. Both ivermectin and diethylcarbamazine are co-administered with albendazole (provided by GlaxoSmithKlein) in order to forestall drug resistance.

In contrast to mass drug administration for STH infections and schistosomiasis, the at-risk populations for onchocerciasis and LF have benefited from much higher drug coverage (30 per cent to 50 per cent). In sub-Saharan Africa where more than 99 per cent of cases of onchocerciasis occurs, the African Programme for Onchocerciasis Control operates in 19 countries, with an estimated 40 million people under treatment in 2005, and 102 million people protected in 16 countries by 2010 (Amazigo and others, 2006). The treatments are provided by an impressive army of more than 100,000 mostly volunteer community drug distributors who provide ivermectin in some of the most remote areas of sub-Saharan Africa, including difficult conflict and post-conflict zones (Amazigo and others, 2006). These treatments are being effected at high economic rates of return approaching 20 per cent. Similarly, the Global Programme to Eliminate LF has led efforts to treat an astonishing 546 million people in 2007 with either ivermectin or diethylcarbamazine, usually together with albendazole. Almost two billion people have received treatments over the past eight years, resulting in an estimated 32 million DALYs averted (Ottesen and others, 2008). Unlike the STH infections and schistosomiasis, which are currently too widespread and suffer from treatment coverage levels that are too low to be considered for elimination, the possibility of elimination is a reality for both onchocerciasis and LF. Hans Remme and his colleagues from the World Health Organization Special Programme on Tropical Disease Research showed that onchocerciasis could eventually be eliminated in areas of two sub-Saharan African countries through multiple rounds of ivermectin annual treatments (Diawara and others, 2009). The Onchocerciasis Elimination Programme for the Americas is also working to achieve elimination targets in six Latin American countries (Hotez and others, 2008a). Evidence is even stronger for LF, as multiple rounds of mass drug administration have resulted in the elimination of this disease in China and the interruption of transmission in several other countries, including Cape Verde, Costa Rica, South Korea, the Solomon Islands, Suriname, and Trinidad and Tobago (WHO, 2008b; Hotez, 2009b). Efforts are underway to consider elimination of LF as a viable target in multiple African and Asian countries, as well as in Latin America and the Caribbean.

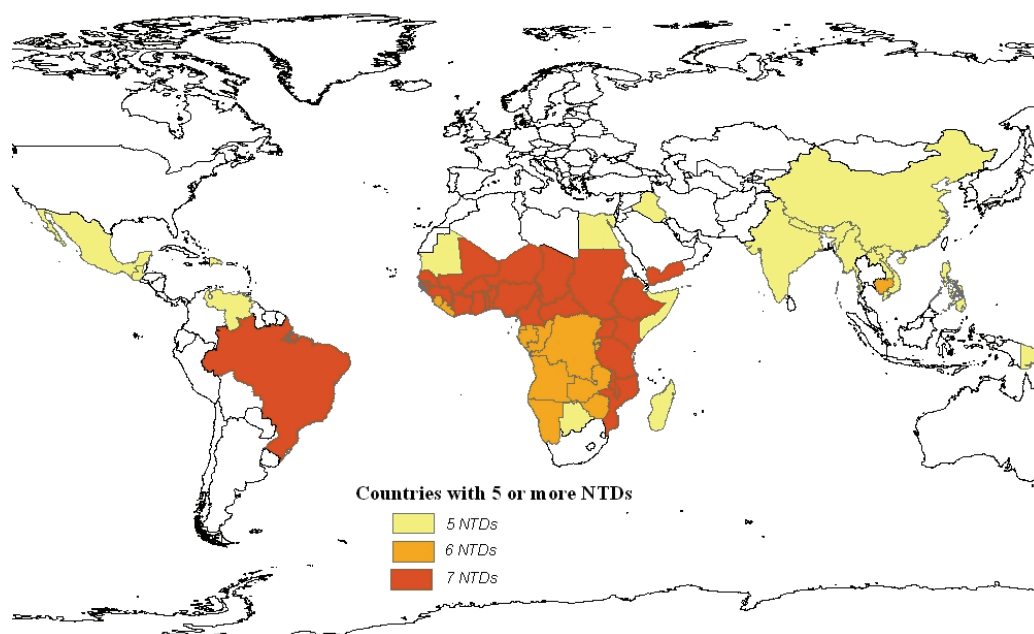
*Trachoma.* For trachoma, a single annual dose of azithromycin (Zithromax®) is provided. Through the International Trachoma Initiative, the drug is donated by Pfizer and used in a comprehensive programme of packaged interventions called SAFE, which includes surgery for trichiasis, azithromycin, facial cleansing, and environmental control and sanitation (Cook, 2008). Using the SAFE strategy, the WHO has established the Global Elimination of Blinding Trachoma by the year 2020 initiative (GET 2020). GET 2020 is feasible in part because of a commitment by Pfizer to provide 135 million doses of Zithromax® over five years (Hotez, 2009b).

*Other NTD control initiatives.* Additional efforts to control or eliminate NTDs include large-scale regional efforts that may or may not include mass drug administration. For example during the first half of the twentieth century, Gambian HAT was almost eliminated in West Africa using mobile health teams that practiced case detection and treatment with pentamidine (Hotez, 2008a). Although civil and international conflicts in Angola, the Democratic Republic of the Congo, and the Sudan have interrupted those efforts and caused a recrudescence or re-emergence of HAT, the possibility remains that such efforts could be scaled in the future with similar results. Similar efforts could be practiced in the Horn of Africa for leishmaniasis. Through vector control and a multinational coordination effort known as INCOSUR, Chagas disease has been eliminated in the southern cone of South America, with similar efforts underway elsewhere in Latin America and the Caribbean, although it is uncertain whether vector control alone will be adequate for elimination of this disease (Hotez and others, 2008a). Finally, as described above, through Carter Center efforts in collaboration with the WHO and multiple NGOs, dracunculiasis is close to elimination, with eradication considered a feasible target (Hopkins and others, 2008; WHO, 2008c; 2008d).

## 2. Integrated NTD Control

The principles and practices of integrated NTD control were summarized previously (Molyneux and others, 2005; Fenwick and others, 2005; Brady and others, 2006; Lammie and others, 2006; WHO, 2006; Hotez, 2009b; Hotez and others, 2006a; 2007a; 2009a). Briefly, in areas of high prevalence, the NTDs exhibit extensive geographic overlap, and a high percentage of the population suffers from polyparasitism with some combination of the three STH infections, schistosomiasis, LF or onchocerciasis (Raso and others, 2004; Richards and others, 2006). With the evidence base to support efficacy (Reddy and others, 2007) and safety of co-administration of albendazole, praziquantel and ivermectin, it is possible to consider integrating mass drug administration for these major NTDs (Hotez, 2009b). Ultimately, it has been proposed to add azithromycin in a “rapid impact package” of drugs to cost less than US\$0.50 per person annually (Molyneux and others, 2005; Hotez and others, 2006a). The WHO has developed treatment guidelines and algorithms to tailor the package in order to suit unique ecologies and regions, such as in Asia and the Caribbean where onchocerciasis is not present and diethylcarbamazine might be substituted (WHO, 2006; Hotez, 2009b) or in areas of Africa, Asia, and Latin America where only some of the major NTDs are endemic.

**Figure I. Map showing geographic overlap and distribution of the seven most common Neglected Tropical Diseases (NTDs)**



Source: Hotez, P. J. (2008a).

In 2008, WHO organized a new Department of Neglected Tropical Diseases. Integrated NTD control programmes are currently underway in 12 African countries, with evidence to date indicating that the remit for community directed ivermectin drug treatments could be expanded to incorporate the rapid impact package for targeting the seven major NTDs (Molyneux and others, 2005; Hotez, 2009b). In contrast, for most of Asia where the STH infections and LF are the predominant infections, the package is often comprised of diethylcarbamazine and albendazole (Hotez, 2010b), while control in Latin America and the Caribbean must consider multiple different

ecologies and vulnerable human populations (Hotez and others, 2008a). Key challenges to integrated NTD control and the major operational research objectives are described in Section J. The global financing of integrated NTD control and its regional variation are described in Section I.

## H. LINKING NTD CONTROL TO MALARIA AND HIV/AIDS

In addition to the NTDs clustering in similar geographic areas, resulting in co-endemicity and causing polyparasitism, there is strong evidence for the co-endemicity of the NTDs with malaria and HIV/AIDS, and thus opportunities to target these infections simultaneously (Hotez and others, 2006a; Hotez and Molyneux, 2008).

### 1. *Malaria and NTD Co-infections*

Evidence for the co-endemicity of selected NTDs with falciparum malaria in sub-Saharan Africa was reviewed by Brooker and colleagues (2006, 2007). Hookworm infection, in particular, was shown to overlap extensively with falciparum malaria throughout sub-Saharan Africa, except in some areas of the Sahel and in South Africa (Brooker and others, 2006). Hookworm and malaria co-infections are two of the most common tropical infections in sub-Saharan Africa. When they occur simultaneously in the same individual, these two NTDs can produce severe anaemia (Brooker and others, 2007). Presumably, IDA from hookworm infection is additive with malaria anaemia resulting from multiple different mechanisms (including hemolysis, dyserythropoiesis, and splenic sequestration). Severe anaemia is of particular concern among girls and women of reproductive age and those who are pregnant, as well as in preschool and school-aged children (Brooker and others, 2007; Hotez, 2010d). There is evidence that hookworm and other helminth infections may increase susceptibility to acquiring falciparum malaria, although there are also data refuting that association (Druilhe and others, 2005; Hotez and others, 2006a).

The severe anaemia resulting from hookworm and malaria co-infections, and possibly schistosomiasis and malaria co-infections, have prompted calls to examine possible links in public health control measures for these diseases (Sachs and Hotez, 2006). Among the opportunities are simultaneous deliveries of deworming drugs (albendazole, mebendazole, and praziquantel) and intermittent preventive treatments (IPT) with antimalarial drugs in pregnancy (IPTp), and deworming with IPT among preschool- and school-aged children (IPTc) (Brooker and others, 2007; Hotez and Molyneux, 2008). In addition, observations made by the Carter Center that use of antimalarial bed nets increases substantially when these are provided by community ivermectin drug distributors have led to suggestions that NTD and malaria control programmes be further linked (Blackburn and others, 2006; Hotez and Molyneux, 2008).

### 2. *HIV/AIDS and NTD Co-infections*

In rural areas of Africa, there is evidence of geographic overlap of HIV/AIDS and selected NTDs. The co-endemicity of urinary tract schistosomiasis (*S. haematobium* infection) with HIV/AIDS in south-eastern Africa, especially in Mozambique, Zimbabwe, and KwaZulu Natal, South Africa is of particular interest (Hotez and others, 2009b). Up to 75 per cent of women with *S. haematobium* infection also suffer from female genital schistosomiasis (FGS). In Zimbabwe, women with FGS had almost a three-fold increase in risk (odds ratio of 2.9) of acquiring HIV/AIDS (Kjetland and others, 2006). Although treatment of FGS-affected women with praziquantel does not reverse the genital pathology and probably does not reduce the risk of acquiring HIV/AIDS, there is substantial interest in determining whether regular and periodic

treatments of school-aged girls with praziquantel might prevent the development of genital lesions and reduce the likelihood of acquiring HIV/AIDS. Given the low cost of preventive chemotherapy for schistosomiasis and the interest of PEPFAR in expanding current remits to take on other global health conditions in low-income countries, there is considerable interest in adding praziquantel treatments for school-aged children to PEPFAR and possibly GFATM initiatives (Hotez and others, 2009b).

In addition to the links between FGS and HIV/AIDS, earlier studies led by a group at Ben Gurion University in Israel indicate that AIDS patients with heminth co-infections exhibit higher viral loads and more rapid depletion of CD4+ T cells (Borkow and Bentwich, 2006; Hotez and others, 2006a). Confirmation of these findings adds to the urgency of linking global AIDS programmes to NTD control, especially in rural areas of sub-Saharan Africa.

## I. GLOBAL FINANCING OF INTEGRATED NTD CONTROL

Substantial funding for several public-private partnerships working together with the WHO and health ministries in low- and middle-income countries has been provided to support mass drug administration for several high prevalence NTDs. In some cases, these public-private partnerships have been supported for decades. For example through multi-donor support, the Merck & Co.-supported Mectizan® Donation Programme and a trust fund managed by the World Bank, the African Programme for Onchocerciasis Control, has provided tens of millions of treatments in 19 countries since 1995. Similarly, the Global Programme to Eliminate LF has received multi-donor support from the British Department for International Development (DFID) and other sources, as has the Schistosomiasis Control Initiative (SCI). SCI and other partnerships have also received significant financing from the Bill & Melinda Gates Foundation. For trachoma, the International Trachoma Initiative, now based at the Task Force for Child Survival and Development, as well as several NGOs including Helen Keller International, Sight Savers, and the Carter Center has received support from Pfizer, Inc. and other donors (Hotez and others, 2007a).

Since 2006, large-scale funds to support the integration of mass drug administration have also been provided (Hotez and others, 2008c). They including an NTD Initiative supported by the United States Agency for International Development (USAID), currently operating through a private contractor known as RTI International in multiple African countries and in Haiti. In addition, DFID has provided support. Together, the United States and British Governments have committed more than US\$400 million in funds to support integrated NTD control and, at a 2008 meeting held at the Atlanta-based Carter Center, United Nations Secretary General Ban Ki-moon committed his office to making NTD control a priority issue at the annual meetings of the G8. Ultimately, some estimates suggest that US\$2 billion to US\$3 billion will be required to support integrated NTD control in all 56 endemic countries with multiple NTDs that require integrated control efforts (Hotez and others, 2009a; Hotez and others, 2008c). Such funds are comparatively modest in comparison to the US\$50 billion recently appropriated for PEPFAR.

Now, together with the WHO, many of the major public-private partnerships committed to the seven NTDs collaborate in a Global Network for NTDs. The 'Global Network' was created in 2006 at the Clinton Global Initiative in New York in order to elevate the profile of these conditions and to mobilize the resources necessary to implement national control programmes in each of the endemic countries (Hotez and others, 2009a). In 2009 at the World Economic Forum in Davos, the Gates Foundation announced a US\$34 million commitment, which the Global Network (hosted by the Sabin Vaccine Institute) would leverage into funds to treat approximately 200 million people. With Kari Stoeber as Managing Director working together with Patrick Lammie from the CDC, the

advocacy and resource mobilization arm of the Global Network will collaborate with the WHO and its regional offices to channel these funds through separate nodes in Africa, Asia and the Americas, respectively, in recognition of the unique regional aspects to NTD control and the importance of empowering national plans for NTDs. In this way, the Global Network aspires to work with existing programmes and structures to leverage and strengthen current health systems. The Latin American regional hub for NTD control was launched in the third quarter of 2009, and will operate as a partnership with the Inter-American Development Bank (IDB), the Pan American Health Organization (PAHO), and the Latin American government health ministries. It is anticipated that the African and Asian regional hubs will be launched in 2010. Discussions are in progress with the Obama administration at the White House and with Department of State to significantly expand the United States commitment to NTDs. To date, no commitments are in place for comparable support from the other G8 countries, although such discussions are underway.

## J. THE RESEARCH AGENDA

In addition to global financing for NTD control there is an urgency to support ongoing research. Among the major gaps are operational research for NTD control, and the development of new drugs, diagnostics, and vaccines.

### 1. *Operational Research*

Some of the operational research priorities surrounding integrated control of mass drug administration have been outlined previously (Hotez and others, 2007a; 2007b; Hotez, 2009b). Among the priorities, further evidence is required to support the safety, efficacy, and increased efficiencies for combining drug therapies. From several randomized clinical trials, there is evidence that albendazole/ivermectin combinations and albendazole/diethylcarbamazine combinations reduce the prevalence of STH and LF with no significant pharmacologic interactions. There is also emerging evidence for the safety of triple therapy combinations with albendazole, ivermectin, and praziquantel (Hotez, 2009b). Adding azithromycin to this triple combination must still await an expanding evidence base, however. Among the other challenges for operational research are attitudes towards patient compliance with the rapid impact package, and how administering the package bundles with other health interventions (i.e., bed nets, micronutrients, and childhood vaccinations, and the health systems in different countries of Africa, Asia, and the Americas) (Hotez and others, 2007a; 2007b). Increasingly, there are concerns regarding how health ministries will cope with providing rapid impact packages when faced with demands for other health interventions, especially those supported by GFATM and PEPFAR. Another concern is the significant gaps in mapping, especially in areas of conflict and post-conflict. Fragmentation of funding and limited availability of selected drugs are also an issue, especially praziquantel, which at roughly US\$0.30 per person annually is still too expensive for many health systems, and albendazole, which is being donated for STH infections only in areas where LF is co-endemic.

### 2. *New drugs and diagnostics*

Not many drugs are available for use in integrated NTD control, especially given the scale of mass drug administration anticipated over the next five to seven years. For example, only mebendazole and albendazole (both belonging to the benzimidazole class) are available for the billion or so people who require treatment for their STH infections, while praziquantel is the only major agent available for schistosomiasis, DEC and ivermectin for LF, ivermectin for onchocerciasis, and azithromycin for trachoma. Therefore, if drug resistance were to develop, there is not an adequate pipeline to ensure replacement for any of these agents. Because, helminths

replicate over a longer time than viruses or bacteria, there are theoretical reasons to believe that anthelmintic drug resistance is less of an imminent threat. However, widespread resistance against the benzimidazoles and ivermectin has been reported for veterinary helminths in livestock, and therefore the possibility for drug resistance developing against STH and other nematode parasites must be entertained.

For the STHs, high rates of drug failure for mebendazole against hookworm infection has already been reported, and confirmed in a recent meta-analysis by a group at the Swiss Tropical Institute (Keiser and Utzinger, 2008). The observation that the efficacy of mebendazole against hookworm diminishes with increasing use adds to this concern (Albonico and others, 2003). In addition, trichuriasis often requires multiple doses of albendazole to be effective. WHO-TDR has expressed interest in examining combination therapies such as albendazole-ivermectin to increase the activity spectrum against trichuriasis, albendazole/mebendazole-pyrantel and albendazole/mebendazole-levamasole combinations for hookworm, and albendazole/mebendazole-nitazoxanide combinations to simultaneously target STHs and some intestinal protozoa. The drug pipeline for back-up anthelmintic drugs against STHs is extremely modest. Tribendimidine has been developed in China and has an adequate antehelminthic spectrum of activity in humans (Hotez and others, 2006b), but it is not clear whether the drug file for this agent is adequate for international regulatory agencies. Novartis has developed an exciting new class of aceto-nitrile compounds for veterinary helminths, but no efforts are underway to translate these discoveries for human STH infections. Currently, no product development partnerships (PDPs) for new STH drugs exist.

For LF and onchocerciasis, both ivermectin and diethylcarbamazine primarily target the microfilarial stages of the parasite and must be administered yearly because the adult female worms can resume production of microfilariae following treatment. A group based at the McGill University Institute of Parasitology has published evidence for ivermectin resistance (Osei-Atweneboana and others, 2007), but this has not been universally accepted (Hotez, 2007). Nonetheless, the need for back-up agents remains great. Wyeth, in collaboration with WHO-TDR is exploring the compound moxidectin, while groups at the Liverpool School of Tropical Medicine and elsewhere are exploring antibiotics for use against the bacterial endosymbionts found in filarial parasites (Hotez and others, 2007a). For schistosomiasis, a new drug target is under development by a group based at Rush University Medical Center in collaboration with the National Institutes of Health Chemical Genomics Center (Simeonov and others, 2008). For both LF and schistosomiasis completed genome projects should facilitate the exploration of new drug targets in the coming years (Scott and Ghedin, 2009; Berriman and others, 2009). There is also a great need for improved field-based diagnostics to detect LF and onchocerciasis

Several PDPs are in place for developing new drugs for kinetoplastid infections (Chirac and others, 2006; Renso and McKerro, 2006). They include the Drugs for Neglected Diseases Initiative, which is exploring nifurtimox and eflornithine combinations for HAT, as well as additional drugs for Chagas disease and leishmaniasis, the Institute for One World Health, which has recently obtained licensure for paromomycin for use against leishmaniasis in India, as well as university-based PDPs at the University of North Carolina, University of California, University of Dundee, and the Seattle Biomedical Research Institute. These activities should increase following completion of genome projects for African trypanosomes, *T. cruzi*, and *Leishmania* spp (El Sayed and others, 2005). In addition to the PDP activities, Sanofi-Aventis has been manufacturing urgently needed existing drugs for HAT and other NTDs.

### 3. *New Vaccines*

Three PDPs have been established for NTD vaccines (Hotez and Brown, 2009; Diemert and others, 2008; Hotez and Ferris, 2006; Bethony and others 2011). For helminth infections, the Sabin Vaccine Institute is developing vaccines to combat hookworm infection caused by *N. americanus* and intestinal schistosomiasis caused by *S. mansoni* (Diemert and others, 2008; Hotez and others, 2008d), while the Institut Pasteur is developing a vaccine for *S. haematobium* infections (Capron and others, 2005). The Sabin vaccines are in early clinical development in Minas Gerais State, Brazil, while the Pasteur vaccine is being tested in Niger and Senegal. These anthelmintic vaccines would be used following deworming in a programme of vaccine-linked chemotherapy (Bergquist and others, 2005). In the case of the human hookworm vaccine, a key target is to overcome mebendazole drug failure (Hotez and Ferris, 2006; Diemert and others, 2008). The Infectious Disease Research Institute (IDRI) is also developing a therapeutic vaccine for leishmaniasis, which is in clinical trials in Latin America and elsewhere. IDRI is also developing several platform adjuvants for use by the PDP community. Both Sabin and IDRI are developing these innovative projects in collaboration with several key Brazilian institutions including the Oswaldo Cruz Foundation (FICOCRUZ) and Instituto Butantan with partial support from the Brazilian government in addition to Gates Foundation support. Brazil and other so-called “innovative developing countries” (IDCs) represent critical elements of future vaccine development for NTDs (Morel and others, 2005). This includes an important role for the members of the Developing Country Vaccine Manufacturers (DCVM). In addition to these PDPs, within the last year, two large multinational pharmaceutical companies have launched global health vaccine institutes. Novartis has established a global health institute for vaccines in Italy, while in a joint venture with the Wellcome Trust, Merck & Co., Inc has established a new global health vaccine initiative in India. Both of these institutes will focus initially on vaccines for neglected bacterial infections.

### 4. *Research financing*

The 10/90 gap refers to the 10 per cent availability of research funds that go to support the diseases afflicting 90 per cent of the world’s population, i.e., diseases of low- and middle-income countries. However, for the NTDs the gap is close to a 1/99 or in some cases even a 1/999 gap. The George Institute in Australia has issued a report on the state of research and development (R&D) for the NTDs and other global health conditions. Currently most of the R&D expenditures for NTDs are from the Bill & Melinda Gates Foundation, the Wellcome Trust, the United States National Institutes of Health, and WHO-TDR. Ultimately, however a global fund for R&D is going to be required to truly make inroads into support for the NTDs.

### K. TRAINING

Training of a new generation of global health scientists will be needed in order to meet workforce demands for the major areas of NTD control. In the areas of mass drug administration and integrated control of the major NTDs, training will be required for the staff of low- and middle-income health ministries not only for drug distribution and administration, but also for the key areas of monitoring and evaluation. This would include elements of whole organismal biology in the areas of medical parasitology and entomology. In addition to health ministries, in Africa and possibly elsewhere, there is a cadre of almost 500,000 community drug distributors and community health workers that were trained through the African Programme for Onchocerciasis Control for purposes of ivermectin distribution, but who now could expand their remit to embrace integrated NTD control. Teachers are also important allies in the administration of NTD drugs to school-aged



children. A programme of expanded training is critical for these community health workers and teachers for future successes in NTD control.

In the area of research and development, there are several high priorities for future training. Among them, at most United States and European public health and medical schools, whole organismal parasitology and entomology, as well as bacteriology and virology have been deprioritized over the last few decades (Hotez, 2008c). As a result very few public health and medical graduates can identify the major pathogens responsible for the NTDs. While adequate training in these appropriate technologies occurs in the major European schools and institutes of tropical medicine, there is no similar entity in the United States. Similarly, these skills are also being de-emphasized in many universities located in low- and middle-income countries.

For product development, much of the new drugs, vaccines, and diagnostics for NTDs are being developed for PDPs. There are needs for training in areas such as process development, formulation, pilot cGMP manufacture, quality control and assurance, and clinical trials (Hotez, 2008c). It has been suggested that a new school for appropriate technology in global health be established (Hotez, 2008c).

#### L. NTDs, HUMAN RIGHTS, AND MEDICAL DIPLOMACY

The NTDs are the most common infections of the world's poor and they disproportionately affect key vulnerable populations including women in low- and middle-income countries, children, aboriginal populations, and people of African descent. In so doing they trap these populations in poverty (Hotez and others, 2009a). For these and other reasons, access to essential medicines for the NTDs have been recognized a fundamental human right, while there is a similar rationale for providing the world's poor with access to innovation through the development of new NTD drugs, diagnostics and vaccines. There is also a potential foreign policy dimension for NTD control (Hotez, 2006; Hotez, 2009c). Hotez and Thompson (2009) have noted a geographic overlap between nations with high prevalence NTDs and the likelihood of civil and international conflict. Some of these nations include those belonging to the Organization of the Islamic Conference (Hotez and others, 2009c). While conflict clearly promotes the breakdown of public health infrastructure, thereby allowing re-emergence of NTDs and other infections (Beyrer and others, 2007), there is also a rationale for the converse, i.e. NTDs promoting conflict. Among the mechanisms proposed for this role of the NTDs are destabilization that results from impaired agricultural productivity, food insecurity, and even abandonment of agriculturally rich areas because of widespread blindness and disability that result from some of the vector-borne NTDs, such as onchocerciasis and LF (Hotez and Thompson, 2009). In addition, the role of childhood NTDs such as hookworm and schistosomiasis in impairing development and cognition and, therefore, ignorance and backwardness should not be underestimated. These concepts of "medical diplomacy" and their relationship to NTD control requires further exploration, as does the role of NTD medical research and development as a viable approach in assuring mutual scientific cooperation between nations.

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