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The Neglected Tropical Diseases: The Ancient Afflictions of Stigma and Poverty and the Prospects for their Control and Elimination

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1. Introduction

The World Health Organizations and other international health agencies identify a select group of 13 tropical infections as the neglected tropical diseases (NTDs). These diseases, which include leprosy, kala-azar, river blindness, guinea worm, schistosomiasis, hookworm and lymphatic filariasis, strike the world's poorest people living in remote and rural areas of low-income countries in Sub-Saharan Africa, Asia and the Americas. They inflict suffering by causing life-long disabilities, disfigurement, reduced economic productivity, and social stigma (WHO, 2003). Unlike better-known global health threats such as HIV-AIDS, malaria, and tuberculosis, the NTDs do not receive enough international attention. Instead, they are neglected diseases among forgotten people found only in the setting of geographic isolation and intense poverty (Molyneux, 2004).

Impoverished and marginalized populations with the NTDs represent the lowest priority markets for U.S. and European pharmaceutical manufacturers. The NTDs do not occur in the industrialized world or even among the substantial wealthy and middle-classes in developing countries. They are not a significant health risk for foreign travelers or the military. This is in contrast to the more substantial commercial markets for HIV-AIDS, malaria and tuberculosis ("the big three"). The recent creation of massive funding schemes for the big three, such as The Global Fund to Fight AIDS, Tuberculosis, and Malaria, and the U.S. President's Emergency Plan for AIDS Relief provides additional financial incentives, as well as a certain amount of panache and luster. In contrast, the commercial market for NTD drug

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and vaccine development is essentially zero, and there is as yet no Bono or equivalent celebrity to champion its cause.

Since the millennium, the hopeless outlook for those afflicted with the NTDs has undergone a surprising turnaround. Through unprecedented advocacy and the creation of new and innovative public-private-partnerships, often based on generous pharmaceutical company donations of effective products, several NTDs have been targeted for control or elimination. Although not well known by the lay public, a silent revolution is gathering, which could alleviate some of our planet's greatest health disparities.

2. The NTDs as the Ancient Afflictions of Stigma and Poverty

The NTDs are caused by parasitic worms, protozoa, and the bacterial agents of leprosy, Buruli ulcer, and trachoma (Table 3.1). Unlike the well-publicized newly emerging infections, such as Ebola, West Nile fever, or avian influenza, the NTDs have burdened humanity since the beginning of recorded history (WHO, 2003). Descriptions of leprosy, schistosomiasis, guinea worm, hookworm, trachoma and other NTDs are found in the Bible (Dirckx, 1985; Hulse, 1971; Ceccarelli, 1994), the Talmud (Ostrer, 2002), *Papyrus Ebers* (c.1550 B.C.), *Kahun papyrus*

Table 3.1. The Neglected Tropical Diseases

Parasitic Diseases (Protozoan)	Etiologic Agent
Kala-azar (Visceral leishmaniasis)	*Leishmania donovani*
African Sleeping Sickness (African trypanosomiasis)	*Trypanosoma gambiense* and *T. rhodesiense*
Chagas Disease (American trypanosomiasis)	*Trypanosoma cruzi*
Parasitic Diseases (Helminth)	
Schistosomiasis	*Schistosoma haematobium, S. mansoni, S. japonicum*
Lymphatic Filariasis (elephantiasis)	*Wuchereria bancrofti* and *Brugia malayi*
Onchocerciasis (river blindness)	*Onchocerca volvulus*
Dracunculiasis (guinea worm)	*Dracunculiasis medinensis*
Soil-transmitted Helminthiases	
Ascariasis (roundworm)	*Ascaris lumbricoides*
Trichuriasis (whipworm)	*Trichuris trichiura*
Hookworm	*Necator americanus* and *Ancylostoma duodenale*
Bacterial Diseases	
Leprosy	*Mycobacterium leprae*
Buruli Ulcer	*Mycobacterium ulcerans*
Trachoma	*Chlamydia trachomitis*

Table 3.2. Annual Deaths from the Neglected Tropical Diseases[1]

Kala-azar	51,000
African Trypansomiasis	48,000
Schistosomiasis	15,000
Chagas disease	14,000
Soil-transmitted Helminthiases[2]	12,000
Leprosy	6,000
Lymphatic Filariaisis	0
Onchocerciasis	0
Guinea Worm	0
Total Neglected Diseases	146,000

[1]World Health Report 2004 (Annex Table 2).
[2]Ascariasis, Hookworm, and Trichuriasis.
[3]Some estimates indicate that African trypanosomiasis causes 100,000 deaths, leishmaniasis 100,000 deaths, hookworm 65,000 deaths, and schistosomiasis 150,000–280,000 deaths annually. Therefore more than 500,000 deaths annually may result from NTDs.

(c.1900 B.C.), the writings of Hippocrates and other ancient texts (Grove, 1990). Joshua's curse and the abandonment of Jerico's walls have been attributed to schistosomiasis (Hulse, 1971), while guinea worms (*Dracunculiasis medinensis*) are believed to be the "fiery serpents" that attacked the Israelites in the desert during their exodus from Egypt (Grove, 1990).

Every year, the NTDs annually kill at least as many people as were killed as a result of the 2004 Christmas tsunami (Table 3.2). Some estimates suggest that more than 500,000 people die annually from NTDs. However, their overall toll cannot be measured by mortality alone. Generally speaking, the NTDs cause much more chronic disability and morbidity rather than death. For instance, Chagas disease causes a chronic and disabling heart condition; hookworm, chronic intestinal blood loss and anemia; onchocerciasis, blindness and intense itching that results in chronic skin changes; guinea worm, localized pain that prevents temporary disuse of a lower limb.

Whereas it is relatively easy to understand the significance of death rates and mortality figures, it is more difficult to translate chronic disability and morbidity into a value that is readily understood by public health officials and health advocates. The human toll from the NTDs is better explained in terms of their disease burden using the disability-adjusted life year (DALY) as a metric. When measured in DALYs (Murray, 1996), the NTDs account for approximately one-quarter of the global disease burden from HIV-AIDS and almost the same burden as malaria (Table 3.3). Even these high DALY figures are probably underestimates based on new studies pointing out the hidden morbidity and mortality of chronic infections with schistosomiasis, onchocerciasis and other NTDs (King et al., 2005; Little et al., 2004; Hotez et al., 2004a).

The NTDs also have a huge social impact due to lost educational potential, reduced economic productivity, and stigma. Schistosomiasis and hookworm impair the ability of school-aged children to learn in school (King et al., 2005; Hotez

Table 3.3. The Neglected Tropical Diseases Ranked by Disease Burden (DALYs 000)[1]

Lymphatic Filariasis	5,654
Soil-transmitted Helminthiases[2]	4,706
Kala-azar	2,357
Trachoma	2,329
Schistosomiasis	1,760
African Sleeping Sickness	1,598
Onchocerciasis	987
Chagas Disease	649
Leprosy	177
Buruli Ulcer	<100
Guinea Worm	<100
Total Neglected Diseases	20,217
Total HIV-AIDS[3]	84,458

[1]WHO, World Health Report 2002.
[2]Ascariasis, Hookworm, Trichuriasis.
[3]WHO, World Health Report 2004.

et al., 2004a), while lymphatic filariasis, guinea worm and river blindness result in missed days of work for adults, especially the family breadwinner (Little et al., 2004). This includes the loss of US $1 billion annually from lymphatic filariasis in India alone (Ramaiah et al., 2000), and $5.3 billion from blinding trachoma (Frick et al., 2003), and substantial reductions in future wage-earning capacity as a result of chronic hookworm infection in childhood (Bleakley, 2003). Therefore, the NTDs not only occur in the context of poverty, but through their adverse social impact they also promote poverty (WHO, 2002). The stigmatizing nature of the NTDs often causes afflicted individuals to shun social contact or seek medical attention (WHO, 2002). There is also an intimate link between the incidence of NTDs and conflict. The interruption of public health services and forced human migrations resulting from decades of wars in Angola, Congo and Sudan, for example, has produced resurgence in African sleeping sickness, kala-azar, and guinea worm (Molyneux, 1997; Ekwanzala et al., 1996; Hotez, 2001).

3. The Role of the Pharmaceutical Industry

By the year 2015 each of the 191 United Nations member states have pledged to meet a set of Millennium Development Goals for global health and human rights (Table 3.4). Considering the NTDs probably impact on more of these goals than any other single entity it is astonishing that the NTDs still retain their neglected status. The global pharmaceutical industry failure to invest in new drugs for these diseases has produced particularly serious consequences. Of the 1,233 drugs commercialized worldwide between 1975 and 1997 only 4 were developed specifically for the NTDs (Pecoul et al., 1999; Kremer and Glennerster, 2004). The Pharmaceutical Manufacturers of America similarly reports that only a single drug for the NTDs was in the

Table 3.4. Reducing Neglected Tropical Disease Burden Impacts on 7 of the 8 UN Millennium Development Goals

1. *Eradicate extreme poverty and hunger*
2. *Achieve universal primary education*
3. *Promote gender equality and empower women*
4. *Reduce child mortality*
5. *Improve maternal health*
6. *Combat HIV/AIDS, malaria and other diseases*
7. Ensure environmental sustainability
8. *Develop a global partnership for development*

pipeline for 2000, compared with 8 for erectile dysfunction, 7 for obesity, and 4 for sleep disorders (Medicins Sans Frontieres, 2001).

The absence of drug research and development (R&D) means that we have only a handful of available drugs for the NTDs and no vaccines. Many of the existing drugs were developed more than 50 years ago, and are themselves highly toxic. For example, the drug of choice used to treat the late stages of African trypanosomiasis is an arsenic-containing compound known as melarsoprol developed in the 1940s. The treatment goal is essentially to use the arsenic to poison the trypanosomes before seriously affecting the patient. A toxic antimony-containing compound is still the treatment of choice for kala-azar (visceral leishmaniasis) in many parts of the world. The absence of R&D and interest in manufacturing new drugs for the NTDs reflects their market failure. The last 50 years have been a dark age for the R&D and manufacture of NTDs drugs and vaccines.

4. New Promise Through Public Private Partnerships

Are we emerging from the dark ages? In 1988, the pharmaceutical giant, Merck & Co., Inc., and later, GlaxoSmithKline and Pfizer, inaugurated a series of extraordinary NTDs drug donation programs. The Ivermectin Donation Program (Merck & Co., Inc.), a partnership with the WHO, the Task Force for Child Survival, and other non-governmental organizations (www.mectizan.org) began after the announcement by Roy Vagelos, Merck CEO, that his company would donate the drug free of charge for as long as needed to anyone with river blindness (Levine, 2004a). Over the last 17 years the Donation Program has provided more than 300 million treatments at roughly $1.50 per dose (Levine, 2004a).

Ivermectin was not in fact developed by Merck to treat river blindness or LF, but rather as part of its veterinary discovery efforts to identify promising new compounds for parasites of livestock. Unlike the NTDs of humans, the parasitic diseases of cattle and sheep represent a market that exceeds US$ 1 billion annually. In 1987, Ivermectin was the ranked as Merck's second best selling drug (Levine, 2004a). When Ivermectin was shown to be safe and effective for the treatment of human river blindness in Africa Merck & Co., Inc. appropriately realized that its small

commercial human market was not worth efforts to sell the drug as a medical product. They chose instead to donate it in an extraordinary and at the time unique gesture of good will and corporate philanthropy. However, the fact that the drug required donation for widespread medical use illustrates the reluctance of the pharmaceutical industry to embark on R&D for the NTDs. Despite the clear success of the Mectizan® Donation Program in relieving human suffering, it did not overcome the hurdles that block R&D and manufacture of new products.

The barriers in NTD product R&D started to erode beginning in the late 1990s through the establishment of a new type of non-profit entity. Known as the Product Development Private-Public-Partnership (PD-PPPs), these non-profits embrace industry practices and collaboration, using private sector approaches to attack R&D challenges, and develop products for developing countries (Widdus and White, 2004). New private public partnerships include vaccine development initiatives for leishmaniasis, hookworm, and infectious diarrheas, and drug development initiatives for leishmaniasis, African trypanosomiasis, and Chagas disease (Table 3.5). This is resulting in an unprecedented involvement of the non-profit sector in the manufacture and testing of new products. A major stimulus to establish PPPs was a quantum leap in funding (referred to as "push mechanisms") that began in 1999 (Hotez, 2004a), including key contributions from the Bill and Melinda Gates Foundation. The U.S. Orphan Drug Act, which provides tax credits and grants for diseases of fewer than 200,000 in the U.S. (Kremer and Glennerster, 2004), and NIH small business innovation grants, which foster academic partnering to manufacture new products, also provided incentives.

Concurrent with the opportunities created by private push mechanisms, many middle-income countries have dramatically increased their contributions to government-sponsored R&D. The term *innovative developing country* (IDC) has been applied to nations such as Brazil, China, Cuba, Egypt, India, South Africa, and South Korea, which have modest economic strength but are relatively advanced with respect to their sophistication in health biotechnology and government-supported research and development (Morel et al., 2005). The IDCs have capacity for producing their own pharmaceuticals and vaccines; at the same time, all except South Korea suffer from endemic NTDs. This creates a unique mix that encourages these

Table 3.5. Major Public Private Partnerships Committed to the Neglected Tropical Diseases

Drugs for Neglected Diseases Initiative – DNDi (Geneva)
WHO Partnership for Parasite Control – PPC (Geneva)
Institute for One World Health (IOWH) (San Francisco CA)
Diseases of the Most Impoverished – DOMI (Seoul Korea)
Human Hookworm Vaccine Initiative – HHVI (Wash DC)
International Trachoma Initiative (New York NY)
Infectious Diseases Research Institute (Seattle WA)
Global Alliance to Eliminate LF (Liverpool UK)
Schistosomiasis Control Initiative (London UK and Boston MA)
African Programme for Onchocerciasis Control (APOC)
Onchocerciasis Elimination Programme in the Americas (OEPA)

nations to begin solving their own NTDs problems with only modest technical or financial assistance from more developed countries.

5. Vertical Control Efforts

The new PPPs and IDCs are providing a new generation of products (often referred to as "tools") to control the NTDs. However, in the meantime, another group of PPPs, which include the Global Alliance to Eliminate Lymphatic Filariasis (GAELF), the Schistosomiasis Control Initiative (SCI), the International Trachoma Initiative (ITI), the African Programme for Onchocerciasis Control (APOC), and several initiatives focused on leprosy, are directly working to apply existing and new tools to disease control. To date, these PPPs are having an enormous impact on reducing NTD disease prevalence and burden through vertical control programs. For example, through APOC, a 15-year partnership of the endemic countries World Bank, WHO, NGDO's and other international organizations, more than 67 million doses of Mectizan® have been distributed and administered through a system of community-directed treatment – ultimately the program aspires to scale up to about 90 million yearly treatments and to prevent 43,000 cases of blindness annually (Levine et al., 2004a). Similarly, through widespread use of two drug combinations comprised of either diethylcarbamazine and albendazole, or Mectizan® and albendazole the GAELF is making dramatic progress in reducing the global disease burden of LF (Molyneux and Zagaria, 2002). The ITI is reducing the global burden of blinding trachoma through use of the Pfizer-donated antibiotic Zithromax®, surgery for trichiasis, and complementary hygienic measures (environmental and sanitation and face washing SAFE strategy) (Mecaskey et al., 2003), and the number of new cases of leprosy has been dramatically reduced through combination antibiotic therapy (Lockwood and Suneetha, 2005). Through the use of a synthetic long-acting pyrethroid insecticide, an initiative known as the Southern Cone Initiative to Control/Eliminate Chagas Disease has dramatically reduced or halted the incidence of new cases of Chagas Disease in Argentina, Bolivia, Brazil, Chile, Paraguay, Uruguay and Peru since it began in 1991 (Levine et al., 2004b). Most dramatic of all, is the progress in guinea worm control with a 98 percent reduction in the number of cases worldwide since control efforts began in the early 1980s (Hopkins et al., 2002). Finally, LF in China and schistosomiasis in Egypt have been controlled beyond expectations by long-term investment in government sponsorship and World Bank investment in control activities. The reasons for these successes include donor commitment, regional approaches, specific technical needs, and the absence of emerging drug or insecticide resistance (WHO, 2003).

If these trends continue the WHO projects that some important NTDs, such as lymphatic filariasis, river blindness, Chagas disease, blinding trachoma, guinea worm, and leprosy, may be eliminated by the year 2020. The term *elimination* refers to the reduction of disease incidence to zero but requiring ongoing public health measures to prevent reemergence (Hotez et al., 2004b; Molyneux et al., 2004). Elimination of some of the NTDs is considered feasible because disease transmission could be interrupted with specific control tools, and does not require sanitation and clean water, which are far more costly (WHO, 2003).

6. Integrated Control

There is additional excitement in the NTD scientific and public health community about the possibility of bundling some of these vertical control efforts in a program of integrated control (Molyneux and Nantulya, 2004; Molyneux et al., 2005). With four drugs, albendazole, Mectizan®, Zithromax®, and praziquantel, it is possible to target seven of the NTDs, namely lymphatic filariasis, onchocerciasis, hookworm, trichuriasis, ascariasis, schistosomiasis, and trachoma in areas where they geographically overlap, such as in Sub-Saharan Africa and focal regions of the Americas (Fenwick et al., 2005; Molyneux et al., 2005). In poor and rural areas in Africa it is not uncommon to identify individuals who are polyparasitized with three or more NTD etiologic agents. The four drugs are mutually compatible in terms of delivery approaches. Through integrated control efforts the international community could potentially control or eliminate morbidity and blindness from these NTDs, and at a fraction of the cost needed to control other diseases (Fenwick et al., 2005).

The Commission for Africa, established by the Britain's Prime Minister Tony Blair recognized the importance of NTDs in their 2005 report (www.commissionforafrica.org). In response to the Commission's calls to implement pro-poor strategies, Fenwick et al. (2005) determined that approximately 500 million people at risk for NTDs in Africa could be treated with all four drugs at a cost of $200 million annually, or $0.40 per patient if these resources were allocated as a package. These figures take into consideration that the multinational corporations Merck, GSK, and Pfizer have committed to donating three of the four drugs, Mectizan®, albendazole, and Zithromax®, respectively.

7. New Generation Control Tools

Despite their promise, the NTD vertical and integrated control efforts are still fragile owing to their one- dimensional reliance on a single chemical agent or drug combination to achieve their intended goals (Hotez, 2004b). Therefore unanticipated drug resistance or other product failures could reverse their success. An example is the near eradication of malaria in India in the early 1960s, which was undermined by the rising costs of DDT to control mosquito populations, outright DDT resistance, and chloroquine anti-malarial drug resistance (Harrison, 1978). As a result, malaria returned to previous levels. Had ongoing R&D continued to generate new control tools, malaria could possibly have been eliminated in India. Similarly, vertical and integrated control efforts directed against hookworm are not likely to be effective in reducing transmission because of the variable efficacy of benzimidazole anthelminthic agents (e.g., albendazole or mebendazole), the high rates of post-treatment hookworm re-infection that occurs in areas of high transmission, and the diminishing efficacy of benzimidazoles with frequent and periodic use (Hotez et al., 2005). These lessons raise the stakes for the activities of the PPPs and IDCs. Unless new control tools are developed the promise for eliminating the NTDs may not be realized.

Successful elimination will therefore require further R&D investment. In 2003, the NIH Director established a Roadmap for the development of new therapies (www.nih.gov/roadmap). Although primarily intended for disease in the industrialized world, this also affords an opportunity to target the NTDs (Hotez, 2004b). In addition, the Bill and Melinda Gates Foundation has made significant investments in the development of new generation vaccines for NTDs including leishmaniasis and hookworm, and new drugs for African sleeping sickness, leishmaniasis, Chagas disease (www.gatesfoundation.org) (Hotez, 2001; Hotez et al., 2005). These new tools could become urgently needed in the face of emerging drug resistance. We might be facing once-in-a-lifetime opportunities to forever eliminate humankind's most ancient scourges. Never has the time been so propitious for ending centuries of neglect.

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