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Neglected Tropical Diseases

0.0 Introduction

Global attention to infectious disease is focused on the HIV/AIDS, tuberculosis and malaria with good reason; the "big three", as they are called, were responsible for 5.6 million deaths in 2001 and are responsible for 39% of all deaths attributed to infectious disease (Engels and Savioli, 2006; Hotez *et al*., 2006a; WHO, 2003). Focus on the big three, as well as acute emerging and re-emerging diseases such as the Ebola virus and avian influenza, has resulted in flurry of funding, research and development and public interest in these areas (Molyneux, 2004; Hotez *et al.,* 2006b; Hotez *et al*., 2007a). Unfortunately, this attention has not extended to a group of parasitic and microbial diseases called the Neglected Tropical Diseases (NTDs). These diseases are largely overlooked due to their low mortality rate and the poverty of their sufferers (Hotez *et al*., 2007a; WHO, 2003). NTDs are responsible for about 534 000 deaths per year; this number does not reflect the long term suffering or the enormous and frequently underestimated socio-economic burden of the billion people who have one or more NTDs (Engels and Savioli, 2006; Hotez *et al*., 2006a; WHO, 2003; WHO, 2006). The bacteria and macro-parasites which characterize the NTDs share a similar distribution among impoverished and mostly tropical environments and typically result in disability and disfigurement (WHO, 2003; WHO, 2006). Although there are inexpensive drugs and treatments available to treat some NTDs, programs to distribute these drugs as well as research and development for new diagnostic tools and pharmaceuticals are seriously lacking (Hotez *et al.*, 2007; Morel, 2003; WHO 2006). Treatment and control of NTDs would alleviate a great deal of the suffering and huge economic burden of endemic countries (WHO, 2007). WHO, other international bodies and private organizations have begun to take notice and measures, such as WHO's "Global Plan", have been put in place (WHO, 2007; Morel, 2003). In the following paragraphs, we set out to describe the NTDs and their socioeconomic burden as well as the possibility of their control, prevention and treatment.

1.0 What are the NTD's?

WHO has identified a list of 13 of the most important NTDs; although not exhaustive, this list includes bacterial and macro-parasitic infections which are frequently vector-borne or spread by unhygienic living conditions (Hotez *et al*., 2006b; WHO, 2006; WHO, 2007). Evidence of the suffering caused by these diseases can be found in the earliest recordings of human history (Hotez *et al*., 2006b). The biologically and medically diverse group of organisms that compose the NTDs are related by their affinity for impoverished and rural environments, overlapping distributions, low mortality, and by their ability to debilitate

and disfigure their hosts (Hotez *et al*., 2006b; Hotez *et al.*, 2007; WHO, 2003). Clean water, sanitation, safe food, and medical resources are frequently unavailable in areas where NTDs are endemic; additionally, NTDs tend to promote conditions of poverty due their negative effects on adult productivity and childhood development (Hotez *et al*., 2006b; WHO, 2007).

There are three bacterial NTDs, three caused by protozoans and seven by helminths (Hotez *et al*., 2006a; Hotez *et al.*, 2007; WHO, 2003). Ranked by annual death rate, they are: leishmaniasis, African trypansomiasis, schistosomiasis, Chagas disease, soil-transmitted helminths, leprosy, lymphatic filiarisis, onchocerciasis, and guinea worm (Hotez *et al*., 2006b).

1.1 Protozoans

Leishmaniasis is an ancient disease caused by protozoans from the *Leishmania* genus and transmitted by the bite of a sandfly. It has four subtypes of varying severity, which include cutaneous and visceral infections. Cutaneous infection results in the formation of disfiguring lesions which frequently occur on the face, arms and legs. Lesions may remain anywhere from a few weeks to over a year; secondary lesions may also occur years after the initial lesion has healed (Heymann, 2004). Visceral cases can result in anaemia, fever, debility and death if left untreated (WHO, 2003).

Sleeping sickness, also called Human African trypanosomiasis, has been devastating Sub-Saran Africa for the last 200 years in intermittent intervals. It is endemic in over 60 countries, and is limited by the distribution of the tsetse fly, which acts as its vector (Heymann, 2004). Depending on the subtype, this disease may take anywhere from a couple of weeks to a few years to progress. Without treatment, this progression is inevitably fatal. It initially affects the lymphatic and circulatory systems and eventually moves to the brain by crossing the blood-brain barrier (WHO, 2003).

Chagas disease, also known as American trypanosomiasis, is transmitted by fecal contamination of the triatomine insect, via insect bites or other compromises of the skin barrier. Symptoms have an acute and chronic phase; the chronic phase may be asymptomatic or may target digestive and/or cardiac tissues (WHO, 2008a). Infection can cause irreversible and chronic damage to affected organs such as the heart; this can be quite dramatic in AIDS patients or others with compromised immune systems (Heymann, 2004; Hotez *et al.,* 2006b).

1.2 Helminths

Schistosomiasis is caused by blood flukes from the *Schistosoma* genus. The disease affects hundreds of millions of people worldwide, typically targets the urinary system, liver, and

kidneys (WHO, 2003). The eggs of the blood fluke are primarily responsible for the symptoms. The severity of the illness depends on the number and location of the eggs. The life cycle of the infectious *Schistosoma* spp. typically require an aquatic molluscan host; human infection occurs via exposure to larvae in contaminated bodies of water (Heymann, 2004).

Soil-transmitted helminthiasis is caused by a group of intestinal worms, namely the hookworms, whipworms (*Trichuris trichiura*) and roundworms (*Ascaris lumbricoides*). As the name implies, these worms are transmitted via contact with contaminated soil; such contamination usually occurs from the deposition of egg-infested fecal matter. The severity of the symptoms depends on the load and type of helminth. Although infection may appear to be asymptomatic, the burden of these diseases is extremely large; infected individuals may suffer from anaemia and nutritional deficiency, which may lead to physical and cognitive development in young children (Heymann, 2004; WHO, 2003).

Lymphatic filiariasis has been a scourge of humanity for at least 4000 years; it is currently the second leading cause of disability worldwide, which is no surprise considering that the causative agents are endemic in over 80 countries (WHO, 2003). It is caused by threadlike worms belonging to a family of mosquito-borne nematodes which inhabit the lymphatic system of infected individuals. Depending on the severity of infection, sufferers may experience anything from sub-clinical levels of lymphatic damage to disfiguring and incapacitating elephantiasis in their extremities (Heymann, 2004; WHO, 2003).

Onchocerciasis, also commonly known as river blindness, is caused by another filial nematode, *Onchocerca volvulus*. It is transmitted by blackflies, which act as an intermediate host, living near fast-moving bodies of water (WHO, 2003). Adult worms may form fibrous nodules in subcutaneous tissues or near the bones and joints of their hosts and may live for up to 14 years causing chronic and nonfatal disease (Heymann, 2004; WHO, 2003). Many of the clinical symptoms of river blindness are a result of the inflammatory response of the immune system to the migration of thousands and thousands of larvae, called microfilariae, discharged by adult worms. The migration and deaths of microfilariae damage surrounding tissue or organs, causing intense itching and disfigurement; ocular degeneration and blindness occur when microfilariae migrate to the eyes (Heymann, 2004; WHO, 2003).

Dracunculiasis, commonly called the guinea worm disease, is caused by the nematode *Dracunculus medinensis*. Individuals are infected by drinking water contaminated with water fleas, which act as an intermediate host and carrier of larvae (WHO, 2003). These nematodes affect the subcutaneous tissue as the adult female migrates through the human

body to the foot, generally, where they eventually create an ulcer when gravid. If left untreated, the nematode will eject larvae when exposed to fresh water, which the host will do to alleviate the burning and itching caused by the worm; the lesion may also acquire a secondary infection if improperly cared for (Heymann, 2004; WHO, 2003). The pain from Guinea worm disease can be disabling, which is of great concern as outbreaks tend to occur at times of agricultural importance (Hotez *et al.,* 2006b; WHO, 2003).

1.3 Bacterial Disease

Leprosy, another ancient scourge of human kind, is a chronic disease caused by *Mycobacterium leprae* (Heymann, 2004). Due to the development of multidrug therapies global prevalence of the disease was reduced by 90% between 1985 and 2001 (WHO, 2003). Unfortunately treatment is not always available to the very poor and sufferers may continue to experience the shunning and social stigma long associated with the disfiguring and disabling effects of the disease (Heymann, 2004). Close personal contact is believed to be required for transmission although the exact mode of transmission is unknown (Heymann, 2004). The disease may take anywhere from 9 months to 20 years to incubate and has a wide array of clinical manifestations varying between lepromatous and tuberculoid forms. The skin, upper respiratory tract, peripheral nerves are typically affected by the disease; sufferers display skin lesions and loss of sensory ability in affected areas (Heymann, 2004; WHO, 2003).

The **Buruli ulcer** is an emerging mycobacterial disease caused by *Mycobacterium ulcerans* which has seen a steady increase in reported cases over the last 25 years (Heymann, 2004). The disease typically affects the skin in the form of a painless ulcer resulting from the damage caused to the subcutaneous fat layer by the bacterium's necrotic toxins; untreated, it can also affect the bones and joints causing permanent disfigurement and disability (Heymann, 2004; WHO, 2003). Like leprosy, the mode of transmission is currently unknown (WHO, 2003). Treatment is very costly, and requires the removal of infected tissue by excision or amputation; there is no pharmacological treatment at this time (WHO, 2003).

Trachoma is caused by several strains of *Chlamydia trachomatis* (Heymann, 2004). Infection typically occurs in the eyelid and may be contracted from direct contact with discharge from the infected area on an infected individual or from contaminated surfaces (Heymann, 2004). Re-infection is very common. Repeated exposure results in the scarring of the eyelid and deformities of the eyelashes, which in turn may scar the cornea and eventually lead to blindness (Heymann, 2004). Of the 84 million people infected with Trachoma, 8 million suffer from visual impairment (WHO, 2008b).

1.4 Expanded list

The aforementioned list is in no way exhaustive. There are many other tropical diseases which are frequently overlooked and meet the poverty-promoting characteristic of the NTDs defined in the above paragraphs. Other NTDs of note, to name just a few, are Dengue/dengue haemorrhaging fever, Treponematoses such as yaws and syphallis, food borne trematodiases such as Fascioliasis, anthrax, rabies and many diarrheal diseases (Hotez *et al*., 2007; WHO, 2006; WHO, 2007).

2.0 Who is affected by the NTDs?

NTDs affect the poorest individuals. Over 70% of the affected areas have low to lower-middle income economies (WHO, 2006). They thrive under poor sanitary conditions, where clean water and food are unavailable and where insect vectors are inescapably abundant (WHO, 2006). Women, children and those geographically isolated from health care are particularly susceptible (Hotez *et al.*, 2006b; WHO, 2006). The NTDs are said to be "poverty-promoting conditions" as the lost worker productivity and impairments they cause to childhood development tends tend to aggravate impoverished conditions (Hotez *et al.*, 2006b; WHO, 2006). Even though there are over 1 billion people are parasitized by one or more NTDs, they are "hidden" from international attention due to their remote locations or lack of political voice, or even because public attention tends to focus on diseases with higher rates of mortality or sensational symptoms (WHO, 2003).

2.1 How are they affected?

NTDs disable, disfigure and debilitate their victims (Molyneux, 2004). Many of the NTDs have been with humanity for much of recorded history and have a significant amount of social stigma attached to them; this stigma also results in social shunning by infected individuals causing them to avoid seeking medical attention (Hotez *et al.*, 2006b). They may affect worker productivity or impair childhood physiological and cognitive growth, affecting the subsequent earning capacity of future generations (Canning, 2006; WHO, 2006). Disabilities caused by NTDs, such as the loss of the use of lower extremeties from Guinea worm infection, have a profound effect on worker productivity, especially in communities reliant on agricultural labour for subsistence farming (WHO, 2003). Parasitism by one or more NTDs may result in anaemia via direct or indirect mechanisms, which is often worsened by co-infection with malaria; this has a particularly adverse affect on the health of children, pregnant women and those infected with HIV (Hotez *et al.*, 2006b). Infected children may not able to maximize available educational potential due to

direct cognitive impairment or reduced general health (WHO, 2003). Children with a high burden of intestinal worms have been documented as having significant improvements in cognitive and physical abilities following deworming (Hotez *et al.*, 2006b). NTD distribution often overlaps with "the big three", HIV/AIDS, TB and malaria; evidence is mounting for a possible relationship between Helminth infection and an increased susceptibility to HIV (Hotez *et al.*, 2006a). Leishmaniasis appears to accelerate the progression of HIV in to AIDS (WHO, 2006). In general, the prognosis of TB, HIV/AIDS and malaria patients is often negatively affected by one or more NTD coinfection(s) (Hotez *et al.*, 2006a; WHO, 2006).

2.2 Drug development

Although cheap treatments are available for some NTDs, with drugs costing between US$ 0.02–$1.50 per day, many of the affected individuals, potentially belonging to the group of 2.7 billion people who live on less than US$ 2.00 per day, are unable to afford or access available treatments (WHO, 2006). There has been a noted absence of research and development for NTDs over the last 50 years; some of the drugs produced prior to this period are also very toxic such as the use of melarsoprol, which essentially treats African sleeping sickness by poisoning the organism with arsenic (Hotez *et al.*, 2006b). The severe lack of pharmaceutical attention has helped propagate and "hide" the suffering and morbidity caused by the NTDs. Pharmaceutical companies often justify this lack of development due to the perceived risk and cost of research and development for NTDs (Trouiller *et al.*, 2002). Trouiller *et al*. found a significant bias towards the pharmaceutical funding of diseases in high-income countries where parasitic infection is typically responsible for only a small portion of disease burden (2002). Countries affected by NTDs frequently do not have the resources or capacity to fund or carry out such research (Trouiller *et al.*, 2002).

2.3 Burden of the NTDs

The decision to prioritize funding for various global health initiatives when based upon traditional measures of disease burden or on moral urgency will inevitably result in increased funding for the "big three" which have a significantly higher rate of mortality than the NTDs (Canning, 2006). WHO measures typically measures disease burden by "disability adjusted life years" (DALYs); this measure often fails to emphasize the importance of the NTDs due to a number of knowledge gaps, an inability to measure subjective losses in quality of life and the very subtle, subclinical and chronic action of many NTDs (Engels & Savioli, 2006). NTD morbidity reduces worker productivity via lost days and reduced physical capacity and reduces the earning potential of infected children (Canning, 2006). For example, it appears that even small parasitic loads can have a subtle and insidious effect (Engels & Savioli, 2006). In order to properly assess the true effect of

the NTDs, burden estimates will need to take in to account subjective feelings of illness, losses of human potential and the often overlapping nature of the NTDs with each other and with the big three (Engels & Savioli, 2006).

When evaluated in terms of cost-effectiveness however, the NTDs appear to be an excellent investment due to the wide variety of cheap treatments and preventative measures and their ability to improve worker productivity and education (Canning, 2006). An investment in the control of NTDs could have a return of 14-30% (Molyneux, 2004). Investments in the health of children and workers are investments in human capital (Canning, 2006).

3.0 Control of NTD's

Combined interventions for multiple NTDs in school or community settings and large scale vector control offer a great deal of hope for the control and prevention of NTDs (Canning, 2006). The key will be executing mass preventative measures, such as improved hygienic conditions and vector control, as well as providing early diagnosis and treatment in remote areas (Engels & Savioli, 2006; WHO, 2006). Mass dewormings in schools for example could have the potential gain of US$ 6-33 DALYs (WHO, 2006). At an extremely low cost, chemical pharmaceuticals have the potential to prevent a large disease burden equivalent to that of either malaria or TB on their own, or one half of the burden caused by HIV/AIDS (Engels & Savioli, 2006).

3.1 Progress

International attention is slowly starting to turn towards the "hidden" diseases and many great steps to reduce their burden have been taken. Guinea worm disease eradication is apparently a realistic goal; to date, 168 countries have eliminated transmission of the disease (WHO, 2006). The eradication of leprosy is also becoming an increasingly realistic goal (WHO, 2006). Brazil has seen a reduction in mortality due to Chagas disease due to widespread pesticide spraying program (WHO, 2006). With help some international help, Cambodia has protected its school-aged children from soil-transmitted Helminths; this group has previously experienced a 70% prevalence of infection (WHO, 2006). Public-private partnerships (PPPs) offer further hope for the treatment and prevention of individual NTDs at minimal costs (Molyneux, 2005). Such partnerships which for example could occur between a pharmaceutical company and a charity allow for the development in previously underfunded areas (Trouiller *et al*., 2002). PPPs also create push mechanisms for government sponsorship (Hotez *et al*., 2006b). Government funding create by private pushing has also enabled "innovative developing countries" to fund NTD research with limited international assistance (Hotez *et al*., 2006b).

3.2 Conclusions

The control and prevention of NTDs is a problem that requires more attention than is being given now. Availability and access to health care, clean living conditions and drinking water, adequate nutrition, education, gender equality and non-discrimination are all elements which will be required for a human-right based approach to intervention (WHO, 2003). International communities and regional efforts will need to align and identify and target vulnerable groups (Hotez *et al.*, 2006a). For example, community-based surveillance systems and the strengthening of existing health care structure will be important steps to take in dealing with NTDs (WHO, 2007). WHO is placing a great deal of emphasis on multi-disease approaches to treating and preventing the NTDS along with the big three (WHO, 2003). They are also offering their support for the integration of NTD prevention in to existing public health packages and for educational campaigns attempting to eliminate the discrimination and social stigma frequently associated with NTD (WHO, 2003). PPPs and other partnerships have shown a great deal of success in preventing and controlling various NTDs; further success in terms of eradication and elimination will depend on these partnerships (Hotez *et al*., 2006a; Hotez *et al.*¸2007). These partnerships will hopefully help precipitate global attention and funding for new pharmaceuticals and control mechanisms, which are sorely missing due to a lack of existing drugs and the potential for resistance to pesticides and existing treatments methods (Hotez *et al.*¸2007). Additionally, the benefits of integrating treatment programs for NTDs with existing programs for AIDS/HIV, malaria and TB could be immense (Hotez *et al*., 2006a). Barriers, political and otherwise, must be crossed as there is such a ridiculously tiny price to pay for such a huge improvement on the quality of life of 1/6th of the world's population.

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