Neglected Tropical Diseases: Infection, Modeling, and Control

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Abstract: We survey the current state of a group of parasitic and microbial diseases called the Neglected Tropical Diseases (NTDs). These diseases currently infect a billion people, primarily in socioeconomically depressed areas of the world, are a leading cause of worldwide disability, and are responsible for approximately 534,000 deaths per year. We focus on several subcategories: protozoans, helminthes and bacterial diseases. We identify the populations most at risk from these diseases, and outline symptoms and other disease burdens. We examine the progress being made in controlling NTDs, including the current state of drug development. We also examine mathematical modeling of NTDs. While mathematical modeling is not bound by many of the strictures of access, data collection and infrastructure funding, we nevertheless demonstrate that few NTDs have received much attention from mathematical models, and that some have received no attention at all. Simple mathematical models could contribute significantly to our understanding of these diseases and the efforts required to control them, at very little cost. Further investment in prevention, treatment and awareness of NTDs is urgently warranted.

Key words: Neglected tropical diseases, mathematical models, leishmaniasis, sleeping sickness, Chagas' disease, schistosomiasis, soil-transmitted helminthiasis, lymphatic filariasis, onchocerciasis, dracunculiasis, leprosy, the Buruli ulcer, trachoma.

Global attention to infectious disease is primarily focused on HIV/AIDS, tuberculosis and malaria; the *big three*, as they are called, were responsible for over five million deaths in 2007 and are responsible for 39% of all deaths attributed to infectious disease.[1–3] 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.[4–6] 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.[3,6] Neglected tropical diseases are responsible for about 534,000 deaths worldwide per year; this number does not reflect the long-term

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suffering or the enormous and frequently underestimated socioeconomic burden of the billion people who have one or more NTDs.[1–3,7] The bacteria and macro-parasites that characterise the NTDs share widespread distribution in impoverished and mostly tropical environments, and typically result in disability and disfigurement.[3,7]

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 lacking.[6–8] Treatment and control of NTDs would alleviate a great deal of the suffering and huge economic burden of endemic countries.[9] International bodies and private organizations have begun to take notice in recent years and have put such measures in place as the World Health Organization's (WHO's) Global Plan.[8,9] In this paper, we set out to describe the NTDs and the socioeconomic burden they impose, as well as the possibility of their prevention, control and treatment. We also survey the current state of mathematical modeling of NTDs, as a window into potential areas of investment.

The WHO has identified a list of 11 of the most important NTDs; although not exhaustive, this list includes bacterial and macro-parasitic infections that are frequently vector-borne or spread by unhygienic living conditions.[5,7,9] The biologically and medically diverse group of organisms that constitute 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.[3,5,6] The big three share many of these characteristics, except for low mortality. Clean water, sanitation, safe food and medical resources are frequently unavailable in areas where NTDs are endemic; additionally, NTDs tend to foster poverty, due their negative effects on adult productivity and childhood development.[5,9]

There are three bacterial NTDs, three caused by protozoans and five by helminths.[2,3,6] Ranked by disease burden, they are lymphatic filariasis, soil-transmitted helminths, leishmaniasis, trachoma, schistosomiasis, African trypansomiasis, onchocerciasis, Chagas' disease, leprosy, the Buruli ulcer and Guinea worm disease.[5]

Protozoans. Leishmaniasis is an ancient disease caused by protozoans from the Leishmania genus and transmitted by the bite of a sandfly.[10] 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 last anywhere from a few weeks to over a year; secondary lesions may also occur years after the initial lesion has healed.[10] Visceral cases can result in anaemia, fever, debility and death if left untreated.[3]

Sleeping sickness, also called Human African trypanosomiasis, has been devastating sub-Saharan Africa for the last 200 years in intermittent intervals.[3] It is endemic in over 60 countries and is limited by the distribution of several tsetse fly species, which act as its vector.[10] Depending on the subtype, this disease may take anywhere from a couple of weeks to a few years to progress; Trypanosoma brucei rhodesiense is thought to be more virulent than T. b. gambiense.[10] Without treatment, the progression is inevitably fatal.[10] It initially affects the lymphatic and circulatory systems and eventually moves to the brain by crossing the blood-brain barrier.[3]

Chagas' disease, also known as American trypanosomiasis, is transmitted by fecal contamination of Reduviidae insects, via insect bites or other compromises of the

skin barrier.[10] Trypanosoma cruzi may also be spread by blood transfusion or organ transplant.[10] Symptoms have an acute and chronic phase; the chronic phase may be asymptomatic or may target digestive and/or cardiac tissues.[11] 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.[5,10]

Helminths. Schistosomiasis is caused by blood flukes from the Schistosoma genus.[10] The disease affects hundreds of millions of people worldwide and typically targets the urinary system, liver and kidneys.[5] 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.[10] The life cycle of the infectious Schistosoma spp. typically requires an aquatic molluscan host; human infection occurs via exposure to larvae in contaminated bodies of water.[10]

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 impairment in young children.[3,10]

Lymphatic filariasis has been a scourge of humanity for at least 4,000 years; it is currently the second leading cause of disability worldwide and its causative agents are endemic in over 80 countries.[3] It is caused by threadlike worms belonging to a family of mosquito-borne nematodes, namely Wucheria bancrofti, Brugia timori and B. malayi, which inhabit the lymphatic system of infected individuals.[10] 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.[3,10]

Onchocerciasis, also commonly known as river blindness, is caused by another filial nematode, Onchocerca volvulus.[10] It is transmitted by blackflies, which act as an intermediate host, living near fast-moving bodies of water.[3] 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.[3,10] 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.[3,10] 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.[3,10]

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.[3] 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.[3,10] The pain from Guinea worm

disease can be disabling, which is of great concern as outbreaks tend to occur at times of agricultural importance.[3,5]

Bacterial disease. Leprosy, another ancient scourge, is a chronic disease caused by Mycobacterium leprae.[10] Due to the development of multidrug therapies, global prevalence of the disease was reduced by 90% between 1985 and 2005.[3] 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.[10] Close personal contact is believed to be required for transmission, although the exact mode of transmission is unknown.[10] The disease may take anywhere from nine 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 and peripheral nerves are typically affected by the disease; sufferers display skin lesions and loss of sensory ability in affected areas.[3,10]

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.[10] 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.[3,10] Like leprosy, the mode of transmission is currently unknown.[3] Treatment is very costly and requires the removal of infected tissue by excision or amputation; there is no pharmacological treatment at this time.[3]

Trachoma is caused by several strains of Chlamydia trachomatis.[10] 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.[10] 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.[10] Of the 84 million people infected with Trachoma, 8 million suffer from visual impairment.[12]

Expanded list. The aforementioned catalogue 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 syphilis), food borne trematodiases (such as Fascioliasis, anthrax, rabies and many diarrheal diseases) and viral zoonoses (such as Rift Valley fever and Lassa fever).[6,7,9]

The Burden of Infection

Neglected tropical diseases affect the poorest individuals. Over 70% of the affected areas have low to lower-middle income economies.[7] They thrive under poor sanitary conditions, where clean water and food are unavailable and where insect vectors are abundant.[7] Women, children and those geographically isolated from health care are particularly susceptible.[5–6] Those in conflict-ridden areas are also particularly susceptible, due to the disruption of any health-care infrastructure.[5] Aside from thriving in poverty, the NTDs are also said to be poverty-promoting conditions, as they reduce

worker productivity and impair childhood development, and, consequently, the future earning abilities of those children.[5–6] The resulting economic loss tends to worsen already impoverished conditions.[5] For example, Hotez et al.[5] cited a $5.3 billion annual loss resulting from lost work days due to blinding trachoma. Even though there are over a billion people who are parasitised 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 incidence and mortality or sensational symptoms.[3]

Neglected tropical diseases disable, disfigure and debilitate their victims.[4] Many of the NTDs have existed for much of recorded history and carry significant social stigma; this stigma also results in social shunning of infected individuals, causing them to avoid seeking medical attention.[5] The NTDs can also affect worker productivity and impair childhood physiological and cognitive growth, affecting the subsequent earning capacity of future generations.[7,13] Disabilities caused by NTDs, such as the loss of the use of lower extremities from Guinea worm infection, have far-reaching effects on worker productivity, especially in communities reliant on agricultural labour for subsistence farming.[3] Parasitism by one or more NTDs may result in anaemia via direct or indirect mechanisms, which is often worsened by coinfection with malaria; this has a particularly adverse effect on the health of children, pregnant women and those infected with HIV.[5] Infected children may not be able to maximise available educational potential, due to direct cognitive impairment or reduced general health.[3] Children with a high burden of intestinal worms have been documented as having significant improvements in cognitive and physical abilities following deworming.[5]

The distribution of NTDs often overlaps with that of the big three; evidence is mounting for a possible relationship between Helminth infection and an increased susceptibility to HIV.[2] Leishmaniasis appears to accelerate the progression of HIV to AIDS.[7] In general, the prognosis of TB, HIV/AIDS and malaria patients is often negatively affected by one or more NTD coinfections.[5,7] Most of the disproportionate investment in the big three is focused on biomedically oriented prevention and treatment efforts. While some NTDs benefit from biomedical interventions, others will only benefit from greater social equity and smaller-scale interventions. Greater socioeconomic equity would, of course, apply to both NTDs and the big three.

The decision to prioritise 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 significantly higher rates of mortality than the NTDs.[13] The WHO typically measures disease burden by "disability-adjusted life years" (DALYs), a time-based measure that combines years of life lost due to premature mortality and years of life lost due to time lived in states of less than full health. However, this method contains explicit value judgements, which are open to strong questioning.[14] Long-term, low-level disabling conditions with a modest incidence rate and low mortality receive lower ratings than diseases with high incidence, intensely disabling conditions with short mortality, or conditons with a high mortality rate. For example, a systematic review of data on disability-associated outcomes for all forms of schistosomiasis suggests that the burden of this disease might be several times higher than the WHO estimate.[15]

Neglected tropical disease morbidity reduces worker productivity via lost days and reduced physical capacity.[13] For example, it appears that even small parasitic loads can have a subtle and insidious effect.[1] In order to assess the true effect of the NTDs, burden estimates must take into 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.[1]

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 capacity to improve worker productivity and education.[13] An investment in the control of NTDs could have a return of 14–30% annually.[4] Investments in the health of children and workers are investments in human capital.[13] Investing in the NTDs also implies investing in the big three, as NTD co-infection tends to influence the prognosis of AIDS, TB and malaria patients.[2]

Mathematical Modeling of NTDs

Many advances in disease management have come from mathematical modeling, including the recognition that mosquito management is the key to malaria control and the realization that smallpox can be eradicated.[16] Mathematical models have the advantage of requiring little investment in infrastructure or data collection. They can evaluate actual or potential control measures simply and cheaply, without the need for expensive or dangerous experiments. Chiefly, this is done by determining R_0, the basic reproductive ratio,[17] which usually predicts eradication if $R_0 < 1$ and persistence if $R_0 > 1$. It might be imagined that NTDs provide the perfect vehicle for examination by mathematical modeling.

However, most NTDs have received very little attention from mathematicians and some have received none whatsoever. We searched Google, Google Scholar and the academic database Scopus for keywords such as "mathematical model leishmaniasis" and "mathematical model leprosy." Where such diseases were known by more common names, we also searched those; hence, we searched both "mathematical model African typanosomiasis" and "mathematical model sleeping sickness." Additionally, we searched for review papers on each disease to see if any referred to modeling papers; we also search the World Health Organization's website using keywords "mathematics" and "models."

Progress. As far as we can tell, to date no mathematical models have been developed for Dracunculiasis or the Buruli ulcer, despite the former being the focus of robust control efforts.[18] With the exception of sleeping sickness, only a few mathematical models have been developed for the remaining NTDs. Multiple models for a given disease are often due to a single research group. This suggests that the diversity of models is even less than it appears.

For leishmaniasis, Dye[19] used mathematical models to compare the effectiveness of various control measures for canine and human zoonotic visceral leishmaniasis. It was found that insecticides would reduce the incidence of human leishmaniasis even more effectively than they reduce the prevalence of canine leishmaniasis and also that vector control would be more effective than canine control. Chaves and Hernandez[20]

developed a model that included a population of incidental hosts for parasites as well as a species that are reservoir hosts. They determined threshold conditions for the persistence of the infection, confirming the existence of incidental hosts for Leishmania parasites. Recently, de Almeida and HN Moreira[21] developed an immunological model to examine the possibility that immune response could have a positive effect on parasite growth. They showed that elimination of the parasite was possible, but depended upon the immune system parameters.

For sleeping sickness, Baker[22] modelled Rickettsia-like organisms (a vertically transmitted symbiont of tsetse) which confer an increased susceptibility to trypanosomiasis infection. It was found that long-term oscillations in trypanosomiasis prevalence in humans and animals could appear, combining with oscillations in host immunity to produce periodic epizootics at a single frequency. Rogers[23] developed a general model involving two vertebrate host species and one insect vector species. It was found that human sleeping sickness cannot be maintained in the human hosts alone; thus, the animal reservoir is crucial in determining not only the continued occurrence of the disease in humans, but its prevalence in these hosts as well. Agur et al.[24] modelled antigenic switches of African trypanosomes occurring randomly at the genetic level. Their study provided a theoretical basis for the appearance of genetic variants in the causative agent of sleeping sickness. Artrouni and Gouteux[25] developed a five-variable compartmental model for the spread of Trypanosoma brucei gambiense. They found that a 50% decrease in vector density would lead to extinction of the epidemic. Chalvet-Monfray et al.[26] developed a model in which human and vector populations migrate between a village and its plantations. They showed that vector control on the plantations can lead to disease eradication. Frank[27] used a mathematical model of parasitaemia and host immunity to examine variations in the rate of switching between antigenic types. It was found that minor modifications of switch rates by natural selection are required to develop a sequence of ordered parasitaemias. Muller et al.[28] introduced a spatialised, agent-based model to account for activity-related movements in humans, the density and mobility of tsetse flies, and the influence of other tsetse-feeding hosts. They found that prevalence is very sensitive to human densities and to the number of tsetse flies initially infected in a given location.

For Chagas' disease, Cohen and Gürtler[29] developed a mathematical model calibrated to detailed household data from three villages in northwest Argentina. They showed that low-cost, locally practicable environmental management combined with intermittent use of insecticides could sustainably control transmission of T. cruzi to humans in rural Argentina. Peterson et al.[30] used ecological niche modeling to identify host relationships of Triatoma species implicated in the transmission of Chagas' disease in Mexico. They predicted a geographic interaction between two species in regions where one of the species had not previously been collected. Inaba and Sekine[31] developed a mathematical model for Chagas' disease with infection-age-dependent infectivity, and considered the effects of vector and blood transfusion transmission. They showed that, under certain conditions, a backward bifurcation could occur, meaning that the disease could persist even if the basic reproductive ratio were reduced to below one.

For schistosomiasis, Chan et al.[32] developed a model of schistosomal morbidity. They used differential equations and Monte Carlo simulations to show that early manifestations

of disease could resolve relatively quickly following treatment, whereas later forms of disease would resolve very slowly or not at all. Chan and Isham[33] derived differential equations for the mean, variance, and co-variance of infection and immunity. They found that heterogeneity in contact rates produced a highly aggregated distribution of parasites with a large variance/mean ratio, while heterogeneity in the immune response had very little effect on the overall dynamics. Feng et al.[34] modelled drug treatment for human hosts, using age and density dependent models of snails. They derived explicit thresholds of treatment rates, above which the infection could be controlled. Williams et al.[35] modelled the transmission dynamics of Schistosoma japonicum, allowing for mammalian host heterogeneity characteristics. They found that, in the lake/marshland areas of the Yangtze River basin, once-yearly mass chemotherapy of humans is little better than twice-yearly mass chemotherapy in reducing human prevalence and that bovine treatment can benefit humans almost as much as human treatment.

For soil-transmitted helminthiasis, Hayashi[36] used a simple mathematical model to evaluate the effects of existing control measures and to assess the efficiency of forthcoming countermeasures. It was found that if the prevalence rate is kept at a low level through a sufficient period, the reinfection rate in the area would decrease. Salazar et al.[37] used Hayashi's models[36] to project the possible outcome of control given the combination of a drug with relatively low cure rate and a highly efficacious drug with low reinfection rates. They found that the intervals of treatment should coincide with the pre-patent period of the parasite. Crompton and Whitehead[38] proposed a mathematical model to explain how human iron metabolism may respond to hookworm infection of varying intensity. They found that high worm burdens were associated with reduced iron stores. Churcher et al.[39] used a composite parameter, the effective transmission contribution, to measure the number of transmission stages resulting from a given worm burden. They found that, when the parasite burden is low, intermediate levels of parasite clustering would maximise transmission.

For lymphatic filariasis, Grenfell et al.[40] examined the relationship between microfilarial burdens and the prevalence of adult (macrofilarial) worms in the human host population. They found that a large proportion of observed microfilariae-negatives arise from the absence of macrofilarial infections or unmated adult worms. Chan et al.[41] developed a dynamic model of filariasis infection intensity and chronic disease using age-stratified data from an Indian epidemic. They showed that the observed infection patterns could be explained by a simple model accounting for only acquired immunity to infection and irreversible progression to disease. Norman et al.[32] examined the effects of control options against filariasis by incorporating age structure. They found that chemotherapy has a larger short-term impact than vector control, but that the effects of vector control can last beyond the treatment period. Michael et al.[43] used a model-based approach for monitoring and evaluating anti-parasite interventions. They found that parasite transmission models can provide a scientific template for informing the optimal design of such monitoring programs.

For onchocerciasis, Basáñez and Boussinesq[44] developed a mathematical framework for humans and vectors. They derived the basic reproductive ratio and related it to the minimum vector density required for parasite persistence in Cameroon. Alley et al.[45] used a microsimulation model to examine the possibility of switching treatment from

the microfilaricide ivermectin to a hypothetical macrofilaricide. The showed that elimination was possible using a macrofilaricide, but that high coverage levels were critical. Filipe et al.[46] developed an age- and sex-structured model for intensity of infection with parasite regulation within humans and vectors. They showed that heterogeneous age and sex exposure could explain location-specific infection patterns of onchocerciasis. Poolman and Galvani[47] incorporated host heterogeneity into a model in order to evaluate intervention strategies targeting specific populations for treatment with ivermectin. They found that targeted allocation of ivermectin in a highly heterogeneous population could reduce the public-health burden of onchocerciasis using 20–25% of the doses of untargeted allocation.

For leprosy, Lietman et al.[48] used a mathematical model to test the hypothesis that individual-level immunity acquired from exposure to tuberculosis may have contributed to the disappearance of leprosy from western Europe. They showed that this was possible, if the basic reproductive ratio of leprosy was low. Meima et al.[49] developed a simulation model to examine the effects of vaccination, case detection and chemotherapy treatment on prevalence, incidence and case detection rates of leprosy. Meima et al.[50] used a computer simulation program to assess the elimination of leprosy. They showed that the predicted annual decline in incidences ranged from 2% to 12%, requiring a long-term strategy for leprosy control. Abubakar[51] used a semi-Markov model in discrete time to investigate relapses from leprosy after treatment. It was found that it was possible to attain zero probabilities for relapse and death from leprosy when treatment regimens were extremely effective.

Finally, for trachoma, Lietman et al.[52] developed a mathematical model to evaluate the WHO-recommended mass-drug administration in order to examine the efficacy of repeat treatment. They found that, in areas where the disease occurs in less than 35% of children, trachoma should be treated annually, whereas in areas where the disease occurs in greater than 50% of children, it should be treated biannually. Ray et al.[53] used a stochastic epidemiological transmission model to examine treatment programs in Ethiopia. They determined that a biannual treatment program implemented for five years would lead to eradication of the disease in 95% of all villages, assuming reintroduction from outside areas could also be controlled.

Impact. Mathematical models are necessary when direct data are not available, as when assessing theoretical intervention methods,[54] and can be used to provide greater understanding of existing control strategies.[55] However, they depend critically upon the assumptions used to construct such models. While no model is a description of reality, understanding the dependence between the assumptions and the theoretical conclusions can provide critical insights for policymakers. Complex models can make specific, quantitative predictions about control strategies, while simple models can elucidate general principles about disease epidemiology.[56]

For example, the successful West African Onchocerciasis Control Program used modeling to supplement intervention programs.[57] Habbema et al.[58] developed a stochastic microsimulation model to examine epidemiological trends in villages with both satisfactory and unsatisfactory vector control. They concluded that 14 years of full vector control would be sufficient to reduce the risk to less than 1%. Subsequently, Guillet et al.[59] used data from river basins in West Africa and Cameroon to refine this

model. They determined the long-term impact of ivermectin treatment on transmission the the feasbility of elimination using treatment alone. By using clearly delineated endpoints, these models helped convince donors and the scientific community that the aims of the program were achievable.[57] Modeling retained a prominent role in subsequent policy discussions.[60]

The World Health Organization has published models describing the HIV/AIDS epidemics in Botswana and India,[61] incorporated modeling in a primer on the effects of climate change,[62,63] used modeling to support the case for completing polio eradication,[64,65] and examined the general usefulness of models in the estimation of disease epidemiology.[66] Public-private partnerships have benefitted from modeling, such as the design and potential impact of human papillomavirus vaccines,[67] the ways in which models have influenced HIV/AIDS policies in the developing world,[68] the use of models for emergency preparedness functions,[69] and their use in response to health crises.[70] The Bill and Melinda Gates Foundation recently funded the largest malaria project known to date, using a network of volunteer computers to run variations of a complex malaria model.[71]

Working papers and policy reports have described the effect that models have had in informing disease control policy,[72] the effect of deterministic models on HIV/AIDS,[73] and the design and impact of HIV vaccines.[74,75] These reports do not just summarise a single conclusion from a single model, but rather focus on the general trends that a plurality of models are predicting. Positioned correctly, mathematical models of NTDs could have a substantial impact on policy and intervention efforts.

Groups most affected by NTDs are disproportionately powerless politically; they are also located in geographical areas remote from political centers of influence. While there have been some modeling attempts to account for these effects for the big three,[68,76–78] this is an area that is sorely lacking in models of NTDs. Other limitations that prevent models from being as good as they can be include lack of access to appropriate data, insufficient communication between modelers and policymakers, lack of education among policymakers as to the strengths and weaknesses of models, and a reliance upon a model's conclusion that does not consider its assumptions. Models must be clear about their limitations, but policymakers must be better educated about the power that models can have.

Requirements. Urgently, deficiencies in mathematical modeling of neglected tropical diseases must be addressed. Mathematical models of Dracunculiasis and the Buruli ulcer are needed immediately. For example, for Dracunculiasis, the method of infection from humans to nematodes is different from that of nematodes to humans, which could be a source of modeling; existing control efforts could also be optimised. For the Buruli ulcer, an economic model for treatment versus prevention would likely provide evidence for the investment of resources into preventing this disease.

In general, spatial modeling of infection in remote areas is vital. There are many models of pesticide spraying to control malaria;[79] these could be adapted to account for the control of vector-borne NTDs, such as Chagas' disease. Modeling access to resources, such as drugs or vaccines, across geographically difficult terrains (e.g., distance to hospitals, swamps, mountains and roads) is crucial. Models that categorise the cost to developing economies due to disabling effects of NTDs could be useful in demon-

strating that tackling these diseases would be cost-effective. Models of NTD research funding could be useful to draw attention to and organise the allocation of money in developed countries. Co-infection models of one or more NTDs could demonstrate the compounding effects of living in prevalent areas. Co-infection models of NTDs with the big three is also necessary: many NTDs contribute to substantially worsened effects or higher incidence of HIV, TB, or malaria.

Control of NTDs

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.[13] Large-scale preventive measures include increasing hygienic conditions and vector control, as well as providing early diagnosis and treatment in remote areas.[1,7,9] These will also affect the big three. Preventive measures specific to NTDs include targeted drug programs, dewormings in schools, tsete traps, monitoring blood transfusions and animal control.[80] For example, mass dewormings in schools could yield $6–33 (U.S.) per gained DALY.[7] 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.[1] Pyrethroid-treated products require no specialised knowledge, achieve up to 100% insect mortality and are cost-effective.[81] Coordination of local, national, and international health services and aid will be necessary for NTD control.[9]

Drug development. Although cheap treatments are available for some NTDs, with drugs costing between $0.02–1.50 (U.S.) per day, many of the affected individuals, potentially belonging to the group of 2.7 billion people who live on less than $2.00 (U.S.) per day, are unable to afford or access available treatments.[7] Research and development for NTDs over the last 50 years has been notably sparse; some of the drugs produced prior to this period are also very toxic (such as melarsoprol, which essentially treats African sleeping sickness by poisoning the organism with arsenic[5]). In an analysis of pharmaceutical research and development over a period of 25 years, Trouiller et al.[82] found a significant bias towards funding for diseases found in high-income countries, where parasitic infection is typically responsible for only a small portion of disease burden; NTD-related pharmaceuticals accounted for only 1% of 1,393 market-approved drugs manufactured between 1975 and 1999. The widespread lack of pharmaceutical attention and investment 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 the cost of research and development for NTDs.[82] Countries affected by NTDs frequently do not have the resources or capacity to fund or carry out such research.[82]

Progress. International attention is slowly starting to turn towards the hidden NTDs and many important steps to reduce their burden have been taken.[9] Guinea worm disease eradication is apparently a realistic goal; to date, 168 countries have eliminated transmission of the disease.[7] The eradication of leprosy is also becoming an increasingly realistic goal.[7] Brazil has seen a reduction in mortality due to Chagas' disease, after widespread pesticide spraying programs.[7] With help some international help, Cambodia

has protected its school-aged children from soil-transmitted helminths; this group previously experienced a 70% prevalence of infection.[7] Public-private partnerships offer further hope for the treatment and prevention of individual NTDs at minimal costs.[83] Such partnerships—which, for example, could occur between a pharmaceutical company and a charity—allow for development in previously underfunded areas.[82] Public-private partnerships also create push mechanisms for government sponsorship.[5] Government funding created by private pushing has also enabled "innovative developing countries"[5[p. 28]] to fund NTD research with limited international assistance.

Conclusions

The control and prevention of NTDs requires more attention than it is being given now. Availability of 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-rights-based approach to intervention.[3] International communities and regional efforts must align, identify and target vulnerable groups.[2] For example, community-based surveillance systems and the strengthening of existing health care infrastructures will be important steps to take in dealing with NTDs.[9] Trouiller et al.[82] have suggested that an overhaul of current drug patent systems would be required to provide incentive for private-sector funding for NTD pharmaceutical research and development.

Specific areas of control have been identified by mathematical modeling: insecticides and vector control for leishmaniasis, sleeping sickness (especially where such vector control is targeted to plantations), Chagas' disease, lymphatic filiariasis and onchocerciasis; control of reservoir animal hosts for sleeping sickness and schistosomiasis; monitoring blood transfusions for Chagas' disease; mass chemotherapy for schistosomiasis, lymphatic filiariasis and leprosy; drug treatments at specific intervals, related to the parasite's biology, for soil-transmitted heminthiasis; targeted microfilaricide and a potential macrofilaricide for onschocerciasis; and targeted drug programs, depending on prevalence, for trachoma. By bringing such biomedical interventions to bear, mathematical models demonstrate how quickly with amelioration of socioeconomic disparities suffering can be relieved, human capital be unleashed, and true development occur. These methods provide insight for future directions, but more modeling is urgently required.

The WHO currently places a great deal of emphasis on multi-disease approaches to treating and preventing the NTDS along with the big three.[3] They are also offering their support for the integration of NTD prevention into existing public-health packages, and for educational campaigns attempting to eliminate the discrimination and social stigma frequently associated with NTDs.[3] Public-private partnerships 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.[2,6] It is hoped that these partnerships will precipitate global attention and funding for new pharmaceuticals and control mechanisms; these are sorely missing, due to a lack of existing drugs and the potential for resistance to pesticides and existing treatments.[6] Additionally, the benefits of integrating treatment programs for NTDs

with existing programs for HIV/AIDS, malaria and TB could be immense.[2] Barriers, political and otherwise, must be crossed, as the price for such a huge improvement on the quality of life of one sixth of the world's population is tiny.

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