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INVITED COMMENTARY

Why Funding for Neglected Tropical Diseases Should Be a Global Priority

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Neglected tropical diseases affect >1 billion of the world's poorest persons. Control programs range from near-elimination (dracunculiasis) to increasing prevalence (dengue and cutaneous leishmaniasis). These are some of the most cost-effective public health interventions and should be a global priority.

Keywords. neglected tropical diseases; parasitic diseases; helminths; protozoans.

Neglected tropical diseases (NTDs) have been defined by the World Health Organization (WHO) as a "diverse group of communicable diseases that prevail in tropical and subtropical conditions, affecting more than one billion people and cost developing economies billions of dollars every year" [1, 2]. The WHO increased the number of targeted diseases to 20 in 2017 [2] (see Table 1). These diseases have a significant effect on the health of >1 billion persons, particularly children, living in poverty with unsafe water, poor sanitation, and inadequate housing [3, 7]. Research on these diseases has been underfunded ($100 million in the United States in 2016) compared with human immunodeficiency virus, malaria, and tuberculosis ($1.5 billion combined) [5, 8].

SCOPE OF THE PROBLEM

The accuracy of prevalence and mortality data from NTDs has significantly improved with Global Burden of Disease Studies [4, 9, 10]. As summarized by Hotez and Aksoy [3] and shown in Table 1, the most common NTDs are intestinal nematode infections, which infect hundreds of millions of persons yearly (ascariasis, hookworm, and trichiuris), along with schistosomiasis [4]. Millions of persons are infected with food-borne trematodes, filariasis, onchocerciasis, Chagas disease, dengue, leishmaniasis, trachoma, and *Echinococcus*. Thousands are infected with leprosy and human African trypanosomiasis [4]. The majority of these diseases have decreased in prevalence in the past decade, with the biggest declines for dracunculiasis (Guinea worm) (decreased 99%) and African trypanosomiasis (decreased 72.5%). In contrast, the prevalence of dengue (up 74.7%) and cutaneous leishmaniasis (up 28.6%) increased during the past decade. It is necessary to examine both the successes and challenges to better understand what lies ahead, and why funding is so important.

SUCCESSFUL APPROACHES

Dracunculiasis (guinea worm) is the NTD closest to eradication, with an incidence decreasing from 3.5 million in 1986 to 25 cases in 2016 (reviewed in [6]). This success required an intensive effort to provide clean or filtered water, larvicides for the intermediate host, and an active surveillance system. Similarly, the major campaign to control human African trypanosomiasis has decreased the global incidence of Gambian human African trypanosomiasis cases to <3000 in 2015 (reviewed in [11]). The campaign focused on active surveillance with better diagnostics and treatment programs involving public-private partnerships with major drug donations from pharmaceutical companies [11]. The other successes in decreasing morbidity from NTDs have resulted from major WHO-led mass drug administration (MDA) campaigns, which decreased filariasis, trachoma, and onchocerciasis by 50% [3], schistosomiasis by 30% (reviewed in [12]), and ascariasis by 20% (reviewed in [13]).

MAJOR CHALLENGES

Vector-borne NTDs, including dengue, leishmaniasis, and Chagas disease, have been the most difficult to control. The prevalence of dengue has increased >75% in the past decade [4]. The dengue vector, *Aedes* mosquitoes, are difficult to control because of widespread urban distribution, aggressive daytime biting, and life-time infection. Global warming and increased rainfall have also increased its spread of the vector [14]. Besides mosquito control, vaccine development has been a major focus for dengue control. Unfortunately, the trials of the only approved tetravalent vaccine were complicated by a variable immune response to the 4 serotypes of dengue virus in circulation [15, 16].

Control of leishmaniasis, spread by phlebotamine sandflies, is particularly challenging because of the involvement

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Table 1. Neglected Tropical Diseases Targeted by the World Health Organization

Disease	Prevalence in 2016, No. of Cases [4]	Change in Last Decade, % [4]	Total 2016 Funding, $ Million [5]	Comments
Close to elimination [3]				
Dranunculiasis (Guinea worm)	25	−99.5	NA	Few remaining cases in Chad (may be linked to dogs) and war-torn areas (South Sudan) [6]
Human African trypanosomiasis	7000	−72.5	37	Active surveillance, better diagnostics, private-public drug partnerships
Lymphatic filariasis	29 382 000	−37.3	16	Mass drug administration
Trachoma	3 338 000	0.5	2.2	Mass drug administration
Visceral leishmaniasis	30 000	−54.2	41[a]	Especially in India without animal vectors
Significant control				
Ascariasis (STH)	799 683 000	−26.7	1.3	Mass drug administration
Cysticercosis	2.676 000	−4.6	3.6	…
Leprosy	523 000	+1.2	11.1	…
Onchocerciasis	14 650 000	−24.0	10	…
Schistosomiasis	189 774 000	−24.5	18	Mass drug administration
Some progress				
Cystic echinococcosis	974 000	−38.3	NA	…
Food-borne trematodes	74 725 000	+6.7	NA	…
Hookworm (STH)	450 683 000	−4.2	3.9	Mass drug administration
Trichuriasis (STH)	435 095 000	−20.0	1.8	Mass drug administration
No control				
Chagas disease	7 201 000	+9.2	25	Spread by triatome bugs, congenital infection, blood supply, immigration
Cutaneous leishmaniasis	4 320 000	+28.6	41[a]	Spread of sandflies with global warming, multiple animal vectors, mass immigration
Dengue	6 046 000	+74.7	113	Widespread *Aedes* mosquitoes with global warming
Newly added diseases [2]				
Buruli ulcer	1900 [5]	NA	2.8	…
Mycetoma and deep mycotic infections	NA			…
Rabies	<1000	−46.7	NA	…
Scabies	146 785 000	NA	NA	…
Snakebite evenomation	NA	NA	NA	…
Yaws	NA	NA	NA	…

Abbreviations: NA, not available; STH, soil-transmitted helminth.

[a]Combined funding for visceral and cutaneous leishmaniasis

of multiple species, vectors, and animal reservoirs affecting the poorest persons (reviewed in [17]). A major effort to control visceral leishmaniasis in the Indian subcontinent has been largely successful, in part because of the lack of animal vectors [17]. In contrast, cutaneous leishmaniasis has increased because of political instability, multiple wild animal vectors, conflicts leading to massive movement of at-risk persons, and the effect of global warming on the spread of sandflies. A multitargeted approach, including new drugs, vaccines, and vector control, will probably be required.

The life cycle and spread of *Trypanosoma cruzi* infection is complex, with local spread in South America by triatomine bugs, but congenital infection, an asymptomatic (but infectious) stage that can contaminate the blood supply, and immigration have resulted in thousands of cases in nonendemic areas such as the United States and Europe. It is now considered an emerging infection in the United States, with an increase of 9% over the past decade (reviewed in [18]). The 2 approved drugs, nifurtimox and benznidazole, are most effective only in early-stage disease and have many adverse effects, and access to drugs is estimated at <1% [18]. New drugs are in the pipeline, but bringing a new drug to clinical trials is very challenging (reviewed in [19]). Disappointing clinical trials of repurposed drugs further highlight the need for better diagnostic assays and biomarkers to follow actual clinical disease progression and not just infection during the chronic phase [18].

IMPORTANCE OF CONTINUED FUNDING TO BUILD ON SUCCESS

NTDs are a world-wide problem with 100% of low-income countries affected by ≥5 NTDs simultaneously [7]. With the ongoing MDA campaigns for lymphatic

filariasis, trachoma, onchocerciasis, and schistosomiasis [3], it is important to build on success with continued funding. The near-control of guinea worm [6] has demonstrated that a major focus on surveillance, clean water, and vector control are critical. The majority of these programs have been vertically driven by outside donors focusing on a single disease. Integration of NTD control into general healthcare delivery systems will allow more sustainable and efficient community-directed treatment for NTDs, along with distribution of vitamin A, malarial therapy, nutrition, and safe water (reviewed in [20]). The synergistic benefit has been shown by using community distributors for the administration of drugs for NTDs, which led to a 9-fold increase in the distribution of bed nets for malaria [20]. Leveraging the resources of well-funded initiatives such as the Global Fund for NTDs in the same geographic areas as AIDS, tuberculosis, and malaria could provide important public health advances.

CONTROL OF NTDs AS COST-EFFECTIVE PUBLIC HEALTH INTERVENTIONS

The cost of the MDA campaigns for onchocerciasis and filariasis with ivermectin, azithromycin for trachoma, and albendazole for filariasis and soil-transmitted helminths using donated drugs is estimated to be <$0.50 per person per year (reviewed in [21]). Costs have been kept low through the major donation programs by pharmaceutical companies. These therapeutic interventions have a major impact on morbidity which can be measured in cost per disability-adjusted life-years of only $5–$10 per disability-adjusted life-year for eliminating lymphatic flariasis, and $10–$23 for schistosomiasis [4, 21]. In addition to health effects, there are significant gains in education, agricultural productivity, and poverty reduction [21]. It has been estimated that for every dollar invested in NTD control, economic productivity will increase 50-fold (reviewed in [22]).

NTD RATES HIGHEST IN COUNTRIES WITH POVERTY AND CONFLICT

Yearly spending on healthcare in the poorest countries is <$10 per capita [20]. It is not surprising that the highest prevalence of 10 NTDs occurs in nations under conflict or with governments near collapse [23]. The least developed countries also have the poorest health and sanitation infrastructure. More than 950 million persons still have inadequate sanitation, and 553 million lack access to clean drinking water [22]. Meeting this public health goal would have a significant impact on NTD control.

FUNDING FOR BASIC AND APPLIED RESEARCH ON NTDs

The funding of basic research on NTDs must be increased to capitalize on new, innovative technology in order to discover new drug targets, biomarkers, and strategies for vector control. Although MDA programs have dispensed millions of drug doses for several targeted diseases, there is concern about reaching areas in politically unstable countries, as well as the potential of MDA programs to accelerate drug resistance [24]. One cost-effective approach is to validate and apply repurposed drugs, such as ivermectin, praziquantel, and fexnidazole [25]. Auranofin, a repurposed drug approved by the Food and Drug Administration for rheumatoid arthritis, is in clinical trials for amebiasis and giardiasis [26, 27]. Funding for all NTDs from the National Institutes of Health was $100 milllion in 2017, with a 25% cut recommended by the White House for 2018 [8].

Finally, basic research for drug therapy can only help to identify new drug targets or at best advance chemical "hits" to optimize efficacy. There is still too little support of the medicinal chemistry required to "translate" basic discoveries into clinical candidates for NTDs. Furthermore, support for preclinical packages (pharmacokinetics/pharmacodynamics, toxicology) and clinical trials is largely lacking.

NTDs AS WORLDWIDE PROBLEM

Although NTDs have their largest impact in the poorest countries, some affect the poor and disenfranchised of all nations. For example, most NTDs occur in the middle-income countries of Brazil, China, and India [23], and a recent surveillance study in rural Alabama found that more than a third of stool samples tested positive for hookworm [28]. Local transmission of dengue and Zika virus in Texas and Florida provided further evidence of the global threat of NTDs [29]. Localized pockets of poverty, immigration, international travel, and climate change present additional challenges to global control of NTDs and underscore the need for additional funding from the wealthiest countries and foundations.

Note

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization. Neglected tropical diseases. Available at: http://www.who.int/neglected_diseases/diseases/en/. Accessed 21 December 2017.
2. World Health Organization. Integrating tropical disease in global health and development. Fourth WHO Report on Neglected Tropical Diseases. Available at: http://www.who.int/neglected_diseases/resources/9789241565448/en/. Accessed 21 December 2017.
3. Hotez P, Aksoy S. PLOS neglected tropical diseases: ten years of progress in neglected tropical disease control and elimination … more or less. PLoS Negl Trop Dis **2017**; 11:e0005355.
4. Vos T, Abajobir AA, Abbafati C, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet **2017**; 390:1211–59.
5. G-FINDER 2017. Neglected tropical disease research and development: reflecting on a decade of global investment. Available at: http://gfinder.policycuresresearch.org. Accessed 2 April 2018.
6. Molyneux D, Sankara DP. Guinea worm eradication: progress and challenges—should we beware of the dog? PLoS Negl Trop Dis **2017**; 11:e0005495.
7. Centers for Disease Control and Prevention. Neglected tropical diseases. Available at: https://www.cdc.gov/globalhealth/ntd/index.html. Accessed 21 December 2017.
8. Henry J. Kaiser Family Foundation. The U.S government and global neglected tropical disease efforts. Available at: https://www.kff.org/global-health-policy/fact-sheet/the-u-s-government-and-global-neglected-tropical-diseases/. Accessed 2 April 2018.

9. Vos T, Allen C, Arora M, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet **2016**; 388:1545–602.
10. Naghavi M, Abajobir AA, Abbafati C, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet **2017**; 390:1151–210.
11. Aksoy S, Buscher P, Lehane M, Solano P, Van Den Abbeele J. Human African trypanosomiasis control: achievements and challenges. PLoS Negl Trop Dis **2017**; 11:e0005454.
12. King CH. The evolving schistosomiasis agenda 2007-2017—why we are moving beyond morbidity control toward elimination of transmission. PLoS Negl Trop Dis **2017**; 11:e0005517.
13. Jourdan PM, Montresor A, Walson JL. Building on the success of soil-transmitted helminth control—the future of deworming. PLoS Negl Trop Dis **2017**; 11:e0005497.
14. Polgreen PM. Infectious diseases, weather, and climate. Clin Infect Dis **2018**; 66:815–7.
15. Hadinegoro SR, Arredondo-García JL, Capeding MR, et al; CYD-TDV Dengue Vaccine Working Group. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med **2015**; 373:1195–206.
16. Dans AL, Dans LF, Lansang MAD, Silvestre MAA, Guyatt GH. Controversy and debate on dengue vaccine series—paper 1: review of a licensed dengue vaccine: inappropriate subgroup analyses and selective reporting may cause harm in mass vaccination programs. J Clin Epidemiol **2018**; 95:137–9.
17. Kamhawi S. The yin and yang of leishmaniasis control. PLoS Negl Trop Dis **2017**; 11:e0005529.
18. Dumonteil E, Herrera C. Ten years of Chagas disease research: looking back to achievements, looking ahead to challenges. PLoS Negl Trop Dis **2017**; 11:e0005422.
19. Sajid M, Robertson SA, Brinen LS, McKerrow JH. Cruzain: the path from target validation to the clinic. Adv Exp Med Biol **2011**; 712:100–15.
20. Gyapong JO, Gyapong M, Yellu N, et al. Integration of control of neglected tropical diseases into health-care systems: challenges and opportunities. Lancet **2010**; 375:160–5.
21. Conteh L, Engels T, Molyneux DH. Socioeconomic aspects of neglected tropical diseases. Lancet **2010**; 375:239–47.
22. Mishra SR, Dhimal M, Bhandari PM, Adhikari B. Sanitation for all: the global opportunity to increase transgenerational health gains and better understand the link between NCDs and NTDs, a scoping review. Trop Dis Travel Med Vaccines **2017**; 3:8.
23. Hotez PJ. The neglected diseases: will a "new world order" reverse global gains? Int Health **2017**; 9:267–8.
24. Hotez PJ. The poverty-related neglected diseases: why basic research matters. PLoS Biol **2017**; 15:2004186.
25. Nwaka S, Hudson A. Innovative lead discovery strategies for tropical diseases. Nat Rev Drug Discov **2006**; 5:941–55.
26. Debnath A, Parsonage D, Andrade RM, et al. A high-throughput drug screen for *Entamoeba histolytica* identifies a new lead and target. Nat Med **2012**; 18:956–60.
27. Tejman-Yarden N, Leitsch D, Debnath A, et al. Auranofin for the treatment of giardiasis. Antimicrob Agents Cheother **2013**; 57:2029–35.
28. McKenna ML, McAtee S, Bryan PE, et al. Human intestinal parasite burden and poor sanitation in rural Alabama. Am J Trop Med Hyg **2017**; 97:1623–8.
29. Sanders JW, Goraleski KA. The hookworm blues: we still got 'em. Am J Trop Med Hyg **2017**; 97:1277–9.