Eliminating the Neglected Tropical Diseases: Translational Science and New Technologies

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Abstract

Today, the World Health Organization recognizes 17 major parasitic and related infections as the neglected tropical diseases (NTDs). Despite recent gains in the understanding of the nature and prevalence of NTDs, as well as successes in recent scaled-up preventive chemotherapy strategies and other health interventions, the NTDs continue to rank among the world’s greatest global health problems. For virtually all of the NTDs (including those slated for elimination under the auspices of a 2012 London Declaration for NTDs and a 2013 World Health Assembly resolution [WHA 66.12]), additional control mechanisms and tools are needed, including new NTD drugs, vaccines, diagnostics, and vector control agents and strategies. Elimination will not be possible without these new tools. Here we summarize some of the key challenges in translational science to develop and introduce these new technologies in order to ensure success in global NTD elimination efforts.

Overview of the Neglected Tropical Diseases

The modern framework for considering a group of parasitic and related infections as neglected tropical diseases (NTDs) was put forward by the World Health Organization (WHO) together with a series of key policy papers published by a community of scientists in the early years following the Millennium Development Goals (MDGs) [1–5]. An original list of more than a dozen NTDs—identified by their disproportionate impact on the world’s poor and for their ability to cause poverty through deleterious effects on worker productivity, child development, and the health of girls and women [2,6]—was subsequently expanded by the WHO to include 17 diseases [7]. Through the Global Burden of Disease Study 2010 (GBD 2010), new information on the prevalence of the NTDs confirms that they rank as the most common afflictions of the world’s poor (led by ascariasis, trichuriasis, and hookworm with more than 400 infections each, followed by schistosomiasis), with practically every person living in conditions of extreme poverty infected by at least one NTD [8].
The GBD 2010 also finds that while some NTDs such as rabies, African sleeping sickness, and visceral leishmaniasis are lethal diseases, most of the NTDs are highly disabling, and many are chronic in nature (Fig 1) [8].

The leading NTDs in terms of disability adjusted life years (DALYs) lost include schistosomiasis, leishmaniasis, and hookworm infection [8]. Additional information has emphasized the social stigmatizing effects from the NTDs and their poverty-promoting features, and their links to regional and global conflict. These elements of the NTDs demand that they remain front and center as we advance to a new set of “sustainable development goals” (SDGs).

Since 2006, a major approach to controlling the NTDs has relied on mass treatment with one or more essential drugs, mostly donated by the major multinational pharmaceutical companies [2–7]. Initially known as the “rapid impact” package—containing up to four drugs that target the three major soil-transmitted helminth infections (albendazole or mebendazole), schistosomiasis (praziquantel), lymphatic filariasis (ivermectin or diethylcarbamazine citrate), onchocerciasis (ivermectin), and trachoma (azithromycin) [2,3]—more than one billion people have now received at least one of these essential NTD medicines. The WHO has designated this approach as “preventive chemotherapy” because for some diseases such as lymphatic filariasis (LF) and trachoma, mass treatment is leading to the interruption of transmission and disease elimination [9]. Moreover, preventive chemotherapy has been shown to result in spillover or collateral public health benefits, including the potential control or elimination of neglected skin diseases such as scabies and yaws [10]. It is estimated that, overall, approximately 36% of the global population living in poverty and requiring preventive chemotherapy actually received treatment in the year 2012 [11], highlighting the urgent need for greater investment worldwide. Based on findings that an unexpectedly high percentage of NTDs occurs among the poor who live in the wealthier group of 20 (G20) nations [12], there is urgency to pressure the G20 to invest more heavily in their own NTDs [13].

Two important post-MDGs policy documents for NTD control and elimination include the 2012 London Declaration on NTDs—which reaffirms a commitment by the multinational pharmaceutical companies to continue donating essential NTD medicines and invest more seriously in research and development (R&D) for new tools [14]—and a 2013 World Health Assembly resolution on the NTDs (WHA66.12) [9]. Both the London Declaration and WHA66.12 highlight opportunities to also eliminate NTDs such as dracunculiasis, human African trypanosomiasis (HAT), leprosy, onchocerciasis in the Americas, and schistosomiasis in China, with more than 74 countries worldwide implementing national NTD master plans [9,11].

New Technologies for Improving Patient Care and Achieving Disease Elimination

Critical disease-specific technologies—drugs, vaccines, diagnostics, and vector control agents—are currently available to facilitate the control or elimination of many of the world’s NTDs [14]. There is particular enthusiasm for the global elimination of the NTDs, lymphatic filariasis, trachoma, and yaws through preventive chemotherapy and mass treatment using currently available drugs. However, for most of the 17 NTDs, drug, vaccine, diagnostic and vector control technologies are imperfect and have limited use because of their toxicities, inadequate efficacies, or because they do not prevent reinfection [15]. For example, a recent survey of almost 400 NTD experts concluded that currently available technologies will not eliminate soil-transmitted helminth (STH) infections or schistosomiasis, two of the most ubiquitous NTDs being targeted (Fig 2) [16].
There is, therefore, an essential need for new or improved technologies to control these diseases [15].

Whether STH infections, schistosomiasis, and onchocerciasis (now targeted by preventive chemotherapy) could be eliminated without new and additional tools has also generated debate. For instance, a recent analysis based on modeling indicates that interruption for STH infections using current mass treatment approaches with benzimidazole anthelminthics may be feasible in areas of low intensity transmission and where strong health systems are in place [17]. For schistosomiasis, efforts are underway in Zimbabwe to evaluate whether mass treatment with praziquantel, together with either behavioral changes or snail control might affect elimination [18]. For onchocerciasis, some modeling indicates that elimination through ivermectin preventive chemotherapy may be achievable if it were continued up to 2030 or even 2040 [19]. Therefore, there is a benefit to increased dialogue between the community of researchers engaged in modeling NTD elimination scenarios and those who are developing next generation tools and products, specifically drugs, diagnostics, vaccines, and vector control agents.

Because many of these NTDs either mostly or exclusively affect people living in poverty, they are being developed primarily by nonprofit product development partnerships focused on specific NTD drugs (e.g., Drugs for Neglected Diseases Initiative [DNDi] and PATH), diagnostics (e.g., Foundation for Innovative New Diagnostics [FIND] and PATH), vaccines (e.g.,...
PATH, Infectious Disease Research Institute [IDRI], and Sabin Vaccine Institute), and vector control agents (e.g., Innovative Vector Control Consortium [IVCC]), working together with industry (including both multinational companies and industrial organizations in developing countries) and academic organizations.

**New NTD Drugs**

The last decade has seen incremental improvements in the development of NTD treatments. An analysis of the neglected disease R&D pipeline from 2000 to 2011 found that most advances entailed repurposing or reformulating existing drugs [20]. Entirely new chemical entities (NCEs) are still needed to improve patient care and meet current elimination targets.

**Drugs for Kinetoplastid Infections**

Until recently, treatment options for kinetoplastids were toxic and ill-adapted. Increased interest in drug discovery is slowly transforming the landscape.

- Human African trypanosomiasis (HAT): An oral short-course treatment for early and advanced stages of the disease and a rapid diagnostic test, are required for sustainable elimination of the disease. While nifurtimox-eflornithine combination therapy, introduced in 2009, has improved case management, it is not practical for large-scale “test and treat” efforts [21]. Two NCEs are currently undergoing clinical evaluation as oral therapies: fexinidazole (Phase IIb/III trials), and the oxaborole SCYX-7158 as a one-dose treatment (Phase I). Several candidates are in lead optimization [22–25].
Chagas disease: Only two drugs exist: benznidazole and nifurtimox. Progress has been made in child-adapted dosage forms (pediatric benznidazole registered in 2011), but the scaling up of treatment in general is far too slow. Posaconazole and a prodrug of ravuconazole (E1224) have shown some promise but are not effective as monotherapies. Currently, shorter courses of benznidazole, as well as E1224 combined with benznidazole, are being evaluated [26].

Leishmaniasis: Treatment has improved over the last decade in Asia, with the development of liposomal amphotericin B, paromomycin, and miltefosine. Nevertheless, adapted treatments are lacking for Africa and Latin America. Oral therapies are being pursued for use in drug combinations to improve treatment for visceral leishmaniasis and coinfection with HIV [27,28]. For cutaneous leishmaniasis, topical creams are currently in clinical trials [29,30]. To ensure that new compounds and back-up molecules are available for kinetoplastids, high-throughput screening of core diversity libraries from several pharmaceutical companies is being conducted. Promising leads from the nitroimidazole and oxaborole series for both leishmaniasis and Chagas are being evaluated.

Drugs for LF and Onchocerciasis
Ironically, the success of mass treatment programs for filarial infections may have undermined support for R&D [31,32]. Nonetheless, promising areas of research are genome sequencing of filarial helminths, the development of drugs against Wolbachia endosymbionts, active screening of repurposing libraries, and specific development projects for new macrofilaricidal drug candidates (e.g., emodepside and flubendazole). Elimination targets will be difficult to achieve without a macrofilaricide.

Drugs for Bacterial and Viral NTDs
There are no drugs in development for leprosy, trachoma, and yaws due to the availability of antibiotics. For Buruli ulcer, experimental substitutions of other antibiotics are being evaluated. One nucleoside inhibitor has completed Phase I for dengue fever. For Ebola virus disease, the West African epidemic has given rise to long overdue attention to and resources for new treatment, though progress remains far too slow and recruitment for trials has been complicated by the otherwise good news that patient numbers are decreasing.

Key Challenges
After years of neglect, NTD drug development efforts are finally intensifying, though not sufficiently. New nonprofit initiatives and increased funding have improved the prospects for NTD drug R&D somewhat, but efforts are still too fragmented and ad hoc. New R&D incentive mechanisms and innovative financing instruments, as well as improved global priority-setting and coordination, will be critical to ensure that treatments are brought out of the pipeline and put into the hands of neglected patients [33].

New NTD Vaccines
The 2014 West African Ebola virus epidemic identified serious gaps in our abilities to advance in a timely manner the development and advanced clinical testing of vaccines to combat the NTDs. Most of these deficiencies were unrelated to the feasibility of making Ebola vaccines, which was established in nonhuman primates almost a decade prior to the outbreak. Instead, our technical abilities outpaced the social, political, economic, and financial institutions for making vaccines for the extremely poor. As a result of absent financial incentives, market
failures, and other socioeconomic forces, we have no licensed NTD vaccines except for rabies, while for the other NTDs only candidate dengue virus vaccines are currently in Phase II and III advanced clinical development. The reason for this situation is mostly that there is a small but substantial market for rabies and dengue biotechnologies among the middle- and high-income countries.

**Anthelminthic Vaccines**

As pointed out previously, it will not be feasible to achieve elimination targets for most helminth infections with preventive chemotherapy alone [16]. Several anthelminthic vaccines for hookworm and other soil-transmitted helminth infections, as well as for schistosomiasis and onchocerciasis, are in varying stages of development. A bivalent recombinant human hookworm vaccine is in Phase I clinical testing in endemic areas of Brazil and Gabon through a HOOKVAC consortium of European partners and the Sabin Vaccine Institute product development partnership (PDP) [34,35], while vaccine antigens for ascariasis and trichuriasis are undergoing preclinical testing [36]. Several vaccines for both urogenital and intestinal schistosomiasis are also in Phase I trials (or at an advanced stage of preclinical development) or later stages of clinical development [37–41]. Finally, through The Onchocerciasis Vaccine for Africa (TOVA) initiative, a new vaccine may soon enter Phase I testing [42]. Most of these anthelminthic vaccines could be used in conjunction with anthelminthic drugs in programs of “vaccine-linked chemotherapy” in order to prevent reinfection following mass drug administration (MDA) [43]. Two transmission-blocking veterinary vaccines are also being developed for zoonotic helminth infections to prevent taeniasis and Asian schistosomiasis [44,45].

**Kinetoplastid Vaccines**

Several candidate leishmaniasis vaccines are under development both for the visceral and cutaneous forms of this disease, by the Infectious Diseases Research Institute (IDRI) PDP, the Sabin PDP, and two European consortia [46–49]. A therapeutic Chagas disease vaccine is also being developed by the Sabin PDP in collaboration with the Carlos Slim Foundation [50], in parallel with other approaches [51,52].

**Key Challenges**

Despite published studies showing the cost-effectiveness or even cost-savings of NTD vaccines [53–56], the major international agencies charged with advancing and introducing new vaccines—such as WHO and Gavi, the Vaccine Alliance—have been slow to adopt and promote them. There are multiple reasons for this situation, including the lack of engagement of major multinational pharmaceutical companies and the fact that NTD vaccines might prevent disability rather than under-five childhood mortality. Another major concern is the significant potential costs attached to advanced clinical development for NTD vaccines in the absence of surrogate correlates of protection. Overcoming these challenges could require developing human challenge models to obtain a “quick read” on vaccine efficacy—an approach that is being pursued for hookworm infection and possibly leishmaniasis—in order to reduce investment risk. Other risk-reducing activities could include combining NTD vaccines with those for malaria or other priority diseases in order to make investments more attractive to the industry and partnering with Developing Country Vaccine Manufacturing Networks (DCVMs) for industrial-scale production.
New NTD Diagnostics

A major challenge to meeting the goals of the London Declaration is the lack of readily available, easy-to-use, reliable, and low-cost diagnostic tools to identify infected patients, confirm cure, monitor the impact of mass treatment programs, and watch for disease re-emergence. Thirteen of the 17 NTDs (as currently defined by WHO) lack essential diagnostics, including seven of the 10 in the London Declaration. While recently there has been greater recognition of the role of diagnostics in meeting 2020 goals, funding commitments are lacking [57,58].

For many of the diseases that need to be managed on a case-by-case basis, notably Chagas disease, HAT, leprosy, visceral leishmaniasis, and Buruli ulcer, the diagnostic pathway is complex, and for some, confirmatory diagnosis requires invasive procedures not usually available at the community level. Investment in the development of appropriate diagnostics will make possible early and comprehensive case detection. For diseases controlled through mass treatment programs, we need tests to identify and map the populations requiring treatment and those in which transmission has been successfully interrupted. New diagnostics are also critically important for monitoring elimination progress and ongoing surveillance [59].

The R&D pipeline for NTD diagnostics overall is not sufficiently robust. For some, such as HAT, schistosomiasis, and onchocerciasis, substantial progress has been made in the development of new point-of-care tests, but they have not yet been widely implemented in endemic countries [60–62]. However, we are still at the biomarker discovery stage for new diagnostics for diseases such as Chagas and soil-transmitted helminthiases. For others, there is very little on the development horizon and no funding available at all. The example of Buruli ulcer, which had nothing new in the diagnostic pipeline until very recently, shows how even limited investment can catalyze R&D progress, with rapid tests expected in the next two years, pending adequate funding.

Key Challenges

In order to foster the development and widespread implementation of new diagnostic tools for NTDs, creative solutions are needed, including the formation of a representative diagnostics coalition that includes countries, researchers, developers, and policymakers to define and prioritize NTD diagnostic needs; improvement of the business case for manufacturers to foster investment by promoting the use of existing and emerging diagnostics platforms [63]; and development of tests to meet multiple diagnostic needs simultaneously. For example, a test that detects both malaria and HAT is now being explored and could become an excellent tool for malaria diagnosis while maintaining surveillance for HAT in an elimination setting. In addition, triaging tests that differentiate various causes of fever or classes of pathogens (bacterial versus viral versus parasitic) could serve multiple purposes: patient management for NTDs such as dengue and leishmaniasis, rational use of drugs to prevent the emergence of drug resistance, and disease surveillance.

The London Declaration has already generated important momentum in the development of new tools to control and eliminate NTDs. The next step is to capitalize on near-term diagnostic successes, such as the HAT rapid test, to build the investment case in support of innovative solutions and ensure that funding commitments match the needs.

New NTD Vector Control Agents and Strategies

Many of the NTDs are transmitted by insects, including mosquitoes, tsetse flies, reduviid bugs, black flies, and sand flies, which continue to plague the health of millions of people worldwide. In many instances, disease control can be effectively achieved by reducing or eliminating vector populations. Furthermore, vector control is necessary where domestic or wild animal reservoirs
contribute to the maintenance of transmission. Current disease control and elimination programs are centered on preventive chemotherapy, with insufficient focus on vector control and source-reduction strategies. It is evident, however, that without enhanced vector control, diseases like LF will take longer to eliminate. In several countries in Africa, the Anopheles mosquito that spreads malaria is also the same mosquito that spreads LF, so there may be opportunities to link NTD- and malaria-control strategies.

Vector control has traditionally been achieved via the application of insecticides, particularly against vectors of Chagas disease in the Americas [64]. Chemical agents used for insecticides typically function by either exhibiting direct toxicity against larvae or adults, or by luring insects away from human hosts and into baited traps. However, insecticides are expensive and their sustained use has been challenged by the rapid emergence of resistance in many insect species, including mosquitoes and black flies [65,66].

Research on the molecular genetics of insecticide resistance will help identify the mechanisms that mediate resistance in field populations. This information can then be exploited to help develop efficient diagnostic assays and management strategies to combat the emergence of resistance [67]. Furthermore, the development of longer-lasting insecticide formulations and more efficacious larvicides [68], coupled with targeted application practices, could increase the efficacy and substantially reduce the cost of these chemical-based methods [69].

Advances in functional genomics research, in conjunction with the growing abundance of insect and pathogen genomic data, now set the stage for the development of novel vector control methods [70,71]. Research into the genetic basis of vector competence (the ability of insect hosts to transmit specific pathogens) has identified molecular mechanisms that contribute to natural insect resistance against disease-causing pathogens. Experimentally derived approaches that fortify hostile disease vector responses can prevent the development of pathogens in their insect hosts and reduce or block disease transmission to the mammalian hosts. In this regard, efforts have focused on modifying the symbiotic bacteria that reside naturally within insect vectors and alter important host physiologies and affect vector competence [72–74].

In addition to methods modifying vector competence, transgenics-based approaches that reduce insect population densities are also attractive. One such approach, designated “Release of Insects with Dominant Lethality” (RIDL), involves releasing genetically engineered male insects that breed with wild females and produce dead progeny [75], or flightless females [76]. Finally, the expanding genomics and functional biology knowledge related to insect smell, or “olfactory physiology,” provides a foundation for the development of novel baits that can enhance the efficacy of targets and traps in the case of tsetse flies [77] and mosquitoes [78,79]. Additionally, relevant technologies can be applied to modify vector host preference and olfaction [80].

**Key Challenges**

The pipeline for new insecticides is limited. Thus, it is imperative to retain the efficacy of existing chemicals. Some of the new, innovative strategies highlighted above, which are designed to reduce human–vector contact or inhibit vector competency, represent promising new strategies. Furthermore, these approaches have the potential to reduce the cost of vector control related to NTDs. Additional new research that aims to improve on existing control tools—including olfaction technologies to alter mosquito behavior or enhanced targets and traps used for tsetse control [81,82]—will also be highly beneficial. The ongoing evaluation of such technologies in endemic settings, together with programs of community advocacy and education could ensure their eventual acceptability.
Integrating New Tools into Elimination Strategies

Eliminating diseases requires not only the right tools, but also the system to deliver them in a timely and efficient manner. This requires a different type of innovation that is dependent on local capacity and implementation science, where we move from the question of “can this work” to “how can it work here?” We have learned that new tools will not deliver themselves. In order for the tools to be meaningful and have an impact, understanding the local context in which the tools will work is key. There is also a need to model how these new tools would promote global elimination efforts for each of the major NTDs.

Discovery science for drug and diagnostics development is often conducted on a global stage, but increasingly we need to recognize that R&D must also consider a local context that involves scientists, clinicians, regulators, and health ministries in disease-endemic countries. Moreover, implementation science must have local context. This requires that multidisciplinary teams including policymakers, social scientists, health administrators, and communication scientists work together in new ways.

A clear message of the recent publication “WHO World Health Report: Research for Universal Health Coverage” is that all countries must become not only research users but

Key Learning Points

- Several new small-molecule drugs are being advanced for the major kinetoplastid infections: human African trypanosomiasis (HAT), Chagas disease, and leishmaniasis, as well as new macrofilaricides and drugs for Buruli ulcer, dengue, and Ebola virus infection. These new drugs will need to be integrated into case detection and management and other control or elimination programs.

- Vaccines for human hookworm infection, schistosomiasis, leishmaniasis, and Ebola virus infection are in clinical trials, while transmission blocking vaccines targeting zoonotic reservoir hosts are in advanced development for taeniasis (cysticercosis) and Asian schistosomiasis.

- There is an urgent need for new point-of-care (POC) diagnostics for most of the NTDs, in addition to tests that meet multiple diagnostic needs simultaneously, such as a test that detects both malaria and HAT.

- Control of vector-transmitted NTDs can be realized through vector reduction or elimination. Many of these approaches, however, rely on the use of chemicals. The presence of high levels of resistance in insects to these chemicals is compromising the major tool available for vector control. There is an urgent need for the development of new chemicals and the need to preserve the efficacy of those currently available. Advances in the genomics and molecular genetics of vectors, together with new transgenic and para-transgenic methodologies, are leading to new and innovative approaches to vector control.

- There is a need to shape public policies for the introduction of these new technologies and ensure they meet World Health Organization (WHO) goals for universal health coverage. In parallel, we need to strengthen capacity for research and development in disease-endemic countries.
For this to happen, there must be strengthening of capacity to conduct research and translate this into policy in the disease-endemic countries themselves. For the last 40 years, the Special Programme for Research and Training in Tropical Diseases (TDR) has been doing just this and has learned a number of important lessons to be considered as we move forward [87].

Defining system bottlenecks and research priorities for addressing them at a country level, and engaging community support, have been critical factors in some of the most successful control programs [88], such as the undisputed success of the development of community-based onchocerciasis control strategies, which treated over 100 million people in 19 African countries as of the end of 2012 [89,90].

Most critical, though, has been long-term commitment to developing individual and institutional capacity in the affected countries [91]. The most important component of research is the researcher, and with endemic country researchers combining local knowledge with quality science, there is great hope for integrating new tools effectively into elimination programs. Let us not forget to invest in this essential part of the research and development cycle.

References

1. Hotez P (2013) Forgotten People, Forgotten Diseases: The Neglected Tropical Diseases and their Impact on Global Health and Development. Washington, D.C.: ASM Press.
2. Molyneux DH, Hotez PJ, Fenwick A (2005) "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. PLoS Med 2: e336. PMID: 16212468
3. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Sachs S, et al. (2006) Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med 3: e102. PMID: 16435908
4. Lammie PJ, Fenwick A, Utzinger J (2006) A blueprint for success: integration of neglected tropical disease control programmes. Trends Parasitol 22: 313–321. PMID: 16713798
5. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, et al. (2007) Control of neglected tropical diseases. N Engl J Med 357: 1018–1027. PMID: 17804846
6. Hotez PJ, Fenwick A, Savioli L, Molyneux DH (2009) Rescuing the bottom billion through control of neglected tropical diseases. Lancet 373: 1570–1575. doi: 10.1016/S0140-6736(09)60233-6 PMID: 19410718

7. World Health Organization (2010) Working to overcome the global impact of neglected tropical diseases: First WHO report on neglected tropical diseases. Geneva. 172 p.

8. Hotez PJ, Alvarado M, Basanez MG, Bolliger I, Bourne R, et al. (2014) The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. PLoS Negl Trop Dis 8: e2865. doi: 10.1371/journal.pntd.0002865 PMID: 25058013

9. World Health Organization (2015) Investing to overcome the global impact of neglected tropical diseases: Third WHO report on neglected tropical diseases. Geneva. 191 p.

10. Hotez PJ, Velasquez RM, Wolf JE Jr. (2014) Neglected tropical skin diseases: their global elimination through integrated mass drug administration? JAMA Dermatol 150: 481–482. doi: 10.1001/jamadermatol.2013.8759 PMID: 24671756

11. World Health Organization (2014) Preventive chemotherapy: planning, requesting medicines, and reporting. Wkly Epidemiol Rec 89: 61–71. PMID: 24707511

12. Hotez PJ (2013) NTDs V.2.0: "blue marble health"—neglected tropical disease control and elimination in a shifting health policy landscape. PLoS Negl Trop Dis 7: e2570. doi: 10.1371/journal.pntd.0002570 PMID: 24278496

13. Hotez P (2014) Blue Marble Health: A New Presidential Roadmap for Global Poverty-Related Diseases. Baker Institute for Public Policy.

14. Uniting to Combat Neglected Tropical Diseases. The London Declaration. http://unitingtocombatntds.org/resource/london-declaration. Accessed February 22, 2015.

15. Hotez P, Pecoul B (2010) "Manifesto" for advancing the control and elimination of neglected tropical diseases. PLoS Negl Trop Dis 4: e718. doi: 10.1371/journal.pntd.0000718 PMID: 20520793

16. Keenan JD, Hotez PJ, Amza A, Stoller NE, Gaynor BD, et al. (2013) Elimination and eradication of neglected tropical diseases with mass drug administrations: a survey of experts. PLoS Negl Trop Dis 7: e2962. doi: 10.1371/journal.pntd.0002962 PMID: 24340111

17. Brooker SJ, Nikolay B, Balabanova D, Pullan RL. Global feasibility assessment of interrupting the transmission of soil-transmitted helminths: a statistical modelling study. Lancet Infect Dis. 2015 Apr 14. pii: S1473-3099(15)70042-3. doi: 10.1016/S1473-3099(15)70042-3 [Epub ahead of print] Global feasibility assessment of interrupting the transmission of soil-transmitted helminths: a statistical modelling study.

18. Colley DG. Morbidity control of schistosomiasis by mass drug administration: how can we do it best and what will it take to move on to elimination? Trop Med Health. 2014 Jun; 42(2 Suppl):25–32. doi: 10.2149/tmh.2014-S04 PMID: 25425948

19. Kim YE, Remme JH, Steinmann P, Stolk WA, Roungou JB, Tediosi F. Control, elimination, and eradication of neglected tropical diseases with mass drug administrations: a systematic assessment. Lancet Infect Dis. 2015 Apr; 15(4):358–69. doi: 10.1016/S1473-3099(15)70042-3 [Epub ahead of print] Global feasibility assessment of interrupting the transmission of soil-transmitted helminths: a statistical modelling study.

20. Pedrique B, Strub-Wourgaft N, Some C, Olliaro P, Trouiller P, et al. (2013) In-hospital safety in field conditions: a systematic review. PLoS Negl Trop Dis 7: e2865. doi: 10.1371/journal.pntd.0002865 PMID: 25058013

21. Schmid C, Kuemmerle A, Blum J, Ghabri S, Kande V, et al. (2012) In-hospital safety in field conditions: a systematic review. PLoS Negl Trop Dis 6: e1249. doi: 10.1371/journal.pntd.0001249 PMID: 22826531

22. Ward CP, Wong PE, Burchmore RJ, de Koning HP, Barrett MP (2011) Trypanocidal furamidine analogues: influence of pyridine nitrogens on trypanocidal activity, transport kinetics, and resistance patterns. Antimicrob Agents Chemother 55: 2352–2361. doi: 10.1128/AAC.01551-10 PMID: 21402852

23. World Health Organization (2012) Research Priorities for Chagas Disease, Human African Trypanosomiasis and Leishmaniasis. Geneva. Technical Report Series Number 975 Technical Report Series Number 975. 100 p.

24. Jackson Y, Chatelain E, Mauris A, Holst M, Miao Q, et al. (2013) Serological and parasitological response in chronic Chagas patients 3 years after nifurtimox treatment. BMC Infect Dis 13: 236. doi: 10.1186/1471-2334-13-236 PMID: 23610718

25. Schmid C, Kuenmerle A, Blum J, Ghabri S, Kande V, et al. (2012) In-hospital safety in field conditions: a systematic review. PLoS Negl Trop Dis 6: e1920. doi: 10.1371/journal.pntd.0001920 PMID: 23209861

26. Chatelain E (2015) Chagas disease drug discovery: toward a new era. J Biomol Screen 20: 22–35. doi: 10.1177/1087057114500585 PMID: 25245887

27. BIO Ventures for Global Health. (2015) Global Health Primer. http://www.bvgh.org/Current-Programs/ Neglected-Disease-Product-Pipelines/Global-Health-Primer.aspx. Accessed February 1, 2015.
28. Loiseau PM, Cojean S, Schrevel J (2011) Sitamaquine as a putative antileishmanial drug candidate: from the mechanism of action to the risk of drug resistance. Parasite 18: 115–119. PMID: 21678786

29. Clinicaltrials.gov Expanded Access WR 279396 Topical Cream Treatment for Uncomplicated Cutaneous Leishmaniasis (WR279396RX).

30. Clinical trials.gov. (2014) Phase 3 Study to Evaluate WR 279,396 vs. Paromomycin Alone to Treat Cutaneous Leishmaniasis (in Tunisia). https://clinicaltrials.gov/ct2/show/NCT00606580. Accessed January 23, 2015.

31. World Health Organization, TDR (2012) Research Priorities for Helminth Infections. Geneva.

32. Olliaro P, Seiler J, Kuesel A, Horton J, Clark JN, et al. (2011) Potential drug development candidates for human soil-transmitted helminthiases. PLoS Negl Trop Dis 5: e1138. doi:10.1371/journal.pntd.0001138 PMID: 21695247

33. Riveau G, Deplanque D, Remoue F, Schacht AM, Vodouhnong H, et al. (2012) Safety and immunogenicity of rSh28GST antigen in humans: phase 1 randomized clinical study of a vaccine candidate against urinary schistosomiasis. PLoS Negl Trop Dis 6: e1704. doi:10.1371/journal.pntd.0001704 PMID: 22802974

34. HOTEZ PJ, Diemert D, Bacon KM, Beaumier C, Bethony JM, et al. (2013) The Human Hookworm Vaccine. Vaccine 31 Suppl 2: B227–232. doi:10.1016/j.vaccine.2012.11.034 PMID: 23598487

35. Zhan B, Beaumier CM, Briggs N, Jones KM, Keegan BP, et al. (2014) Advancing a multivalent ‘Pananthelmintic’ vaccine against soil-transmitted nematode infections. Expert Rev Vaccines 13: 321–331. doi:10.1586/14760584.2014.872035 PMID: 24982641

36. HOTEZ PJ, Bottazzi ME, Zhan B, Makepeace BL, Klei TR, et al. (2015) The Onchocerciasis Vaccine for Africa—TOVA—Initiative. PLoS Negl Trop Dis 9: e0003422. doi:10.1371/journal.pntd.0003422 PMID: 25634641

37. Bergquist R, Lustigman S (2010) Control of Taenia solium taeniasis/cysticercosis: past practices and new possibilities. Parasitology 140: 1566–1577. doi:10.1017/S0031182013001005 PMID: 23947762

38. Lightowlers MW (2013) Control of Taenia solium taeniasis/cysticercosis: practical past practices and new possibilities. Parasitology 140: 1566–1577. doi:10.1017/S0031182013001005 PMID: 23947762

39. You H, McManus DP (2015) Vaccines and diagnostics for zoonotic schistosomiasis japonica. Parasitology 142: 271–289. doi:10.1017/S0031182014001310 PMID: 25395056

40. Gurney RS, Duthie MS, Fox CB, Matlashewski G, Reed SG (2012) Adjuvants for Leishmania vaccines: from models to clinical application. Front Immunol 3: 144. doi:10.3389/fimmu.2012.00144 PMID: 22701453

41. Kamhawi S, Aslan H, Valenzuela JG (2014) Vector saliva in vaccines for visceral leishmaniasis: a brief encounter of high consequence? Front Public Health 2: 99. doi:10.3389/fpubh.2014.00099 PMID: 25152872

42. Marooof A, Brown N, Smith B, Hodgkinson MR, Maxwell A, et al. (2012) Therapeutic vaccination with recombinant adenovirus reduces splenic parasite burden in experimental visceral leishmaniasis. J Infect Dis 205: 853–863. doi:10.1093/infdis/jir842 PMID: 22301630

43. Hotez PJ, Diemert D, Bacon KM, Beaumier C, Bethony JM, et al. (2013) The Human Hookworm Vaccine. Vaccine 31 Suppl 2: B227–232. doi:10.1016/j.vaccine.2012.11.034 PMID: 23598487

44. You H, McManus DP (2015) Vaccines and diagnostics for zoonotic schistosomiasis japonica. Parasitology 142: 271–289. doi:10.1017/S0031182014001310 PMID: 25395056

45. Alvar J, Croft SL, Kaye P, Khamesipour A, Sundar S, et al. (2013) Case study for a vaccine against leishmaniasis. Vaccine 31 Suppl 2: B244–249. doi:10.1016/j.vaccine.2012.11.080 PMID: 23598489

46. Raman VS, Duthie MS, Fox CB, Matlashewski G, Reed SG (2012) Adjuvants for Leishmania vaccines: from models to clinical application. Front Immunol 3: 144. doi:10.3389/fimmu.2012.00144 PMID: 22701453

47. Kamhawi S, Aslan H, Valenzuela JG (2014) Vector saliva in vaccines for visceral leishmaniasis: a brief encounter of high consequence? Front Public Health 2: 99. doi:10.3389/fpubh.2014.00099 PMID: 25152872

48. Marooof A, Brown N, Smith B, Hodgkinson MR, Maxwell A, et al. (2012) Therapeutic vaccination with recombinant adenovirus reduces splenic parasite burden in experimental visceral leishmaniasis. J Infect Dis 205: 853–863. doi:10.1093/infdis/jir842 PMID: 22301630
50. Dumonteil E, Bottazzi ME, Zhan B, Heffernan MJ, Jones K, et al. (2012) Accelerating the development of a therapeutic vaccine for human Chagas disease: rationale and prospects. Expert Rev Vaccines 11: 1043–1055. doi: 10.1586/erv.12.85 PMID: 23151163

51. Gupta S, Wan X, Zago MP, Sellers VC, Silva TS, et al. (2013) Antigenicity and diagnostic potential of vaccine candidates in human Chagas disease. PLoS Negl Trop Dis 7: e2018. doi: 10.1371/journal.pntd.0002018 PMID: 23350012

52. Pereira IR, Vilar-Pereira G, Marques V, da Silva AA, Caetano B, et al. (2015) A human type 5 adenovirus-based Trypanosoma cruzi therapeutic vaccine reprograms immune response and reverses chronic cardiomyopathy. PLoS Pathog 11: e1004594. doi: 10.1371/journal.ppat.1004594 PMID: 25617628

53. Lee BY, Bacon KM, Bailey R, Wiringa AE, Smith KJ (2011) The potential economic value of a hookworm vaccine. Vaccine 29: 1201–1210. doi: 10.1016/j.vaccine.2010.12.004 PMID: 21167860

54. Lee BY, Bacon KM, Shah M, Kitchen SB, Connor DL, et al. (2012) The economic value of a visceral leishmaniasis vaccine in Bihar state, India. Am J Trop Med Hyg 86: 417–425. doi: 10.4269/ajtmh.2012.10-0415 PMID: 22403311

55. Bacon KM, Hotez PJ, Kruchten SD, Kamhawi S, Bottazzi ME, et al. (2013) The potential economic value of a cutaneous leishmaniasis vaccine in seven endemic countries in the Americas. Vaccine 31: 480–486. doi: 10.1016/j.vaccine.2012.11.032 PMID: 23176979

56. Lee BY, Bacon KM, Wateska AR, Bottazzi ME, Dumonteil E, et al. (2012) Modeling the economic value of a Chagas’ disease therapeutic vaccine. Hum Vaccin Immunother 8: 1293–1301. doi: 10.4161/hv.20966 PMID: 22894964

57. Policy Cures (2013) G-Finder Factsheet: Diagnostic R&D for Neglected Diseases.

58. Molyneux DH (2014) Neglected tropical diseases: now more than just ‘other diseases’—the post-2015 agenda. Int Health 6: 172–180. doi: 10.1093/inthealth/ihu037 PMID: 24969646

59. Murray S (2014) Diagnostic tools as essential as drugs in the fight to control disease. ftcom: The Financial Times Ltd.

60. Buscher P, Gillemann Q, Lejon V (2013) Rapid diagnostic test for sleeping sickness. N Engl J Med 368: 1069–1070. doi: 10.1056/NEJMec1210373 PMID: 23484849

61. Sterenberg JM, Gierlinski M, Bieler S, Ferguson MA, Ndung’u JM (2014) Evaluation of the diagnostic accuracy of prototype rapid tests for human African trypanosomiasis. PLoS Negl Trop Dis 8: e3373. doi: 10.1371/journal.pntd.0003373 PMID: 25521120

62. Ochodo EA, Gopalakrishna G, Spek B, Reitsma JB, van Lieshout L, Polman K, Lamberton P, Bossuyt PM, Leeflang MM. Circulating antigen tests and urine reagent strips for diagnosis of active schistosomiasis in endemic areas. Cochrane Database Syst Rev. 2015 Mar 11; 3:CD009579. doi:10.1002/14651858.CD009579.pub2 PMID: 25758180

63. Ndung’u JM, Bieler S, Roscigno G (2010) "Piggy-backing" on diagnostic platforms brings hope to neglected diseases: the case of sleeping sickness. PLoS Negl Trop Dis 4: e715. doi: 10.1371/journal.pntd.0000715 PMID: 20520801

64. Schofield CJ, Dias JC (1999) The Southern Cone Initiative against Chagas disease. Adv Parasitol 42: 1–27. PMID: 10050271

65. Mallet J (1989) The evolution of insecticide resistance: Have the insects won? Trends Ecol Evol 4: 336–340. doi: 10.1016/0169-5347(89)90088-8 PMID: 21227375

66. Davies JB (1994) Sixty years of onchocerciasis vector control: a chronological summary with comments on eradication, reinvasion, and insecticide resistance. Annu Rev Entomol 39: 23–45. PMID: 8135499

67. Marcombe S, Poupardin R, Darriet F, Reynaud S, Bonnet J, et al. (2009) Exploring the molecular basis of insecticide resistance in the dengue vector Aedes aegypti: a case study in Martinique Island (French West Indies). BMC Genomics 10: 494. doi: 10.1186/1471-2164-10-494 PMID: 19857255

68. Rowland M, Boko P, Odjo A, Asidi A, Akogbeto M, et al. (2013) A new long-lasting indoor residual formulation of the organophosphate insecticide pirimiphos methyl for prolonged control of pyrethroid-resistant mosquitoes: an experimental hut trial in Benin. PLoS One 8: e69516. doi: 10.1371/journal.pone.0069516 PMID: 23936033

69. Federici B, Park H-W, Sakano Y (2006) Insecticidal Protein Crystals of Bacillus thuringiensis. In: Shively J, editor. Inclusions in Prokaryotes: Springer Berlin Heidelberg, pp. 195–236.

70. Thomsen EK, Strode C, Hemmings K, Hughes AJ, Chanda E, et al. (2014) Underpinning sustainable vector control through informed insecticide resistance management. PLoS One 9: e99822. doi: 10.1371/journal.pone.0099822 PMID: 24932861
71. International Glossina Genome I (2014) Genome sequence of the tsetse fly (Glossina morsitans): vector of African trypanosomiasis. Science 344: 380–386. doi: 10.1126/science.1249656 PMID: 24763584

72. Neafsey DE, Waterhouse RM, Abai MR, Aganezov SS, Alekseyev MA, et al. (2015) Mosquito genomics. Highly evolvable malaria vectors: the genomes of 16 Anopheles mosquitoes. Science 347: 1258522. doi: 10.1126/science.1258522 PMID: 25554792

73. Cirimotich CM, Ramirez JL, Dimopoulos G (2011) Native microbiota shape insect vector competence for human pathogens. Cell Host Microbe 10: 307–310. doi: 10.1016/j.chom.2011.09.006 PMID: 22018231

74. Dennison NJ, Jupatanakul N, Dimopoulos G (2014) The mosquito microbiota influences vector competence for human pathogens. Curr Opin Insect Sci 3: 6–13. PMID: 25584199

75. Marinotti O, Jasinskiene N, Fazekas A, Scaife S, Fu G, et al. (2013) Development of a population suppression strain of the human malaria vector mosquito, Anopheles stephensi. Malar J 12: 142. doi: 10.1186/1475-2875-12-142 PMID: 23622561

76. Fu G, Lees RS, Nimmo D, Aw D, Jin L, et al. (2010) Female-specific flightless phenotype for mosquito control. Proc Natl Acad Sci U S A 107: 4550–4554. doi: 10.1073/pnas.1000251107 PMID: 20176967

77. Masiga D, Obiero G, Macharia R, Mireji P, Christoffels A (2014) Chemosensory receptors in tsetse flies provide link between chemical and behavioural ecology. Trends Parasitol 30: 426–428. doi: 10.1016/j.pt.2014.06.007 PMID: 25017128

78. Xu P, Choo YM, De La Rosa A, Leal WS (2014) Mosquito odorant receptor for DEET and methyl jasmonate. Proc Natl Acad Sci U S A 111: 16592–16597. doi: 10.1073/pnas.1417244111 PMID: 25349401

79. McBride CS, Baier F, Omondi AB, Spitzer SA, Lutomiah J, et al. (2014) Evolution of mosquito preference for humans linked to an odorant receptor. Nature 515: 222–227. doi: 10.1038/nature13964 PMID: 25391959

80. Potter CJ (2014) Stop the biting: targeting a mosquito's sense of smell. Cell 156: 878–881. doi: 10.1016/j.cell.2014.02.003 PMID: 24581489

81. Esterhuizen J, Rayaisse JB, Tirados I, Mpiana S, Solano P, et al. (2011) Improving the cost-effectiveness of visual devices for the control of riverine tsetse flies, the major vectors of human African trypanosomiasis. PLoS Negl Trop Dis 5: e1257. doi: 10.1371/journal.pntd.0001257 PMID: 21829743

82. Solano P, Torr SJ, Lehané MJ (2013) Is vector control needed to eliminate gambiense human African trypanosomiasis? Front Cell Infect Microbiol 3: 33. doi: 10.3389/fcimb.2013.00033 PMID: 23914350

83. World Health Organization, TDR. (2015) TDR For Research on Diseases of Poverty. Implementation Research Toolkit. http://www.who.int/tdr/publications/topics/ir-toolkit/en/. Accessed February 5, 2015.

84. Peters D, Tran N, Adam T, Research AfHPaS, Organization WH. (2013) Implementation research in health: a practical guide. http://www.who.int/iris/handle/10665/91758#. Accessed March 2, 2015.

85. World Health Organization (2013) Research for universal health coverage: World health report 2013. 168 p.

86. Terry RF, Salm JF Jr., Nannei C, Dye C (2014) Creating a global observatory for health R&D. Science 345: 1302–1304. doi: 10.1126/science.1258737 PMID: 25214621

87. Reeder JC, Guth JA (2015) What have we learned from 40 years of supporting research and capacity building? PLoS Negl Trop Dis 9: e3355. doi: 10.1371/journal.pntd.0003355 PMID: 25569291

88. Certain E, Terry RF, Zicker F (2015) Shaping the research agenda. PLoS Negl Trop Dis 9: e3350. doi: 10.1371/journal.pntd.0003390 PMID: 25569230

89. Group CDIS (2010) Community-directed interventions for priority health problems in Africa: results of a multicountry study. Bull World Health Organ. 88: 509–518. doi: 10.2471/BLT.09.069203 PMID: 20616970

90. World Health Organization. (2015) African Programme for Onchocerciasis Control. Achievements of Community-directed treatment with ivermectin. http://www.who.int/apoc/cdti/achievements/en/. Accessed February 9, 2015.

91. Ogundahunsi OA, Vahedi M, Kamau EM, Aslanyan G, Terry RF, et al. (2015) Strengthening Research Capacity-TDR’s Evolving Experience in Low- and Middle-Income Countries. PLoS Negl Trop Dis 9: e3380. doi: 10.1371/journal.pntd.0003380 PMID: 25569232