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Neglected Tropical Diseases (A Sanchez, Section Editor)

Human Hookworm Disease: Alternative Strategies to Achieve the Global Health Agenda for Elimination

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Opinion statement

This year marks the fifth anniversary of the World Health Organization's roadmap and the activities spearheaded by the coalition Uniting to Combat Neglected Tropical Diseases for the control and elimination by the year 2020 of these diseases. It also marks a decade of integrated scaled-up mass drug administration efforts supported by the US Agency for International Development. Through the 2012 London Declaration for NTDs, the soil-transmitted helminths were targeted for control through mass drug administration (MDA) or preventive chemotherapy, together with basic sanitation and clean water (WASH). However, recent reports show there are multiple forces that provide substantial challenges for advancing the control or elimination of this subset of diseases (especially for hookworm disease) by relying solely on preventive chemotherapy or PC together with WASH. This review provides a summary of the recent publications that highlight the achievements and challenges of the global health agenda to control and eliminate the neglected tropical diseases, summarizes the reports of the current knowledge of hookworm disease, and focuses on the outlook of the alternative and innovative research and development strategies (diagnostics and vaccine development) that are an essential component to accelerate the global health agenda for their control and elimination.

Introduction

The modern concept of Neglected Tropical Diseases, first coined in the 2000s [1•], describes the collection of a group of 17 chronic and debilitating diseases that affect the poorest populations in the world, hence considered the diseases of inequity [2]. In 2010, the *Lancet* published a series of reviews on Neglected Tropical Diseases (NTDs) highlighting the diseases and their socioeconomic impact, the existing programs for elimination and control, the challenges and opportunities, and the policy framework [3•, 4–7].

The World Health Organization (WHO) in 2012 updated the roadmap for NTDs to provide guidelines on how to develop, improve, and implement integrated control programs for the diagnosis, treatment, and prevention of these diseases with the goal of reducing burden of disease towards their elimination by the year 2020 [8]. Member states in a World Health Assembly Resolution in 2013 endorsed the 2020 targets [9].

This roadmap for elimination was followed by the launch of the London Declaration on NTDs, where global health leading organizations, pharmaceutical companies, donors, endemic countries, and non-government organizations joined collectively in the effort towards the achievement of the WHO 2020 targets for a selected group of NTDs [10]. A coalition of these partners called Uniting to Combat NTDs was created [11] and four diseases (lymphatic filariasis, leprosy, sleeping sickness, and blinding trachoma) were targeted for elimination, while schistosomiasis, soil-transmitted helminth infections (STH), Chagas disease, and visceral leishmaniasis were targeted for control through mass drug administration (MDA) (also known as preventive chemotherapy) or other interventions [12]. Dracunculiasis was also targeted for disease eradication.

The global challenges of preventive chemotherapy

This year, a *Lancet* review by Molyneux et al. [13••] provides an elegant and detailed update of the global health agenda for the control and elimination of NTDs marking this year's fifth anniversary of the London Declaration and the plans for NTD control and elimination included in the United Nations Sustainable Development Goal targets [14].

Even though reports show that more than one billion people in 88 countries have received preventive chemotherapy, the Global Burden of Disease studies and other reports show that there are multiple forces presenting substantial challenges for control and elimination by relying solely on preventive chemotherapy or disease management [14–16]. Global poverty and economic development, weak health systems, and the increasing areas of political conflict and war zones as well as epidemiological surprises clearly prevent the ability of implementing or even scaling WHO's proposed integrated approaches. Instead, these studies support the notion that there are ample opportunities to tackle these issues by the establishment and expansion of ventures and cohesive collaborations to advance new research and development innovation complementing MDA and disease management such as vaccines, new drugs, and better diagnostic tools.

Control strategies for soil-transmitted helminths

Amongst the NTDs, the soil-transmitted helminths [*Ascaris lumbricoides*, *Trichuris trichiura*, and the major human hookworm (*Necator americanus*)], which are intestinal worms acquired via contaminated water or via penetration

of an infective larvae through the skin, are to be targeted for elimination via MDA. Even though the number of treated school-age children has increased since 2012, global coverage remains on average only 50% and the burden of disease has not significantly diminished. Deworming efforts are now advancing to include pre-school children and adult populations. However, as mentioned in previous reports by our group and others, and based on modeling studies, MDA alone or even the promotion of access to clean water, sanitation, and hygiene may not, in the long term, interrupt helminth transmission [13••, 16, 17]. This has been reaffirmed in the recent 2013 Global Burden of Disease study where data shows that MDA is not having the impact that was expected for these intestinal parasites. Indeed, there has only been a modest percentage change from 1990 to 2013 for ascariasis (25.5% reduction) and trichuriasis (11.6% reduction) while for hookworm, an increase in prevalence was observed (5.1% increase) during this period [18]. Finally, a survey of NTD experts, asked to provide thoughts on the effectiveness of MDA for the control and elimination of soil-transmitted helminths, confirmed it is unlikely that preventive chemotherapy would eliminate infection but rather additional measures would be needed to complement such an approach [19].

Emerging solutions for effective control

The current guidelines for STH MDA approaches could be revised and strengthened by expanding treatment for adult populations and folding in additional deworming medicines [20]. Even then, however, a recent systematic review suggests that the health benefits of deworming may not be as pronounced as initially believed [21]. The reasons for these findings are under investigation but may include rapid reinfection after treatment and low efficacies for hookworm and *T. trichiura* infections.

In the last decade, several groups and initiatives have focused on research and development of innovative tools to improve both diagnostics as well as alternative interventions (vaccine and new drugs) for the control of soil-transmitted infections. In the field and in low-resource settings, depending on their intensities, these infections can be a challenge to diagnose especially if they only rely on clinical manifestations. In addition, their detection, which in these settings is primarily based on traditional stool-based microscopic methods (requiring qualified technicians), can be hampered because infected individuals have irregular shedding of eggs and/or larvae. For the last two decades, new technologies, applying the "omics," have substantially advanced towards the use of molecular diagnosis. These new techniques have been extremely useful to monitor and assess prevalence and intensities during immune-epidemiological field studies and during clinical trials. These advances in molecular diagnostics for soil-transmitted infections are summarized in detail by O'Connell and Nutman [22••].

Our Product Development Partnership (PDP), Texas Children's Hospital Center for Vaccine Development, based in Houston Texas has more than 16 years of evaluating viable alternative research and development solutions for the prevention of intestinal helminths [23•]. Using a global partnership approach, we join forces and form coalitions with scientists from academic

institutions, government agencies, and non-governmental establishments to develop and test low-cost vaccines such as the human hookworm vaccine [24•].

Hookworm disease

Amongst the soil-transmitted helminths, hookworm disease caused by *N. americanus*, the major species pathogenic to humans, causes iron deficiency anemia and chronic morbidity symptoms (lethargy, physical, and cognitive impaired development) afflicting more than half a billion people primarily children and women in child-bearing age and leading to drastic productivity and economic losses [24•, 25••].

For the past decade, multiple articles have been published that summarize in detail the pathology, epidemiology, immunology, and host switches of hookworm disease as well as modeling studies to better understand the global economic and health burden [16, 24•, 25••, 26–28]. Briefly, it is well known that patients infected with hookworm do not mount a protective immune response, explained primarily because the host-parasite interactions create an immune-tolerant environment allowing the worms to survive for a long period of time. Starting from the infective larva penetration through the skin, the parasite creates an environment of immune evasion producing and releasing macromolecules, which facilitate invasion, migration, and development of the larvae into mature adult worms. The pathophysiology caused by the adult hookworm is a consequence of massive blood losses while the adult worm is lodged in the intestinal mucosa and actively feeds on the blood. Furthermore, and to reduce the amount of pathology, the worm modulates the immune response with switches towards immune tolerance or suppression permitting a symbiotic relationship where hookworm burden is tolerated. Unfortunately, even though there may be an interdependent relationship between the host and the parasite, having moderate to heavy infections can lead to a depletion of iron reserves in the host or the so-called chronic iron deficiency anemia, which in turn can lead to a reduction of cognition and physical and intellectual development in school-age children. Lastly, hookworm infections in women of child-bearing age can also lead to infertility or poor birth outcomes [16, 24•, 25••, 26–28].

Therefore, understanding the global economic and health burden of hookworm disease is a crucial and needed step that facilitates in-country officials, policy makers, researchers, and funders when selecting the best intervention strategies for control and elimination and in support of the need of innovation in research and development approaches. These data have now revealed that the economic impact caused by hookworm disease can range from $7.5 billion to $138.9 billion annually, which surpasses the impact of some of the mortality diseases, i.e., tuberculosis, dengue, and rotavirus [26].

Human hookworm vaccine initiative

Alternative or complementary interventions (such as vaccines, new drugs, or community-wide programs) are essential to ensure there is a positive influence in hookworm burden of disease and alleviate the disability it causes amongst the populations. As highlighted above, the development of a human

hookworm vaccine would be an attractive strategy to be integrated within the framework of MDA campaigns. Cost modeling studies predict that this approach could be highly cost-effective leading towards a decline of reinfection rates, improve individual and population health, and at the same time provide healthcare cost savings [27, 28].

In terms of pharmacological treatment for hookworm disease, a Cochrane analysis identified minimal efficacy for a single-dose mebendazole, with cure rates of approximately 15% (range 0–68%) against *N. americanus*. Similarly, single-dose albendazole treatment provides variable efficacies and rapid rebound infection. These findings demonstrate the need to develop a vaccine that can be combined with preventive chemotherapy [29].

Advancements of the human hookworm vaccine development to date are described in recent articles [16, 24•, 30••]. In recent years, there has been an increased interest for strategies that could accelerate clinical development of vaccine interventions, especially for those diseases that require complex field-based clinical studies in resource poor areas of the world. The development of controlled human challenge models are increasingly being adopted to establish clinical proof of concept [31]. Interestingly, a controlled human hookworm infection model is in progress with the goal to test efficacy of vaccine formulations before entering field-based clinical trials but also as a model to validate the proteome of hookworms in search of new immunotherapies [16, 32].

Conclusion

The soil-transmitted helminths and particularly hookworm infections contribute a substantial level of burden of disease globally. These parasites have developed complex and sophisticated biological and physiological mechanisms to maintain a symbiotic relationship within the host producing a collection of proteins, enzymes, and immune responses aiding to their penetration, movement, development, and survival. The development of new diagnostics, new drugs, and vaccines would represent a new generation of cost-effective biotechnology approaches for the control of these diseases. Even though these interventions may not fully tackle total prevention of infection, they may be successful at reducing the burden of disease or the magnitude of the intensity of infections.

To achieve the global health agenda for the elimination of soil-transmitted diseases and hookworm disease, alternative strategies will need to be incorporated and adopted within the strategies designed for the sustainable development goals and within the WHO and London Declaration disease elimination frameworks. In particular, it is imperative that hookworm disease-endemic countries and emerging economies will require to be fully committed towards the 2020 elimination and meeting control targets.

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Compliance with Ethical Standards

Conflict of Interest

Maria Elena Bottazzi is an Associate Dean of the National School of Tropical Medicine, Professor of Pediatrics, and the Deputy Director of Texas Children's Hospital Center for Vaccine Development, a Product Development Partnership with ongoing programs for the development and testing of vaccines against neglected tropical diseases including hookworm, schistosomiasis, onchocerciasis, Chagas disease, and leishmaniasis. She has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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