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Helminth infections: Enabling the World Health Organization Road Map

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ABSTRACT

Helminthiases are considered among the most persistent public health problems. Control and/or elimination remains a global health challenge and the World Health Organization Road Map highlights critical gaps and actions required to reach the 2030 targets, among them the need for new and more effective treatment options. Stronger collaborations across different fields are required to reach these goals. The helminth elimination platform is one example of how knowledge of two different disease areas can be aligned to fuse expertise and break disease silos.

One-sixth of the world's population - approximately 1 billion people - is infected with pathogens that cause neglected tropical diseases (NTDs). The World Health Organization (WHO) identifies 20 major conditions as NTDs, led in prevalence or incidence by the four major soil transmitted helminth (STH) infections (ascariasis, hookworm infections, trichuriasis and strongyloidiasis), followed by lymphatic filariasis (LF), schistosomiasis, scabies, leishmaniasis, Chagas disease and onchocerciasis (https://www.who.int/teams/control-of-neglected-tropical-diseases/overview). It is likely that all of the world's population living below the World Bank poverty line of USD 1.90 per day are infected with one or more of the 20 NTDs listed by the WHO, corresponding to at least 10 % of the global population (Hotez, 2020). Five NTDs are currently controlled to a large extend through mass drug administration (MDA) programs using safe, single-dose or combination medicines: LF, onchocerciasis, schistosomiasis, soil-transmitted helminthiases and trachoma. MDA is a means of delivering essential medicines based on the principles of preventive chemotherapy, in which populations or sub-populations are offered treatment without an individual diagnosis. It aims to prevent and alleviate symptoms and morbidity on the one hand, and reduce transmission on the other, improving global health in endemic areas (Webster et al., 2014). Whereas MDA programs have successfully reduced infection intensity, elimination has not been achieved in many countries for most diseases. Many factors, however, hinder the necessary coverage required for program success, such as primarily targeting specific populations (school-aged children) rather than the population as a whole (schistosomiasis, STHs) or the suboptimal efficacy of MDA drugs (ivermectin (IVM), onchocerciasis). It has also been clearly described that increasing the MDA treatment schedule (e.g. annual to biannual delivery) can improve the impact of MDA. In both cases however, countries may not be equipped to implement such strategies. Another factor influencing adequate coverage is the lack of compliance. Previous experience of adverse events when taking the drugs (onchocerciasis), rumors about the drugs or areas that simply cannot be reached (ongoing conflict, migration of populations) are only a few examples. Underlying all of the above is the overall lack of financial resources for drug access and inadequate political engagement (Kim et al., 2015).

Less than a handful of drugs are registered for treatment and control of helminth infections in humans, all of which have limitations. Onchocerciasis, or river blindness, is a vector-transmitted tropical disease caused by *Onchocerca volvulus* that mainly occurs in sub-Saharan Africa (SSA); approximately 21 million people are infected, of whom millions suffer from vision impairment and severe forms of dermatitis (Vinkeles Melchers et al., 2021), and 218 million people live at risk of infection (Zhou et al., 2019). The most effective and safe drug used to treat onchocerciasis is IVM. Treat-

Abbreviations: NTD, Neglected Tropical Diseases; STH, Soil transmitted helminths; MDA, Mass Drug Administration.

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ment results in near elimination of the filarial progeny, microfilariae (mf), from the skin and temporary prevention of new release by the adult worms (Basanez et al., 2008). However, within 6–8 months mf levels are once again high enough to sustain transmission of the infection, thus MDA needs to be repeated for many years. This has been a successful strategy to reduce disease burden, but after three decades of MDA, elimination has only been achieved in a few countries and it is clear that additional tools would be beneficial. In addition, many areas co-endemic with the filaria *Loa loa* do not receive MDA due to the risk of life-threatening adverse events in patients with a high *L. loa* burden (Boussinesq et al., 2003).

An estimated 1.5 billion people are infected with at least one of the STHs, while an estimated 5.3 billion people are at risk of infection (Jourdan et al., 2018). The disease results in disability, which compromises school attendance, child development and overall economic productivity. Albendazole, albendazole-IVM, mebendazole, levamisole and pyrantel pamoate are currently on the WHO list of essential medicines for the treatment of STH infections. The two benzimidazoles, albendazole and mebendazole, are widely used in preventive chemotherapy programs against STH infections. While albendazole and mebendazole are highly effective against *Ascaris lumbricoides*, and moderately effective against hookworm, they are poorly efficacious against *Trichuris trichiura* at single doses (Moser et al., 2017). Furthermore, there is an enhanced risk of development of drug resistance, as has already been described for STH infections in livestock (Wolstenholme et al., 2004).

The WHO recently published three critical actions to achieve the targeted elimination (interruption of transmission) of onchocerciasis, i) start MDA in all endemic areas after mapping and implement new strategies where appropriate, ii) develop improved diagnostics to facilitate mapping and decisions to eliminate transmission and iii) develop a macrofilaricide to accelerate interruption of transmission (World Health Organization, 2020. Ending the neglect to attain the sustainable development goals: a road map for neglected tropical diseases 2021–2030: overview. https://apps.who.int/iris/handle/10665/332094. License: CC BY-NC-SA 3.0 IGO). The WHO Road Map 2021–2030 (https://www.who.int/teams/control-of-neglected-tropical-diseases/ending-ntds-together-towards-2030) also suggests a multisectorial action for deworming programs for STH. Hence, to control and eliminate both gastrointestinal and tissue-dwelling nematode infections, more collaborative research and joint access strategies are needed to improve the coverage of MDA, but also develop improved drugs with better efficacy. In the STH field, these drugs should be effective against all, not just some, gastrointestinal helminth species and, in filariasis, they need to either eliminate adult worms or render them permanently sterile (Hotez et al., 2008).

Drug development is handicapped by high attrition rates, and many promising molecules fail during preclinical development or subsequent toxicological, safety and efficacy testing, making research and development (R&D) costs very high. The annual Global Funding of Innovation for Neglected Diseases (G-FINDER) surveys report the level of investment into R&D for new products for NTDs, and shows that NTDs receive nowhere near the level of funding required and that funding, when it is available, is rarely allocated in a manner likely to move products through the pipeline to patients (https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2022/01/02212458/2021-G-FINDER-Neglected-Disease.pdf). Only 1 % of all new drugs to reach the market in the past 25 years were for neglected diseases (Trouiller et al., 2002; Pedrique et al., 2013). As a result, no dedicated drug development pipeline for human helminthiases is in place.

It is essential to adopt a cooperative approach and share responsibility to reduce risks and overcome these obstacles. To enable new drug products for NTDs, high-risk development programs must be avoided, development costs minimized and significant development attrition rates overcome. Drug repurposing is one approach that has numerous advantages over starting drug discovery from scratch, including reduced development time-lines (averaging 5–7 years) and lower overall development costs. Some impressive examples demonstrate successful repurposing of veterinary drugs for human use, including IVM, praziquantel, moxidectin and triclabendazole (de Moraes and Geary, 2020). Success rates are higher due to a proven mode of action, often across several parasite species, and comprehensive information on the drug target, pharmacology, dose, toxicity data and formulation is already available.

To leverage expertise in different helminth disease areas and further break down disease silos, the Helminth Drug Development Platform (HELP, https://www.eliminateworms.org, see Table 1), has been created to establish a pan-nematode drug development pipeline, acting on multiple helminth infections to optimize the efforts. It is focusing on two main nematode infections, namely STH and filariasis, with support from the European Union (EU) Horizon 2020 framework program. HELP brings together a large amount of experience and draws from a pool of disease specialists, experts in clinical trials in remote settings, and pharmaceutical development and access professionals. Its networks within endemic countries and in the global health environment aims to further shape access strategies to deliver drugs according to the needs of specific countries. The HELP platform is investigating promising candidates derived from advanced compound libraries provided by Elanco and Celgene and compounds with the best profile will be progressed through the preclinical stage. A potential new pan-nematode molecule is SLO-1, which is targeted by emodepside, a broad-spectrum anthelmintic used for the treatment of parasitic infections in cats and dogs (Krucken et al., 2021). Having successfully completed a first-in-human study, it is currently being tested for efficacy against onchocerciasis and STH (Clinicaltrials.gov registraions numbers NCT05180461, NCT05017194). Moreover, corallopyronin A, a new compound already proven to have efficacy against *Wolbachia* endosymbionts in filariae (Schiefer et al., 2012), superior to the current 'gold standard' doxycycline, and

Table 1
Strength, Weakness, Opportunities and Threats (SWOT) Analysis of current helminth control.

Strength	**Weakness**
Elimination programs achieve reduced morbidity due to helminth infections Abrogation of transmission in some areas and countries Awareness for neglected patient groups increases	Control programs rely on an extremely limited number of tools Current drugs do not kill/eliminate adult worms (Onchocerciasis, Trichuriasis) Transmission unbroken in many areas No drug availability outside of Mass Drug Administration (MDA) programs Vulnerable populations often not targeted
Opportunities	**Threats**
Common drug targets in various helminth species Large body of knowledge on the animal health market Advanced compounds that have a complete toxicology package or have already been used in humans, but that have no registration	Potential spread of drug resistance Compliance issues with drug treatment Migration of infected individuals into post-control regions

with excellent bioavailability and safety data (in exploratory toxicology), will undergo state of the art toxicity profiling to further advance it for use in phase 1 trials.

In addition, two advanced clinical leads are being studied, oxfendazole and oxantel pamoate. Oxfendazole has been approved for veterinary use in oral and topical formulations in the United States (US) and the EU since the early 1990s. It is a benzimidazole anthelmintic indicated for the treatment of gastrointestinal roundworms, lung worms and tapeworms in cattle, sheep, horses and dogs, demonstrating its capacity to act across many helminth species. It is easy to manufacture and the cost of goods is low, suggesting an affordable treatment that, once registered for human use, could be produced in SSA. Thus, it is a promising addition to the limited portfolio of anthelmintics currently available to treat worm infections in humans. Preclinical data (Hubner et al., 2020) indicate that oxfendazole is a promising macrofilaricide; since it has no activity against mf, it is potentially a safe treatment option for patients coinfected with *L. loa*, and due to its pan-nematode activity, it might be useful for treatment of loiasis itself, a disease that has not yet been included in the NTD list. A tablet appropriate for field use is currently being tested for bioavailability by Swiss TPH and Ifakara Health Institute within the HELP consortium, one of the first phase 1 studies of a new chemical entity being performed in SSA. Oxantel pamoate is a nicotinic acetylcholine receptor agonist whose excellent anthelminthic activity against *T. trichiuria* was initially described in 1972. It has been used in veterinary practice for over 40 years but is not registered for human use (alone or in combination) in any country with a stringent regulatory authority (SRA). An oxantel pamoate-pyrantel combination product was marketed for human use (including children) under the brand name Quantrel® in the Philippines (Johnson & Johnson, Philippines) and Latin American countries (Pfizer, Venezuela), but the current marketing status is unclear. HELP will develop a child-friendly formulation of oxantel pamoate to be studied in a clinical phase 1b study aiming at evaluating safety, tolerability and pharmacokinetic properties in participants infected with *T. trichiura* (Palmeirim et al., 2021). To allow individual patient care, such new medicines must be registered and approved for use within the country where they are needed, which is currently not the case and existing drugs are not available outside of MDA campaigns. The African Vaccine Regulatory Forum (AVAREF), strongly supported by the European and Developing Countries Clinical Trials Partnership (EDCTP), enforces registration processes across multiple African countries and supportive programs by the US Good and Drug Administration] (priority voucher program), EMA (European Union (EU)-M4all) or Swissmedic (MAGHP; Switzerland) aim to enable a faster approval process and also stimulate companies to engage in drug development and access for NTDs.

Other aspects to be considered in the framework of successful drug development are differences in exposure, vulnerability, access to treatment and health outcomes that exist between different ethnicities but also between men and women. They may respond differently to a given drug treatment and drug development processes in general often suffer from an underrepresentation of women, and patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug**.** Such differences are neither well understood nor systematically documented (Hotez, 2009; Rilkoff et al., 2013). While the International Conference on Harmonization (ICH) has developed specific guidelines that deal with the participation of geriatric and pediatric subjects in the drug development process, this has not been the case for gender differences, and female underrepresentation has persisted. Additional work is required to identify drivers of such disparity. Differences in exposure and vulnerability may also be due to inequities stemming from traditional gender roles, with high prevalence of several helminth infections often observed in women. Gender norms may impede socioeconomically disadvantaged women in endemic areas from accessing necessary preventive interventions or morbidity services. For women, disability and disfigurement resulting from helminth infection limit their employment and marriageability, impacting their so and economic well-being (Hotez, 2009; Rilkoff et al., 2013). Even women and girls who are not infected with NTDs may suffer social and economic consequences if they are expected to take time away from education or work to care for family members with severe NTD morbidity (United to Combat NTDs: ‘‘NTDs: Women and Girls in Focus”, Summary Report, 2016, https://unitingtocombatntds.org/wp-content/uploads/2017/11/women_and_girls_in_focus_english.pdf). Helminth disease-specific aspects are that pregnant women are usually excluded from treatment in MDA programs, as no investment has been made in studies to demonstrate safety of the drug in special populations, including pregnant women or children under the age of 5 years. Pregnancy for example can cause females with chronic helminth infections to be more vulnerable to severe helminth-associated anaemia (Aderoba et al., 2015). Furthermore, several studies have shown that in utero exposure to maternal filarial infections increases the susceptibility to infections in children by immunomodulation (Bal et al., 2018). Such aspects should be factored into the clinical development plan.

With its registration also for specific populations, a new drug has not yet reached the finish line. Access to new NTD interventions is another consideration that needs to be taken into account very early in the development process. Successful implementation of a novel intervention strongly depends on the environment, in which it is planned to be placed. For NTDs, these are resource-poor settings with structural inequalities in access to health services, infrastructure, education, political influence and weak markets. Currently, the dominant strategy to ensure access to medicines for NTDs is drug donation from Western pharmaceutical companies. Moxidectin for example, a repurposed drug recently approved for onchocerciasis, has a better efficacy profile than IVM, but its implementation is hindered by the lack of drug donation. Such a dependence on profit-driven organizations is precarious and a more sustainable approach is required. A competitive national pharmaceutical industry should be fostered with the potential to ensure country-tailored, sustainable and affordable drug delivery for NTDs. As a starting point, it is important to obtain as accurate information as possible on the target population to estimate acceptable levels of cost for the formulated drug, based on data provided by health care workers, physicians and policy makers from disease-endemic countries. The cost estimate further depends on the use of a new drug, i.e., in MDA programs delivering billions of treatments to the population at risk or in a more targeted approach. If the cost of goods is too high and/or drug manufacturing processes too complicated, the end product will not be affordable for patients and health systems in SSA. For onchocerciasis, economic analyses are currently being conducted (Turner et al., 2019), comparing the cost-effectiveness of current elimination strategies with other potential interventions, such as test-and-treat approaches. It must be noted that many obstacles affect the accuracy of modelling, such as insufficient data capture, assumptions based on old data and unknowns in the real world, which may differ from country to country. Thus, information based on modelling should be used as guidance for strategic decisions but no more.

More recently, MDA program fatigue has been reported decades after its implementation: an individual in an endemic area may find repeated MDA inconvenient or may lose confidence in the MDA campaign (Coulibaly et al., 2018). As the population is treated as a whole, irrespective of individual infection status, there is a fine balance between making MDA compulsory, potentially limiting

individual autonomy, and allowing individuals to opt-out, jeopardizing the entire campaign if diseases are re-introduced to the treated community; this should be constantly re-evaluated as it is also the case for malaria (Cheah and White, 2016). Whereas MDA has been the only option at the time, more patient-centric solutions should be moved into focus in the future. Test and treat programs, for example, would specifically target infected individuals and improve the mapping of disease areas to provide a more targeted approach, which may be more sustainable and cost effective.

However, in the absence of consolidated and clear global forecasts, serious commitment is needed to foster patients' drug access. Facing these challenges, the signatories of the London Declaration made a clear statement that it is important to take the initiative now to develop new drugs to avoid a scenario in 2030, when elimination targets may not have been achieved and valuable time may have been wasted (Group, 2019). These commitments have been renewed in 2022 in the Kigali Declaration.

In conclusion, drug development and drug access for NTDs, in particular helminth infections, is urgently needed. For a program to be successful, many factors must be considered upfront and expertise and capacity from various disease areas need to synergize more effectively, since the parasites are often closely related and the issues to be tackled are often very similar. To improve a patient's well being goes well beyond drug discovery and development processes, with aspects ranging from technology transfers and logistics for local manufacturing and distribution of the drug, to social mobilisation and acceptance by the population need to be carefully revisited. New pathways should be identified, in which disease control technologies are adopted and used by local health systems and target populations. The landscape has changed over the past years and new consortia, such as HELP, are being set up to join forces, overcome silos and make drug development and access affordable.

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