AN UNMET NEED FOR SOIL-TRANSMITTED HELMINTH DRUGS

Soil-transmitted helminths (STHs) are parasitic worms that cause disease in humans, and are transmitted through ingesting or coming into contact with contaminated food, water or soil. The main species that infect humans are hookworm (Necator americanus and Ancylostoma duodenale), roundworm (Ascaris lumbricoides), and whipworm (Trichuris trichiura). Soil-transmitted helminths cause significant morbidity by residing in the intestines and other organs, causing malnutrition and impaired cognitive development.

More than 1.5 billion people worldwide are infected with soil-transmitted helminths.[1] While soil-transmitted helminth infection does not cause death in the majority of cases, it does place a significant burden on sufferers' quality of life. In 2019, the global burden of hookworm infection was 984,000 disability-adjusted life years (DALYs), roundworm accounted for a further 754,000 DALYs and 2,090 deaths, and whipworm was responsible for 236,000 DALYs.[2] A significant proportion of the disease burden of soil-transmitted helminths could be prevented by the development and deployment of novel chemotherapeutic agents.

R&D gaps and clinical use cases

Development of STH vaccines remains a high priority to provide long term protection, prevent reinfection and reduce the likelihood of emerging drug resistance, but, even with increased investment, they will take significant time and resources to develop, partly due to the complex lifecycles of the parasites which make it challenging to develop a vaccine which will target parasites at all stages of development. In the absence of vaccines, disease control efforts for STH infections currently rely on mass drug administration with albendazole or mebendazole. However, the continued use of these treatments promotes growing drug resistance, highlighting the need for several kinds of novel therapeutics:

Target 1: Preventive chemotherapy in endemic areas

Current mass drug administration has a low efficacy against T. trichiura, resulting in low cure rates and an increased risk of reinfection. Improving cure rates will require new combinations of existing and novel or repurposed drugs with improved efficacy. Initial trials of combinations of ivermectin-albendazole and moxidectin-albendazole have shown promising results, but larger clinical trials are needed to provide more conclusive evidence.

1 World Health Organization, Fact Sheets – Soil-transmitted helminth infections

2 Institute for Health Metrics and Evaluation, Global Burden of Disease 2019 Results Tool.

Target 2: Management of drug resistance in endemic areas currently using WHO recommended preventive chemotherapy

New, high efficacy drugs with novel modes of action are needed to both deal with existing drug resistance and to prevent the development of further resistance by improving cure rates and reducing the required frequency of treatment.

Target 3: Preventive chemotherapy for women in the first trimester of pregnancy

Current treatment options are only recommended after the first trimester of pregnancy. However pregnant women, with their elevated iron requirements, are particularly vulnerable to iron-deficiency anaemia, which is the primary cause of morbidity in hookworm infection. They are at a higher risk of serious harm from STH infection than the rest of the population.

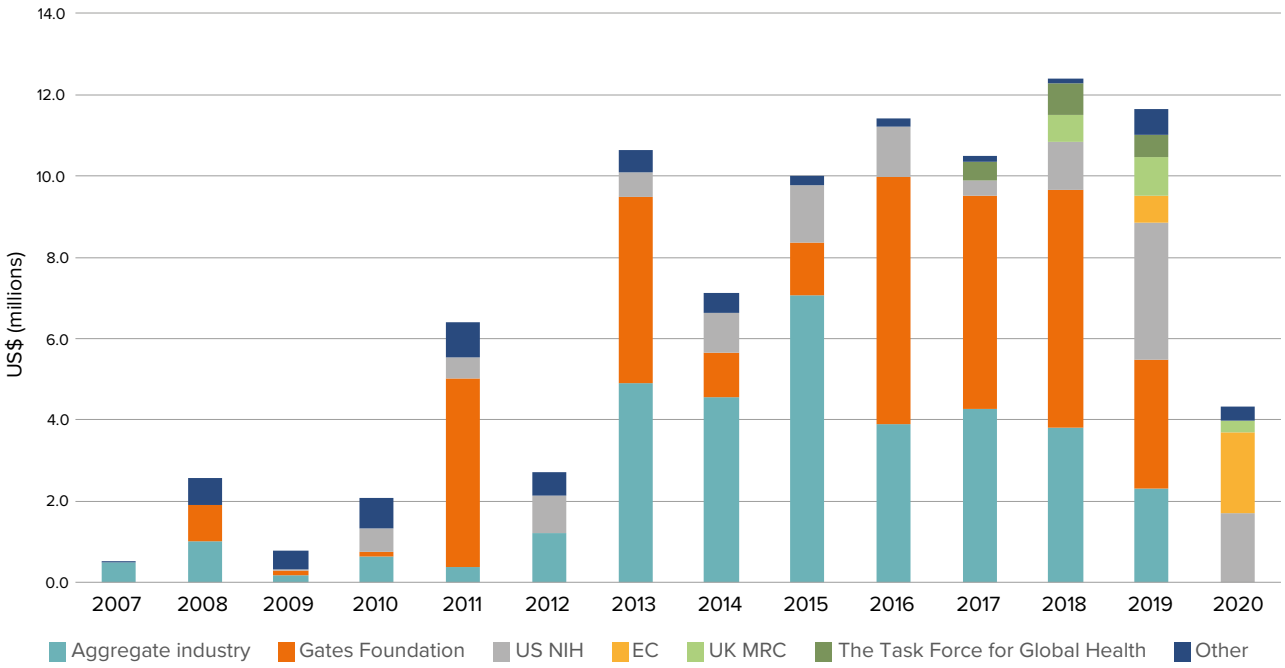
Trends in funding for STH drug R&D

Funding for STH drug R&D fell to $4.3m in 2020, a $7.3m (-63%) decline from 2019. This was the second consecutive year of declining funding, leaving it below its long-term average of $6.6m and far beneath its 2018 peak of $12.4m.

After averaging just $2.5m of investment over the first six years of the G-FINDER survey, funding grew rapidly in 2013, and remained high thanks to sustained contributions from the Bill & Melinda Gates Foundation, industry, and to a lesser extent, the US National Institutes of Health (US NIH). The sharp fall in 2020 funding was the result of the complete cessation of funding from the Gates Foundation and industry, each having already declined steeply in 2019. Over the preceding five years (2014-2018), the Gates Foundation and industry had been jointly responsible for 84% of STH drug R&D, but 2019 saw the completion of both the Foundation's ongoing multi-helminth funding streams to DND*i* and the Swiss Tropical & Public Health Institute (Swiss TPH), as well as the conclusion of post-registration studies by a major industry funder.

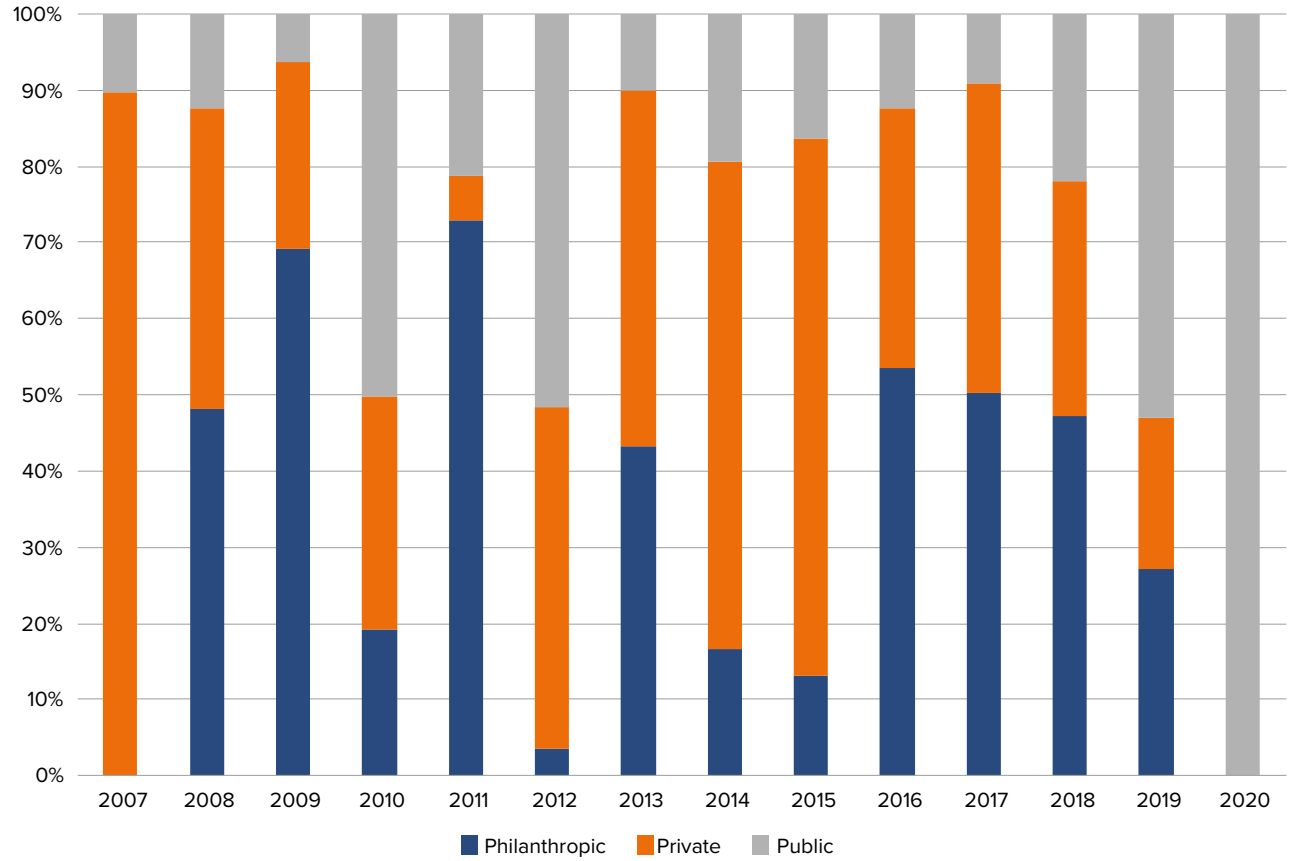
Following the sharp falls in funding from the Gates Foundation, industry and the US NIH – the top funder in 2019 – the European Commission (EC) was left as the top funder of STH drug R&D in 2020, providing just under half of the reduced total ($2.0m, 46%) – more than three times its 2019 level. The majority of the remaining funding came from the US NIH ($1.7m, 39%), down by nearly half from its peak in 2019.

FIGURE 1 **STH drug R&D, by funder 2007-2020**



As a result of the cessation of Gates and industry funding, in 2020 funding was exclusively provided by high-income country (HIC) public funders, well above the average share of 20% over the previous 13 years, representing a significant break from the pattern of philanthropic and industry-dominated funding which had prevailed since 2013. In the previous 13 years, around 40% of funding came from each of the philanthropic sector and industry funders, with HIC public funders providing an average of 20%.

FIGURE 2 **STH drug R&D funding, by sector 2007-2020**



Around half (53%) of the funding for STH drugs in 2020 was invested in basic and early-stage research, with the remainder not specifying an R&D stage. No STH drug funding was reported as specifically for clinical development or post-registration studies in 2020, a big drop from its two-thirds share of funding in each of the previous two years. This reflects the conclusion of two Gates-funded clinical trials, and of an industry-led post-registration study.

The pipeline for STH drugs

Product/Candidate name	Archetype	R&D stage (P2I)	Developer(s)
Tribendimidine	Repurposed drugs	Phase III	Swiss TPH
Emodepside	New chemical entity	Phase IIA	University of Basel DND*i*
Moxidectin	Repurposed drugs	Phase II	Swiss TPH
Albendazole/Ivermectin	Repurposed drugs	Phase III	Swiss TPH
Albendazole/Moxidectin	Repurposed drugs	Phase III	Swiss TPH

There are numerous repurposed or combination drugs in the pipeline explicitly targetting improved efficacy of treatment against T.trichiura.

The recently concluded Gates Foundation-funded phase III trials have shown that treatment with ivermectin-albendazole resulted in higher efficacy than treatment with albendazole alone, making it a promising combination therapy in regions with high T. trichiura prevalence, particularly in regions where ivermectin will be beneficial against other endemic helminth infections.

Phase II trials of combination therapy of moxidectin-albendazole are being conducted by the Swiss TPH, primarily to determine the efficacy against T. trichiura, with secondary outcomes examining the cure rates and egg reduction rates in cases of coinfection with A. lumbricoides and hookworm.

Emodepside is a marketed veterinary anthelmintic which is undergoing early-stage research within trials funded by both the EC and the Gates Foundation to determine its applicability to a number of human soil-transmitted helminth infections, including hookworm and whipworm.

Tribendimidine is a repurposed drug which has reached phase III clinical trials. It has shown to be efficacious against hookworm infection when used in combination with either ivermectin or oxantel pamoate and could therefore be an appropriate addition to mass drug administration regimens to help reduce the risk of drug resistance.

Oxantel pamaote has been shown to be highly efficacious against T. trichiura, and shows promise for use in preventive chemotherapy for whipworm, alone or as a combination treatment. Efficacies of oxantel pamoate against A. lumbricoides and hookworm infections were low, however, except when used in combination with another drug, such as albendazole or mebendazole.

Other areas of unmet need

Neither the currently approved treatments, nor any of the drugs presently in development address the unmet need for drugs that are safe and recommended for use during the first trimester of pregnancy. WHO recommendations encourage the use of albendazole or medendazole as preventive chemotherapy after the first trimester, but state that anthelmintic medicines must not be given during the first trimester.[3] Pregnant women are one of the most vulnerable groups to helminth infection due to their increased iron requirements, meaning that helminth infection can result in adverse health effects on both mother and foetus, including maternal anaemia, pre-term birth and low birth weight.

The funding landscape for soil-transmitted helminth drugs changed dramatically in 2020, both in terms of the overall funding trends, and a shift in the sectoral split of funding. However, since much of this change can be attributed to the conclusion of relevant clinical trials, future investments into drugs to treat STH infections, particularly in late-stage clinical trials, will be important to secure increased investment from new and traditional funders of STH drug R&D will be essential to allow effective treatment of vulnerable populations.

3 World Health Organisation, Guidance summaries - deworming in pregnancy