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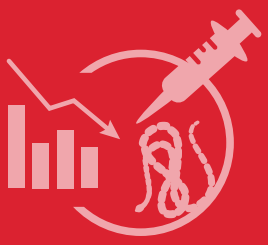

Promoting Private Sector Involvement in Neglected Tropical Disease Research and Development

Jeremy Barofsky and Jake Schneider

About the Brookings Private Sector Global Health R&D Project

Global health remains one of the world's most pressing challenges. Particularly in developing economies, a complex set of factors impede development, deployment, and affordability of medications, vaccines, and diagnostic tests. While there is no single solution to this challenge, an important part of the overall solution lies in incentivizing investors and pharmaceutical companies to raise their investment in global health R&D.

The Brookings Private Sector Global Health R&D Project seeks to find ways to address this investment shortfall. The project recognizes the need to complement the research on the social returns to global health R&D by examining the potential financial returns to private sector global health R&D investors, and offers policy solutions that can boost those returns. This publication is the fourth in a series of reports published by the Private Sector Global Health R&D Project. To contact the report authors, please email HealthRD@brookings.edu.

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Executive Summary

After rapid declines in the burden of disease in the developing world since 2000, funding for global health treatment and research is in decline. The World Health Organization (WHO) estimates that $150 billion is required to restore the pipeline of drugs for neglected tropical disease (NTDs) and Tuberculosis to the necessary levels.[1] However, research from West, Villasenor and Schneider finds that $5.6 billion is currently spent on global health R&D overall annually. Even if research and development funding for neglected diseases increased sharply today, the average 8 year timeline from preclinical testing to approval, means that drug and vaccine development for NTDs will be inadequate for the foreseeable future compared to disease burden.

In this paper, we explore the current drug and vaccine development environment for NTDs and investigate ways to stimulate more investment. This is the fourth in a series of reports in the Brookings Private Sector Global Health R&D Project on ways to strengthen private investment to expand available drugs and vaccines against NTDs. Earlier papers examined health R&D spending levels, the literature on barriers to investment, and health governance.

This analysis focuses on specific examples of successful or promising NTD drug and vaccine development, tells the story of how novel compounds are being turned into viable products, and describes the private sector's role. To examine these topics, we investigate the landscape of NTD public-private partnerships for drug and vaccine development and then use case studies and economic modelling to explore prospects for greater private investment. Using interviews from key experts, we develop case studies of recent public-private partnerships that are moving small molecule drugs through the research pipeline for treatment of Human African trypanosomiasis (Fexinidazole and Acoziborole) and Chagas disease (Benznidazole and E1224) as well as current prospects for vaccine development to prevent hookworm and schistosomiasis.

In addition, we analyze the development costs for small molecule drugs compared to estimates of potential revenue to identify expected private investment returns. We investigate under what circumstances and for what type of drugs we can expect positive returns if NTD R&D was executed by a private post-market biopharmaceutical firm. The analysis estimates the net present value of costs for neglected disease R&D both for an average NTD drug as well as using the specific expenditure and timeline for three NTD drug candidates (Fexinidazole,

Acoziborole, and Benznidazole). The private return on investment that would have prevailed for each drug candidate is calculated, adjusting for available tax credits, capitalizing costs, and incorporating estimates of drug failure risk. The primary source of potential revenue is the priority review voucher (PRV), in which firms that develop an eligible drug are awarded expedited FDA review for another drug candidate. Expected PRV revenue is calculated by estimating its resale value from earlier drug approval, larger market share, and longer patent exclusivity and under various supply scenarios. We also qualitatively describe other potential sources of revenue including secondary market sales and the benefit private firms obtain when engaging in socially responsible drug development on employee motivation and retention.

We find that the current neglected tropical disease research and development landscape is driven by non-profit entities in partnership with the private sector. We find that private firms are driven by pre-existing commitments to disease elimination and geographic areas as well as interest in aligning their work with social goals.

We find that the current neglected tropical disease research and development landscape is driven by non-profit entities in partnership with the private sector. Although the PRV is an important incentive for drug development, companies report that it is not the primary motivator to encourage investment. Instead, we find that private firms are driven by pre-existing commitments to disease elimination and geographic areas as well as interest in aligning their work with social goals. In the NTD R&D partnerships we explore, the non-profit entity is responsible for identifying a promising compound, stewardship of the partnership, and the clinical development costs. The private entity manages the manufacturing process, drug registration, and approval. In addition, private sector entities are found to provide in-kind contributions through their compound library.

We compare the net present value of development costs for an average NTD small molecule drug, adjusting for both the orphan drug and general R&D tax credits, against potential revenue from a PRV and find that under most scenarios revenue is insufficient to support a positive private return on investment (ROI). We then explore the most important drivers of private-sector drug costs and find that risk of failure and PRV value (determined by PRV supply) are most important in determining ROI. Using data on phase development costs specific to Fexinidazole and Acoziborole and assuming that the supply of priority review vouchers is restricted, we find the return on investment to be break even for Fexinidazole and slightly negative for Acoziborole.

If we also incorporate the fact that probability of success through each clinical phase is likely higher than for private-market drugs, we find a range of approval probabilities indicating positive private returns. In addition, relatively high phase II versus phase III clinical development costs for Fexinidazole and Acoziborole mean that private ROI is likely to be higher if orphan drug designation is achieved such that the tax credit can be applied starting in phase II.

Moreover, we find that the returns on investment for Benznidazole or a similar project, if undertaken by a private firm, are positive in the current policy environment. Given that this is an already created drug without approval in the U.S., costs were substantially lower than for novel compound synthesis. Nevertheless, this approval can produce health benefits through greater access to treatment. Furthermore, private biopharmaceutical companies are well placed to invest in neglected diseases because their financial structure

allows them to internalize many of the benefits, including taking advantage of tax credits and the intangible value of greater employee motivation for work toward social goals.

Our case studies on the current environment in vaccine development reveal a challenging landscape for private sector involvement given the size of investments needed and the average length of development timelines. Specific to vaccine development for schistosomiasis and hookworm, we compare funding outlays against projected needs for approval and find that current annual levels are inadequate to produce final vaccines under any reasonable timeline. We also note the public health risk from expanding mass drug administration (MDA) combined with an empty drug and vaccine pipeline given the danger of antimicrobial resistance. The creation of a public sector pull mechanism to encourage private sector investment, namely an Advanced Market Commitment, for hookworm and schistosomiasis would help spur private-sector support and vaccine innovation. Moreover, there is growing evidence that reduced childhood exposure to hookworm and schistosomiasis produces long-term benefits in cognition, educational attainment, and labor market returns. That is, in addition to their primary health impact, treating both hookworm and schistosomiasis fosters human capital formation and increases earnings opportunities in adulthood. Given the positive social returns and opportunities for economic development, pull mechanisms that guarantee public support for development of these vaccines would generate significant health and economic benefits as well as avoid the scenario of antimicrobial resistance when current treatments become ineffective.

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Based on this analysis, we make several recommendations for future action:

1. **Alignment of public funding with social return.** Our analysis shows the restricted circumstances in which private sector R&D generates a positive return on investment in the current policy environment. To increase the range of activities that receive private funding, we propose public funding that is explicitly tied to health gain (disability adjusted life years [DALYs] averted). There are various financing mechanisms that have been developed that would allow governments to pay for results, including Development Impact Bonds and cash-on-delivery models. These arrangements allow public funders to provide financing contingent on results, as verified by a third party, and do not require outlays otherwise.

2. **Private sector late-stage investment and risk sharing.** Our quantitative analysis finds that the most important drivers of private sector development cost are long development timelines and failure risk. Complementary to recommendation #1, we therefore propose additional private sector investment focused on phase III clinical trials to minimize risk-adjusted, capitalized private sector costs. In addition, to further minimize risk, private sector biopharmecutical firms could enter into investment agreements that would spread the risk and benefits of these trials. This risk-sharing arrangement would be particularly oriented toward social impact investors that want to both diversify market risk (R&D risk being orthogonal to market risk) and generate positive social returns.

3. **Public funding coordination and stewardship.** Our case studies indicated the importance of stewardship and coordination of product development partnerships by non-profit entities. Greater stewardship from governments to determine priority areas for NTD investment as well as coordinate joint funding of early stage R&D with nonprofit actors would both increase the likelihood of private sector involvement in late stage R&D as well as increase the likelihood that innovation maximizes public health.

4. **Advanced market commitment for hookworm and schistosomiasis:** Our analysis highlighted the challenges for NTD vaccine development and the mismatch in scale between current resources compared to the funding necessary for successful development. The creation of an advanced market commitment ensuring a set price for certain number of treatments purchased would increase the likelihood of private involvement in vaccine development.

5. **Tiered PRV based on social return and clinical stage:** One specific policy change that may be more feasible in the near term to align financial incentives and health impact includes an adjustment to the PRV such that the PRV varies based on the level of innovation produced compared to current clinical practice.

6. **Targeted domestic resource mobilization:** Although there are limited resources available for NTD R&D in the developing world, we recommend a targeted strategy of domestic resource mobilization mediated through and conditioned by low-interest loans from multilateral institutions like the World Bank or the African Union.

The Challenging Economics of Neglected Tropical Disease Research and Development

There are several difficulties facing biopharmaceutical firms regarding research and development (R&D) for drugs and vaccines against neglected tropical diseases. The development of a new drug or vaccine is time-intensive, risky, and expensive. A company in the private market decides to invest in a given product if expected revenue is favorable compared to costs over time. If the expected capitalized cost of R&D expenditure is less than the discounted stream of profits, then a firm will invest.[2] Unsurprisingly, larger R&D expenditures occur for drugs with higher expected returns.[3] Purchasing power is in general too low in developing nations and among those affected by NTDs to incentivize drug and vaccine development and greater patent protection in the developing world is insufficient to mitigate this underinvestment.[4]

To underscore the weak incentives for NTD development, from 2000 to 2011, a total of five new therapeutic products for NTDs were approved by regulatory bodies worldwide. This constituted less than 1 percent of total worldwide product approvals. In addition, none of these were new chemical entities, but instead were expanded indications, new formulations, or combinations of existing therapies.[5] This missing market threatens future global health goals. One study found that there are 145 'missing' drugs, vaccines, and diagnostics that will be required to achieve the Sustainable Development Goals' health targets.[6]

There are multiple market failures that impede the development of drugs and vaccines for neglected tropical diseases. These include:

1. Time-inconsistency: governments and institutions that buy vaccines have a time-inconsistency problem. They can promise to pay prices that would lead to a profitable product for the firm, but then would be pressured to provide the product for a lower price. Later, governments could renege using their roles as dominant purchasers and arbiters of property rights.
2. Global public goods: Since the creation of a drug or vaccine to treat NTDs is a global public good, there is a free-rider problem since the many small

nations that would benefit from the product would not have an incentive to unilaterally pay higher prices for drugs to make drug development profitable. Meanwhile, there are either no or very small private commercial markets for individual purchases of these drugs and vaccines because the population that experiences the vast majority of the NTD burden is in poverty and/or living in low-income nations.

3. Lumpy investments: Given that an innovation for drug or vaccine development requires substantial fixed costs before any revenue or social benefit accrues and large uncertainty exists in whether the investment will produce sufficient clinical efficacy for compound approval, incremental investments are wasted if not continued to the end of the development pipeline. Therefore, if liquidity or coordination constraints exist, even if the product would be, in expected value, profitable, the nature of this production function means that risk-averse investors would not act unless compensated for this uncertainty.

Production of public knowledge where the social benefits are large, but the private economic incentives are low, is a critical failing that limits our ability to use market incentives to produce social innovation. As noted in our report "Private Sector Investment in Global Health R&D: Spending Levels, Barriers, and Opportunities," West, Villasenor and Schneider find that one-half of one percent of total private sector R&D ($511 million) went toward neglected disease R&D in 2016.[7]

However, it is vital to make progress by bringing greater resources to bear toward NTD drug development because the stakes are high. Addressing diseases borne by the poorest would improve health and help reduce poverty (given that health constitutes an important input to a household production function). Yet without solutions to these market failures, private production of innovation for NTD drugs and vaccines will be inefficiently low.

Overcoming Market Limitations in Global Health R&D

Given the market failures identified above that limit private sector R&D for NTDs, non-profit product development partnerships (PDPs) are the primary organizational structure that currently invest in drugs and vaccines for these vulnerable populations. In this paper, we focus on two major PDPs: efforts by the Drugs for Neglected Diseases Initiative (DND*i*) to develop small molecule drugs and work by the Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine (Texas Children's Hospital) in vaccines. DND*i* is a collaborative, non-profit drug R&D organization dedicated to developing new treatments for neglected diseases. Texas Children's Hospital coordinates various public and private sector actors to contribute their expertise toward small-molecule and/or vaccine development. DND*i* attracts more private sector interest with their focus on small molecule drugs, although its focus on social goals and public gain attracts philanthropic donors and government funding as well. In addition to public and philanthropic funding, mechanisms such as PRVs, advanced market commitments, social marketing, and orphan drug development could be used by these PDPs and private biopharmaceutical firms to support greater NTD R&D investment.

Priority Review Voucher

After being proposed in a paper by Ridley et al. (2006), the US Congress created the PRV program in 2007 to incentivize NTD drug development.[8] The United States Food and Drug Administration (FDA) aims to review a standard drug application in 10 months. The FDA also offers priority review of drugs, which are intended to take 6 months. Initially, the PRV program awarded a voucher for fast-tracked FDA review to the sponsors of a successful new tropical disease drug application only. In 2012, the program was expanded to make rare pediatric diseases also eligible for PRV designation.[9] Through the PRV program, an eligible neglected disease or rare pediatric drug candidate undergoes expedited

regulatory review itself. In addition, a bonus PRV is awarded that can be used by a drug company to speed up review for another drug. Because the PRV can be sold, the value of this expedited review can be transferred to another company. Thus far, 16 PRVs have been awarded, including 4 in 2017. Six PRVs have been sold for prices ranging from $67.5 to $350 million and two PRVs have been used by their developers. Later, we describe in detail how we estimate the value of PRVs, given per year supply assumptions.[10]

Advanced Market Commitments

The ideas behind Advanced Market Commitments (AMCs) were set down in a 2005 paper.[11] An AMC is an agreement made by G8 nations to provide a guaranteed price to a biopharmaceutical company conditional on successful drug or vaccine development. If no vaccine or drug is developed, then no donor funds are expended. The AMC represents another potential solution to the market failures that impede drug and vaccine development for purchasers (development aid agencies and nations) to commit to fully or partially finance purchases at a pre-specified price. Currently, no AMC has been created to encourage development of an NTD. The only example of the creation of an AMC in practice is a pilot AMC for pneumococcal disease. Because this is not an NTD, we do not describe it in detail here.

Social Marketing

During our interviews with representatives from private-sector biopharmaceutical companies, we found widespread interest in and motivation to support the development of drugs that generate a social return. Private sector representatives reported that, conditional on being able understand the risks involved and the amount of spending that would be needed, they were motivated to engage in NTD research to more closely align their work with the company's social values.

This is consistent with an analysis that scientists value the ability to engage in knowledge production as a public good.[12] Using data from the job offers received by post-doctoral candidates in biology, a paper by Stern (2004) analyzes the economic implications of private firms adopting a science-oriented approach to knowledge production. The paper exploits the fact that many professionals receive multiple job offers when choosing their employment status. The data includes both a wage offer and job characteristics for post-doctoral candidates in biology, with specific information by job offer on opportunities to engage in science.

One finding is firms that do not allow their employees to publish must offer on average a 25 percent wage premium. This intangible value for the production of scientific knowledge by a private firm, although difficult to quantify specific to NTDs, represents real value that can be used to motivate, attract, and retain highly skilled researchers. Put another way, for all people and individual scientists in particular given their career selection, one element in their utility function includes the production of altruistic knowledge intended to improve lives.

In addition, there is a separate value for scientists to work on scientifically interesting problems even if they are not commercializable. Or researchers may have an intrinsic preference for interacting with the broader scientific community and receiving recognition for discoveries. That is, scientists have a "taste" for science. Nevertheless, this taste is not uniform across all scientists as other research suggests that the "taste for science" varies with some researchers valuing salary and access to resources above the ability to engage in publication.[13]

A sustained commitment to the production of socially valuable drugs and vaccines would permit biopharmaceutical firms to compete for an expanded pool of scientists, which could translate into gains either in researcher quality or motivation as well as willingness to accept lower wages for the ability to contribute to social welfare. Further discussion of this effect can be found in the appendix.

Orphan Drug Tax Credits

Over the past few decades, most of the developed world has passed legislation that offers tax credits to encourage private-sector investment in orphan drugs. The US Congress passed the first such law in 1984 as the Orphan Drug Act (ODA). Similar laws were passed by Japan in 1993, Australia in 1998, and the European Union in 2000.[14] Although there is some variation, orphan drugs are generally defined by two criteria: the product is intended to cure or treat a disease with low prevalence and/or there is no reasonable expectation that the product, irrespective of prevalence, will provide revenues that cover R&D and production costs in the country where orphan status is granted.

In the US, an orphan drug designation includes the orphan drug tax credit (ODTC), which provides drug developers with a tax credit that equals 50 percent of qualified clinical trial expenses. In addition, orphan drug designation provides 7 years of market exclusivity as well as limited grants for pre-clinical research. Because the ODTC is a non-refundable credit, drug developers without tax liability cannot take immediate (and therefore full) advantage of the credit. However, for pre-market developers, the ODTC can be carried forward to future tax years when sufficient tax liability has accrued, up to 20 years.[15] An example of the ODTC's use for neglected diseases in the US is the FDA's recent approval of Chemo Group's application for Benznidazole, where it received both a Tropical Disease PRV and as well as orphan product designation.[16,17] In the US, in addition to the ODTC, there is a general nonrefundable R&D tax credit that can be applied to pre-clinical expenditure. One recent analysis calculated that the value of this general R&D investment tax credit averages 6% of total pre-clinical costs for orphan drug development.[18] We apply this 6% reduction as well as the ODTC in our analysis.

Neglected Tropical Disease Case Studies

In this paper, we focus on four neglected tropical diseases: Chagas disease, human African trypanosomiasis (commonly referred to as "HAT"), hookworm infection and schistosomiasis. We selected these diseases based on their large global burden (in terms of both DALYs and prevalence), as well as their promise for scientific innovation. Table 1 provides basic and pertinent information about each disease.

TABLE 1 | **Overview of the Four Diseases Included in this Study**

Disease	Global Burden (DALYs, Thous.)[19]	Clinical Features	Candidate(s)	Partnership/Latest Phase Entered
Chagas disease	219.0	Vector spread by insect *Trypanosoma cruzi*	Benznidazole, E1224	FDA Approval
HAT	128.4	Vector spread by tsetse flies	Fexinidazole, Acoziborole (SCYX-7158)	Phase II/III
Hookworm	1,863.6	Worms spread by infected defecation.	Na-GST-1, Na-APR-1, Na-GST-1 plus Na-APR-1 (M74)	Phase I/II
Schistosomiasis	1,685.4	Vector spread by water-born snails	Bilhvax, Sm14, Sm-TSP-2	Phase III

Source: Authors' compilation. We present DALY estimates from IHME here for hookworm and schistosomiasis.

Human African Trypanosomiasis

Human African trypanosomiasis (HAT), commonly referred to as sleeping sickness, is a major neglected tropical disease. HAT is caused by infection with a protozoan parasite and transmitted via tsetse flies. Sleeping sickness can manifest in an acute form, predominant in East Africa (mostly Uganda and Tanzania) or in a chronic form that is found in fifteen nations in West or Central Africa with Democratic Republic of the Congo, Angola, South Sudan and the Central African Republic most seriously affected.[20] Both forms of the disease ultimately progress to involve the central nervous system (CNS) and are considered universally fatal without treatment (within three months for the acute form and within two years for the chronic form).

The incidence of acute HAT reached 38,000 cases per year at its peak in the late 1990s. With public health prevention and treatment initiatives, the incidence of acute HAT decreased from 700 in 2000 to around 100 in 2014.[21] Over the same period, the incidence of new cases of chronic HAT decreased from more than 25,000 new cases per year as of 2000 to 3,600 new cases per year by 2014.[22] Thus, in recent years the total number of cases of HAT each year has not exceeded 3,000. However, the disease is associated with very severe morbidity as well, with early stage disease causing headaches, arthralgias, fevers and lymphadenopathy and later stages causing meningoencephalitis and parenchymal edema of the brain with resulting progressive neurological disturbances.

The drugs currently available to treat HAT are all sub-standard in terms of toxicities and mode of administration, and as such, there is an urgent need for novel, effective therapeutics.[23] For treatment of the acute form of HAT, Suramin is the only drug available to treat early infection and melarsoprol the only drug to treat late infection. Suramin is associated with several adverse effects while melarsoprol is a highly toxic, arsenic-containing drug with a multitude of serious side effects that is only available by injection. Consequently, the health benefits and improvement in access from new treatments would be substantial.

In the following, we describe two recent public-private partnerships that have produced promising new treatments for HAT: Fexinidazole and Acoziborole (SCYX-7158).

In 1995, Aventis—the company that preceded what is now Sanofi-Aventis—announced that the production of drugs to treat HAT—including eflornithine—would be discontinued. If discontinued, this would have left healthcare providers without any avenue for treating patients with this disease. Following this announcement, the WHO and Aventis signed an agreement in May 2001 to ensure a continued supply of three of the four drugs to treat HAT and establish a program for donation of these essential medicines. In addition, Aventis supplemented the donation of medicines with an additional 25 million USD per year to support the WHO's program against African trypanosomiasis.[24] This donation program was renewed in 2006, 2011 and 2016. Currently, Sanofi-Aventis has guaranteed an unlimited quantity of all three drugs through 2020.[25]

Given the goal to eliminate HAT and the dearth of safe drugs to treat this disease, DND*i* chose HAT as an early priority condition for drug discovery. Early on in its existence, DND*i* undertook a systematic review and profiling of more than 700 nitroheterocyclic compounds from diverse sources and assessed these compounds for their antiparasitic activity. In the process of screening drug libraries, DND*i* uncovered Fexinidazole as a promising candidate that was effective against single-celled parasites. This drug had been the subject of development efforts in the 1970s and 1980s and its activity against trypanosomes had been confirmed in that process, but later stages of development had been abandoned. DND*i* then approached Sanofi-Aventis to form a public-private partnership to advance the approval of Fexinidazole. In September 2009, the drug entered clinical trials and Fexinidazole is currently being studied in a randomized Phase II/III clinical trial.[26] Ultimately, DND*i* aims to evaluate and register Fexinidazole as a treatment for adults and children over 6 years of age with either stage of HAT.

In this partnership, DND*i* has assumed much of the responsibility for the clinical and pharmaceutical development activities while Sanofi-Aventis is primarily responsible for the industrial development and production. In particular, DND*i* has designed and executed data collection for human studies of Fexinidazole, working with the National HAT Control Programme to recruit adult patients with stage 2 HAT in the Democratic Republic of the Congo (DRC) and the Central African Republic. The two organizations have agreed to share any benefits that result from the development of this drug.

The Sanofi-DND*i* Partnership for Fexinidazole intends to apply for initial approval of the medicine under the European Medicines Agency's (EMA) Article 58. According to the EMA, "article 58 of Regulation (EC) No 726/2004 allows the Agency's Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the World Health Organization (WHO), on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU)."[27] This regulatory mechanism considers medicines or vaccines for a public health priority disease. The CHMP performs a scientific assessment of the product, and, after consultation with the WHO, adopts a scientific opinion. This option was selected by Sanofi and DND*i* because it is will "facilitate faster WHO prequalification of the medicine as well as regulatory approvals and implementation in endemic countries."[28] Given that HAT is among the eligible diseases for the tropical disease PRV, the DND*i*-Sanofi-Aventis PPP would have the option to pursue FDA approval for the drug in the future in exchange for a PRV, if desired.

Acoziborole was selected as a pre-clinical candidate for HAT in late 2009. A Phase I study of Acoziborole was conducted in 2015 in France. This first phase assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of Acoziborole after single oral dose in 128 healthy human volunteers of sub-Saharan origin. The results from this study showed that the drug penetrates the brain, which is crucial to treat the late stage of HAT, where the parasite crosses the blood-brain barrier and kills patients if no treatment is given. In 2016, the single dose treatment began testing in patients with HAT in a Phase II/III trial in the DRC.[29]

The drugs currently available to treat HAT are all sub-standard in terms of toxicities and mode of administration, and as such, there is an urgent need for novel, effective therapeutics.

Acoziborole resulted from the private company Anacor's pre-existing compound library, which has produced various compounds with anti-infective properties. Anacor, with the help of the Sandler Center for Drug Discovery at the University of California, San Francisco (UCSF), screened its library of boron-based compounds for activity against the sleeping sickness parasites and identified an attractive lead series. To advance the development of this compound, Anacor approached DND*i*, which was seeking compounds for its lead optimization programme. DND*i*, Anacor and a consortium of academic institutions such as Pace University and the Swiss Tropical and Public Health Institute then worked on the series of molecules in pre-clinical studies that subsequently led to DND*i*-led Phase I study that has been completed and a Phase II/III study that is underway. In 2012, Acoziborole became DNDi's first new chemical entity resulting from its own lead optimization programme to enter clinical development.[30]

Chagas Disease

Chagas disease is a neglected vector-borne disease with an estimated burden of 8–10 million cases worldwide. Infection with *Trypanosoma cruzi* (*T. cruzi*), the etiologic agent of Chagas disease, and its clinical

sequelae of Chagas cardiomyopathy and gastrointestinal disease are responsible for as many as 15,000 deaths each year. Despite this substantial burden, evidence has shown that less than one percent of infected patients receive treatment with benznidazole or nifurtimox, the two antitrypanosomal medicines currently available to treat Chagas disease.[31]

The burden of Chagas disease has historically been concentrated among the poor in Latin America due to the living conditions that create suitable vector habitats for repeated domestic vector-borne transmission by the Triatomine insects (commonly called "kissing bugs"). In addition to vector-borne transmission, the *T. cruzi* parasite can be transmitted congenitally from infected mother to child and through blood and organ donation. In recent years, human migration has resulted in increasing prevalence of this disease in developed countries such as the United States, Switzerland, and Spain. Although prevalence data are limited, the most recent estimate suggests that about 300,000 individuals living in the United States are infected with *T. cruzi* and that the majority of these cases are chronic infections in people who have migrated from high-prevalence regions of Latin America.[32] Detection of infection has increased in the United States since screening of the blood supply was initiated in 2007.

Following the addition of Chagas disease to the list of PRV eligible conditions, market activities for Chagas disease increased substantially.

Chagas disease is clinically manifested in two stages—an acute stage and a chronic stage. The acute stage begins when the parasite enters the body and typically lasts for approximately 4–8 weeks. Symptoms are usually non-specific and can include fever and a flu-like syndrome, though many patients remain asymptomatic during this phase.[33] Following the acute phase, parasitemia falls to undetectable levels and patients enter the latent or indeterminate chronic form of the disease. In many patients, the indeterminate form does not progress further; however, 20–30 percent of patients go on to develop clinically evident chronic Chagas disease. Chronic Chagas disease manifests most often as cardiovascular disease, though gastrointestinal disease is also present in a minority of patients. The cardiac form of chronic Chagas disease leads to Chagas cardiomyopathy, cardiac conduction abnormalities, thromboembolism, congestive heart failure and sudden cardiac death. In contrast, the digestive form of Chagas disease causes damage to the nervous system resulting in dysphagia, weight loss, and megaesophagus or toxic megacolon.

There are currently only two antitrypanosomal drugs that have proven clinical efficacy against the *T. cruzi* parasite. The first is called benznidazole and the second is a nitrofuran derivative called nifurtimox, manufactured by Bayer Health Care. Benznidazole is generally regarded as the first line therapy for treatment of Chagas disease in most of the world because the clinical evidence for its efficacy is more robust and it is better tolerated by most patients.

As of August 2017, benzinidazole was approved for use in the US by the FDA. Previously, access to care for Chagas disease in the US was limited because treatment was only available through investigational protocols administered by the US Centers for Disease Control. In addition, production interruptions and periodic shortages of benznidazole as well as the lack of a pediatric formulation limited Chagas treatment.[34] In 2012, a pharmaceutical company based in Argentina, ELEA, announced that they would begin production of a generic form of benznidazole. DND*i* and the Mundo Sano Foundation, along with the associated parent pharmaceutical company Chemo Research, S.L. (hereafter Chemo Group), announced a plan to secure FDA approval of benznidazole. They initiated this discussion

with the FDA in September 2013 during which they obtained an orphan drug designation and ultimately filed an application with the FDA for approval of benznidazole in December 2016.

Chemo Group—and specifically their US-based division Exeltis—led the registration process for benznidazole with the FDA, along with their corporate social responsibility partner, Mundo Sano Foundation, and DND*i*. Together, these organizations formed a public-private partnership that enabled this application to move forward successfully. Chemo Group's role in this partnership has been to lead and submit the new drug application to the FDA with their internal regulatory oversight. They also produce and distribute the product. DND*i* provided technical expertise, including data from two DND*i*-led clinical trials of benznidazole in children that were used in the FDA application.[35] Chemo Group first engaged with the FDA in 2013. They secured Orphan Drug Designation for benznidazole in April of 2014. In December of 2016, they then submitted a new drug application to the FDA via the Accelerated Approval pathway.[36]

Following the addition of Chagas disease to the list of PRV eligible conditions, market activities for Chagas disease increased substantially. This included the new drug application process initiated by the Chemo Group-DND*i* partnership as well as a competing and very public application by another private pharmaceutical company, KaloBios (renamed as Humanigen as of July 2017), who also had obtained the orphan drug designation in July of 2017 and had intended to obtain a PRV through this application process.[37]

Benznidazole was approved on August 29, 2017 via the Accelerated Approvals Pathway, with an orphan drug designation. The FDA granted benznidazole this orphan product designation because Chagas disease is neglected and until this time there were no approved drugs for Chagas disease in the United States. With this approval, Chemo Group was also awarded a Tropical Disease PRV. According to the terms of the collaboration between Chemo Group and DND*i*, a substantial portion (reportedly 50 percent) of the revenue derived from the future sale of the PRV will be directed toward access initiatives for Chagas patients and improving patient health in other neglected tropical disease areas.

DND*i* has also taken a leading role in preclinical research and early phase clinical trials for a new treatment for Chagas disease. In 2009, DND*i* partnered with a Japanese pharmaceutical company, Eisai Co Ltd., to begin developing an azole compound called E1224 that it had discovered. In 2011, early phase clinical trials were begun on this compound, which was again before the PRV program included Chagas. The initial trial evaluated E1224 as a monotherapy for Chagas disease. The preliminary results showed that E1224 was effective at clearing *T. cruzi*, but that efficacy was not sustained one year after treatment and safety concerns remained. As such, the development of E1224 as a monotherapy has been discontinued and focus has shifted to its use in a combination therapy with benznidazole for Chagas disease.[38] Research on this combination therapy is being funded by the Global Health Innovative Technology Fund (GHIT) a collaboration that pools funding between the Gates Foundation, the Japanese government, and private-sector Japanese biopharmaceutical firms. The discovery of E1224 was via its known anti-fungal activity. A scientist working on Chagas disease had identified that anti-fungals had efficacy against the *T. cruzi* parasite that causes Chagas disease. Tests were then undertaken to determine if the compound had efficacy against *T. cruzi* and it did; as such there was no formal drug screening process for this particular compound.

Eisai's interest in joining this partnership is motivated by its corporate philosophy and mission to play a role in interrupting cycles of poverty among poor populations globally. One representative of the company stated, "Eisai has a slightly different take on these activities. We strongly believe that addressing these diseases have a strong impact on the circle of poverty....By trying to break this spiral of poverty, we

believe in the long-run we will improve these societies and economies. As these economies advance, we see this as a very long-term investmen ... Some call this a non-financial capital investment. These investments will be very good for these societies and our company as well."[39]

In 2009, Eisai and DND*i* announced the formation of a public-private partnership for the development of E1224 for Chagas disease. Under the terms of the agreement, DND*i* retained primary responsibility for the clinical development assessing the safety and efficacy of E1224 for Chagas patients. Eisai provided scientific expertise in clinical development and supplied the drug for clinical trials. Eisai also retained the option to become the industrial partner with DND*i* to manufacture and register E1224 during the Phase I/II trials. This partnership between DND*i* and Eisai also preceded the inclusion of Chagas disease in the PRV program. Moreover, DND*i* has remained the sponsor of the drug so they would be the primary awardee should a PRV be sought in the future.

Generalizable Findings from the Case Studies

In this section, we discuss generalizable findings on the motivations for and successes related to the four NTD drug cases discussed: Fexinidazole and Acoziborole for HAT and Benznidazole and E1224 for Chagas disease. Across all private-sector firms interviewed, we found a high level of interest and support for involvement in NTD drug development. One important factor driving this interest was pre-existing philanthropic efforts for a given disease or geographic area. For example, when DND*i* approached Sanofi-Aventis regarding a partnership for the development of Fexinidazole, Sanofi was already contributing substantial resources to HAT elimination through its drug production and donation program with the WHO. These resources were being expended indefinitely and without the promise of disease elimination. The PPP for Fexinidazole offered a clear strategy to improve upon an existing donation infrastructure in the form of a more efficacious and better-tolerated drug that could be more easily made accessible to patients with HAT. Moreover, Sanofi-Aventis grew increasingly invested in their key role in the global HAT elimination effort, appealing to their sense of corporate responsibility, and allowing opportunities to display company achievements as the key actor combating HAT. Similarly in the case of Chagas disease, given Chemo group's extensive presence in Latin America, working toward FDA approval for Benznidazole was a natural fit.

In addition, across all private-sector partners, there was widespread support for ensuring that the social goals of the company and its employees were aligned with company actions. Given the opportunity to be involved in these partnerships, with coordination driven by DND*i*, firms agreed. One motivation expressed during interviews was how NTD investments could serve to attract top scientific talent and motivate scientific staff internally due to the value and emphasis the company has and continues to place on the investment in these medicines based on need instead of profit maximization. In Sanofi's case, scientific staff stressed that the development of drugs for neglected diseases is treated as an equal priority to other, more obviously profitable disease areas and the investment in Fexinidazole is seen as concrete evidence of this commitment.

Another finding that came out of these studies is that the availability of the PRV, although helpful, is not the only motivation for NTD drug development. Nevertheless, other private-sector behaviors indicated its value. For example, we also examined a situation where the PRV's incentive structure caused two private entities—Chemo Group and Kalobios/Humanigen—to compete to receive approval for benznidazole and the resultant PRV. This time pressure may have led to benznidazole's initial approval for a more limited age range (children 2 to 12) than would have been the case without the PRV. Nevertheless, if Chemo Group had not worked with DND*i* to obtain FDA approval and the neglected tropical PRV, Humanigen may have received the voucher instead

and decided not to use any of the proceeds toward the social goal of increasing treatment access. We also observed that funding from GHIT was essential in supporting continued development of E1224 as a combination therapy, even after it failed in clinical trials as a stand-alone Chagas treatment.

We investigate the important role that public-private partnerships played in coordination and prioritizing given disease areas and compounds, as well as collecting necessary data and reducing private-sector risk. By screening compound libraries, DND*i* lowered both the risk and costs associated with identifying novel compounds for activity against neglected disease. In interviews with individuals within Sanofi, for example, the role of risk sharing in this area of drug discovery was repeatedly highlighted. Moreover, particularly in the case of HAT, DND*i* has had an important role in both the design and execution of complicated human studies in unfamiliar locations where it can be difficult to reach patients and administer necessary medications due to weak health infrastructure.[40] For benznidazole, DND*i* helped secure the data needed for FDA approval and helped organize clinical trials for E1224. Overall, performing these functions of stewardship, risk-mitigation, and data collection complemented private sector expertise in the creation of novel compound libraries early in the development process and application submission, manufacture, and drug registration at the end.

Quantitative Analysis of Private Sector Investment Returns

In this section, we investigate the return on investment (ROI) from the small-molecule drugs described in our case studies, if they had been developed by a private-sector entity instead of the non-profit DND*i*. To calculate an expected ROI, we use information on development costs for Fexinidazole, Acoziborole, and Benznidazole compared to potential revenue sources.

We estimate development costs following methods from Joseph DiMasi's 2003 and 2016 studies.[41] In addition, we estimate revenue sources from awarding of a PRV and discuss qualitatively the benefits of secondary market sales, the value to a private entity of engaging in socially-oriented R&D, and the value of orphan drug and general R&D tax credits, where applicable. From these, we create a private ROI that can be expected across various scenarios based on eligibility for the ODTC, compound approval probabilities, and assumptions on PRV supply.

The most often cited estimate of drug development costs comes from the research and development costs of 106 randomly selected new drugs collected in a survey of 10 biopharmecutical firms.[42] The paper estimates the average pre-tax cost of new drug and biologics development. The estimated average OOP cost per approved compound is $1,395 million (2013 dollars) and capitalizing these costs to the point of market approval with a real discount rate of 10.5 percent yields a pre-approval cost of $2,558 million in 2013 dollars ($2.7 billion in 2017). Table 2 summarizes the assumptions that form the basis of DiMasi et al.'s (2016) average drug R&D costs calculations including the cost for each clinical phase, the average time per phase, and the opportunity cost of capital based on the capital structure of the biopharmecutical industry. The study finds that the average probability of clinical success for a novel compound entering clinical testing to approval is 11.83 percent. In contrast, using earlier data, DiMasi found that overall approval probability for a given novel compound was 21.5 percent.[43] This probability includes stoppage in clinical development both from lack of safety and efficacy as well as for reasons of profitability; whereas the only considerations for NTD drug development would be safety and clinical efficacy. For this reason, we judge the 11.83 percent total approval probability to be a lower-bound estimate for NTDs.

TABLE 2 | Drug Development Phase Costs and Time for Small Molecule Drugs

Transition Probabilities Between Phases				
	Phase I-II	**Phase II-III**	**Phase III-NDA/BLA**	**NDA/BLA Sub**
Probability	59.52%	35.52%	61.95%	90.35%
Pre-Approval Statistics				
	Phase I	**Phase II**	**Phase III**	**Total**
Mean Time (months)	33.1	37.9	45.1	116.1
Mean Time to Next Phase (months)	19.8	30.3	30.7	80.8
Mean Time (years)	2.8	3.2	3.8	9.7
Mean Time to Next Phase (years)	1.7	2.5	2.6	6.7
Probability of Entering Phase (%)	100.00%	59.50%	21.10%	
Additional Parameters				
Total Transition Probability Between Phases	11.83%			
Average Cost of Capital (Discrete)	10.5%			
Average Cost of Capital (Continuous)	9.98%			

Source: DiMasi et al. (2016) and Authors' compilation. Note: Probability of entering a given clinical phase represents the cumulative probability of transition through all previous phases.

Others argue that drug development costs are significantly lower than the Dimasi et al. (2016) study. For example, an analysis of the development of 10 recent cancer drugs found that median out-of-pocket costs was 648 million, 5 drugs received regular approval and 5 accelerated approval.[44] Median time to development was 7.3 years. Using an opportunity cost of capital of 7 percent, total costs were $793.6 million. However, these estimates do not account for risk nor capitalized costs and we therefore use more conservative cost estimates based on Dimasi et al. (2016).

We obtained compound-level data on the costs of development at each stage for 3 of the 4 compounds in our case studies: Fexinidazole and Acoziborole for treatment of HAT and Benznidazole for treatment of Chagas disease. When compound specific information is not available, we use data from table 2 for Fexinidazole and Acoziborole.[45]

Qualified expenses under the ODTC only can be applied to costs incurred after the date of orphan drug designation. Given that this designation often occurs during clinical phase II or III, we conservatively assume that the ODTC can be applied only to phase III costs, decreasing by 50 percent out-of-pocket phase III costs per investigational drug. In sensitivity analysis, we also explore how costs and ROI change if the ODTC is used starting at phase II instead. All other development costs are assumed to be eligible for the general R&D business tax credit and decreased by 6 percent.

To estimate preclinical costs, Dimasi et al. (2016)'s assumptions on pre-human period costs are followed

for our average NTD drug analysis, but compound specific pre-clinical costs are used for Fexinidazole and Acoziborole. From data on 78 compounds, Dimasi et al. (2016) find that the average pre-clinical period (the time between compound synthesis to first human testing) is 31.2 months. In addition, using their data, Dimasi et al. (2016) calculate a ratio of pre-human to total R&D expenditure of 30.8% per approved drug with a five-year lag. This percent is robust to variation in the time lag used. However, since actual pre-clinical spending is known for Fexinidazole and Acoziborole, these data are used instead of the ratio estimate.

Revenue could include the PRV, secondary sales, and the value of social returns from NTD R&D. Expected revenue from the PRV is estimated quantitatively, while the other two possible revenue streams are not, so the ROI compares an estimate of the PRV's value against the capitalized costs per approved drug. Capitalized costs account for the opportunity cost of capital since firms can invest in other profit-making opportunities and approved drug costs incorporate the risk of drug failure.

Following Ridley and Regnier,[46] we reproduce their estimates of the value of the PRV by calculating the value of its three sub-components:

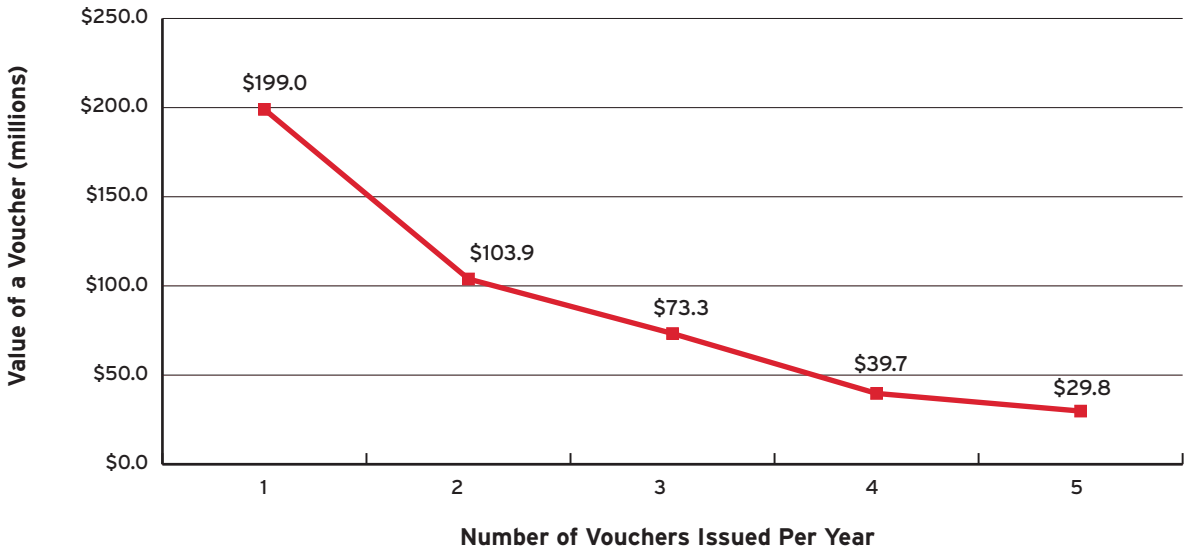
1. Competitive Effects: a drug earlier to market has a first-mover advantage that locks in a larger market share compared to competition,
2. Time Value of Money: revenue from drug sales is received earlier and so reduces the opportunity cost of time to obtain revenue from drug investments
3. Exclusivity Effects: market exclusivity still expires at the same date, meaning that earlier approval produces a longer period of patent exclusivity.[47]

Utilizing the methodology set forth by Ridley and Regnier, we re-estimated the values of PRVs associated with the number of vouchers issued per year. In figure 1, we estimate that a PRVs expected value is roughly $200 million if one is issued per year, and approximately $40 million if four vouchers per year are awarded. These values are commensurate with the prices that Ridley and Regnier calculated in their previous studies and observed sales.[48] We calculate the ROI implications if PRV supply remains constant at current levels (averaging 4 per year) and if PRV eligibility criteria are tightened to only NTDs and PRV supply is restricted to one per year.

The value of a PRV is a function of the projected sales of the drug receiving expedited review. The distribution of yearly drug sales is highly skewed, where a small number of blockbuster drugs receive $1 billion or more in sales per year with a rapid decline in sales thereafter. Because of this underlying sales distribution, the value of PRVs also drop rapidly as the supply increases. Figure 1 shows that the expected value of a PRV drops by nearly half if the number of PRVs issued per year increases from one to two. The figure therefore makes clear that the revenue stream from the PRV program cannot be used to sustainably increase private-sector NTD novel compound development activity.

To estimate private-sector return on investment (ROI) for small-molecule NTD drugs, we compare development costs against potential revenues. Table 3 shows our results. The first row shows the most conservative estimates of ROI if we assume that small molecule drug development costs are similar to the average biopharmaceutical costs identified by DiMasi et al.'s 2016 study.[49] That is "Average Drug" in table 3 reproduces those results as a reference. "Average NTD drug" then calculates costs and the ROI under both current (4 per year) and restricted (1 per year) PRV supply scenarios. Both the ODTC for clinical phase III costs and general R&D tax credits are applied. We observe that the expected private ROI compared to capitalized costs per approved drug is substantially negative for an average NTD drug (if approval probabilities and costs were similar to pharmaceutical norms).

FIGURE 1 | **Value of Priority Review Vouchers, by Number of Vouchers Issued Per Year**



Source: Authors' calculations, Ridley and Regnier (2016, 2015, 2010, Appendix)

TABLE 3 | **Return on Investment by Small Molecule Drug**

	OOP costs per investigational drug	Capitalized costs per approved drug			Return on investment	
	Total	Pre-clinical	Clinical	Total	Current	Restricted
Avg. Drug	339	1098	1460	2558	-98.4%	-92.2%
Avg. NTD Drug	207	752	1120	1872	-97.9%	-89.4%
Fexinidazole	43	32	298	330	-88.0%	-39.7%
Acoziborole	55	106	240	347	-88.5%	-42.6%
Benzinadozole	9	N/A	28	28	41.1%	607.3%

Sources: Authors' calculations, DND*i*, DiMasi et al. (2016), and Ridley and Regnier (2016). The estimated PRV value given current market supply is $40 million and estimated PRV value given restricted supply $200 million. OOP refers to out-of-pocket (not capitalized) costs. Costs in million $US.

In addition, we calculate costs, revenue, and private ROI for three of the four specific drug case studies: Fexinidazole, Acoziborole, and Benznidazole. To make these calculations, we use compound specific costs and time per development phase when available. When out-of-pocket phase costs or clinical development phase lengths are not available, we use values from DiMasi et al. (2016) as conservative estimates.

First, table 3 shows that in the current policy environment, returns are negative for all drugs except for the pre-existing compound, Benznidazole. This is consistent with the type of NTD drug development that has been generated through the PRV incentive mechanism previously. Of the five NTD PRVs awarded thus far, three (including Benznidazole) were awarded to drugs that were developed and registered outside of the U.S. for years. The other two (Coartem for malaria and Vaxchora for cholera) have a secondary travelers market where a positive return is possible. Our analysis also shows that for Benznidazole, and presumably other already developed drugs, the PRV provides significant opportunities for positive returns. In the case of Benznidazole, the ROI calculated accounts for half of the PRVs value being pledged toward medication access, however this is not required for PRV eligibility. Although Chagas is classified as an NTD, there will also be revenues from secondary market sales in the US for Benznidazole, further increasing returns.

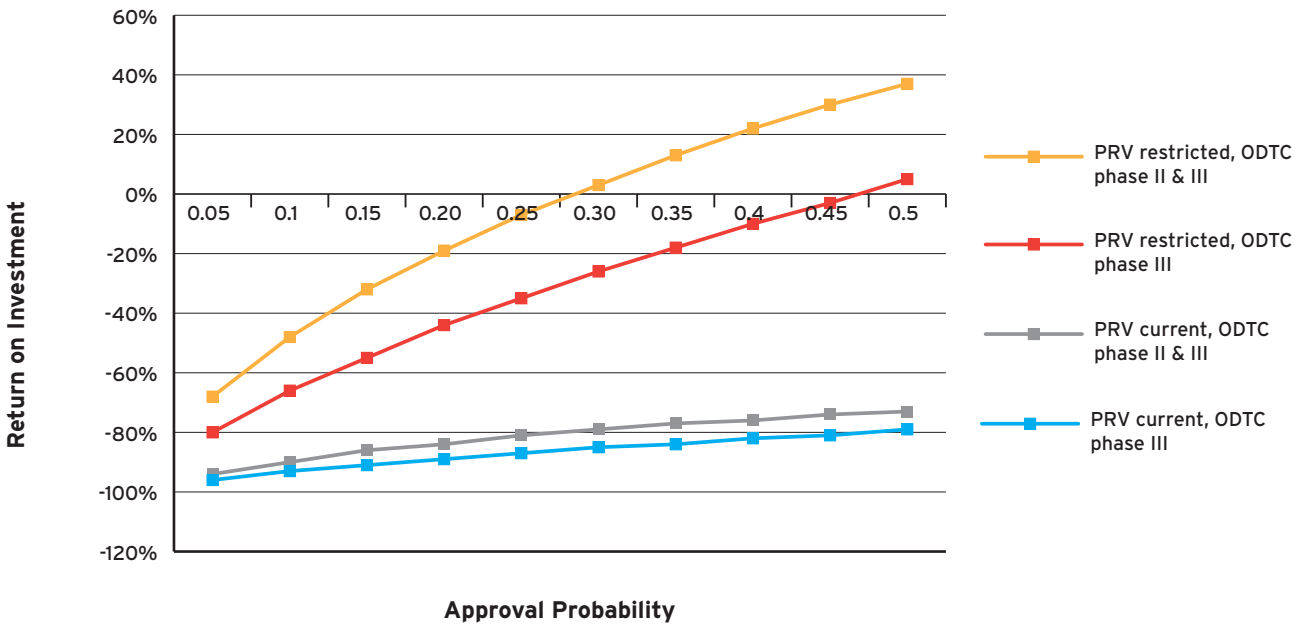
Table 3 elucidates two additional points: 1) once we incorporate risk and the opportunity cost of capital, costs are substantially higher for the private sector, making end to end investment particularly challenging, and 2) reported out of pocket costs for NTD drugs are an order of magnitude smaller than the industry average costs for private market new chemical entities. Table 3 also shows that Acoziborole's pre-clinical capitalized costs are three times larger than those of Fexinidazole , indicating both the importance of basic research support to making private-investment viable and the high variance in pre-clinical costs.

Even though table 3 demonstrates that all drug candidates except for Benznidazole have negative ROIs, these negative rates of return can largely be attributed to the very low transition probability of 11.83%. This transition probability implies that about one in eight drug candidates will reach viability, while the others will fail at some point in the development process. However, this value is a very conservative estimate. To explore how variation in approval probabilities affects investment incentives, we graph private ROI as approval probabilities vary from 5% to 50%. Figures 2 and 3 show ROI across this range of approval probabilities for Fexinidazole, and Acoziborole, respectively, where each figure shows ROI with both current and restricted PRV supply and when the ODTC is applied to either phase III or both phase II and III clinical costs.

The figures show that the most important determinant of a positive ROI is a restricted supply of PRVs per year, but this of course implies fewer overall new small-molecule drugs for NTDs being generated as well. Figures 2 and 3 also indicate the importance of applying the ODTC to clinical phase II and III. This change impacts private ROI because for both Fexinidazole, and Acoziborole, the ratio of phase II to phase III development costs is significantly higher than the ratio for the industry average.

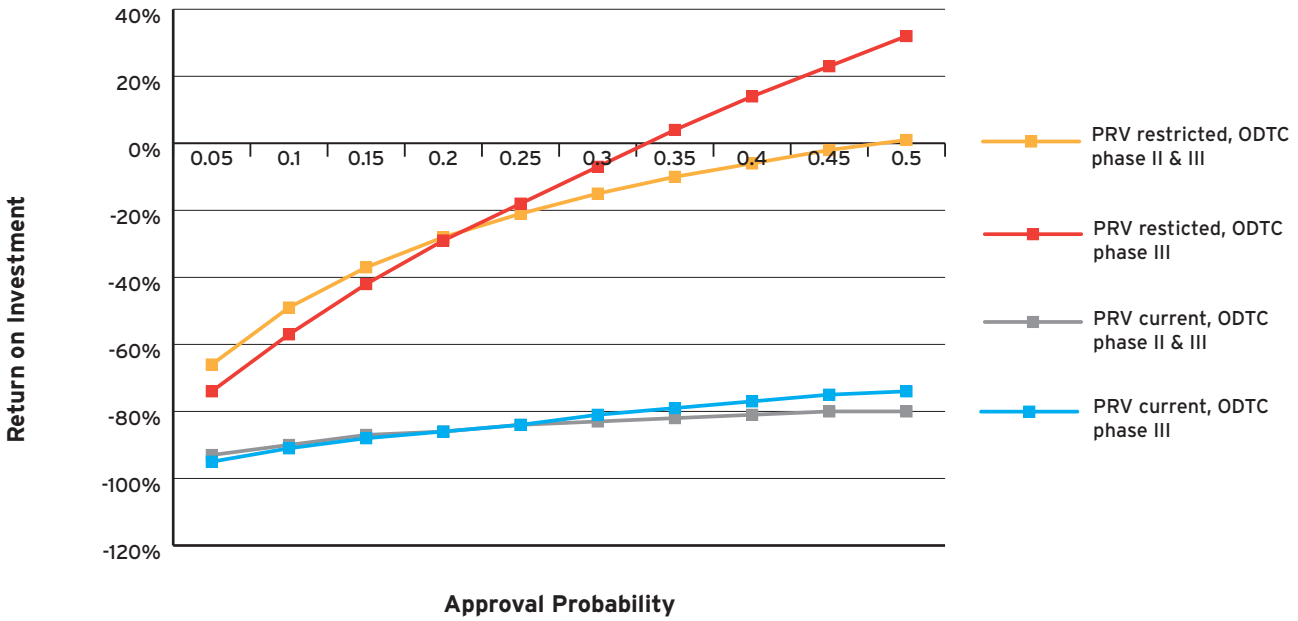
Figure 2 shows that positive ROIs could be obtained by the private sector for an NTD drug with costs similar to Fexinidazole if the PRV supply was restricted and especially if the ODTC applied to both clinical phases II and III within a feasible range of approval probabilities. For Acoziborole, because of its higher relative pre-clinical cost, figure 3 shows a limited range of policy conditions that would generate a positive private ROI for the development of an Acoziborole-like drug. This analysis demonstrates that even without including returns from drug sales, investments in some NTD medications can be financially profitable if failures rates are lower than average and PRV values are high. Further research in our series will calculate the potential returns to pharmaceutical sales, which will move ROIs further in the positive direction, if included.

FIGURE 2 | Return on Investment Sensitivity Analysis for Fexinidazole



Source: Authors' calculations

FIGURE 3 | Return on Investment Sensitivity Analysis for Acoziborole



Source: Authors' calculations

Vaccine Case Studies: Schistosomiasis and Hookworm

Schistosomiasis

The Institute for Health Metrics and Evaluation (IHME) at the University of Washington reports that in 2015, 252.3 million people worldwide were infected with schistosomes, the parasite that causes schistosomiasis.[50] In fact, schistosomiasis ranks second only to malaria as the most common parasitic disease according to the Sabin Vaccine Institute and the highest among neglected diseases, as our definition does not include malaria.[51]

"Schistosomiasis is an acute and chronic disease caused by blood flukes (trematode worms) of the genus, *Schistosoma*," reports the World Health Organization (WHO).[52] Primarily transmitted by snails, schistosomes are water-borne parasites that are present in fresh water in developing countries. Fresh-water cercariae (larvae) penetrate the skin of human hosts and move throughout the host's body without multiplying within the human. Many of the parasites are excreted out of the host's body through feces or urine, but those left behind (including the eggs) may become embedded in the intestines or bladder.[53] This leads to irritation and inflammation, which begins the pathogenesis of the disease.

As schistosomiasis primarily affects the world's "bottom billion," they often lack medical care or medications necessary to treat the illness and access to sanitation to mitigate transmission.[54] Thus, the disease persists and causes irreparable damage to the host. In the case of schistosomiasis, this can include cirrhosis of the liver or renal disease, ultimately leading to kidney failure. Schistosomiasis also causes anemia, malnutrition, and retards childhood development. Suggesting the *Schistosoma* eggs are carcinogenic, Hotez contends that schistosomiasis may actually lead to cancer later on in life as well.[55] There are three main strains of schistosomiasis that effect human beings, as well as several other local strains (see appendix for more detail).

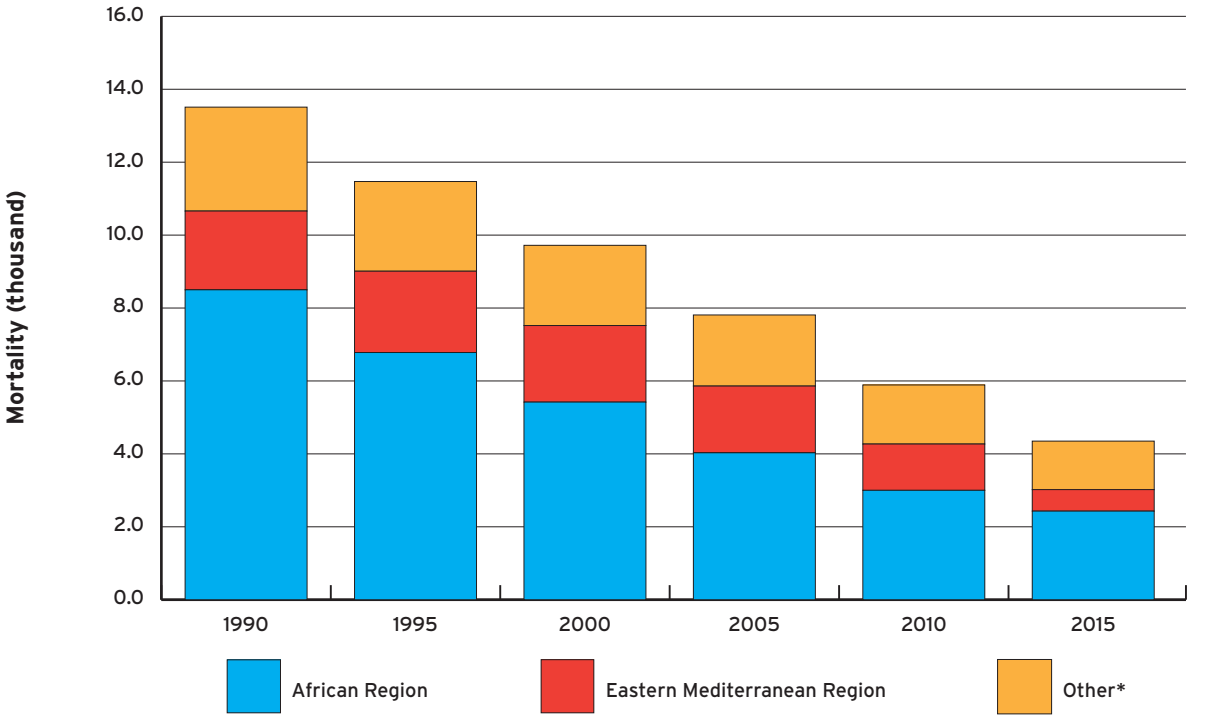
Schistosomiasis accounts for a substantial proportion of the world's NTD burden. Merrifield et al. write, "Schistosomiasis, together with hookworm and leishmaniasis, rank as those neglected tropical diseases with the highest burden as defined by disability-adjusted life years (DALYs)."[56] The Sabin Institute reports: "Schistosomiasis infects ... people in as many as 78 countries, with a vast majority of the burden occurring in Africa."[57] After Africa, the WHO's Eastern Mediterranean Region (consisting of the Middle East, North Africa, the Horn of Africa and Central Asia) had the highest burden of disease. Figure 4 shows that the majority of schistosomiasis-related mortality occurs in sub-Saharan Africa (SSA). Figure 5 shows that about 90% of the burden of disease caused by schistosomiasis comes from morbidity, much of which is also in SSA. In 2015, therefore, 90.8 percent of total schistosomiasis burden occurred in SSA and 6.7 percent in the Eastern Mediterranean Region. Although the DALY burden reached a peak in 2005, the distribution of the burden has shifted toward SSA because relative decline has been slower there. Figure 5 also shows that the DALY burden from schistomiasis rose from 1990 to 2005, but has declined by 24% since.

The frontline medication for treating schistosomiasis is Praziquantel (PZQ), a preventive chemotherapeutic. According to Hotez: "A key point about the essential NTD medicines required to practice preventive chemotherapy is that most are donated by the major pharmaceutical companies, and in 2010 these companies reaffirmed their commitment to continue these donations for as long as necessary through a London Declaration for NTDs."[58] Merck, for instance, donates PZQ. Best practices for treatment dictate not only treatment with mass drug administration (MDA) in areas with endemic schistosomiasis, but also with vector control, such as de-molluscing. Tebeje et al. argue for an integrated approach for treating schistosomiasis, including the use of mass chemotherapy, targeted molluscicding, environmental modification, health education, improved sanitation, and vaccination.[59] In endemic areas, reinfection rates are high even after MDA. King writes that even after

improvements in the prevention of schistosomiasis, research demonstrates that MDA is "likely never to be fully curative."[60] Therefore, preventive chemotherapy and transmission control (PCT) are best when MDA is combined with vector control. For schistosomiasis, with evidence that "the impact of MDA was seen to plateau over time," practitioners began to consider not only attempts at prevention of the disease through MDA, but also techniques at suppressing transmission through snail control and comprehensive water, sanitation and hygiene (WaSH).[61] WaSH, in addition to MDA, has been shown to be more effective than MDA alone. For example, the WHO reports, "Safe water was associated with significantly reduced odds of *Schistosoma* infection, and that access to adequate sanitation was associated with significantly lower odds of infection with both *S. mansoni* and *S. haematobium* (the two most prevalent schistosomes)."[62]

The continued decline in schistosomiasis prevalence driven particularly by wider use of PZQ MDA could be counterproductive in the long term. Because PZQ is the only available treatment for schistosomiasis, as its use increases, the risk of antimicrobial resistance (AMR) increases as well. As Tebeje et al. states: "Having been used for more than three decades, the emergence of PZQ-resistant schistosomes is a constant threat."[63] This contradiction at the heart of currently successful schistosomiasis control efforts underlines the importance of investment in the vaccine pipeline. In addition to the health benefit from prevented reinfection, a schistosomiasis vaccine would also reduce the likelihood of PZQ resistance and prevent onset of female genital schistosomiasis, a known cofactor in HIV transmission.

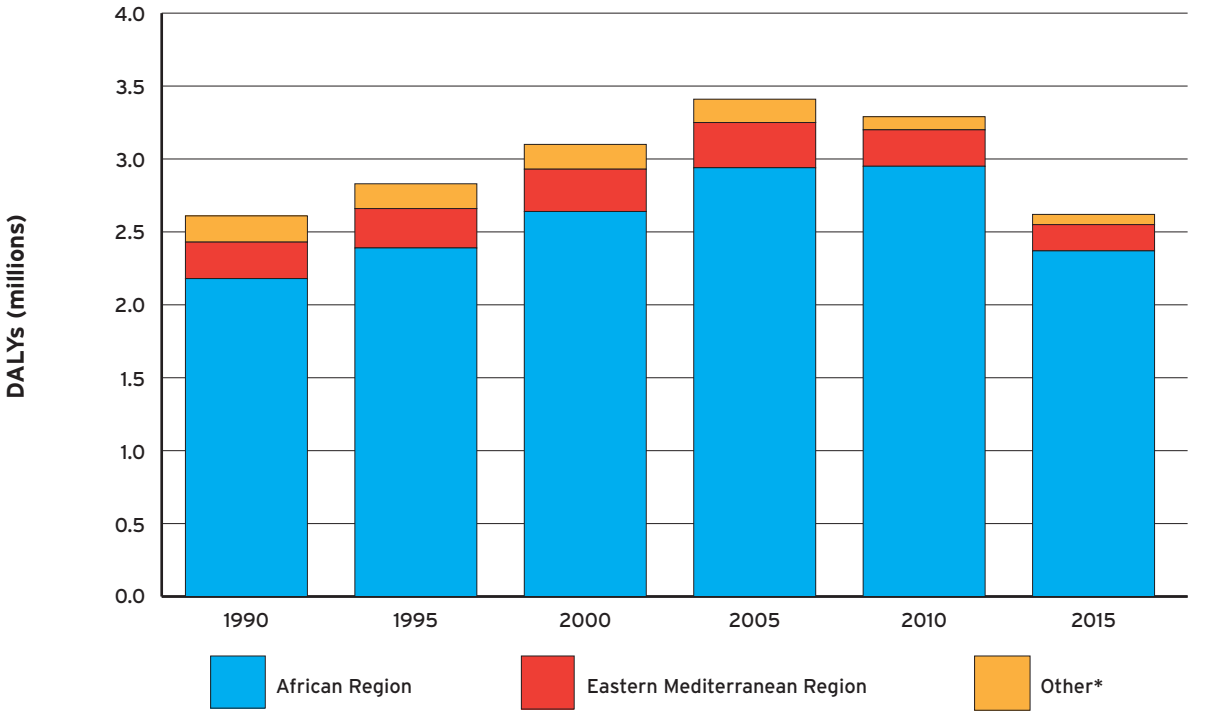
FIGURE 4 | **Schistosomiasis Mortality, 1990–2015**



Source: Institute for Health Metrics and Evaluation (IHME) and Authors' calculations.

* Other includes European Region, Region of the Americas, South-East Asia Region and Western Pacific Region.

FIGURE 5 | **Schistosomiasis DALY Burden by Region, 1990–2015**



Source: Institute for Health Metrics and Evaluation (IHME) and Authors' calculations.

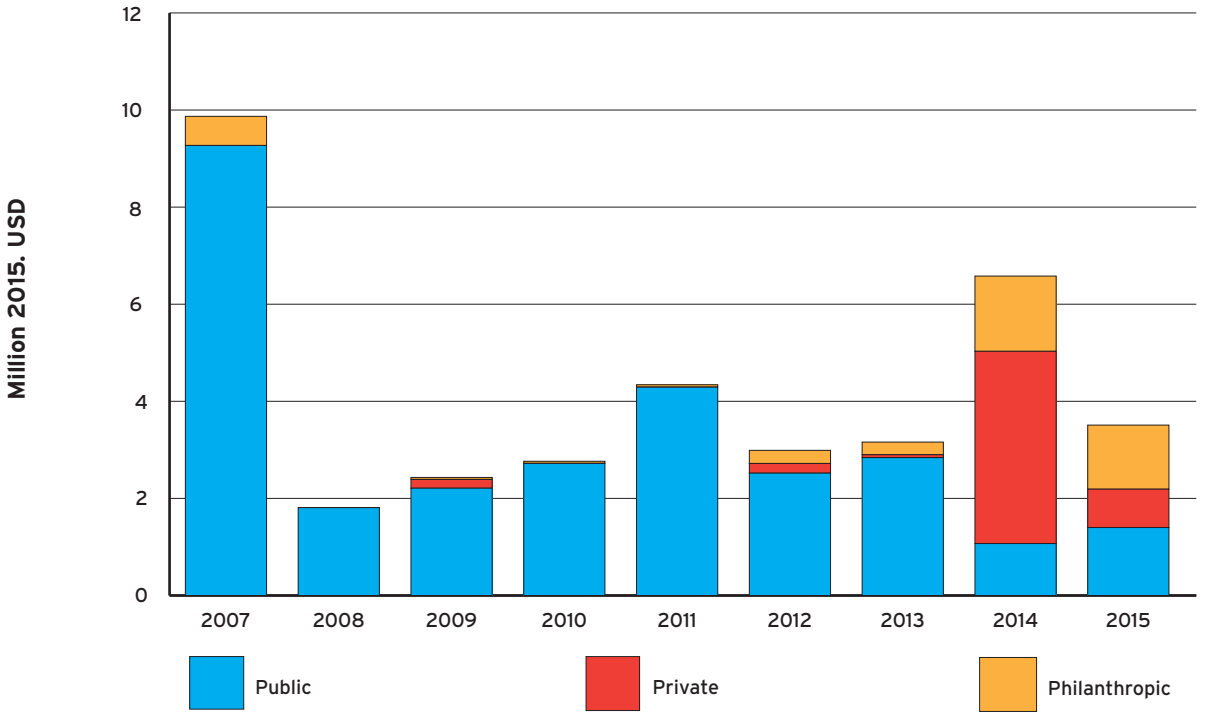
* Other includes European Region, Region of the Americas, South-East Asia Region and Western Pacific Region.

A vaccine for schistosomiasis still does not exist. However, the synthesis of one is most likely possible. As Merrifield et al. note, "Immunity as a result of natural exposure to a pathogen is … evidence of the biological feasibility for vaccine development."[64] Research confirms that people do gain immunity to schistosomiasis through exposure over time (as demonstrated through lower infection rates as age progresses). However, it is unclear if a person could ever actually gain full immunity to the disease (as opposed to increased immune protection). Therefore, the goal of a schistosomiasis vaccine should not necessarily be complete immunity, but rather reduction in the pathogenicity and disease transmission.[65]

The leading candidate for a schistosomiasis vaccine was ostensibly Bilhvax (*sh*28GST), which underwent phase III clinical trials between 2009 and 2012. However, as Ricciardi and Ndao report in their 2015 paper, "Unfortunately, no new information has been made available about the status of the vaccine, thereby, rendering specialists in the field skeptical of its future."[66] And as of our interviews in Quarter 3 2017, no additional information on Bilhvax had been released.

Table 4 provides a summary of the most promising vaccine candidates for both schistosomiasis and hookworm. Other than Bilhvax, which we assume to have failed in phase III given the paucity of reported information since 2012 and our interviews (Hotez and

FIGURE 6 | **R&D Spending on a Schistosomiasis Vaccine, FY 2007–FY 2015**



Source: G-Finder, NBER, World Bank and Authors' calculations.

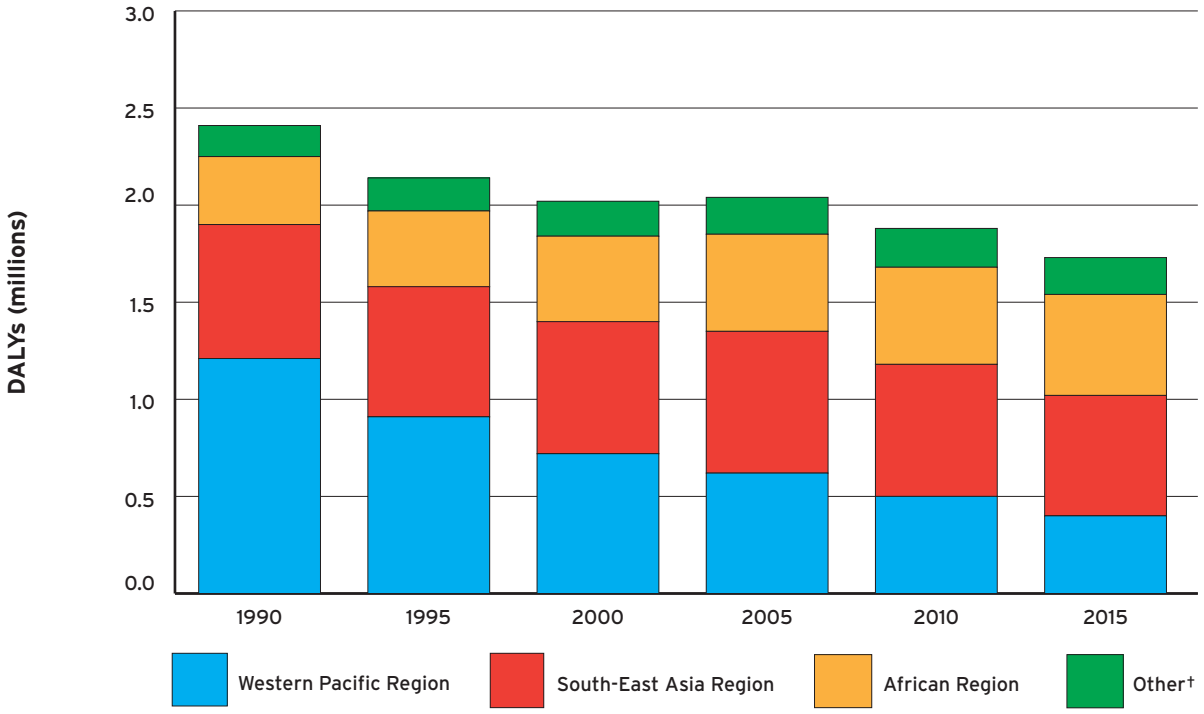
Bottazi), there are two vaccine candidates moving from phase I to II trials currently, Sm14 and Sm-TSP-2.

Between FY 2007 and FY 2015, the public, private and philanthropic sectors spent over $38 million dollars on R&D for a new vaccine for schistosomiasis according to the G-Finder study.[67] In the public sector, the largest funder has historically been the U.S. government. The largest private sector funder has been an amalgamation of spending by the pharmaceutical and biotechnology companies and the largest philanthropic funder was the Bill & Melinda Gates Foundation, followed by the Blavatnik Family Foundation. As figure 6 shows, funding for R&D for a schistosomiasis vaccine has increased marginally (in real terms) since FY 2008, but annual levels have not been above $10 million per year even in 2007, the highest year in the series.

Hookworm

Hookworm infection is acquired by infective larval stages that penetrate the skin, typically occurring when people walk barefoot on contaminated soil. Once inside the host body, the larvae move through the circulatory system, lungs, and other tissues before entering the gastrointestinal track to mature into adult worms that feed on human blood. These adult worms produce up to 30,000 eggs per day, which pass through the feces of infected people, driving a cycle of transmission.[68] Hookworm intensity usually increases

FIGURE 7 | **Hookworm DALY Burden, 1990–2015**



Source: Institute for Health Metrics and Evaluation (IHME) and Authors' Calculations.
† Other includes: Eastern Mediterranean Region, European Region, and Region of the Americas.

with age or plateaus in adulthood.[69] If left untreated, high-intensity hookworm infection can lead to internal blood loss, the development of iron-deficiency anemia, and protein malnutrition—the drivers of hookworm morbidity. Further, chronic infection in children retards physical growth and cognition.[70] Hookworm along with roundworm and whipworm make up a family of parasites known as soil-transmitted helminths (STHs).

Hookworm infection is most prevalent in warm, moist climates—conditions that facilitate the development of the worms' eggs in soil. Ranking by DALYs, the Southeast Asia region currently suffers the world's highest burden of hookworm infections. The African and Western Pacific regions follow closely (figure 7). However, since 1990, the Western Pacific has experienced an extraordinary reduction in DALYs burden from hookworm, while DALYs lost from hookworm infection in the African region has increased.

Studies have demonstrated that treating hookworm has long-term, positive impact beyond better health outcomes. Dewormed children demonstrated better cognitive function, are more likely to regularly attend and do well in school, pursue higher education, and ultimately earn more in adulthood.[71] Moreover, children treated for STHs were more likely to work in non-agricultural, more specialized segments of the labor market later on in life.[72] Although the importance of the economic effects of childhood STH treatment has

been debated,[73] the evidence indicates that children enjoy both health and long-term economic gains from reduced early life worm exposure.

Similar to other STHs, hookworm control and eradication can be achieved through economic development and urbanization. In densely populated areas, the fixed cost of municipally provided sanitation systems drops dramatically. These sanitation services reduce the practice of open defecation and subsequently lower the population's risk of hookworm transmission from contact with human feces.

Like schistosomiasis, WHO currently recommends periodic MDAs to control hookworm disease. MDAs use medicinal treatment of albendazole and mebendazole to all people at-risk for hookworm, even those without an individual diagnosis. However, albendazole and mebendazole do not protect users against reinfection. MDAs are often hosted in conjunction with sanitation and education efforts. Schools serve as a convenient and popular channel to administer the deworming medication, as teachers can be trained to deliver the pills.[74] However, these school campaigns do not usually reach adult populations, who tend to have high hookworm intensities or children too young for school. There is evidence that school-based treatment provides spillover health benefits for young children through their school-aged siblings.[75]

One of the primary benefits of developing a hookworm vaccine is the opportunity for elimination in areas without economic development, sanitation infrastructure, and local governance capacity to organize public health programs.

Even before current treatments were available, public health campaigns were successful in raising hookworm awareness. After scientific advances in the early 1900s, the Rockefeller Foundation created the Rockefeller Sanitary Commission for the Eradication of Hookworm Disease, which operated from 1909 to 1914 in the southern United States. This produced a sharp increase in awareness of hookworm and ultimately a drop in childhood hookworm prevalence. Later studies attributed a significant portion of the difference in schooling rates between the US North and South to childhood exposure to hookworm. In addition, the Rockefeller Foundation extended eradication efforts into Latin America, which led to dramatic declines in hookworm infection there too. Nevertheless, social inequality among rural populations, the urban poor, and within indigenous areas in Latin America means that hookworm infection remains (see appendix).[76]

More recently, a large decline in hookworm disease burden in the Western Pacific between 1990 and 2015 has been achieved. This success can be attributed to progress in the People's Republic of China, where prevalence of STHs overall dropped from 57.5 percent in 1990 to 18.6 percent in 2010.[77] The "National Control Program on Important Parasitic Disease" 2006–2015 program assumed a three-pronged approach: large-scale deworming or MDAs, rebuilding sanitation systems in rural areas, and health education.[78] Economic development concurrent with strong support from China's Ministry of Health allowed China to control the burden of intestinal STHs.[79]

One of the primary benefits of developing a hookworm vaccine is the opportunity for elimination in areas without economic development, sanitation infrastructure, and local governance capacity to organize public health programs. Some argue that current hookworm control methods—such as MDA preventive chemotherapy, health education, and building sanitation system infrastructure—can lead to global control of hookworm.[80] However, overall hookworm burden has declined by 14% since 2000 (figure 7) where successes in China have been mitigated by increases in SSA, indicating that

current methods are insufficient without large-scale social change. Second, as MDA has spread, researchers have grown increasingly wary of hookworm drug resistance and reduced drug efficacy.[81] The same contradiction exists with hookworm and schistosomiasis MDA. As drug administration expands, the risks of drug resistance increase as well. Given treatment failure and emerging resistance, limited pipeline R&D investments today, risk significant future health consequences among the most vulnerable. Third, high rates of hookworm reinfection after treatment mean that under certain circumstances vaccine development both improves health and is cost-effective[82] compared to continued MDA.

Recent efforts by the scientific community have opened the possibility for an alternative method of treating hookworm—a vaccine.[83] Collaborators and researchers at Texas Children's are investigating two vaccine candidates: Na-GST-1 as a human hookworm vaccine candidate, completing one set of phase I trials in Brazil 2014. Researchers also completed a separate set of phase I trials in the US in 2017, as well as a trial in Gabon testing the co-administration of Na-GST-1 with another antigen Na-APR-1. Na-GST-1 is the second candidate that has been clinically tested for efficacy as a human hookworm vaccine.[84]

Figure 8 shows funding for hookworm vaccines by public, private, and philanthropic sources from 2007 to 2015. The figure demonstrates an overall fall in funding, particularly after 2009. In addition, we observe a shift from most of that funding coming from philanthropic sources to most of the funding coming from public sources after 2012. This is consistent with previous efforts by the Gates Foundation to fund a hookworm vaccine. In total, Gates provided approximately $35 million toward a hookworm vaccine (Stuart, L. interview).[85] However, eventually Gates did not believe that development was feasible given available resources and therefore ceased support. Indicating the importance of resource coordination for these large investments, this decision also impacted efforts to raise funding from other philanthropies.

TABLE 4 **Summary of Current Vaccine Candidates for Hookworm and Schistosomiasis**

Vaccine Candidate	Disease	Development Stage	Developer
Bilhvax (*sh*28GST)	*Schistosoma haematobium*	Clinical Phase III	Inserm & Eurogentec
Sm14	*Schistosoma mansoni*	Clinical Phase I	FIOCRUZ, Brazilian Governement Financial Agency (FINEP), and Alvos Biotecnologia
Sm-TSP-2	*Schistosoma mansoni*	Clinical Phase I	Texas Children's Hospital Center for Vaccine Development PDP
Na-GST-1	*Hookworm*	Phase I/II	Texas Children's Hospital Center for Vaccine Development PDP
Na-APR-1	*Hookworm*	Phase I/II	Texas Children's Hospital Center for Vaccine Development PDP
Na-GST-1 plus Na-APR-1 (M74)	*Hookworm*	Phase I/ II	Texas Children's Hospital Center for Vaccine Development PDP

Source: Ricciardi and Ndao, Workshop Report: Schistosomiasis Vaccine Clinical Development and Product Characteristics, and Authors' compilation.

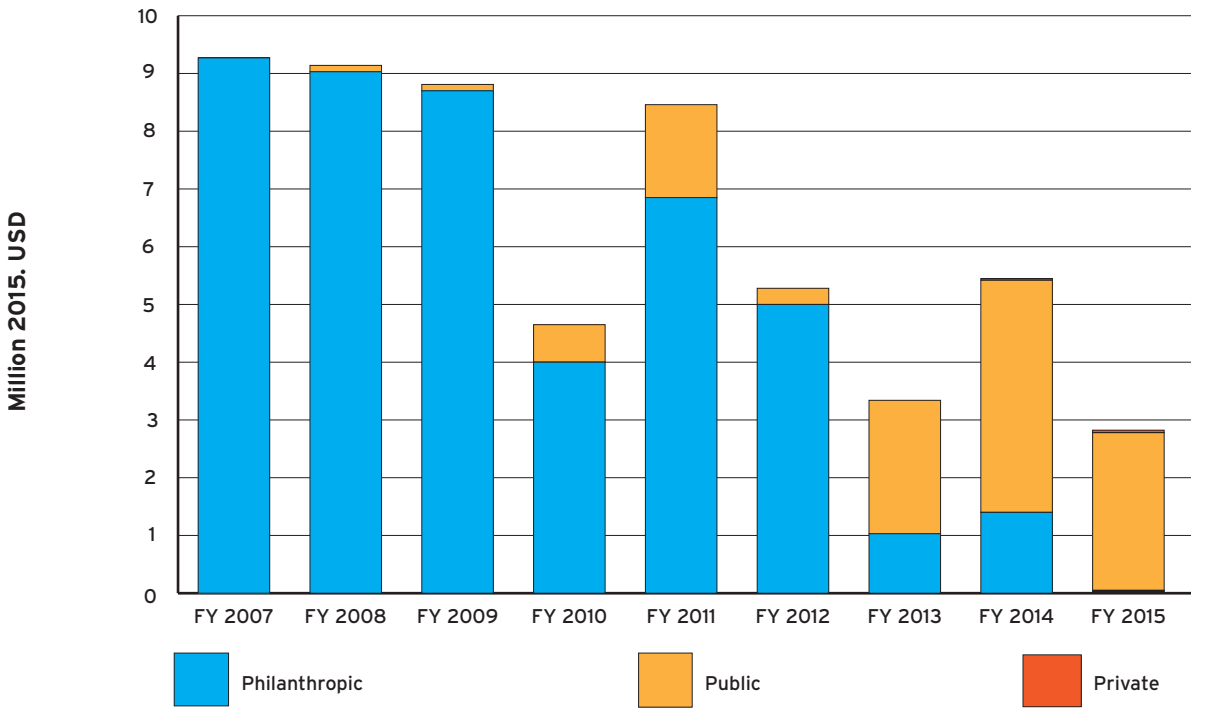
Texas Children's Hospital Center PDP includes leading public, private, and academic institutions around the world and receives the majority of its funding via donor grants for individual projects. For the most part, donors are public or nonprofit entities, including governments of the European Union and Brazil, the Hoffman Family Foundation, and Gavi Alliance. The National Institutes of Health in the United States supports Texas Children's activities by funding research grants to universities in the network.[86]

In table 5, we display cost per development phase and transition probability data for the large molecule vaccine candidates of schistosomiasis and hookworm currently in development, provided by Texas Children's Hospital. Comparing the annual funding per year in figures 6 and 8 for schistosomiasis and hookworm against the costs per development phase in table 5 indicates the scale of the unmet funding need for vaccine development. Particularly for phase III development, which averages $53.3 million per for the three vaccine candidates in table 5, there is a clear discrepancy between current funding levels and need.

Conclusions about Vaccine Development and Private Incentives

Based on the analysis we have undertaken, we can make multiple generalizable conclusions. First, overall funding for NTD vaccine development for hookworm and schistosomiasis is significantly lower than what would be needed to make any progress toward an effective vaccine. In general, creating a vaccine implies greater uncertainty, takes more time, and requires

FIGURE 8 | **R&D Funding for Hookworm Vaccines, FY 2007–FY 2015**



Source: G-Finder, NBER, World Bank, and Authors' calculations.

TABLE 5 Summary Data for Vaccine Candidates for Schistosomiasis and Hookworm

Vaccine Candidate / Statistics	Phase I	Phase II	Phase III	Total
Sm-TSP-2 *(Schistosomiasis)*				
Estimated costs	5 million	10 million	60 million	75 million
Probability of Entering Phase	100%	75%	50%	37.50%
Dates of phase duration	Completed	2 years	3–5 years	5–7 years
Na-GST-1 *(Hookworm)*				
Estimated costs	5 million	10 million	25 million	40 million
Probability of Entering Phase	100%	75%	50%	37.50%
Dates of phase duration	Completed	2 years	3–5 years	5–7 years
Na-APR-1 *(Hookworm)*				
Estimated costs	5 million	N/A	N/A	5 million
Probability of Entering Phase	100%	N/A	N/A	N/A
Dates of phase duration	Completed	N/A	N/A	N/A
Na-GST-1 plus Na-APR-1 (M74) *(Hookworm)*				
Estimated costs	5 million	25 million	75 million	105 million
Probability of Entering Phase	100%	65%	40%	26%
Dates of phase duration	Completed	2 years	3–5 years	5–7 years

Source: Bottazzi and Hotez.

more expensive testing at each development phase than for small-molecule drugs. Estimates of the time for clinical development phases for a vaccine are longer than DiMasi's 2003 and 2016 studies and estimated probabilities of success are lower at each stage.[87,88,89] As all vaccines are biologics, testing is also more expensive than for small molecule drugs.[90] Given that no commercial entities are organized to consistently create vaccines and they are discovered infrequently, there are no reliable estimates of average development costs. In fact, an important analysis of AMCs does not attempt to estimate average costs.[91] Of course, the potential benefits of vaccine development are also larger and longer lasting, so these investments may be highly cost-effective. But the uncertainty around the effect of this funding, means that the marginal benefit for incremental funding for small-molecule treatments is seen as relatively more attractive.

In addition, the lumpy nature of these investments is such that they only generate returns, in expected value, when investments are continued until a determination on clinical efficacy is made. Even the largest philanthropic investors such as the Gates Foundation made the determination that they cannot guarantee

the consistent funding stream needed to support these large investments. As demonstrated by figures 6 and 8, the investment profile for schistosomiasis vaccines have been more heavily concentrated on the public and private sector in comparison to hookworm vaccines, which was dominated by philanthropic entities until a sharp decline after 2009.

Second, private-sector partners exhibit lower levels of involvement in vaccine development in the NTDs we investigated compared to small-molecule drugs. This is a function of the fact that private-sector compound libraries are not as useful for vaccine development as they are for small-molecule development and many of the current vaccines are too early in their development to benefit from private-sector expertise. An exception is Texas Hospital Center's recent partnership with a private sector entity for the development of their schistosomiasis vaccine candidate. Merck KGaA will work with Texas Children's to move the vaccine candidate from pilot to industrial manufacturing via an in-kind contribution and technical input. It is also a function of the more limited pull funding mechanisms to entice private participation in vaccine development. Although proposed at approximately the same time as the PRV, the AMC funding model has not been set-up to encourage vaccine development, with the exception of a pilot program for pneumococcal vaccine.

Third, another form of uncertainty related to vaccine development is that their social value is determined by predicted disease prevalence levels approximately a decade from when investment decisions are made. Because developing nations have had significant success in reducing the burden of disease from infectious tropical diseases over the last decade using existing public health measures and MDA, funder support has waned for vaccine development with their uncertain effect, long timeline, and high total cost. Nevertheless, there is no uncertainty on whether AMR will erode efficacy of current treatment options only the timing. In fact and paradoxically, the more successful and widespread MDA becomes, the greater the likelihood AMR will make these treatments obsolete. This is a particular danger for schistosomiasis where only one treatment exists without any replacement on the near-term horizon. Therefore, the success that has reduced funder motivation may represent a myopic perspective that ultimately increases the likelihood of epidemic retrenchment if vaccine and drug pipelines are allowed to remain empty. Given the timelines for vaccine and drug development, having an empty pipeline puts at risk the international community's years of previous investments.

Moreover, the history of partial hookworm eradication in Latin America indicates that burden may persist even in middle-income nations. Because MDA requires persistent follow-up treatment, areas with high poverty or weak governance are less likely to have the capacity to disseminate certain types of technology compared to others. Vaccines are a technology that, because of their long lasting benefits and minimal infrastructure required for dissemination can be effectively introduced in areas with low incomes, weak governance, or instability. Given the higher marginal cost of MDA in more rural and poor areas, the availability of a vaccine becomes more valuable in reaching those less likely to be consistently treated with MDA or environmental measures.

Recommendations for Future Action

We conclude this report with a series of recommendations intended to increase the resources available from the private sector to address the global burden of disease from neglected tropical diseases. New sources of neglected disease R&D finance are crucial to achieve the Sustainable Development Goals. After consistent increases in public and philanthropic funding for global health beginning in the 2000s, the so-called "Golden Age" of support, public funding to the developing world has either plateaued or is in decline. At the same time, the 2000s were characterized by rapid and widespread economic growth in LMICs and therefore greater

domestic resources were put toward global health as well. Since growth has faltered, greater domestic resources are unlikely to be forthcoming either.

On the other hand, for large biopharmaceutical companies, the last decade has been characterized by substantial profit margins with decreasing opportunities for highly productive R&D in developed markets. Consequently, in addition to R&D investments, companies have engaged in significant distribution of dividends to stockholders and stock buybacks. One analysis finds that stock buybacks between 2006 and 2015 among the 18 US pharmaceutical companies continuously list on the S&P 500 Index during that time totaled US$261 billion, which was equivalent to 56 percent of their combined R&D expenditures over the same period.[92] More generally, the extent to which the current business environment does not align profit-making with social goals and as profit-making opportunities from previously created intellectual property remain, private-sector led investment in NTDs will remain challenging since the opportunity costs of foregone private sector investments are bigger. That is, if private biopharmaceutical continues to have high profit margins from previous innovation such that a significant amount of their capital is not being invested, but instead going to share buybacks, encouraging greater private sector involvement in global health R&D will remain challenging.

Given the foregoing analysis, we recommend the following policy changes to increase the level of private funding for NTD drug and vaccine development, strengthen the NTD research pipeline, and improve health in the developing world:

1. **Alignment of public funding with social return**. Our analysis showed that the current policy environment does support a positive ROI for private entities when companies obtain approval for pre-existing drugs such as Benznidazole. However, the social benefit of approval for existing treatments is limited because health gains come exclusively from improved treatment access. In addition, we find that with a restricted supply for PRVs, there may be sufficient revenue to support novel drug development in some circumstances.

If private biopharmaceutical continues to have high profit margins from previous innovation such that a significant amount of their capital is not being invested, but instead going to share buybacks, encouraging greater private sector involvement in global health R&D will remain challenging.

Yet, the binary nature of the PRV and the skewed distribution of private sector drug revenue (which determines the PRV's value) limits its widespread use to incentivize innovation. Moreover, tax expenditure via the orphan drug and general R&D tax credit represent the opportunity cost of public resources without a determination of whether the return in better health is worthwhile for a given investment. Since PRV access is binary, there is an incentive to invest the minimum amount necessary to obtain FDA approval, irrespective of health impact and access. In addition, the orphan drug tax credit incentivizes any form of R&D, without regard to marginal clinical efficacy. Finally, the policy environment is not supportive currently for substantial private-sector involvement in vaccine development.

To more closely align publicly provided financial incentives with social benefit, we propose direct OECD government funding for and competitive contracting for pre-clinical, clinical phase I and II NTD drug development. This would allow public funders to create specific benchmarks to be reached and direct financing to the compounds

mostly likely to generate social gain. These measures of social gain would be based on DALYs averted from the development and implementation of a new NTD drug. Although relatively new, Development Impact Bonds (DIBs) and the cash-on-delivery concept permit private investors to provide upfront capital for—in this case—neglected disease R&D and could be repaid with some profit margin contingent on successful results (the approval of a new chemical entity to fight neglected disease). These bonds could be indexed for successful clinical trial results as well as effective access efforts that demonstrably reduce disease.

2. **Private sector late-stage investment and risk sharing.** Our quantitative analysis finds that the most important drivers of private sector development cost are long development timelines and failure risk. Complementary to recommendation #1, we therefore propose additional private sector investment focused on phase III clinical trials to minimize risk-adjusted, capitalized private sector costs. In addition, to further minimize risk, private sector biopharmecutical firms could enter into investment agreements that would spread the risk and benefits of these trials. This risk-sharing arrangement would be particularly oriented toward social impact investors that want to both diversify market risk (R&D risk being orthogonal to market risk) and generate positive social returns. This model of risk-sharing during phase III clinical trials is increasingly being used in the commericialzable market and, if well-designed, could also be effective to promote private sector participation in NTD R&D. In this model, private equity invests because the biopharmaceutical company has already evaluated the technical risk and chosen to invest. By sharing in the risk and potential rewards, the private equity firm is able to take on risk uncorrelated to market returns. In return, taking on investments reduces the biopharmaceutical firm's technical risk. Potential investors include social impact investors or sovereign wealth funds (SWFs), pools of capital that a national or subnational entity owns jointly, a subset of which are often designated toward strategic development objectives including promotion of national development goals. Given recent commodity discoveries there are now multiple SWFs in sub-Saharan Africa (including Botswana, Ghana, and Nigeria) and these could be used as additional pools of finance to promote NTD drug development in collaboration with OECD support.

3. **Public funding coordination and stewardship.** Our case studies indicated the importance of stewardship and coordination of product development partnerships by non-profit entities. Greater stewardship from governments to determine priority areas for NTD investment as well as coordinate joint funding of early stage R&D with nonprofit actors would both increase the likelihood of private sector involvement in late stage R&D as well as increase the likelihood that innovation maximizes public health.

4. **Advanced market commitment for hookworm and schistosomiasis.** Our analysis highlighted the challenges for NTD vaccine development and the mismatch in scale between current resources compared to the funding necessary for successful development. The creation of an advanced market commitment ensuring a set price for a certain number of treatments purchased would increase the likelihood of private involvement in vaccine development.

The creation of an advanced market commitment ensuring a set price for a certain number of treatments purchased would increase the likelihood of private involvement in vaccine development.

5. **Tiered PRV based on social return and clinical stage:** One specific policy change that may be more feasible in the near term to better align financial incentives and health impact includes an adjustment to the PRV such that the PRV varies based on the level of innovation produced. Our analysis elucidates the trade-offs between expanded PRV eligibility and PRV value. Given that the binary nature of the PRV does not necessarily promote innovation with high social value, we propose creating a tiered PRV depending on the level of innovation a new treatment generates compared to current clinical practice. Shorter review periods therefore would be provided for the development of a new chemical entity compared to an already existing product. Another option, as suggested by Ridley in a recent paper, is that PRV eligibility could be restricted for drugs that have been available outside the US for over 3 years.[93] Congress could require the manufacturer to certify it conducted new clinical investigations and also specify its access plan.

6. **Targeted domestic resource mobilization:** We acknowledge the current slowdown in economic growth throughout the developing world and the increasing levels of public debt being held by a significant number of low-income nations. Nevertheless, we recommend a targeted strategy of domestic resource mobilization mediated through and conditioned by low-interest loans from multilateral institutions like the World Bank and the African Union. Funding commitments to public-private partnerships would be solicited for drug and vaccine R&D initially from multilateral institutions. However, given the emerging literature documenting the long-term health, schooling, and ultimately earning gains produced by NTD treatment (particularly hookworm), conditional on successful development and treatment expansion in a nation with high burden, a nation would be required to pay a percentage of tax receipts from the generation of children that benefited from a childhood with lower disease exposure. This would be used as partial payment to the multilateral institution for supporting the NTD R&D that improved health and welfare. For example, if this arrangement were to be undertaken to develop a new drug for HAT and it were developed and disseminated successfully in high burden nations such as Tanzania and Uganda, the World Bank's loan would then be paid back using a percentage of the tax receipts from the age cohorts who benefited from childhood treatment.

The challenges to seeding the drug and vaccine development pipeline with promising treatments through private-market incentives are significant. Nevertheless, this paper elucidates pre-existing public-private efforts that have or are moving toward successful development. The current policy environment supports drug development through tax credits, regulatory changes, and extended exclusivity. The foregoing analysis outlines additional ways private sector entities could pool risk and the public sector could design incentives to increase the pace of socially beneficial R&D. With continued partnership and the recommendations above, the health challenges of the world's most vulnerable populations can be addressed more rapidly and effectively.

Appendices

List of Expert Consultations

Name	Organization
Meg DeRonghe	Gates Foundation
Lynda Stuart	Gates Foundation, Director in Discovery and Translational Sciences, NTDs
Jeffrey Moe	Duke University
Francois Bompart	Sanofi
Peter Hotez and Maria Elena Bottazzi	Baylor University College of Medicine
Michael Reich	Harvard Chan School of Public Health
Rachel Cohen	Drugs for Neglected Tropical Diseases Initiative
David Ridley	Duke University
Laurent Fraisse	Sanofi
Enrico Colli	Chemo Group, Chief Scientific Officer, BZN project
BT Slinsby	Global Health Innovative Technology Fund
Simon Brooker	Gates Foundation, LSTHM, Schisto
Thomas Saugnac	DND*i*, Operations Director
Fabian Gusovsky	Eisai, Scientific Leader of Eisai's World Health Initiative
Harald Nusser	Novartis Social Business
Jonathan Spector	Novartis
Ron Wooten, John Bradley, William Robb, Jonathan Tunnicliffe, and Gregory Dodge	NovaQuest
Stephane Regnier and David Ridley	Novartis and Duke University

Appendix A: Additional Background on Chagas Disease

Over the past two decades, both benznidazole and nifurtimox were only available in the United States through investigational protocols administered by the US Centers for Disease Control and Prevention due to their lack of regulatory approval. This created a relatively complex system for end-users—including both healthcare providers and patients—to obtain the drug. In addition, production interruptions and periodic shortages of benznidazole as well as the lack of a pediatric formulation all conspired to limit efforts to treat Chagas disease.[94]

Benznidazole, first registered in 1971, was manufactured by Roche for approximately three decades. In 2003, Roche announced that it would no longer produce this medication and instead donated all rights and the technology to manufacture benznidazole to the Laboratorio Farmaceutico do Estado Pernambuco (LAFEPE), with a plan that it would then manufacture and market the drug.[95] During the period from 2004–2010, LAFEPE made efforts to produce the active ingredient in benznidazole but was unable to do so. LAFEPE then announced in the summer of 2011 that they were unable to produce a sufficient supply to meet global need for this drug.[96]

Appendix B: Economic Modeling—Continued

This section describes in greater detail additional potential revenue streams related to R&D for neglected tropical diseases.

Secondary Sales Market

Although in general neglected diseases have limited secondary markets because they are prevalent in low-income nations and among populations that do not have an ability to pay, there are situations where a secondary market exists. For example, although Chagas is defined by the the WHO and the FDA as a neglected tropical disease, it is both eligible for a tropical disease PRV while an estimated 300,000 people in the U.S. suffer from its chronic form. Given the FDA's recent approval of Benznidazole, a secondary market could develop that would provide additional revenue to the Chemo Group as screening and treatment increase in the U.S. Although it is currently undetermined, it is likely the state Medicaid programs will cover Benznidazole and will therefore represent a potentially significant additional revenue source for Chemo group. In addition, given continued economic growth in the developing world as well as expansions of health system coverage to lower income nations (Ghana, for example, has substantially expanded it publicly-financed health insurance coverage in the last decade), a larger percentage of middle and low-middle income nations engage resources toward what were previously NTDs. Nevertheless, given the geography of acute and chronic HAT and the ease with which travelers can avoid it, we assume that no secondary market exists.

Calculation of Value of Priority Review Voucher

Utilizing the methodology set forth by Ridley and Regnier, we calculated the sale function for a pharmaceutical product with peak shares of $914 million in fifth year sales. Then using a product adoption function from Ridley and Regnier, we modeled total revenues using the logarithmic function:

$$y = 19.686\ln(x) - 0.9227$$

We calculated revenues monthly for the sales function, then offset the function by four months to model the non-PRV sales. Subtracting the expedited sales (with PRV) from the non-expedited sales curves yields the time value of money component of the PRV's value. We used a similar methodology (with annualized discounting instead of monthly) to calculate the exclusivity effect.

Finally, the competitive effects were modeled using the regression output (from Ridley and Regnier's 2015 study):

$$\begin{aligned}\text{peak\_share} = {} & 0.23 + 0.46(\text{promotional\_share}) \\ & - 0.18(\text{third}) - 0.23(\text{fourth}) - \\ & 0.009(\text{time}) + 0.007(\text{time*third}) \\ & + 0.01(\text{time*fourth}) \\ & - 0.06(\text{new\_competitor})\end{aligned}$$

We reproduced the output coefficients and utilized the economic theory that each entrant results in a loss of 8% market share. Using the methodology set forth from Ridley and Regnier, we calculated each entrants competitive advantage, multiplied this scale-up factor by the sales function, then subtracted the calculated competitive effects curve from the expedited curve to yield the competitive effects component. Summing the three components produces our estimates for the value of a PRV based upon the number of vouchers issued.

Calculation of ROI Sensitivity Analysis

To model how private ROI changes for various probabilities of success based on transition probabilities for Fexinidazole and Acoziborole, we discounted the clinical costs by the transition probabilities plus the pre-clinical costs. To model this, we estimated the proportions of the transition probabilities from Phase I-II:Phase II-III:Phase III-NDA as 2:1:2 as an approximation of the probabilities found by DiMasi et al. (2016).

Appendix C: Additional Background on Hookworm Disease Burden, Etiology, and Treatment

Human hookworm infection is caused by nematode parasites of the genus Ancylostoma and species Necator americanus. Globally, N. americanus remains the predominant etiology in comparison to A. duodenale. These two hookworms, the roundworm Ascaris lumbricoides, and the whipworm Trichuris trichiura, make up a family of parasites known as soil-transmitted helminths (STHs).

In 2001, delegates at the World Health Assembly (WHA) unanimously endorsed a resolution urging endemic countries to seriously tackle worms. The current global target is to eliminate morbidity due to all STHs in children by 2020.

Hookworm infection is acquired by infective larval stages that penetrate the skin, typically occurring when people walk barefoot on contaminated soil. (A. duodenale larvae may also infect humans via ingestion of the worm's larvae.) Hookworms do not replicate in the human body, so the morbidity of hookworm is highest among patients that harbor large numbers of adult parasites. The intensity of a hookworm infection can be measured with quantitative fecal egg counts as a proxy marker.

In 1902, a medical zoologist identified the first hookworm victims in the American South. After this realization, the Rockefeller Foundation was convinced to take up the cause of hookworm eradication, as it was a common, easy to treat, and easy to prevent disease. From 1909–1914, the Rockefeller Foundation campaigned for hookworm treatment and prevention through the Rockefeller Sanitary Commission for the Eradication of Hookworm Disease. The program taught young doctors to educate the public on hookworm infection and advise people on prevention techniques, such as constructing of a sanitary privy or wearing shoes. Makeshift clinics tested and treated individuals. The Rockefeller campaign cut hookworm prevalence significantly in the South where child prevalence was 43 percent before the campaign. More importantly, the campaign successfully boosted development of the Southern public health systems. As the South urbanized, hookworm prevalence continued to drop until hookworm was no longer endemic in the American South. However, more recent evidence suggests that hookworm prevalence in the Southern United States is may have returned in at least one rural county with sanitation problems, but further studies are needed to determine whether this limited prevalence estimated is widespread (McKenna et al., 2017).

In the early 20th century, the Rockefeller Foundation, through its International Health Board, extended hookworm eradication efforts into Latin American countries (LAC). As a result, hookworm infection rates in the LAC declined dramatically and led to the establishment of local health agencies run by national governments, who continued the hookworm reduction efforts. Despite the economic and social growth of the LAC region since the early 1900s, social inequality still remains an issue and impediment to control of hookworm infection in the area. The marginalization of both the rural and urban poor as well as indigenous peoples in LAC countries has prevented control of hookworm (Gaze et al., 2015).

Appendix D: Additional Background on Schistosomiasis Disease Burden, Etiology, and Treatment

The three main strains are *S. haematobium*, *S. mansoni*, and *S. japonicum*, each primarily endemic to different areas. *S. haematobium* makes up the largest proportion of schistosomiasis cases (close to two-thirds) and is located primarily in Africa and the Middle East. This strain causes urogenital diseases, and is highly correlated with contracting HIV/AIDs through so-called "sandy patches."[97] *S. mansoni* causes intestinal and hepatic schistosomiasis and accounts for nearly one-third of the disease. Finally, *S. Japonicum* also causes intestinal disease, accounts for about 1 percent of the known cases, and is located primarily in East Asia

Other local strains include *S. mekongi, S. guineensis and S. intercalatum*. *S. mekongi* is endemic to the Mekong river basin and *S. guineensis* and *S. intercalatum* exist in West and Central Africa.[99]

An important organization contributing to the reduction in the schistosomiasis burden is the schistosomiasis Control Initiative (SCI). The SCI began in 2002 with a £20 million grant from the Bill & Melinda Gates Foundation with the goal of delivering schistosomiasis and intestinal worm treatments to Sub-Sahara Africa. In 2006, it was a founding partner of the Global Network for Neglected Tropical Disease Control (GNNTDC), and "expanded its remit to integrating the control of elimination of seven NTDs."[100] By 2013, the SCI announced the delivery of its 100 millionth treatment of Praziquantel (PZQ) against schistosomiasis. This trend is confirmed by the chart below (Figure 3), which shows deaths attributable to schistosomiasis decliniing, but still transmission and re-infection are significant.

TABLE 6 | **The Major Human *Schistosoma***

Species	Length as adult	Disease	Percentage of cases worldwide	Major geographic locations
Schistosoma haematobium	10–22 mm (0.4–0.8 in.)	Urogenital schistosomiasis	63%	Africa, Middle East
Schistosoma mansoni	6–17 mm (0.0–0.7 in.)	Intestinal and hepatic schistosomiasis	35%	Africa, Middle East, Americas
Schistosoma japonicum and Schistosoma mekongi	12–26 mm (0.5–1.0 in.)	Intestinal and hepatic schistosomiasis	1%	China, the Philippines, Southeast Asia

Source: Hotez[98]

Appendix E: Data

G-Finder

All funding data for schistosomiasis and hookworm within this report comes from the G-FINDER survey, conducted annually by Policy Cures Research. The G-FINDER survey has tracked global investment in R&D for neglected diseases since 2008, and for Ebola and select VHFs since 2014. It covers basic research, drugs, vaccines, diagnostics, microbicides, and vector control products, as well as platform technologies (adjuvants, delivery technologies, and diagnostic platforms).

Endnotes

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