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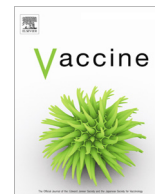
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Neglected tropical disease vaccines: hookworm, leishmaniasis, and schistosomiasis

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1. Introduction and a brief history of neglected diseases

The modern health and equity framework for a group of chronic and debilitating infections known as the neglected tropical diseases or 'NTDs' emerged in the 2000s in response to global calls by the United Nations to address HIV/AIDS, malaria, and other poverty-related diseases [1]. Some of the most important "other diseases" as defined by the Millennium Development Goals for poverty reduction included the major human parasitic infections, such as hookworm infection, schistosomiasis, and leishmaniasis. These illnesses were first labeled as 'neglected' by the Rockefeller Foundation during the 1980s because of their high prevalence, severe and debilitating clinical manifestations, and disproportionate impact on people living in low- and middle-income countries (LMICs) [2]. It was subsequently determined that such infections essentially affect almost everyone living in extreme poverty in LMICs; they also reinforce or cause poverty because of their long-term effects on the intellectual and cognitive development of children, their ability to impair worker efficiency or productivity; and their deleterious effects on women's reproductive health [3]. For that reason, biopharmaceutical interventions to prevent or cure the NTDs represent potential anti-poverty measures [4].

2. Disease burden of the neglected tropical diseases

The Global Burden of Disease Study (GBD) 2019 finds that together, malaria and the NTDs account for almost 750,000 annual deaths and 63 million disability-adjusted life years (DALYs) [5]. However, subtracting for malaria, the NTDs together cause approximately 100,000 deaths annually and 16.5 million DALYs. Hookworm infection, schistosomiasis, and leishmaniasis represent three of the most common and highest burden NTDs (in terms of DALYs) now considered targets of vaccines (Table 1).

Human hookworm infection is a leading cause of iron deficiency anemia, especially in children and women of reproductive age with

low underlying iron reserves [7]. Because hookworms in the gastrointestinal tract feed on blood, both iron deficiency and plasma protein losses ensue and result in significant malnutrition globally. In Africa, hookworm frequently combines with malaria and/or Schistosomiasis to cause profound and life-threatening anemia, especially during pregnancy [8].

Schistosomiasis also predominantly affects children and adolescents, and is an important cause of impaired reproductive health through the condition known as female genital schistosomiasis [9]. Chronic infection can also lead to chronic hepatic and renal impairments, and even neoplastic changes resulting in a unique bladder cancer.

Leishmaniasis in its cutaneous form causes one or more ulcers, which are especially pernicious and disfiguring when they appear on the face [10]. Cutaneous leishmaniasis has become hyperendemic in parts of the Middle East where sandfly vector control efforts were interrupted due to conflict and political instability [11]. In South and Central America, a metastatic form of the disease (mucocutaneous leishmaniasis) causes severe disfigurement. In war-torn South Sudan and elsewhere in East Africa and the Indian subcontinent, a visceral form of leishmaniasis is a significant cause of mortality [12]. Refugee populations as well as women and children are also disproportionately affected.

Because these three major NTDs are not ordinarily killer diseases, it has been problematic to explain to biopharmaceutical developers and policymakers their full health impact. While the GBD uses DALYs as an alternative metric, this approach often fails to convey the complete global health burden. For example, the mortality of profound anemia of pregnancy in Africa from combined hookworm and malaria is not always attributed to the former, while the social stigma and mental health effects of female genital schistosomiasis and cutaneous leishmaniasis, especially among girls and women, frequently go unreported [13]. Moreover, because the NTDs comprise stealth causes of poverty, this feature presents opportunities to appeal to finance ministers both in LMICs and the group of 7 (G7) nations, as well as the World Bank, International Monetary Fund, and regional banks.

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Table 1

Hookworm infection, schistosomiasis, and leishmaniasis – three major NTDs in LMICs. Data from Global Burden of Disease (GBD) 2019 Cause and Risk Summaries [6].

Disease	Estimated Disease Prevalence	Major disease sequelae	Disability-adjusted life years (DALYs)	Major locations
Hookworm disease	173 million	Iron deficiency anemia Protein malnutrition Intellectual and growth impairments	1.0 million	Sahelian West Africa Central and East Africa India, Laos, and Papua New Guinea Brazil
Schistosomiasis	140 million	Chronic inflammation Intestinal and hepatic dysfunction Renal and urogenital impairments Bladder cancer	1.6 million	Sahelian West Africa Central and East Africa Middle East Brazil
Leishmaniasis	4–5 million	Cutaneous scarring and disfigurement Pancytopenia and hepatosplenomegaly	0.7 million	Middle East and North and East Africa Central Asia Central Latin America

3. Opening the door for NTD Vaccines: a changing vaccine ecosystem

Despite the availability of anti-parasitic drugs such as albendazole and praziquantel for hookworm and schistosomiasis, respectively, and their widespread administration through programs of mass drug administration (MDA) [1,2], both of these human helminth infections remain highly prevalent. The reasons for this include varying levels of drug effectiveness in resource-poor settings, as well as high rates of post-treatment reinfection in areas of high transmission [14,15]. Moreover, some of the worst effects, including the urogenital lesions of schistosomiasis, can occur early in childhood prior to access to mass treatment programs [9]. Similarly, in areas of high leishmaniasis transmission such as in the Middle East and East Africa, sandfly control or mass treatment approaches have not been possible in the setting of conflict, urbanization, and political instability [11,12]. The zoonotic transmission of leishmaniasis in many regions also acts as a barrier to the success of treatment campaigns. These realities along with the fact that vaccines have had an integral part of many successful global disease control efforts such as smallpox, polio, and measles over the past century, provide a strong rationale for developing, testing, and distributing new vaccines to protect against NTDs. In fact, modeling studies find that various NTD vaccines could be not only cost-effective but even cost-saving (meaning that they can provide health benefits and save money at the same time) in many circumstances [14–17].

Yet, there remains the perception among multinational pharma companies that they have no financial incentive to embrace vaccines for NTDs. This apparently has left them reluctant to participate in the product and clinical development of NTD vaccines, leaving vaccine candidates for hookworm infection, schistosomiasis, and leishmaniasis stuck at the phase 1–2 stage for clinical testing. This may represent a persistent disconnect between supply and demand. Typically, advocates for free market economies argue that in a free market anyone who can satisfy any existing major demand will end up benefiting financially. There is clearly a demand for NTD vaccines with the substantial clinical and economic burden imposed by NTDs. For example, a study published in *PLOS Neglected Tropical Diseases* estimated productivity losses due to anemia from hookworm infection to be between \$7.5 billion to \$138.9 billion annually [18]. Such losses exceed published estimates for a number of diseases that have received comparatively more attention than hookworm. Productivity losses can have reverberating negative effects throughout a country's economy as well, preventing further overall development and thus compounding other problems. Yet, when multinational pharma companies do not view a potential solution to such a significant problem as prof-

itable enough, that suggests that free market forces may not be fully at work. Instead, other forces such as investor perception of the company's overall value and in turn a company's stock share price may take precedence.

NTD vaccines face the double indemnity of being vaccines and being for NTDs. Over the past several decades, many multinational pharma companies have moved away from vaccine manufacturing in favor of medications that have higher profit margins (e.g., higher prices can be charged), can be used repeatedly, have markets that can be readily expanded via direct-to-consumer advertising, and used to treat conditions that a greater proportion of the public may be actively experiencing, regardless the actual burden [19]. Vaccines tend to be longer-term investments and may not offer the short-term bursts in profits that may have a greater immediate effect on a company's stock share price. At the same time, many including investors may not fully comprehend the longer-term impact of NTDs and the value of interventions such as vaccines to prevent or mitigate them.

The hope is that this situation might change following some important insights and policy shifts generated by the ongoing COVID-19 pandemic. The COVID-19 pandemic is showing how an infectious disease can have considerable direct and indirect effects on local, regional, and national economies [20]. Efforts like Operation Warp Speed have further demonstrated how policy levers can incentivize companies to develop and bring to market new vaccines. Meanwhile, NTDs have remained widely prevalent and in fact may have even accelerated because of the diversion of funds and resources to COVID-19 prevention efforts [21]. But there has also been a new understanding of the devastation caused by vaccine access inequalities that delayed the availability of mRNA and other vaccines to LMICs [22]. Now with NTDs, a strong case can be made that vaccine inequality does not end with COVID-19 vaccines. Instead, the COVID-19 pandemic represents a new awakening for the importance of global attention towards NTD vaccines.

4. Decolonizing the vaccine ecosystem

Even though the importance of making affordable, effective, and safe NTD vaccines available has become more widely and generally accepted, there remain formidable challenges in actually carrying NTD vaccines “across the finish line” in terms of the transition towards large scale manufacturing, pivotal or phase 3 clinical trials, global licensure, and ultimately distribution and use. Among the good news on this front is how the first malaria vaccine recently achieved these key milestones [23] and might help to blaze a path for hookworm, schistosomiasis, and leishmaniasis vaccines.

Included among those key scientific and technical challenges for developing vaccines de novo, are the complexities related size

of eukaryotic parasite genomes and the absence of high throughput approaches for conducting reverse vaccinology [24] as well as the establishment of correlates of protection. Other problems include patent protections on cutting-edge technologies and adjuvants. But even assuming that these problems are obviated by the fact that several lead candidate vaccines have now entered phase 2 clinical testing, their ultimate adoption by a vaccine producer for end-stage development is not assured. At the same time, mergers and acquisitions have led to greater consolidation, fewer players, and less diversity among the multinational pharmaceutical companies. The major multinational companies may not see enough of a return on investment for NTD vaccines to divide their attention from what they perceive as greater short-term gains, despite evidence for significant global demand [25] and modeling that supports an ability of health systems to pay [26]. Further, NTD vaccines are not viewed with the status of “pandemic threat” vaccines such as those for COVID-19, Nipah virus infection, or other emerging virus threats. To date, for instance, the Coalition for Epidemic Preparedness Innovation (CEPI) has not prioritized donor support for NTD vaccines.

There is an emerging consensus among global policymakers for the concept of “decolonizing” the vaccine ecosystem to promote and enhance LMIC vaccine producers as first-rate innovators and leaders in the NTD vaccine space [27]. This could include building capacity for new vaccine technologies and adjuvants, especially for the African continent where NTDs remain highly endemic, and local or regional development of early phase testing capacity using controlled human infection models [28]. This could also include encouraging new vaccine manufacturers to emerge throughout the world, ones that may not be beholden to the same type of shareholder demands and view NTDs as growth opportunities.

While LMIC vaccine producers, primarily those that form part of the Developing Countries Vaccine Manufacturers Network (DCVMN) [29] have shown some interest in taking on NTD vaccine projects, overall they lack the funds for both phase 3 trials and industrial scale production. Despite evidence for the cost effectiveness and even economic dominance (cost-savings), this alone has not been an incentive for LMIC governments and producers to create strategies for adopting NTD vaccine development programs. Another consideration is the fact that no national regulatory authority based in an LMIC enjoys the same stringent status from the World Health Organization as do regulators in North America, Europe, Japan, or Australia. As a result, all current and future NTD vaccines will depend on the WHO prequalification process and/or on the evaluation by high-income nation regulators to enable their global distribution.

Finally, from a policy perspective an additional hurdle is the irony that currently employed mass treatments do provide some mitigation on the global health burden of hookworm infection and schistosomiasis, even though these anti-parasitic drugs have largely failed to produce substantial disease burden reductions. Nevertheless, a “one shot on goal” mentality, meaning one intervention per NTD, has permeated the global health policy space. This is similarly the case for leishmaniasis, where there is often an assumption of one drug for all disease forms. This view has further discouraged policymakers from enthusiastically assuming the costs and navigating the formidable regulatory hurdles during the development of new vaccines.

All of this means that perhaps some market shaping efforts are needed, efforts to re-align the potential supply of new NTD vaccines with the obvious need/demand for them. Both “pull” and “push” mechanisms are available. On the pull side, market shaping initiatives have been very successful throughout history with the Gavi advanced market commitments (AMCs) being one prominent example for vaccines. In the AMC case, Gavi established contracts with vaccine manufacturers in which they would a guaranteed cus-

tomers base among LMICs for years, as long as the manufacturers were willing to maintain supply and accept price ceilings. This was a win-win solution for both manufacturers and LMICs. Market shaping initiatives can also entail providing investments for smaller businesses willing to tackle underappreciated problems like NTDs so that they compete on a more level playing field with larger multinational companies. The disadvantage of AMCs or other pull mechanisms is that companies or their consortium partners still require up-front funds to undertake vaccine development and testing. Therefore, AMCs by themselves may not be sufficient, requiring push funding support from philanthropic donors, governments, or innovative financing such as priority review vouchers (PRVs).

5. Traditional vaccine technologies and adjuvant access

Several exciting vaccine candidates for hookworm, schistosomiasis, and leishmaniasis are now advancing through a clinical pipeline even with the substantial hurdles discussed here. These primarily rely on well-vetted technologies, especially recombinant protein antigens or more traditional virus vectors. Their preliminary successes derive from the enthusiasm of academic investigators and non-profit product development partnerships willing to champion NTD vaccines, together with forward thinking public and private donors. The fact that they rely on more traditional vaccine technologies for antigen production should not diminish their importance, reliability, or performance expectations. Indeed, there may be distinct advantages for traditional technologies, including their acceptance by communities, low cost, and more straightforward refrigeration requirements (compared to mRNA vaccines that require deep freezing temperature storage). Therefore, decolonization relies on both acceptance of traditional technologies and commitments to help them achieve licensure in LMICs or globally, while continuing to support capacity building in terms of both new and traditional approaches.

Adjuvant access also remains a problem, with only a handful of adjuvants currently available through open sources, including aluminum derivatives (alum, aluminum phosphate, and aluminum hydroxide) or limited and relatively affordable licenses including the lipid A derivatives such as monophosphoryl lipid A or synthetic lipid A moieties, and deoxyoligonucleotides. It will be essential to establish better partnerships, contractual arrangements, or patent-waivers between LMIC vaccine producers and multinational pharma companies to ensure adjuvant availability for NTD vaccines.

6. Concluding statement

The hope is that the series of three papers that highlight the value of vaccines for hookworm, schistosomiasis and leishmaniasis found in the two volumes of this supplement might help to drive further actions to get NTD vaccines fully tested and through stringent regulatory pathways. Despite the formidable hurdles outlined above, several important new NTD vaccines for hookworm, schistosomiasis, and leishmaniasis, respectively, are moving through a pipeline of clinical trials and development. These aspects will be detailed in the series. It remains a priority to both accelerate the development of these current vaccines, while offering opportunities to greatly expand the list of vaccines that enter critical path activities leading to pilot manufacturing, toxicology testing and ultimately first-in-human trials.

CRedit authorship contribution statement

Peter J. Hotez: Conceptualization, Data curation, Visualization, Writing original draft, Writing review and editing.

Maria Elena Bottazzi: Conceptualization, Writing review and editing. **Paul M. Kaye:** Conceptualization, Writing review and editing. **Bruce Y. Lee:** Conceptualization, Writing review and editing. **Karl Philipp Puchner:** Conceptualization, Writing review and editing.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PMK is co-inventor of a patent for a gene sequence used in the candidate ChAd63-KH leishmaniasis vaccine and has received funding from the UK Medical Research Council, the Wellcome Trust and the European & Developing Countries Clinical Trials Partnership for the development of vaccines against leishmaniasis. PJH and MEB are inventors on various patents relating to vaccines against hookworm and schistosomiasis.

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