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EDITORIAL

Controlled human infection models to evaluate schistosomiasis and hookworm vaccines: where are we now?

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Expert commentary

Controlled human hookworm and *Schistosoma* infections are a valuable tool to advance vaccine development and can be used to efficiently test new vaccine candidates as well as provide insight into immunological responses that could help identify correlates of protection or novel vaccine targets.

Neglected tropical diseases (NTDs), among hookworm and schistosomiasis, contribute significantly to the global disease burden and disproportionately affect the most vulnerable populations. Combined estimated 650 million people are infected and in many regions hookworm infection and schistosomiasis are co-endemic [1]. Control of these two diseases relies heavily on mass drug administration (MDA) with anthelmintics. As a result, prevalence has reduced in the past years, but much effort is still needed to achieve the WHO elimination targets of 2030 [1]. Moreover, modeling studies indicate that disease control through MDA alone may take decades in case of hookworm [2], or may not at all be achieved in high transmission settings for schistosomiasis [3]. This is in part due to frequent reinfections after MDA. An efficacious vaccine against any of these infections can potentially be a pivotal tool to advance the control or even eradication of these diseases [2,3]. However, intrinsic to the field of NTDs, research funding into vaccine development is limited and hampered by a lack of commercial interest. Controlled human infection model (CHIM) studies can be a cost-effective way to accelerate vaccine development. In these studies, a small number of healthy volunteers are deliberately exposed to the parasite at the same time point. As such, valuable information is obtained on the preliminary efficacy of a vaccine in a relatively short period of time [4]. This is in contrast to field studies, where it may take longer for natural infection to accrue. CHIMs for vaccines ideally serve as proof-of-concept studies before moving to larger, more expensive field studies. In addition, CHIMs can also be used to study immune responses following infection and help identify correlates of protection. Particularly in the field of malaria, CHIMs have helped advance vaccine candidates such as the RTS,S malaria vaccine, whereby initial efficacy was demonstrated in a proof-of-concept CHIM study, and later confirmed in a phase 3 clinical trial in African children (~30% protective vaccine efficacy) [4]. In analogy with malaria, CHIMs for hookworm and schistosomiasis can play an important role in vaccine development.

1. Hookworm challenges: from self-inoculation to controlled human infection models

Worldwide, estimated 450 million people are infected with hookworms [1]. Two main species are responsible for human infection, namely *Necator americanus* and *Ancylostoma duodenale*. Hookworm infection predominantly affects children and pregnant women who consequently are at increased risk of developing iron-deficiency, anemia, and protein loss [2]. Human hookworm infection is notoriously difficult to replicate in animal models [5], which complicates preclinical efficacy testing of vaccines. A controlled human hookworm infection (CHHI) model is not only of value for vaccine testing but can also increase our understanding of hookworm induced immune responses and potentially identify correlates of protection. Thus far, CHHI research has focused on its therapeutic potential for immune-mediated diseases, such as allergy, asthma, irritable bowel disease, and celiac disease due to its immunoregulatory mechanisms [6]. One of the earliest experimental hookworm infections was of a researcher who inoculated himself to relieve allergic symptoms in the mid-1970s [7]. Controlled human hookworm infections have come a long way since, with rigorous clinical studies now being performed in various countries. To date, only controlled human infections with *N. americanus* larvae have been performed. Doses of up to 50 larvae are generally well-tolerated; however, in some cases, severe abdominal symptoms have been reported [8]. The endpoint of the majority of these studies focusses on disease progression of autoimmune diseases, for instance duodenal villous height:crypt depth ratio and IgA tissue transglutaminase levels for celiac disease [6], with a view of using hookworm larvae to treat or ameliorate autoimmune disease. However, for vaccine studies trial endpoints would preferably

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be related to clinical endpoints as a consequence of the hookworm infection itself. Given the fact that clinical consequences of hookworm infection only occur after years of high burden infections, controlled infection studies assessing vaccine effect will therefore use protection from infection or a reduction in egg load as a surrogate endpoint. However, the high day-to-day variability complicates the reliability of this endpoint. To overcome this issue, a highly standardized method of preparing Kato-Katz slides and feces homogenization is advised. Moreover, we showed that repeated dosing, e.g. 2 × 50 larvae, decreases egg output variability and leads to egg counts comparable to field setting, without increasing adverse events and should therefore be advised for future vaccine studies [8].

So far, two subunit vaccine candidates, *Na*-GST-1 and *Na*-APR-1, have shown to be safe and immunogenic in healthy adults; however, their efficacy still needs to be evaluated [9,10]. For this purpose, a vaccination-infection trial is currently ongoing, which will be the first study to evaluate vaccine efficacy with controlled human hookworm infection to date (NCT03172975). In contrast with vaccines for viruses or bacteria, relying on a single antigen target might not be sufficient for a hookworm vaccine which is why the two vaccine candidates have already been tested in tandem [10]. Proof-of-concept immunization studies with attenuated larvae may provide useful new insights into complex (protective) immune responses and correlates of protection that complement the hookworm vaccine pipeline. Protective immunity through vaccination with radiation-attenuated larvae has already been successfully demonstrated in dogs [5]. A human study exploring this method in combination with a CHHI was recently completed in Australia, and its results are eagerly awaited [ACTRN12617001007325]. Another interesting approach to map immunological responses, is a study that combines sequential hookworm immunizations abrogated with albendazole treatment in the early infection stage, i.e. 2 weeks after infection [NCT03702530]. This timing coincides with the lung stage of the parasite, where killing of worms is believed to be strong inducers of potentially protective immune responses. Similar to malaria, where such studies have led to the identification of multifunctional T cells and γδT cells as important correlates or protection [11], these studies could revolutionize hookworm vaccine development through the identification of markers or signatures of protection, and selection of antigen targets.

2. Controlled human *Schistosoma* infections using single-sex parasites

Schistosomiasis affects the lives of more than 200 million people. The most significant health risks related to schistosomiasis are caused by eggs that get trapped in tissue triggering a local granulomatous, inflammatory response. The subsequent scarring and fibrosis is a safety concern for a controlled human infection with schistosomes (CHI-S). One way of minimizing egg-associated pathology is using male or female worms only. Molecular techniques make it possible to reliably determine the sex of the infective larval stage [12]. Highly sensitive assays can be used to detect worm-derived circulating anodic antigen (CAA) [13]. So far, 17 healthy, Schistosoma-naïve volunteers were exposed to 10, 20, or 30 male *Schistosoma mansoni* cercariae. Infection was detectable in 82% of participants exposed to 20 male cercariae [14]. Multiple systemic symptoms, such as (nocturnal) fever, myalgia, and headache, were reported, indicating that acute schistosomiasis syndrome can occur even without the presence of eggs [14].

Three vaccine candidates are currently in development. The rSm14/GLA-SE showed high seroconversion rates (92%) in Senegalese adults, and is now being evaluated in Senegalese children in a phase IIb study. The Sm-TSP-2 has been tested in a phase I study (NCT02337855) and its results are expected soon, while phase I studies for Sm-p80 are underway in the US, Burkina Faso, and Madagascar. Although the single-sex CHI-S model differs substantially from a natural infection in terms of infection dose and the lack of egg-induced immune responses in the absence of eggs, it can still be used to obtain preliminary efficacy data on these vaccines based on worm reduction and would only require 11 participants per group to detect a 75% reduction in CAA levels. More recently, a single-sex female CHI-S model is being developed (NCT04269915) that when proven to be safe, can serve as an additional tool and is particularly useful for vaccines that target antigens which are preferentially expressed on female worms, such as for Sm-p80 [15].

CHI-S also offers opportunities to investigate the effects of repeated exposure to cercariae. In mice and non-human primates, immunization with irradiated cercariae lead to 80% reduction in worm burden after challenge [16]. Immunological markers associated with protection included upregulated Th1 polarized CD4+ cells and increased IgG, which are responses also observed in male single-sex CHI-S [14,16]. If indeed repeated CHI-S leads to protection, this provides a unique opportunity to identify correlates of protection that improve our understanding of immunity and may lead to the discovery of new vaccine targets.

3. Transferring hookworm and schistosomiasis CHIMs to endemic settings

So far, these CHIM studies have only taken place in non-endemic settings. However, immune responses in endemic settings may be substantially different due to prior exposure to the parasites, coinfections, or differential environmental exposures [17]. To further understand the consequences of these differing immunological setpoints for vaccine development, CHIM models should be transferred to endemic settings. The first steps have been taken to set up a CHI-S in Uganda [18], while CHHI studies are planned to take place in Brazil [19] and Gabon [20]. By harmonizing study procedures across different study sites, (vaccine) immune responses can be compared between non-endemic and endemic populations, which will further our understanding of these parasitic diseases and aid vaccine development.

4. Conclusion

In conclusion, controlled human infections with hookworm or schistosomiasis are a valuable tool to advance vaccine development for these neglected tropical diseases. Although limitations of such models need to be recognized, their strengths lie in their ability to efficiently establish preliminary vaccine efficacy and provide insight into immunological responses that could help identify correlates of protection or novel vaccine targets.

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Declaration of interest

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