Most commercially available vaccines work by activating B-cell responses, which result in the long-lasting production of protective antibodies. Widespread use of vaccines has helped to control and even eradicate several devastating infectious diseases, including smallpox, polio, measles, mumps, and rubella. Therefore, vaccines have been acknowledged as one of the major achievements of modern biomedicine. Cutting-edge vaccinology continues to push the boundaries by utilising innovative technologies such as genome-wide sequencing, gene editing, and systems biology to identify novel targets and develop the next generations of vaccines. Despite the enormous success of vaccine therapies, there are currently no licensed commercially available vaccines for any human disease caused by endoparasites. What is the reason for this absence?

Protozoan and metazoan endoparasite infections affect billions of people worldwide, causing extensive morbidity and mortality. Among the infectious diseases caused by unicellular protozoan parasites, malaria (Plasmodium spp) is the largest killer. According to WHO, malaria accounts for approximately 435,000 deaths each year. Other high-burden diseases caused by protozoan parasites include human African trypanosomiasis or sleeping sickness (Trypanosoma brucei), Chagas disease (Trypanosoma cruzi), and cutaneous and visceral (kala-azar) leishmaniasis (Leishmania spp). Diseases caused by metazoan endoparasites also represent a huge public health burden, in particular those caused by infection with helminths, such as schistosomiasis (Schistosoma spp) lymphatic filariasis (Brugia malayi), and hookworm disease (Necator americanus and Ankylostoma duodenale).

Few chemotherapies are available for most of the diseases caused by endoparasites, and for some of these diseases, no chemotherapies are available. In many cases, available drugs present potentially serious side effects and drug resistance has started to emerge. Moreover, several of these endoparasites are zoonotic; therefore, complete eradication will be difficult to achieve. Efforts to control the spread of parasitic infections can be dramatically affected by political instability, as in the case of the recent resurgence in malaria and Chagas disease in Venezuela, reported by The Lancet Infectious Diseases on Feb 21, 2019. Thus, availability of vaccines would dramatically aid in the control of endoparasite diseases by providing long-term protection to individuals and communities.

One of the reasons for the lack of vaccines for endoparasites is plain negligence. Indeed, 11 of the 20 neglected tropical diseases currently recognised by WHO are caused by endoparasites. These diseases mostly affect populations living in poverty, often neglected by national governments, and which do not represent attractive markets for traditional vaccine developers. Therefore, despite the pressing need for vaccines, they have been largely overlooked.

But are negligence and lack of financial incentive the only causes? According to WHO, total funding for malaria control and elimination reached an estimated US $3 · 1 billion in 2017. It could be argued that this investment is still not enough. However, it is certainly not negligible. Indeed, malaria has received considerable attention by both the private and public sector. Recent completion of a phase 3 trial of RTS,S/AS01, the most advanced subunit vaccine for malaria, resulted in approximately 30% protection from clinical infection as evaluated over 4 years. Although promising, this finding lays behind the great successes achieved by other vaccines and suggests that classic vaccination strategies might need a revision in the case of endoparasites.

Nonetheless, there is hope on the horizon, and lessons from research in the malaria field can inform directions in the case of other diseases caused by endoparasites. Field studies have shown that the breadth and magnitude of the antibody response (ie, the extent of antigens targeted by robust antibody responses) correlates with protection from clinical malaria. Thus, a single or a few antigen targets might not be enough to bring about sufficient levels of protection in the case of endoparasites. Instead, complex multi-target vaccine formulations might be required. “Old-fashioned” attenuated parasites might cover this requirement; however, unlike recombinant subunit vaccines, attenuated whole-organism strategies carry intrinsically higher safety risks and present major mass-scale production and distribution challenges. Nonetheless, Sanaria, led by Stephen Hoffman, has produced a purified, aseptic, vialled, and cryopreserved attenuated P. falciparum sporozoite candidate vaccine, which is currently undergoing evaluation (PSPZ vaccine). In addition, a gentamicin-attenuated Leishmania major vaccine is currently being evaluated in a phase 3 study (IRCT20151019024604N3, Kerman University, Iran).

Both protozoan and metazoan parasites have very complex life cycles, in many cases involving different life stages within the mammalian host. Moreover, several protozoan parasites (e.g., Leishmania spp, Plasmodium sp., and T. cruzi, among others) present intracellular forms. In these cases, a cellular immune component in addition to antibodies might be required to achieve full protection. With this in mind, a third-generation therapeutic vaccine for human visceral leishmaniasis and post kala-azar dermal leishmaniasis is currently being evaluated in a phase 2 study (ISRCTN11285604, University of York, UK and Institute of Endemic Diseases and Centre for Tropical Diseases, Sudan). This vaccine candidate was specifically designed to elicit CD8+ T-cell responses to Leishmania donovani. If proven effective, this strategy
might inform the design of vaccines to other protozoan parasites which present intracellular stages.

Several parasite species present different strains. Thus, identifying protective immune responses targeted to conserved antigens might be a promising strategy. In a study published in Nature Medicine on March 19, 2018, Neville Kisalu, Azza Idris, and colleagues reported the isolation of several monoclonal antibodies specific to Plasmodium falciparum circumsporozoite protein from people immunised with the PfSPZ vaccine mentioned above. One of these antibodies conferred high levels of protection in adoptive transference experiments and was shown to bind an epitope highly conserved among thousands of P. falciparum strains. Thus, structure-based vaccine design can help identifying conserved epitopes which represent excellent candidates for next-generation vaccines.

Several endoparasites present rapid antigenic variation, which can affect antigenic offer and, therefore, negatively impact vaccine success. Thus, understanding the mechanisms of antigenic variation can help improve vaccine efficacy. The laboratory led by Hugo Lujan (Catholic University of Cordoba, Argentina) has shown that the underlying mechanism of antigenic variation in the protozoan parasite Giardia lamblia depends on the RNA interference (RNAi) pathway. Vaccination of domestic mammals with a RNAi machinery-deficient mutant G. lamblia strain, which expresses the whole array of variant-specific surface proteins, led to high levels of protection against wild-type parasites. In a report published in Nature Communications on Jan 21, 2019, the same group showed that variant-specific surface proteins are promising tools to improve oral vaccination because of their physicochemical characteristics.

Efforts to develop vaccines to metazoan parasites are also underway. Three different candidate vaccines for urogenital and intestinal schistosomiasis are currently being clinically evaluated (NCT03041766, NCT03110757, and 5R44AI103983-05, USA), and a European consortium is currently working towards the development of the first human hookworm vaccine (Hookvac).

Still, increased efforts to generate vaccines to endoparasites remain urgently needed. Major attention should be paid by those countries of the Group of Twenty (G20) in which populations are particularly affected by neglected tropical diseases. To accelerate advances from basic research to tangible clinical tools, close collaboration and communication between academics, clinicians, governments, and the private sector is key. EBioMedicine aims to be a platform to further communication between these different actors, and welcomes studies aimed at providing novel insights to facilitate the development of tools to control diseases cause by infections with endoparasites.

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