Editorial: Safe and effective treatments are needed for cryptosporidiosis, a truly neglected tropical disease

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Safe and effective treatments are needed for cryptosporidiosis, a truly neglected tropical disease

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Early childhood cryptosporidiosis causes acute disease and mortality, as well as lasting malnutrition and developmental delay. However, there are no safe and effective therapeutics for cryptosporidiosis. Developing such therapeutics will save hundreds and thousands of lives in young children and spare millions of disability-adjusted life years lost (DALYs). This white paper discusses the global public health impact of *Cryptosporidium* infections, the immediate need for more effective treatment of cryptosporidiosis, and recent advances that are yielding multiple promising leads for therapeutic development. We will discuss the remaining challenges, which is to complete the preclinical and clinical steps to bring these novel therapeutics to children in urgent need of treatment.

Diarrhoeal diseases cause unacceptable loss of life, mainly among infants and children in low-income and middle-income countries (LMICs). The Global Enteric Multicentre Study (GEMS) revealed the pathogens associated with diarrhoea in children in LMICs.[1] Of particular prevalence, as cause of severe disease, were rotavirus, *Cryptosporidium spp*, enterotoxigenic *Escherichia coli* and *Shigella*. The parasite *Cryptosporidium* (*C. hominis and C. parvum*) remains one of the most lethal pathogens for malnourished infants and children, with a devastating health impact on those under 2 years of age. The GEMS study estimated about 7.5 million cases of *Cryptosporidium* infection occur every year within this population in Africa and Asia resulting in over 200 000 *Cryptosporidium*-attributable deaths due to moderate-to-severe diarrhoea, with an excess of 59 000 deaths compared with children with similar symptoms that were *Cryptosporidium* negative.[2]

Cryptosporidium infection in these malnourished children is also significantly associated with debilitating stunted growth contributing to excess mortality.[3–6] This *Cryptosporidium*-associated stunting and wasting leads to poor physical and neurological health with poor childhood development, resulting in a lasting effect on population health in LMICs.[5] This burden falls disproportionately on children in sub-Saharan Africa, but also in South America and Asia (figure 1). In 2018, Dr Khalil and coworkers at the Institute for Health Metrics and Evaluation reported that acute *Cryptosporidium* infection was associated with an annual loss of greater than 4.2 million DALYs.[3] Each DALY represents the loss of a full year of healthy life. In 2019, the Global Burden of Disease study revised the number of deaths and DALYs attributable to *Cryptosporidium* to 133 422 deaths and 8.2 million DALYs per year, taking into account both the acute and long-term effects of *Cryptosporidium* infection.[7] To put this in perspective with other diarrhoeal diseases within the same 2019 study, cholera is attributable to less deaths (117 000) and DALYs (7.1 million), and both *Shigella* and Rotavirus were responsible for only slightly more deaths (148 000 and 235 000, respectively) and DALYs (10 million and 17 million).[7] In contrast to cryptosporidiosis, vaccines or treatments are available or in advanced development for these infections. Notably, when comparing *Cryptosporidium* with WHO recognised neglected tropical diseases (NTDs), it greatly exceeds both the deaths and DALYs associated with essentially all of these diseases (figure 2).[8]

Effective treatment to mitigate the impact of cryptosporidiosis on child health and survival is woefully lacking. Nitazoxanide is the only US Food and Drug Administration (FDA) approved therapeutic for treating *Cryptosporidium* infection. It has been shown to be ineffective in immunocompromised individuals

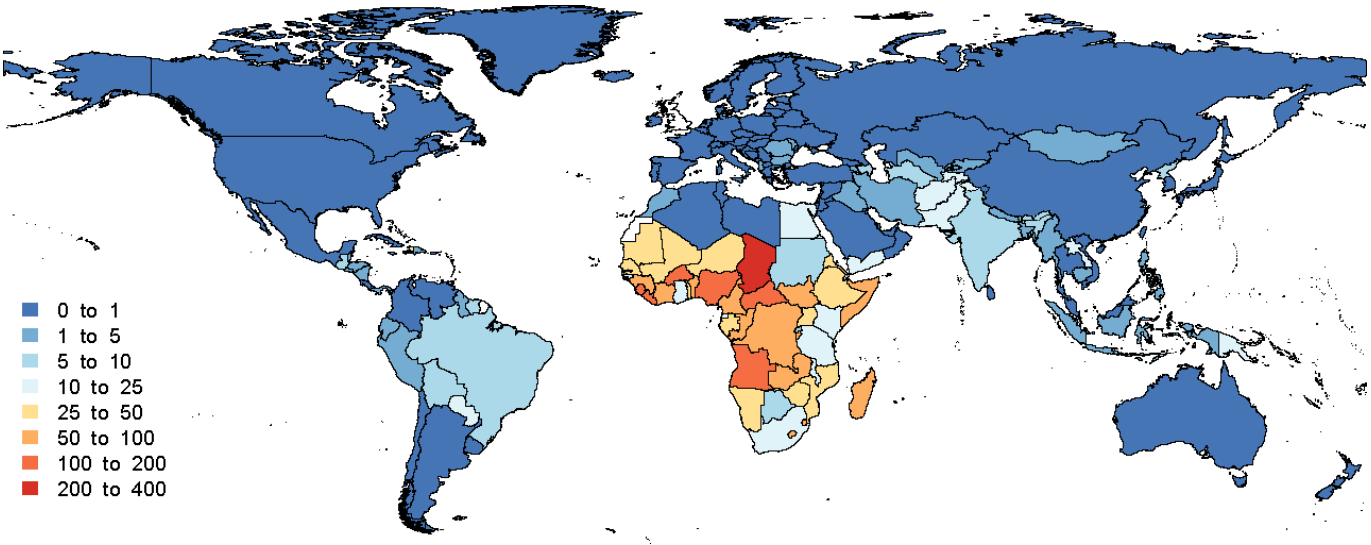

Figure 1 Total (acute and long-term) *Cryptosporidium* DALYs per 1000 child-years among children under 5 (GBD estimates and geographic distribution, Ibrahim Khalil). DALYs after accounting for undernutrition-associated DALYs due to cryptosporidiosis.[7] DALYs, disability-adjusted life years lost; GBD, Global Burden of Disease.

and less than 50% effective in malnourished children less than 5 years old.[9] Nitazoxanide in vitro does have direct activity against *Cryptosporidium*, but only at concentrations much higher than those achieved during therapy. Animal models suggest nitazoxanide likely relies on stimulation of the immune system to expel *Cryptosporidium*. Those most threatened by infection, malnourished children and the immunocompromised cannot mount the immune response required for effective therapy with nitazoxanide.[10 11]

This unmet medical need inspired a recent surge in *Cryptosporidium* research that has yielded the modern experimental tools and facile animal models needed to discover antiparasitic compounds and validate their targets.[12–23] Most importantly, safe and effective compounds in preclinical models with direct action against *Cryptosporidium* have emerged.[13 15 16 18 24–31] This represents a major advance, significantly expanding the quality and quantity of the portfolio. Multiple drug candidates are now progressing towards preclinical development and clinical trials at an uneven pace (table 1). The initial high-risk research that led to these compounds was conducted by multiple academic and industry groups, often with extensive academic and industry collaboration and with governmental and philanthropic support. Now further investments are needed to capitalise on this rich portfolio and accelerate the development and registration of transformative therapies for this largely unmet medical need.

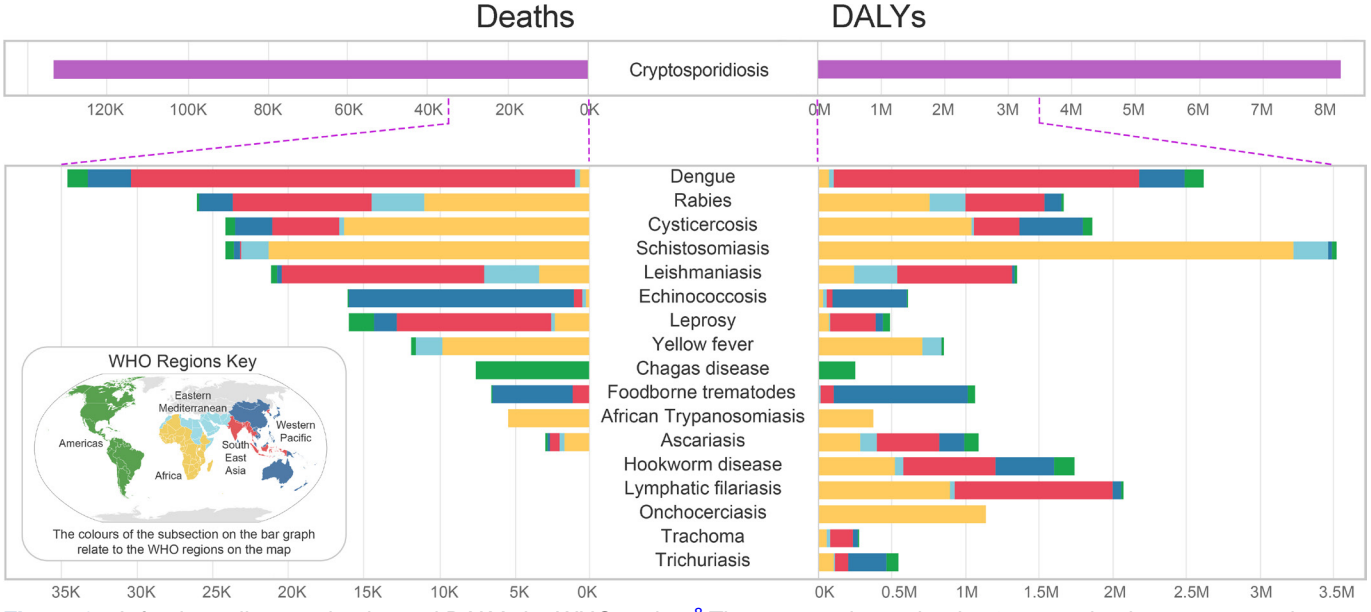

Figure 2 Infectious disease deaths and DALYs by WHO region.[8] There are estimated to be 133 000 deaths per year and 8200K DALYs due to cryptosporidiosis (pink), which greatly exceed the WHO NTDs, note differences in scales. DALYs, disability-adjusted life years lost; NTDs, neglected tropical diseases.

Table 1 Examples of compounds in preclinical development

Inhibitor/compound series	Lead laboratory	Effective in animal models	Stage	References
Phosphatidylinositol 4-kinase	Novartis	Yes	Phase 1 human trials	15
Bumped kinase inhibitors	University of Washington	Yes	Preclinical candidate	26
Lysyl tRNA synthetase	DDU, University of Dundee	Yes	Late lead profiling	13
Benzoxaborole	Anacor, University of Vermont	Yes	Late lead profiling	29
SLU-2633/MMV665917	St. Louis University, University of Vermont	Yes	Late lead profiling	31
Phenylalanine tRNA synthetase	BROAD Institute, University of Vermont	Yes	Early lead profiling	16

A vaccine that prevents *Cryptosporidium* morbidity and mortality would be of great benefit to childhood health in LMICs, and research towards vaccination should be supported. However, natural immunity to *Cryptosporidium* is non-sterile and requires multiple infections, highlighting the parasite's potential to evade immunity. Developing vaccines to address parasitic infections, like *Cryptosporidium*, has been difficult and we are probably at least a decade from having a safe and effective vaccine. Developing a therapeutic will allow us to address child health in LMICs in a much faster time frame. Even after vaccines arrive, there will be a need for drugs because of insufficient protection, lack of coverage and challenges of roll-out and delivery.

Multiple recent efforts centred in academia, industry and in joint venture have produced highly promising late preclinical therapeutic leads that are markedly superior to nitazoxanide in preclinical models (table 1). This is a truly transformative advance in both quality and quantity offering a viable path towards treatment. These compounds now require varying degrees of advanced preclinical testing, and clinical trials performed before they can be deployed. The target population is infants, however, for a proof of concept (phase 2a) study, testing in infants is inadvisable due to safety, pharmacokinetic and ethical challenges. Cryptosporidiosis is typically rare in adults living in high transmission areas due to acquired immunity, except in HIV/AIDS patients. Recent advances in the clinical evaluation of novel antimalarials provide critical guidance forward. Human challenge models using healthy volunteers have proven an invaluable tool[32 33] providing an insight into efficacy without the risks associated with highly vulnerable populations. Multiple such studies have been conducted with *Cryptosporidium* in the past and were found to be safe[34–36] and the model has recently be updated.[37] We support a clinical trial plan proposed in which the proof of concept (phase 2a study) is conducted with volunteers intentionally infected with *C. parvum*, followed by phase 2b and 3 studies in children in endemic areas.[37]

Since malaria and *Cryptosporidium* belong to the same phylum Apicomplexa, they share some conserved drug targets, and thus there is a synergy possibility in research and development of malaria and *Cryptosporidium* therapeutics. But like malaria, *Cryptosporidium* may develop resistance to monotherapy, given the high numbers of parasites during infection. Indeed, emergence of resistance has been documented in the newborn calf model of infection for one compound that targets methionyl-tRNA-synthetase.[38] Therefore, it is probably necessary to take several compounds through clinical development to provide the possibility of combination treatment (table 1). There are also possibilities for synergy with the animal health market, particularly for dairy cattle, where in some areas nearly 100% of newborn calves acquire *C. parvum* infection, and *Cryptosporidium* infection has been shown to lead to lasting weight loss and reduced milk production.[39–41]

A challenge to be addressed is the clinical usage of an anti-*Cryptosporidium* drug. Studies indicate that there are multiple causes of diarrhoea; as indicated above, causative organisms include *Shigella spp,* enterotoxigenic *E. coli*, *Campylobacter jejuni* and rotavirus. There is current compelling evidence of unmet therapeutic need for enteric cryptosporidiosis found in three patient groups: (1) young children aged 0–24 months in LMICs; (2) malnourished children under age 5 and (3) immunosuppressed individuals of any age.[42 43] A recent publication outlines an effective therapeutic could be used to reduce the large burden of *Cryptosporidium* in LMICs (table 2).[42] *Cryptosporidium* therapy could be used syndromically, for instance in children less than 2 years old with moderate-to-severe diarrhoea, probably combined with an antibacterial to cover the major treatable causes, *E. coli*, *Shigella spp.* and *C. jejuni*. Treatment could be carried out with a diagnostic, such as a point-of care rapid antigen detection test, or a PCR, similar to that used in SARS-CoV-2 detection. This diagnostic-directed therapy might be especially helpful in malnourished children less than 5 years old, where asymptomatic and mildly symptomatic *Cryptosporidium* has been shown to be highly associated with poor outcomes, such as stunting, poor physical and mental development and excess deaths from other causes. These diagnostic tools are available now, and the rapid antigen detection test can be done at small village clinics where sick and malnourished children are first

Table 2 Use case scenarios for an anti-*Cryptosporidium* therapeutic for LMICs adapted from[42]

Target population	Disease burden	Potential treatment sites	Potential treatment strategies	Current applicability: nitazoxanide
Young children aged 0–24 months	7.5 million cases with moderate-to-severe diarrhoea,[2] 133 000 deaths and 8.2M DALYs annually in LMICs[7]	Primary, secondary and tertiary health facilities in LMICs	Diagnosis-based treatment	Not approved in children under 12 months, only ~30% efficacy in malnourished[9]
			Empiric treatment in high-risk populations where diagnostic tools are not available	Insufficient evidence and guidelines
		Community based treatment	Mass drug administration in seasons with high prevalence	Insufficient evidence and guidelines
Malnourished children	Estimated 50 million wasted children globally.[45] Recent studies indicate 10%–20% prevalence of cryptosporidiosis in children with acute malnourishment.[9 46–48]	Primary, secondary and tertiary health facilities in LMICs. Malnutrition care centres in clinics and hospitals	Diagnosis-based treatment	Poorly effective (~30% efficacious)[9]
			Empiric treatment in high-risk populations where diagnostic tools are not available	Insufficient evidence and guidelines. Nitazoxanide poorly effective[9]
Immunocompromised patients	Estimates range from 5% to 50% of PLWHA and up to 30% of solid organ transplant recipients.[49–53]	Primary, secondary and tertiary health facilities in LMICs. HIV/AIDS treatment programmes. Transplant centres in any global setting	Diagnosis-based treatment	Poorly or non-effective for PLWHA[9 43 54]
			Empiric treatment in high-risk populations where diagnostic tools are not available	Insufficient evidence and guidelines Poorly or non-effective for PLWHA[9 43 54]

Adapted from Ashigbie *et al.*[42]
DALYs, disability-adjusted life years lost; LMICs, low-income and middle-income countries; PLWHA, people living with HIV/AIDS.

seen. In the event that a compound or combination with appropriate safety profile can be developed, mass drug administration could be used, particularly given the high infectivity of the parasite and the fact that many infants are likely to be chronically infected.

Beyond this, the authors believe that *Cryptosporidium* should be formally recognised as a NTD by the WHO, for its major impact is in LMICs and predominantly affects infants and young children. As noted above, *Cryptosporidium* has a very significant impact compared with many other NTDs currently listed by the WHO (figure 2). This status will bring the critical medical need of *Cryptosporidium* treatment to the attention of funding bodies, foundations, international health organisations and pharmaceutical companies. *Cryptosporidium* should also be on the list of tropical infections eligible for a priority review voucher (PRV) by US FDA.[44] The PRV programme has proven to be an important financial incentive to pharmaceutical companies wishing to develop drugs for NTDs.

There are some exciting compounds at a later preclinical or early clinical stage. This calls for more funding to move these leads into clinical trials, to properly evaluate the effect that they will have on millions of people (primarily infants and young children). Going into the clinic will enable us to determine the profile of a drug that can have clinical impact and to establish a way for its use.

Thus, in summary, using either deaths or DALYs as parameters, the unmet medical need for *Cryptosporidium* infection exceeds that of most NTDs and causes a huge impact on Africa and Asia. The current therapeutic available is inadequate for the vast majority of this unmet medical need. Tenable use case scenarios exist for how more effective therapeutics for *Cryptosporidium* infection could be deployed to reduce deaths and DALYs. *Cryptosporidium* should be recognised as a major unmet medical need and designated a NTD by the WHO and as a tropical disease with PRV status by the US FDA. The fastest way to address the unmet need is to close funding gaps in preclinical candidates and clinical trials, and this should lead to an effective *Cryptosporidium* therapeutic in a few years.

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