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PROTOZOA (L BARTELT, SECTION EDITOR)

The Global Burden of Pediatric *Cryptosporidium* Infections

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Abstract Cryptosporidiosis has been identified as a leading cause of diarrhea in young children worldwide. Infection results in significant short-term morbidity as well as long-term sequelae. Recent advancements in molecular diagnostics used in large multicenter prospective studies have led to the discovery that burden of *Cryptosporidium* disease is higher than previously recognized; however, the implications of this discovery are not fully understood. Epidemiologic studies suggest infection impacts long-term growth; however, the mechanisms driving this vicious cycle have yet to be elucidated, and it remains to be seen why malnutrition renders such high susceptibility to *Cryptosporidium*. Whole-genome sequencing has refined classification of anthroponotic and zoonotic strains and may shed light on novel modes of transmission and species -specific pathogenicity. As *Cryptosporidium* has been recognized as a significant pathogen with implications on child health it challenges us to determine the mechanisms of pathogenesis for this difficult to study parasite and also enforces the need to continue advancing innovative technologies in resource-limited settings to curb the impact of this neglected tropical disease.

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Introduction

The apicomplexan protozoan *Cryptosporidium* spp. is the agent of cryptosporidiosis, best known for causing diarrhea in malnourished children and individuals living with HIV/AIDS. Due to the parasite's widespread global distribution, environmental hardiness with zoonotic potential, high rates of waterborne transmission in low resource settings, insufficient diagnostics, and lack of highly effective targeted therapy or vaccine, *Cryptosporidium* joined the list of neglected tropical diseases in 2006. Advancements in diagnostics since that time have revealed that the burden of *Cryptosporidium* is greater than previously recognized, including new associations attributing *Cryptosporidium* as a major cause of moderate to severe pediatric diarrhea, mortality, and chronic long-term sequelae. While advancements have been made in the study of *Cryptosporidium* biology, pathogenesis, immune response, and transmission, several limitations including a paucity of experimental models continue to limit understanding of the parasite [1]. In this edition, we will review updates in our understanding of the impact of *Cryptosporidium* on children and then address important advancements and technologies, remaining knowledge gaps, and strategies towards achieving the goal of reducing the burden of *Cryptosporidium*.

Endemic and Resource-Limited Settings/Morbidity and Mortality

While advances have been made in reducing the mortality related to infectious diarrhea, largely due to improved efforts

of symptomatic therapy with oral rehydrating solutions and intensified community-based care, the frequency of enteric pathogen exposure and long-term morbidities related to these infections remains high. In 2008, the United Nations estimated 4.4 million deaths in children under age five, with diarrheal disease and pneumonia as the leading causes of death [2]. Furthermore, diarrheal disease in early childhood has been associated with delayed age of starting school, cognitive impairment, decreased work productivity, and growth short falls [3–6].

It is now understood that the etiology of diarrhea in children living in low-income countries can be attributed to multiple enteropathogens due to lack of adequate sewage systems, overcrowding, and lack of access to potable water. In a prospective analysis examining both diarrheal and non-diarrheal stool specimens from children in Bangladesh, Taniuchi et al. recently identified not only diverse sequential enteropathogen exposures but the presence of greater than three different infectious agents per diarrheal episode [7]. There is growing evidence that certain pathogens are responsible for the greatest burden of diarrheal disease. *Cryptosporidium* is now recognized as one of these major diarrheal-associated pathogens across multiple recent studies [8••, 9, 10].

Many recent studies from South Asia and Africa have identified high rates of cryptosporidiosis in young children [11•, 12]. In India, it is estimated that cryptosporidiosis is responsible for up to 249,000 hospitalizations and 14,600 deaths per year in children under the age of two [11•]. The largest prospective study of pediatric morbidity and mortality from diarrhea to date, the Global Enteric Multicenter Study (GEMS), a case–control study over the first 3 years of life across seven different sites, with almost 500,000 child-years of observation, sought to identify leading etiologies of diarrhea in young children. GEMS demonstrated that *Cryptosporidium* species were responsible for the highest burden of diarrhea, second only to rotavirus. Furthermore, despite implementation of World Health Organization recommended management of diarrheal disease, *Cryptosporidium* was among the leading pathogens associated with prolonged symptoms and stood alone with increased mortality risk in children ages 12–23 months [8••].

In children, infection with *Cryptosporidium* spp. has been associated with prolonged diarrheal episodes lasting longer than 7 days [13–15]. Perhaps, even more important, earlier studies from Peru and Brazil suggest association of infection with long-term sequelae on child growth and development. In Peru, children with *Cryptosporidium* infection had persistent growth short falls 3–6 months after infection [16]. In Brazil, Guerrant et al. reported that *Cryptosporidium* infection during the first 2 years of life was significantly associated with decreased physical fitness 4–7 years later [4]. More recently, a larger cohort study from Bangladesh has described a significant association of infection in the first 2 years of life and stunted growth at age two (Korpe et al., unpublished).

Beyond these epidemiologic associations, we are lacking in studies in humans that might shed light on the mechanism between infection and malnutrition. In vitro and animal studies suggest a role between infection and inflammation causing deranged immune signaling leading to enteropathy and poor growth [17–19]. These models, which need further validation in human studies, demonstrate that specific nutrient deprivation has a profound impact on the character and intensity of inflammation [19, 20], such as an apparent bias away from Th1-type primary immune responses (Bartelt, unpublished) similar to what has been shown in malnourished children in Haiti with cryptosporidiosis [21]. Also, the field observation that the *APOE4/4* allelotype was protective against early childhood diarrhea and the cognitive impacts in malnourished children [22] was also shown to protect malnourished transgenic mice from weight loss and parasite burden following *Cryptosporidium parvum* challenge [23].

The impact of cryptosporidiosis may be much larger than what is apparent by measuring diarrheal burden alone. In a study of almost 400 children in Bangladesh, over 70 % of children had at least one non-diarrheal infection with *Cryptosporidium* during the first 2 years of life [24]. In Southern India, a study of 186 young children documented asymptomatic infection in 60 % [25]. And asymptomatic *Cryptosporidium* infection has also been documented at high rates in adults in endemic regions [26].

With the advent of molecular diagnostics, we are better able to detect enteric pathogens in stool and, in particular, describe otherwise difficult to detect organisms like enteric protozoa with far greater granularity than ever before [27]. While quantitative molecular diagnostics can associate parasite burden with severity of diarrhea during cryptosporidiosis [28••], what is the significance of low burden detection in asymptomatic children living in endemic countries? Is this simply a symptom of highly sensitive diagnostic techniques? Increasingly, there are findings to suggest when it comes to *Cryptosporidium* infection in young children; even non-diarrheal detections cannot be ignored. Few studies have suggested a relationship between non-diarrheal infection and poor growth [16]. In Bangladesh, children with non-diarrheal infection have twice the risk of becoming stunted compare to children without infection (Korpe, Duggal, Petri, unpublished). The impact of non-diarrheal infection on a child's growth and developmental potential need further study, since the burden of non-diarrheal infection in children in low-income countries is so great. Additionally, the asymptomatic carriage of *Cryptosporidium* may provide a greater reservoir for spread of infection.

Table 1 Most notable insights into *Cryptosporidium*

	Reference
Cryptosporidiosis is a leading cause of morbidity and mortality from diarrhea in children under five.	[8••]
Country-wide estimate of *Cryptosporidium* burden shows that *Cryptosporidium* spp. is responsible for almost 15,000 deaths per year in children under two in India.	[11•]
Advanced molecular diagnostics demonstrate that burden of parasite correlates with phenotype of disease.	[28••]
Genotyping of *Cryptosporidium* spp. identifies unique risk factors for infection.	[40•, 41•]

Transmission

In addition to significant morbidity due to *Cryptosporidium* infection, children likely play an important role in the transmission cycle. *Cryptosporidium* is transmitted by fecal-oral spread and poses a challenge to public health systems due to resistance to chlorination and low infective dose. Sporadic outbreaks have been associated with contaminated water supplies [29] and notoriously in swimming pools [30]. However, in impoverished settings, direct anthroponotic or zoonotic spread may play a larger role than waterborne disease. A study from India demonstrated that households given bottled drinking water had just as high rates of cryptosporidiosis as households that used the municipal water supply, indicating that water source made no difference in risk of infection [26].

Using a serum IgG ELISA to the *Cryptosporidium* gp15 protein, it was determined that most children in South India experience their first exposure between 3 and 9 months of age, presumably prior to the introduction of non-breast milk supplementary food and water [31]. A 1994 study in Brazil identified a secondary attack rate of 39 % in households with a child infected with *Cryptosporidium*. However, only half of these secondary cases manifested with diarrhea; the others had asymptomatic carriage [32]. An outbreak in Norwegian school children demonstrated a secondary attack rate of 17 % [33]. Additionally, living in a

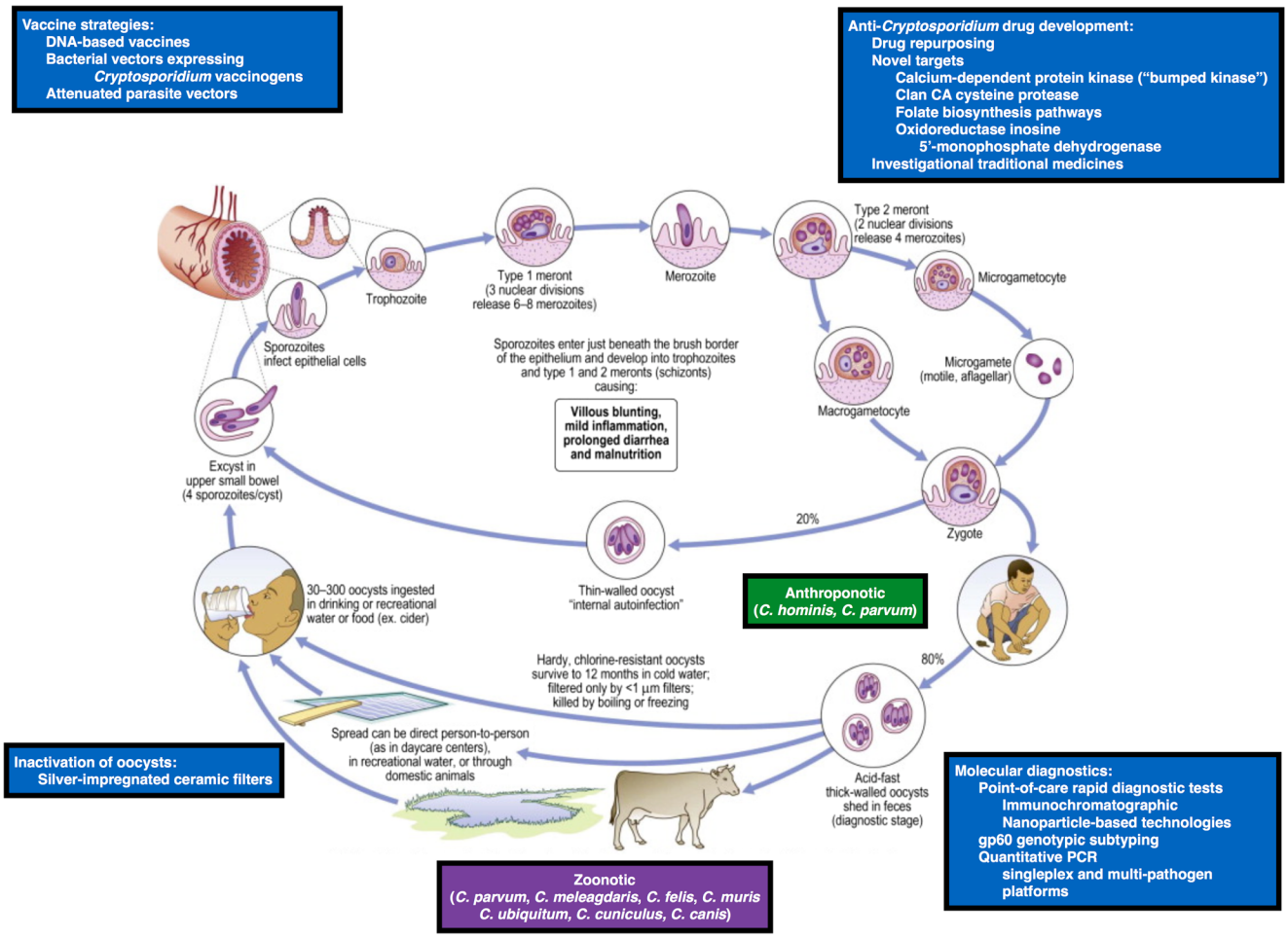

Fig. 1 The life cycle of *Cryptosporidium* and examples of investigational approaches to treat and control disease transmission. Adapted from "Cryptosporidiosis" Lima, Samie, and Guerrant in Tropical Infectious Diseases: Principles, Pathogens, and Practice, 3rd Edition, Guerrant, Walker, Weller editors

household with young children has consistently been identified as a risk factor for infection [11•, 34]. Thus, person-to-person spread likely plays an important role for spread of disease among children.

Furthermore, genotypic analyses demonstrate that despite close contact with domestic animals, anthroponotic spread may play a larger role in transmission, even among communities involved in animal husbandry [35–38].

In addition to fecal-oral spread, there is now emerging evidence that *Cryptosporidium* spp. may be a respiratory pathogen. Among children presenting with diarrhea to an acute care center in Uganda, 1/3 of children with *Cryptosporidium* infection also had sputum positive for *Cryptosporidium* by PCR [39•]. In Bangladesh, children presenting with *Cryptosporidium* diarrhea were over 2 times more likely to have concurrent pneumonia compared to children with non-cryptosporidium associated diarrhea (adjusted Odds Ratio 2.7, CI 1.04, 7.2, p =0.04)[Leung DT, Das SK, Malek MA et al., in press]. Therefore, respiratory spread may be an overlooked source of *Cryptosporidium* transmission.

Strain and Species Variability

To date, over 26 species in the genus *Cryptosporidium* have been described, with even further diversity within species. Advanced genotyping techniques are improving our understanding of the global distribution of specific subtypes (see Table 1 in accompanying article by Samie et al.) and may provide insight into species specific pathogenicity. For example, *C. parvum* has been associated with zoonotic transmission, but Widmer et al. applied whole-genome sequencing to determine that *C. parvum* isolate TU114 has more similarity to the anthroponotic *Cryptosporidium hominis*, explaining differences in this isolate's host range [40•]. In addition, molecular work has helped to better define risk factors for infection [42]. Chalmers et al. genotyped over 8000 *Cryptosporidium* isolates and found that a majority were *C. parvum* or *C. hominis*, and less than 1 % were six other species. In this study, *C. parvum* infection was associated with younger age, and *C. hominis* was associated with recent travel [42]. Molecular techniques have also paved the way for identification of other species that infect humans, such as the cervine genotype, *Cryptosporidium ubiquitum* [41•].

Furthermore, we now see differences in geographic distribution of species and genotypes by subtyping of gp60 polymorphisms. In Spain, *C. hominis* 1bA10G2 was the predominant subtype identified [43]. In contrast, a long-term study of Bangladeshi children identified *C. hominis* subtypes *Ie* and *Id* in greater than 90 % of samples tested [Gilchrist, Petri, personal communication]. Further studies are needed to determine how subtype predicts pathogenicity and whether cross-immunity exists between subtypes.

Conclusion

The important impact of *Cryptosporidium* on the health of children living in under-resourced settings continues to be reinforced and refined [1, 44]. The burden of *Cryptosporidium* challenges our current best advances in supportive care for diarrheal diseases, pathogen detection in human stools and environmental samples, transmission of waterborne and fecal-oral enterics, and understandings of immunity to pathogens in intestinal mucosal compartment. This edition addresses examples of advances and strategies for responding to this heavy burden of *Cryptosporidium* through the application of improved and accessible point-of-care diagnostics for both clinical means and water quality testing measures, interrupting the *Cryptosporidium* transmission cycle, targeted anti-cryptosporidium drug development, and novel approaches to vaccine development (Fig. 1).

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008. With regard to the authors' animal research, all institutional and national guidelines for the care and use of laboratory animals were followed.

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