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Epidemiology and control of human gastrointestinal parasites in children

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Abstract

Parasites found in the human gastrointestinal tract can be largely categorized into two groups, protozoa and helminths. The soil-transmitted helminths (*Ascaris lumbricoides*, hookworm and *Trichuris trichiura*) are the most prevalent, infecting an estimated one-sixth of the global population. Infection rates are highest in children living in sub-Saharan Africa, followed by Asia and then Latin America and the Caribbean. The current momentum towards global drug delivery for their control is at a historical high through the efforts of numerous initiatives increasingly acting in coordination with donors, governments and local communities. Together, they have delivered enormous quantities of drugs, especially anthelmintics to children through nationwide annual or biannual mass drug administration largely coordinated through schools. However, a much larger and rapidly growing childhood population in these regions remains untreated and suffering from more than one parasite. Mass drug administration has profound potential for control but is not without considerable challenges and concerns. A principal barrier is funding. Stimulating a research and development pipeline, supporting the necessary clinical trials to refine treatment, in addition to procuring and deploying drugs (and sustaining these supply chains), requires substantial funding and resources that do not presently exist. Limited options for chemotherapy raise concerns about drug resistance developing through overuse, however, satisfactory pharmacoepidemiology and monitoring for drug resistance requires more developed health infrastructures than are generally available. Further, the

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limited pharmacopeia does not include any effective second-line options if resistance emerges, and the research and development pipeline is severely depressed. Herein, we discuss the major gastrointestinal protozoa and helminths reviewing their impact on child health, changing epidemiology and how this relates to their control.

Keywords

cestodes; child health; children; drug resistance; epidemiology; helminth; intestinal; mass drug administration; nematodes; parasite; pediatric; protozoa; public health; soil-transmitted helminths; trematodes

Gastrointestinal (GI) protozoa and helminths (Table 1) flourish in settings characterized by warm temperatures, humidity, poor sanitation, dirty water, and substandard and crowded housing. Infection rates are highest in children living in sub-Saharan Africa (SSA), followed by Asia and then Latin America and the Caribbean (LAC) [1,2]. In SSA, it is estimated that approximately a quarter of the total population is infected with one or more helminths, typically the nematode worms, which are the most prevalent of all GI parasites [1,2]. The 2006 estimates propose that of the then 181 million school-aged children in SSA, almost half (89 million) were affected by one or more of these parasitic worms [2,3]. While whole populations will be geographically at risk, children are observed to disproportionally carry the greatest burden of infection [2,4–6]. This disproportion has behavioral, biological and environmental bases. Children tend to be more active in the infected environment and rarely employ good sanitary behaviors. Frequently, these potential carriers are crowded together for large periods of time (e.g., schools, orphanages or slums), increasing the likelihood of transmission or environmental contamination with the parasite. In addition, helminths are “masterful immunoregulators” [7], able to elicit a complex and mixed Th1/Th2 response that both wards off and subverts an immune response from the human host for months or even years.

While evidence of many of these parasites can be found in the oldest human civilizations, including their presence in mummified feces, writings of Hippocrates and in the Ebers Papyrus, a medical treatise from 1500 BC [8–11], our knowledge of how these parasites modulate and sustain host–parasite relationships and their complex interplay with human immune systems has only begun to emerge in recent years and is far from complete [12]. This is partly attributable to the fact that these parasites had been largely brought under control in wealthier Europe and the USA during the time of their sanitation revolution at the turn of the 19th Century [13]. Consequently, the biomedical era of vaccines and therapies in the mid-1900s left these parasites neglected, with only a small number of basic science laboratories having any interest in them. Until fairly recently, these parasites have silently ravaged the worlds most impoverished. However, the recent surge of donor activity and government action towards improving global public health is encouraging [14–16].

This renewed attention is desperately needed as the tendency for infection to be in children is particularly concerning since the population structure of endemic regions is predominantly under the age of 14 years [201]. As a result, children are the primary sufferers, an essential vector for the reintroduction of the pathogens to the local environment and, consequently, the focus for control initiatives for GI parasitic diseases. Another important group for consideration is pregnant women since one-quarter to one-third are also heavily infected with hookworm in SSA [17]. Exacerbating the large numbers at-risk in SSA, Asia and LAC is the intense level of poverty in these regions. Almost all of the ‘bottom billion’, that is, the estimated 1.4 billion people who live below the World Bank poverty level of US$1.25 per day, live in SSA, Asia and LAC, and almost all of the children of the bottom billion are infected with one or more GI parasites [18]. Given the current population structure, the focus and concern for these parasites

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on human and child development becomes ever more urgent [19]. The social and economic impact of chronic GI parasites on human development (e.g., malabsorption, malnutrition and resultant stunting, and chronic anemia) and capacity (e.g., diminished cognition, missed school and inability to work) can destabilize endemic communities and reinforce local poverty. This consequently hinders national and regional economic development out of poverty [18,20,21]. Our failure to improve the situation for these communities continues to limit global development and attainment of the Millennium Development Goals.

Global epidemiology

GI parasites are infectious diseases of poverty. Thus, while still found in North America and Europe, their prevalence is highest in areas of intense poverty in low- and middle-income countries in the tropical and subtropical regions of SSA, Asia and LAC [2,3,22–26]. In North America and Europe, these infections are most prevalent within immigrant and refugee communities [27–29]. In a general sense and compared with the nematode worms, the epidemiological data for GI protozoa, cestodes and trematodes (excluding schistosomiasis) is limited, none of which have been studied systematically or included in any of the Global Burden of Disease studies [202,203]. Accurate figures for the prevalence of these infections are almost impossible to obtain, and despite their relative low frequency compared with the nematodes, they can cause significant morbidity and mortality in a large number of individuals [30].

Protozoa

GI protozoa cause significant morbidity in children and as opportunistic infections in HIV/AIDS and immunosuppressed patients in developing countries who are already malnourished or have limited access to medical services [31]. Consequently, these patients will suffer from repeated severe diarrheal episodes that can be fatal [32–36]. *Giardia* cysts are highly resistant to environ mental conditions, being able to survive in cold mountain streams, stomach acid, chlorine and even in UV-treated wastewater [37–39]. *Giardia* is consequently the cause of many of the outbreaks occurring in recreational water facilities [40]. Acknowledging the resilience of these cysts, it is conceivable that protozoan infections are much more frequent in settings of tropical poverty than estimated, even in the absence of reported outbreaks and epidemio logical surveys [41,42]. Outbreaks (along with an increase in bacterial infections such as cholera) occur in periods of heavy rain when water management systems are overwhelmed, such as the annual floods in Bangladesh or India.

Amoebic dysentery from *Entamoeba histolytica* is the second most common cause of death from parasitic disease worldwide after malaria [43–45]. It is estimated that *E. histolytica* infects 40–50 million people and results in approximately 100,000 deaths annually worldwide [46–48]. However, these numbers are somewhat dated, and partly estimated based on data using diagnostic methods that did not effectively differentiate *E. histolytica* from the nonpathogenic *Entamoeba dispar*. Outbreaks, which often provide the best epidemiological evidence for cryptosporidiosis and giardiasis, tend to be associated with municipal and recreational water systems [49–56] and crowded human ecologies, such as daycare centers [57–60], orphanages [61] or slums. *Cryptosporidium* and *Giardia* are potential zoonotic threats from commercial livestock [62–64] and domesticated animals [65,66]. This is a factor to consider with children living in more impoverished settings where animals and livestock are closely integrated in the community.

Nematodes

There are dozens of species of nematode worms; however, only a small subset accounts for their enormous amount of human infection. Known also as the soil-transmitted helminths (STHs), *Ancylostoma duodenale*, *Necator americanus*, *Ascaris lumbricoides* and *Trichuris*

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trichiura are among the most prevalent organisms on the planet, estimated to infect almost one-sixth of the global population [18]. We know that burdens are high in children, primarily owing to the large array of surveillance and control activities occurring in school and public education systems in endemic countries. The dynamics of infection throughout life, however, are less well known as data tend to be scattered, dated or based on small sample populations (see for example the review of studies in [67]). However, we can see that on a very basic level for the intestinal nematodes, the prevalence curves for *A. lumbricoides* and *T. trichiura* follow very similar lines with a steady rise from infancy to mid teens, and then declining into the adult age classes. This is different from the hookworms (although *Necator* and *Ancylostoma* differ somewhat), as they can begin in early childhood and adolescence but then rise through adult life either reaching a plateau or only declining from 40 years or so. There are, to our knowledge, no data on age-associated prevalence or intensity for human *Strongyloides stercoralis* in the literature, and all STHs present challenges of interpreting worm burden from the diagnostic tests used [68].

One feature of nematodes that must be considered given their estimated global prevalence is the connection between the prevalence and intensity of infection. While prevalence represents the population affected with anything from one (asymptomatic infection) to thousands (heavy infection) of worms, the number of false negatives depends on the diagnostic method used. However, morbidity is dependent on infection intensity, and most worm burdens are highly over-dispersed with a theoretical proportion of 80% of all worms in less than 20% of those infected. Thus, while you might have a prevalence of 80%, measurable morbidity would only be present in perhaps 15%. Most diagnostic methods provide indirect measures of infection, relying on the presence of eggs in the feces, and at best are only semiquantitative, since the relationship between egg output and the number of adult worms is complex. A Kato–Katz test will probably only pick up 50% of all low-intensity infections, while a concentration test has much higher sensitivity, and PCR-based tests are the most sensitive. Thus, the reported prevalence will be dependent on test sensitivity [69]. The development of improved quantitative diagnostics, capable of field implementation in resource-poor settings, is central to effective monitoring for resistance in addition to enhanced understanding of the epidemiology of nematodes.

Cestodes

In general, little is known about the global epidemiology and burden of disease due to cestodes (tapeworms). It has been suggested that cestode infection is not frequent in children living in tropical poverty as they have limited access to meats that serve as sources of infection [67]. In addition, there are low rates of tapeworm infections in large Muslim populations in parts of Asia and Africa. However, there are reports from communities in Africa [70–74] and South Asia [75–79], suggesting that intestinal cestode infection is a concern in these regions. While detection of *Taenia* in stools is not common, the incidence of neurocysticercosis (larval *Taenia solium* infection) can be an indicator of the presence of this tape worm, and is a leading cause of epilepsy in the developing world [72,80–82].

Trematodes

Humans become infected with intestinal flukes by consuming food or water that is contaminated with intermediate hosts such as infected fish and aquatic animals (e.g., crustaceans and clams). Death from infection is rare, and light infections can be asymptomatic. However, heavy worm burdens can cause cachexia and prostration. The major intestinal flukes include fasciolopsiasis (*Fasciolopsis buski*), heterophyiasis (*Heterophyes heterophyes*), metagonimiasis (*Metagonimus yokogawai*) and echinostomiasis (*Echinostoma ilocanum*).

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In addition, *Schistosoma mansoni* and *Schistosoma japonicum* can cause severe intestinal complications. They are, however, blood rather than intestinal flukes and live in blood vessels, but their eggs penetrate into the intestine causing intestinal damage, portal hypertension, and progressive enlargement of the liver and spleen. The number of children in the overall population suffering from intestinal schistosomiasis is unknown. *S. mansoni* is found in SSA, Eastern Mediterranean and LAC, and *S. japonicum* found in Southeast Asia and in the Western Pacific region can cause intestinal schistosomiasis [83]. A recent review suggests that other trematode infections such as fascioliasis and clonorchiasis (neither are strictly intestinal flukes, since they live in the biliary system, but may serve as an indicator of existence of other flukes in an ecosystem), while infrequently discussed, are increasing in global prevalence with approximately 750 million people at risk of infection [84], especially in Asia. How this correlates with the health impact of intestinal trematodes has not yet been studied.

Increasing importance of urban foci

There appears to be a shift in the epidemiology of some of these parasites related to population growth and crowded living conditions in urban and slum environments [85–87]. This shift requires further understanding to enable control efforts to advance in urban settings [2]. Many diseases, especially helminths, have historically occurred mainly in rural populations. However, in several low and middle-income countries [88–91], urban migration has led to the creation of urban squatter settlements with high rates of polyparasitism with both protozoa and helminths. Studies on urban ecology highlight general risk factors for polyparasitism in these settings [92,93]. These include houses without cemented floors, lack of health and hygiene education (e.g., use of soap), lack of clean piped water, poorly maintained latrines and children walking barefoot. While urbanization can promote access to health services and public works, overcrowding and poor sanitation will lead to higher infection rates through closer proximity of the infected to larger vulnerable populations. Some parasite transmission will thrive in these urban conditions, especially the protozoa (*Giardia* and *Cryptosporidia*) and helminths such as *A. lumbricoides* and *T. trichiura* [2], while others such as the hookworms will be less affected.

Impact on child health & development

Generally, symptoms signaling the presence of a GI parasite are related to the intensity of infection. Thus, a light protozoan or helminth infection is often asymptomatic whereas a mild to heavy infection can be associated with painful and severe symptoms. However, subtle damage and dysregulation can occur in the absence of any noticeable infection. For example, it has been observed that minor levels of GI nematodes impair functions such as milk production in animals [94,95]. Summary findings of two major studies of the literature [67,96] found that in humans:

- The effects of GI parasites depend on the species, the mixture of species, the duration of infection and the number of worms;
- The distribution of worms among hosts is highly skewed such that a minority of individuals, almost entirely young, have moderate-to-heavy infections and are more likely to be clinically affected;
- The intensity of infections depends on the size and nutritional status of the host;
- Treating worms can lead to improvements in growth and nutritional status, but deworming alone does not treat any underlying nutritional deficits that have been caused or made worse by infection.

The predominant mechanisms by which GI parasites harm human hosts are by:

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- Feeding on host tissues, including blood, leading to a loss of iron and protein (especially with hookworm);
- Causing maldigestion or malabsorption of nutrients;
- Provoking inflammatory responses that may affect appetite and food intake or modify the metabolism and storage of key nutrients such as iron;
- Eliciting typical responses to infection, such as fever and increased metabolic rate;
- Eliciting immune responses to infection (which results in the diversion or use of nutrients and energy for purposes that would not have been necessary had worms not been present).

While it is likely that impaired child development operates through the mechanisms outlined above, the causal links underlying stunted physical and intellectual development are still not well established.

Polyparasitism, or coinfection with either multiple GI helminths and/or protozoa in the young is widespread [97–106]. There is also evidence of *Plasmodium* (malaria)–helminth coinfection across SSA that is associated with exacerbated anemia [107–109]. Coinfection between the helminths themselves or with protozoa and the synergistic impact on the health and nutritional status of the host is not well understood and is understudied [110–112]. Some research has shown that coinfection with hookworm and either *S. japonicum* or *T. trichiura* is associated with higher levels of anemia than would be expected with single infections [113]. Individually, it has been well documented that persistent infection with a nematode can impair physical [114] and mental growth [115,116], and affect the nutritional status [114] and general development of children [117–124]. Similarly, there are few studies on the impairment of human or child development caused by chronic infection with protozoa. In one study, children with *E. histolytica*-associated diarrhea during the first 2 years of life were 2.93-times more likely to be malnourished and 4.69-times more likely to be stunted [125]. Another study demonstrated that malnutrition and amoebic dysentery were associated with cognitive deficiencies [126]. Studies of *S. japonicum* (one cause of intestinal schistosomiasis) in children have shown that infection causes anemia and can severely disrupt the nutritional status of the host [127–129]. To our knowledge, the specific impact of cestodes and trematodes on children and adolescents has not been studied longitudinally, specifically or systematically. However, it is conceivable, given the known consequences of GI infection generally such as malabsorption and malnutrition, that medium- to high-intensity infections would have similar effects on a child.

Burden of disease

In setting public-health priorities and policy, metrics for assessing and comparing relative burdens of different diseases are often employed. Often called ‘summary measures of population health’ (SMPH), these metrics have driven the Global Burden of Disease program, which is now undergoing a major revision and update. There is ongoing dispute that metrics such as the disability-adjusted life year (DALY) do not capture the true impact of these diseases and their subtle morbidities on human development and endemic communities [130]. This failure partly contributes to sustain their neglected status, thus delaying the necessary global attention to escalate efforts toward their control. Although calculations of years of potential life lost (YLL) and DALYs are useful, they are limited in their account of the spectrum of economic and public-health burdens of GI parasites, particularly when applied in resource-poor settings [131]. Furthermore, these metrics have only been calculated for the nematodes and schistosomiasis. The numbers derived for these parasites are considered to be low as they rarely cause death, which is heavily weighted in these metrics, but rather persist chronically, making their burden difficult to quantify. For example, estimated intestinal nematode-related

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deaths vary widely from 12,000 to 135,000 and consequently DALY estimations range from 4.7 to 39 million [4].

The protozoa are driven much more by basic sanitation and other environmental factors. Thus, point incidences fluctuate wildly depending on season, weather, sanitation, nutrition and other factors. As protozoan infections are not chronic infections in general, prevalence figures do not mean much. Most protozoa represent a public-health threat because of their water- and/or food-borne transmission. Owing to the dynamics of protozoa infections, SMPH provide little in terms of quantifying their impact. This, unfortunately, can undermine the attention and importance paid to some diseases. The same could be said about cestodes and trematodes for which our knowledge suffers from a lack of epidemiological data and systematic investigation.

Furthermore, SMPH ignore the impact of polyparasitism and coinfection on human and child development [130], yet mixed GI protozoan and helminth infection, as discussed previously, is widespread and a common characteristic of children living in the tropics and subtropics.

Prevention, treatment & control

Typical public-health interventions (such as the provision of clean water, community health education, observation of food hygiene, and maintenance of functioning sanitation systems) are essential to long-term control in a community. However, the implementation and sustainability of interventions is complex, and variable between local contexts. Slum living is an increasingly common phenomenon that is creating a new urban parasitology where poly parasitism is magnified, and this will require a new way of thinking for the development and implementation of community control endeavors. Large-scale epidemiological surveys with concomitant cartographic modeling using morbidity questionnaires are increasingly used to guide targeted, spatially explicit and cost-effective sanitation [89] and pharmaceutical interventions [132–134], such as Mass Drug Administration (MDA). MDA entails the large scale, often nationwide, deployment of drugs based on local needs gathered from these parasitological surveys and geospatial modeling of infected populations [16,133,134]. Examples of other geospatial parasitological surveys are available from East Africa [135, 136] and Zanzibar [137].

Chemotherapy

An extensive technical review of MDA for the nematodes and other nonintestinal parasites has been published in the February 2009 edition of *Expert Review of Anti-infective Therapy* [138] and elsewhere [16,18]. Pharmacotherapy options for helminths [139] and for protozoa in children [42] have also been recently reviewed elsewhere. Thus, in the following section we aim to survey the history and the major themes and concepts related to current and future control efforts.

Anthelmintics for the treatment of nematodes and other helminth diseases were originally designed to be used for individuals with diagnosed infections and have largely evolved from veterinary applications. Starting in the 1960s then developing through the late 1970s, it was recognized that in order to impact global helminth burdens it was necessary to expand the use of such drugs massively. Pioneering work in the 1980s by Bundy [140], Stephenson [141, 142] and others provided the evidence that interventions targeting children without diagnosis would substantially reduce the burden in the community, not only on those treated but also in the untreated portions of the population, principally adults. For many years, interventions have been given regularly to children through schools and primary healthcare centers, and then increasingly with community participation. Initially, these programs were haphazard, dependent on the availability of funding. Gradually, it became apparent that a more coordinated approach was needed, encompassing the whole population to have the greatest effect.

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Today, the morbidity of the helminths (and other prevalent tropical diseases, for example, lymphatic filariasis, onchocerciasis and trachoma), is largely controlled through annual or biannual integrated MDA (see Table 2 for 2008 MDA data from SSA) [16,138]. In 2001, World Health Assembly Resolution 54.19 urged all member states endemic for schistosomiasis and nematodiasis to attain "a minimum target of regular administration of chemotherapy to at least 75% and up to 100% of all school-age children at risk of morbidity by 2010" [204]. This strategy has been termed 'preventive chemotherapy'. The most recent year for which a complete summary and analysis of these efforts is available is 2006 [205]. Table 2 shows that while coverage may be limited or nonexistent in many countries, where it exists, MDA is highly effective. The African region has the highest regional coverage and the highest coverage of all countries/territories reporting data. Southeast Asia, Western Pacific, LAC and Eastern Mediterranean regions all report lower regional coverage despite overall good coverage in countries/territories reporting data (~50%). This suggests that deworming activities targeting children perform reasonably well when and where implemented, but are carried out only in a limited number of countries and territories that represent only a small proportion of the population at risk in each region. Neither India nor China reported data on their MDA activities in 2008.

Nationwide school-based MDA allows for multiple efforts to be aligned, in theory cutting overall program costs and allowing increased numbers of the population to be treated [143–145]. The drugs used in MDA [138] include combinations of a benzimidazole (albendazole [ALB] or mebendazole [MBZ]) for the nematodes, praziquantel (PZQ) for schistosomiasis, and commonly, due to coinfection, ALB and diethylcarbamazine (DEC) or ALB and ivermectin (IVM) for lymphatic filariasis [146], IVM for onchocerciasis and azithromycin (AZM) for trachoma. The advancement and refinement of the use of already existing compounds is essential since the compounds mentioned above essentially represent the full pharmacopeia available for helminth treatment. Furthermore, the drug research and development (R&D) pipeline is severely depressed, with only a limited number of candidates, such as moxidectin as a macrofilaricide for onchocerciasis, in clinical development. Older drugs, such as levamisole and pyrantel, are other options but their therapeutic position needs to be further defined and developed [139,147]. Tribendimidine is another anthelmintic drug with a broad spectrum of activity. In 2004 the drug was approved by Chinese authorities for human use [148]. The efficacy of tribendimidine against nematodes has been established in populations in China, and new laboratory investigations point to activity against cestodes and GI polyparasitism with the nematodes and other helminths [147,149,150], yet there is limited testing of tribendimidine outside of China in other endemic populations. Artemisinin derivatives, which act also on juvenile schistosomes (PZQ is only effective against fully mature adult schistosomes) are still controversial, largely because their use as antimalarials takes precedence and schistosomiasis and malaria are often co-endemic.

The chemotherapeutic arsenal against protozoa is less vulnerable to resistance than that of the anthelmintics [42] and, if history is suggestive, may perhaps supply a few alternative therapeutic options after further R&D. The 5-nitroimidazoles are the drugs of choice for both *E. histolytica* and *Giardia* and include metronidazole, tinidazole and ornidazole [42]. ALB was originally developed as a veterinary anthelmintic, then as a human anthelmintic but also has some utility for the treatment of *Giardia*. Nitazoxanide (NTZ) has been shown to be effective for the treatment of cryptosporidiosis [151,152] and has recently been reviewed in *Expert Review of Anti-infective Therapy* [153]; however, access is limited due to factors related to licensing, and we exercise caution in overstating its use for human therapy as its efficacy appears to be somewhat unpredictable and modest. NTZ was first developed as a veterinary drug for tapeworm in the 1970s and discussions about potential synergies with NTZ have emerged recently since it has been observed to have activity against a variety of microorganisms, including not just protozoa but also helminths in endemic communities

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[154–157]. The use of NTZ as an anthelmintic requires additional research for its therapeutic position to become clearer. PZQ and triclabendazole are the only treatment options for the trematodes [84], while PZQ and niclosamide are the recommended drugs for intestinal *Taenia* spp. infections [158].

Role of vaccines

As MDA efforts expand and coverage increases throughout endemic communities, monitoring and evaluation efforts will be required to anticipate the possibility of emerging drug resistance [16,159]. In anticipation of both emerging drug resistance and the high rates of post-treatment reinfection to hookworm infection [160], a nonprofit product development partnership (PDP), known as the Human Hookworm Vaccine Initiative (HHVI) was established in 2000. Based at the Sabin Vaccine Institute (DC, USA) and George Washington University (DC, USA), the HHVI is transitioning a pipeline of *N. americanus* hookworm antigens from discovery, through process development, to pilot manufacture under current good manufacturing practices (cGMPs) and clinical testing. Both manufacturing and clinical development are being conducted in collaboration with the Brazilian Ministry of Health and two major Brazilian institutions, the Oswaldo Cruz Foundation (FIOCRUZ) and Instituto Butanan. Several antigens formulated with Alhydrogel® and other adjuvants are either completing manufacture or are entering Phase I clinical testing [161]. Among the current lead target candidates are two recombinant enzymes required for parasite blood feeding [162,163]. Ultimately, the human hookworm vaccine is expected to stimulate a host immune response that results in substantially reduced hookworm burdens and blood loss, thereby preventing moderate and severe iron-deficiency anemia, the hallmark of hookworm disease [164].

In addition to the hookworm vaccine, the HHVI has begun efforts to develop a vaccine against intestinal schistosomiasis [165], with an extracellular domain of a parasite surface tetraspanin as a lead candidate [166]. Manufacture and clinical testing of the major schistosome antigens will also undergo development in Brazil, and ultimately, the hookworm and schistosome antigens may be coformulated in a multivalent anthelmintic vaccine [165]. While the greatest number of cases of hookworm and schistosomiasis in the Americas occur in Brazil [24], the expectation is that such anthelmintic vaccines could be used throughout the developing world. It is likely that these vaccines could be used in conjunction with anthelmintic drugs in a program of vaccine-linked chemotherapy[167], thereby reducing global dependence on the benzimidazoles and PZQ.

Recognizing the limits of improved global sanitation in the foreseeable future, some researchers have looked to vaccines for amoebiasis and other protozoan infections [168]; however, none has progressed into clinical development. Generally, over the past decade, progress in vaccine development has been facilitated by new animal models that allow better testing of potential vaccine candidates and the application of recombinant technology to vaccine design. However, active initiatives are presently limited to two targets of a vast array of helminth parasites, with challenging economic barriers to developing vaccines and varying views about their potential role within current control programs.

Expert commentary & five-year view

The current momentum towards global drug delivery for control of the nematodes and schistosomiasis is at a historical high through the efforts of numerous nongovernmental organizations [206] increasingly acting in coordination with donors, governments and local communities [13,18]. Thus far, enormous quantities of drugs, especially anthelmintics, have been distributed to children in SSA, Asia and LAC. Yet, a much larger and growing population remains untreated (Table 2) [18]. MDA has profound potential for control but is not without considerable challenges and concerns. A principal barrier is sustainable funding for both the

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drugs (most of these programs rely upon donations by the manufactures while others must be purchased) and their delivery. Procuring and deploying drugs requires funding and resources greater than that which is available now or in the near future. In addition, there is the potential for resistance [149,169–172] which would have dire consequences for control efforts if it were to become widespread. Although treatments for GI helminth infections appear adequate at present, experience from veterinary medicine shows that drug resistance can easily occur to all the classes of compounds in current use [30,173]. Human drug exposure levels are far lower, both individually and in the community, compared with use in animals, but the compounds in use have not necessarily been optimized for human use [13,30]. The mechanisms of action of many drugs are currently poorly understood and their dosage and regimens are not based on detailed pharmacokinetic and pharmacodynamic information, which in most cases is lacking. Furthermore, the proximity between humans and livestock and the potential cycling of resistant pathogens into the environment has only just begun to be explored [174].

Novel drugs (new chemical classes and modes of action) would be needed to replace current drugs should resistance emerge and spread. However, the R&D pipeline for these parasites is almost nonexistent, although new leads may be coming from animal health research. Given the large overlap in the epidemiology of helminths and protozoa, especially in slum environments, it makes sense to further explore areas for synergy and combined therapy. This is also important given the severely limited pharmacopeia and second-line therapies available if resistance does arise. NTZ, the first-line treatment for cryptosporidiosis and with efficacy in other protozoan infections, has shown promising efficacy in early helminth studies, which after further research could present new treatment options either used alone or in combination with existing treatments. There is also some interest in MBZ–NTZ combinations. It is likely, given early data, that use of tribendimidine will increase, but additional studies outside of China in other endemic populations are necessary. Other approaches to evade resistance could include the use of different combinations of drugs in each MDA cycle, an approach used in the management of helminth infections in livestock. As shown in a small set of countries in Table 2, the combinations may change for each round of biannual MDA between age groups. Current MDA coverage will also be greatly challenged by the increase in the numbers of young individuals in endemic communities. As one coauthor calculated in 2003, the sheer scale of the undertaking of global control of the nematodes is incredible [13]:

> “500 million children would need to be regularly treated for ascariasis (one to three times a year for several years) over the next 25 years for the absolute numbers to stay the same (estimates based on data in [175]). A further 300 million would have to be added in the next 25 years. For a reduction to occur, these figures would need to be at least doubled and, to treat all infections, perhaps doubled again.”

It is clear that the cycle of infection and environmental contamination by these parasites will continue unless radical steps are taken. It has been shown in the past that neither improvements in sanitation or the scaling-up of drugs alone can lead to elimination of infection in the short term. Sanitation revolutions can and have occurred in Israel, South Korea and Japan this past century, but this is not feasible in the near term in most communities. One estimate by Pawlowski proposes that sanitation would take 15–25 years to achieve control levels of parasites in an ecosystem, while the addition of drugs and health education would reduce this to a more manageable 5–10 years [176]. Even though in some areas success has been achieved, especially with the integration of multiple programs to control filariasis, schisto-somiasis and nematodes, much remains to be done [18,177]. When considering children, it is clear that they play an important part in control strategies. They are the principal source of infection through environmental contamination, and the principal sufferers from the effects. Perhaps apart for hookworm, which also affects older age classes as well, the bulk of the disease burden is on children who suffer from the effects of infection over both the short and long term. Acute infections with protozoa such as *Giardia* and, to a lesser extent, *E. histolytica*, lead to weight

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loss, acute malnutrition and wasting. *Giardia* can also cause a chronic wasting syndrome in children, referred to as ‘ failure to thrive’. By contrast, helminth infections are more insidious, having chronic impacts such as growth limitation, stunting, chronic anemia and effects on cognition. Taken together, the impact of GI polyparasitism severely limits the development of children as key future members of their community and society.

Given the association between crowded living and polyparasitism, the role of the community in participating in its own disease control is paramount. In many countries, endemic GI parasitic infections are closely related to economic and social issues (e.g., ethnic diaspora and conflict [29,178]) and may be a sensitive issue. Yet, in many communities these infections can serve as an useful entry point for other community and primary healthcare activities, bringing together different sectors, such as family medicine, child care, health education and nutritional programs [177]. Indeed, this integration with the community is the philosophy and key to success for MDA. Community-directed approaches may however be more difficult to apply in urban and peri-urban settings, where the traditional community structure has been disrupted. The development of vaccines is encouraging, although the linkage of vaccines to control programs will not be an option for many years.

In summary, GI parasitic infection will remain responsible for untold childhood morbidity as long as poverty exists. Yet efforts to reduce GI parasites in communities have shown potential to be highly effective when they focus on reducing exposure and increased drug delivery in the local context. Additional research on recent global demographic shifts and these parasites will need to be actively pursued to guide control endeavors. Since 2008, more than half of the world’s population (3 billion people) has migrated to or been born in urban areas, including approximately 50,000 settlements of at least 50,000 people [179]. Forecasts suggest that by 2015, and for the foreseeable future, population growth will be predominantly urban, principally in the 500 or so cities that have 1–10 million inhabitants, and mainly in poorer countries. While the majority of the ‘bottom billion’ remain in rural areas, the proportion and number of poor people living in urban areas is rising [179–181]. About one in three urban inhabitants – approximately 1 billion people – now live in slums, but the proportion is much higher than this in SSA and South Asia [87,179–181]. Improvement in domestic water supplies with the introduction of piped and closed sewerage systems is likely to have the most marked impact in decreasing overall infection rates. Investment in public works at large would also go a long way. Improved diagnostics, such as the FLOTAC technique [182–184] are also essential as the more effective interventions become in reducing helminth egg excretion, the less useful direct parasitological tests become [69]. The integration of these measures using improved cartographic and census data, in conjunction with the innovative use of existing drugs, are the foundation for ultimate control of GI parasites.

Key issues

- Children are both the principal sufferers of the effects of gastrointestinal (GI) parasites and the source of the continued maintenance of transmission. As such, children are the targets of disease control interventions.
- The population structure of endemic regions shows a predominance of children under the age of 14 years. As a result, the social and economic impact of chronic GI parasites on a child’s development (e.g., malabsorption, malnutrition and resultant stunting, and chronic anemia) and capacity (e.g., diminished cognition, missed school and inability to work) can destabilize endemic communities and reinforce local poverty. This consequently hinders national and regional economic development out of poverty.

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- In general and compared with the nematodes (also known as soil-transmitted helminths), the epidemiological data for GI protozoa, cestodes and trematodes (excluding schistosomiasis) is limited, none of which have been studied systematically or included in any of the Global Burden of Disease studies. Accurate figures for the prevalence of these infections are almost impossible to obtain, and despite their relative low frequency compared with the nematodes, they can cause significant morbidity and mortality in a large number of individuals.
- There appears to be a changing epidemiology related to population growth and crowded living in urban and slum ecosystems that requires further understanding to advance control efforts.
- The health impact of GI parasites depends on a number of variables including the nutritional status of the host, the species of parasite, the mixture of species, the duration of infection and the number of parasites in the human host.
- The main objective of current control efforts is to reduce morbidity in children by decreasing their parasite biomass of GI nematodes. This is achieved by treating target groups, generally children, with anthelmintics (benzimidazoles).
- The pharmacopeia for the GI parasites is very limited and the R&D pipeline inadequate. Thus, the advancement and refinement of the use of already existing compounds and approaches is vital.
- Limited options for chemotherapy raise concerns about drug resistance developing through overuse. Although treatments for GI helminth infections appear to be sufficient at present, experience from veterinary medicine shows that drug resistance can occur easily in all classes of compound used thus far. Human drug exposure levels are far lower, both individually and in the community, compared with use in animals, but the compounds in use have not necessarily been optimized for human use. The mechanisms of action of many drugs are currently poorly understood and their dosage and regimens are not based on detailed pharmacokinetic and pharmacodynamic information, which in most cases is lacking.
- The development of vaccines, if they advance further, is encouraging, but the linkage of vaccines to control programs will not be an option for some years to come. Operational research studying the costs of these vaccines and their potential delivery strategy should continue to guide R&D.
- Efforts to reduce GI parasites should focus on reducing exposure in the local context. Improvement in domestic water supplies with the introduction of a piped and closed sewerage system is likely to have the most marked impact in decreasing overall infection rates. The integration of these measures using improved cartographic and census data, in conjunction with the innovative use of existing drugs, are the foundation to ultimate control of GI parasites.

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Table 1

Comparison of major gastrointestinal protozoa and helminths.

Organism		Reservoir	Mode of transmission	Clinical manifestations
Protozoa				
Entamoeba histolytica		Infected humans	Fecal–oral transmission by ingestion of feces containing infectious cysts	Bloody diarrhea (dysentery), intestinal and/or liver abscesses, asymptomatic intestinal infection
Giardia intestinalis		Infected human and other mammals	Fecal–oral transmission by ingestion of feces containing infectious cysts	Watery diarrhea, steatorrhea and malabsorption
Cryptosporidium parvum		Infected human and a variety of animal hosts (zoonosis)	Fecal–oral transmission by ingestion of feces containing infectious cysts	Watery diarrhea; intractable diarrhea in patients with AIDS
Cyclospora cayetanensis		Unknown	Foodborne and waterborne	Watery diarrhea
Helminths				
Nematodes	*Ascaris lumbricoides*	Infected humans	Fecal–oral transmission by ingestion of eggs	Intestinal or biliary obstruction
	Hookworms (*Ancylostoma uodenale* and *Necator americanus*)	Infected humans	Fecal–oral transmission by ingestion (*A. duodenale* only) of larvae or passage through skin	Iron deficiency anemia from chronic gastrointestinal blood loss
	Trichuris trichiura	Infected humans	Fecal-oral transmission by ingestion of eggs	Damage to intestinal mucosa; malnutrition and/or anemia
Cestodes		Pigs, cattle and fish	Ingestion of raw or undercooked meat	Asymptomatic taeniasis to medium to heavy infection causing malabsorption and related mineral and vitamin imbalances. Cysticercosis (*Taenia solium*). Hydatid cysts (*Echinococcus granulosus/multilocularis*)
Trematodes		Aquatic plants and animals	Contaminated water or ingestion	Asymptomatic light infection to medium to heavy infections that can cause intestinal obstruction, ulceration and hemorrhage

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Table 2

Mass Drug Administration coverage for the nematodes in sub-Saharan Africa (2008).

Country	Pre-school-aged children (1–5 years of age)				School-aged children (5–15 years of age)			
	Reported Number treated	*Drug used*	*Program Coverage (%)*	*Epidemiological coverage (%)**	*Reported number treated*	*Drug used*	*Program Coverage (%)*	*Epidemiological coverage (%)**
Angola	3,195,425	ALB/MBZ - round 1	65.36	128.02				
	3,856,436	ALB/MBZ - round 2	78.88	154.50				
Benin	1,119,856	ALB/MBZ -round 1	96.31	98.46	244,289	IVM + ALB		10.65
	2,132,163	ALB/MBZ -round 2	98.87	187.47				
Burkina Faso					3,371,729	IVM + ALB		82.27
Burundi	1,190,403	ALB/MBZ -round 1		131.57	1,684,349	ALB/MBZ -round 1	94.42	84.58
	970,870	ALB/MBZ -round 2		107.31	1,444,609	ALB/MBZ -round 2	99.49	72.54
Cameroon	1,166,987	ALB/MBZ -round 1	43.60	49.37	94,453	IVM + ALB		1.96
	1,923,909	ALB/MBZ -round 2	71.88	81.39				
Cape Verde					95,008	MBZ		76.10
Cote d'Ivoire	3,002,474	ALB/MBZ	92.97	120.96	374,923	MBZ		7.11
Democratic Republic of the Congo	10,154,588	ALB/MBZ -round 1		109.28				
	9,063,242	ALB/MBZ -round 2		97.54				
Ethiopia	3,653,566	ALB/MBZ		34.92	266,724	MBZ		1.21
Gambia	217,075	ALB/MBZ	83.00	103.04	66,594	MBZ		15.18
Ghana	2,574,215	ALB/MBZ	91.88	98.37	177,603	IVM + ALB		3.10

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Country	Pre-school-aged children (1–5 years of age)				School-aged children (5–15 years of age)			
	Reported Number treated	*Drug used*	*Program Coverage (%)*	*Epidemiological coverage (%)**	*Reported number treated*	*Drug used*	*Program Coverage (%)*	*Epidemiological coverage (%)**
Guinea	1,676,915	ALB/MBZ -round 1	97.00	130.77	215,000	MBZ		8.31
	1,655,642	ALB/MBZ -round 2	95.77	129.11				
Guinea-Bissau	182,332	ALB/MBZ - round 1	93.17	88.04	110,702	MBZ		27.17
	181,955	ALB/MBZ - round 2	92.98	87.86				
Kenya	109,207	DEC + ALB		2.13	633,938	DEC + ALB, MBZ		6.32
Madagascar	489,186	DEC + ALB		20.22	1,320,803	DEC + ALB		25.34
	2,845,627	ALB/MBZ - round 1	97.07	117.60	4,067,772	MBZ		78.06
	2,941,710	ALB/MBZ - round 2	100.34	121.57				
Malawi	1,861,245	ALB/MBZ	113.79	90.83	893,481	IVM + ALB, MBZ		20.77
Mali					1,469,393	IVM + ALB		43.04
Mauritania	398,760	MBZ		106.34				
Mozambique	1,934,474	ALB/MBZ - round 1	63.55	63.96	220,000	MBZ		3.64
	3,017,790	ALB/MBZ - round 2	99.14	99.77				
Niger					1,077,835	IVM + ALB		25.74
Nigeria	2,617,494	ALB/MBZ	97.58	13.35	1,048,854	IVM + ALB		2.65
Rwanda	1,263,407	ALB		97.87	2,454,947	ALB		99.94
Senegal					116,374	IVM + ALB		3.53
Sierra Leone	734,381	ALB/MBZ	98.56	98.27	794,777	IVM + ALB		54.50

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	Reported Number treated	*Drug used*	*Program Coverage (%)*	*Epidemiological coverage (%)**	*Reported number treated*	*Drug used*	*Program Coverage (%)*	*Epidemiological coverage (%)**
Swaziland					77,970	MBZ		25.38
Togo	849,208	ALB/MBZ		112.98	252,949			15.31
Uganda					670,166	IVM + ALB, ALB + PZQ		7.18
United Republic of Tanzania	5,457,302	ALB/MBZ	77.83	92.19	952,707	IVM + ALB, MBZ		8.35
Zambia					70,000	MBZ		1.97

Countries without any reported data on Mass Drug Administration for the nematodes in sub-Saharan Africa: Botswana, Central African Republic, Chad, Comoros, Congo, Equatorial Guinea, Eritrea, Gabon, Lesotho, Liberia, Mauritius, Namibia, Sao Tome and Principe, Seychelles, South Africa and Zimbabwe.

*The reasons for instances where epidemiological coverage is markedly greater than 100% include: re-treatment of the same population due to geographical overlap; different drug delivery channels (e.g., school-based and community-based) by the same intervention; inaccuracies in calculating the population at risk; and incorrect inclusion/exclusion of individuals in/from the group targeted for treatment.

ALB: Albendazole; DEC: Diethylcarbamazine; IVM: Ivermectin; MBZ: Mebendazole; PZQ: Praziquantel.

Data taken from [207].