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The Global State of Helminth Control and Elimination in Children

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INTRODUCTION

Helminth infections, including hookworm (*Necator americanus*, *Ancylostoma duedenale*), roundworm (*Ascaris lumbricoides*), and whipworm (*Trichuris trichiura*), collectively known as intestinal (or soil) transmitted helminths, as well as schistosomiasis, are among the most common infections found in children worldwide, infecting almost 2 billion people (Table 1).[1,2] Although intestinal helminth infections and schistosomiasis are not the only major parasites affecting children, their overwhelming numbers in terms of pediatric cases globally requires special attention. New estimates from the Global Burden of Disease Study 2015 indicate that together these helminth infections resulted in more than 6 million disability-adjusted life-years (DALYs), a number roughly equivalent to the DALYs caused by measles, *Haemophilus influenzae* type B meningitis, or other better-known pediatric conditions.[2] However, even these DALY estimates may represent "low-ball" figures based on revised estimates of more than 4 million DALYs from hookworm alone.[3] Thus, although intestinal helminth infections are not leading causes of death,[4] they are profoundly important causes of childhood disability and even future economic disrupters, with calculated adverse effects on future wage earning. Overwhelmingly, these worms affect children living in extreme poverty, particularly those living in rural communities or urban communities that lack adequate water, sanitation, and hygiene (WASH).[5] Contrary to previous assumptions, helminths and other neglected tropical diseases are not restricted exclusively to resource-

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limited countries. For some worm infections, there is a significant burden of disease found in poor communities living in countries with robust economies, including areas of the United States.[6]

The most common and most profound disabilities resulting from each of the major intestinal helminth infections and schistosomiasis are shown in Table 2. Children acquire their primary infection as they begin interacting with the environment during their preschool years and reach maximum worm burden for roundworm and whipworm (transmission via oral ingestion of embryonated eggs) by school age, whereas for hookworm and schistosomiasis (transmission via direct percutaneous invasion of larvae) in adolescence or young adulthood.[8,9] Overall, children infected with intestinal helminths and/or schistosomiasis often suffer from restrictions in cognitive development, impairment in memory, and reduced education attendance and performance.[5,9,10] These deficits lead to impaired school achievement.[9,11] Preschool- and school-aged children are at particular risk of poor long-term outcomes because they harbor the greatest burden of worms.[5] Children infected with roundworm are at increased risk of abdominal pain, abdominal distention, vitamin A deficiency, wheezing, and asthma, whereas children with whipworm may have colitis and other forms of inflammatory bowel disease (IBD) or Trichuris dysentery syndrome.[9] These findings go against the commonly held, but erroneous, belief that somehow worms protect children from asthma or IBD.[12] Children with hookworm experience iron-deficiency and iron-deficiency anemia, in addition to intestinal protein losses.[3] Young adults are also at risk of significant morbidity secondary to helminths. In resource-poor areas, women of reproductive age or those that are pregnant are at high risk of hookworm-induced iron-deficiency anemia.[5,13] In Africa and elsewhere, hookworm-induced anemia is also exacerbated by malaria coinfections.[14] Similarly, schistosomiasis is a major cause of chronic pediatric inflammation and anemia.[15] In addition, schistosomiasis caused by *Schistosoma haematobium* causes lesions in the female genital tract that result in a 2.9-to 4-fold increase in HIV transmission and increased risk of progress to AIDS.[13] Schistosomiasis has also been linked to female infertility and the development of noncommunicable diseases such as cancer.[16–18] Because these infections commonly have subclinical symptoms in children and young adults, the evidence of morbidity may not become apparent until adulthood, leading to limitations in adult workforce capability and wage potential, creating a cycle of poverty within the community.[1] Beyond poverty, pediatric helminth infections can exhibit a devastating social impact within communities.[19]

Previously, in the United States and other wealthy nations, helminth infections were thought to be isolated to immigrant communities, refugees, and adoptees from endemic regions. In refugees settling in North America, the prevalence of soil-transmitted helminths and schistosomiasis has been documented as high as 86%.[21] However, with the expansion of global networking and international travel and a high prevalence of worms in children living in poverty within wealthy countries, the pediatric clinician practicing within North America and Europe must be increasingly aware of the impact of worm infections in children. Two pediatric populations need to be considered. First, children and young adults with appropriate epidemiologic risk factors and geographic origins from Africa, Asia, and Latin America who present with acute symptoms, such as abdominal distention, abdominal pain, and wheezing, as well as more chronic symptoms, such as asthma, colitis, HIV, and bladder

cancer, should be evaluated for helminth infections. Second, helminth infection transmission may be more common in North America and Europe than previously thought.[6] For example, toxocariasis, a zoonotic helminth infection from dogs, is widespread in the Southern United States and Eastern Europe,[22–24] whereas the intestinal helminth infections highlighted above may still occur in the Southern United States and parts of Europe,[24,25] and schistosomiasis transmission was recently documented in Corsica.[26]

DIAGNOSIS AND TREATMENT

The diagnosis of helminths has traditionally been based on serologic evaluation for schistosomiasis or visualization of eggs, in stool for intestinal helminth and intestinal schistosomiasis (*Schistosoma mansoni* or *Schistosoma japonicum*), or in urine for urogenital schistosomiasis (*S haematobium*), using microscopy. The subjective declaration of eggs and/or larvae can be a fickle and arduous task that suffers from laborious preparation, the need for skilled microscopists, with sensitivities that range from 50% to 85%.[27] Modern molecular techniques have revolutionized helminth diagnoses with greatly improved detection rates and 10-fold increases in detection of 2 or more parasitic infections (polyparasitism).[28,29] By using multiparallel quantitative real-time polymerase chain reaction with a stool bead beating DNA extraction method to reduce the cost, the assay can be used in a capacity-building setting in resource-limited countries.[28–30] Newer techniques continue to be developed allowing for more rapid, sensitive diagnostics particularly in settings of polyparasitism and low worm burden.[28]

Current therapy for children with helminth infections is based on adult dosing and adult formulations, including benzimidazoles and praziquantel. For treatment of hookworm or roundworm administration of either albendazole 400 mg orally once taken with food or mebendazole 100 mg orally twice a day for 3 days is recommended. For whipworm, albendazole 400 mg orally for 3 to 7 days or mebendazole 100 mg for 3 to 7 days is required, and for schistosomiasis, treatment consists of praziquantel 20 mg/kg orally twice a day for 1 day (see Table 2).[9,20]

It is evident that as the global community becomes smaller, worm infections in children may become a more common occurrence in pediatric clinics within the United States and other wealthy countries. As a result, it is imperative for the pediatric clinician to understand the historic, current, and prospective landscape of helminth disease in children around the world.

INTRODUCTION TO MASS DRUG ADMINISTRATION

The significant life-long morbidity of helminths has led to the commitment of public and private leaders to address controlling and even eliminating these pathogens globally.[5] Early goals focused primarily on WASH through improved sanitation, reducing soil and water contamination, and implementing health education within communities.[5] These strategies to improve community infrastructure incurred high cost without immediate, noticeable change, prompting a shift toward mass drug administration (MDA), also now referred to by the World Health Organization (WHO) as preventive chemotherapy.[5] MDA programs are centered on the regular, repeated administration of preventive chemotherapies, such as

benzimidazoles (albendazole, mebendazole) for intestinal helminth infections, ivermectin or diethylcarbamazine citrate for filarial worms, and praziquantel for schistosomiasis.[31] It has been anticipated that repeated MDA at regular intervals will reduce worm burden to reduce morbidity, and in areas with low prevalence possibly even inhibit transmission and eventually allow for elimination of helminth infection.[5] Early precedent for a mass treatment approach was seen in the United States in the early 1900s.[32] In 1910, the Rockefeller Sanitary Commission for the Eradication of Hookworm Disease (RSC) estimated 40% of the population of Southern United States was infected with hookworm. The RSC sponsored treatment administration for more than 400,000 individuals through mobile dispensaries, implemented education campaigns, invested in public health infrastructure, and completed disease mapping among 11 southern states in efforts to reduce hookworm disease.[33] Interestingly, in school systems with the highest levels of hookworm burden, children that received therapeutic intervention were found to have greater increases in school enrollment, school attendance, and literacy by 1920. Furthermore, as children that received treatment for hookworm aged into adulthood, they had a substantial gain in income.[34] However, the success of this program was multifactorial, relying not only on MDA but also on changes in education, shifts away from agrarian activities toward urbanization, and overall economic development of the Southern United States.[34–36] Similar economic reforms led to reductions in intestinal helminth infections in Japan and South Korea beginning in the 1950s, as well as in Eastern China beginning in the 1990s.[6]

MASS DRUG ADMINISTRATION PHASE 1 (2001): REDUCTION IN MORBIDITY

Anthelmintics MDA programs gained momentum in 2001, after the release of the 2000 Millennium Development goals,[17] and with the adoption of a World Health Assembly Resolution specifically committed to intestinal helminth infections and schistosomiasis.[37] Initially, MDA programs focused on controlling worm burden within a community to reduce morbidity within an individual.[38] In order to accomplish this goal, a joint statement by WHO and UNICEF in 2004 supported the target of “high-risk” communities, including preschool- and school-aged children, adolescent girls, and women of childbearing age based on worm prevalence.[10] Because young children often harbor the greatest burden of worms, focusing on these “high-risk” communities was predicted to generate the greatest impact on morbidity while minimizing the cost for clinical diagnosis.[5,39–41] To achieve worm control, the WHO estimated that at least 75% of all school-aged children in endemic regions were in need of regular treatment or approximately 875 million children.[5,16,42] Early programs administered a single dose of benzimidazole (albendazole or mebendazole) for the treatment of soil-transmitted helminths and a single dose of praziquantel for the treatment of schistosomiasis.[38] The medications were found to be generally well tolerated and often administered by community health workers or teachers in school-based programs.[38] Furthermore, administration of regular anthelmintics treatment to high-risk groups was found to be affordable and sometimes sustainable.[10] However, it has been noted that a single-dose mebendazole or albendazole can exhibit low efficacy against whipworm or hookworm in some settings,[43,44] and in some cases, paradoxic drug failure[45] or diminished efficacy with repeated use.[46] Possibly, some of these findings explain why a Cochrane

analysis of randomized clinical trials using MDA approaches failed to conclusively confirm child-health benefits in terms of nutritional benefits, hemoglobin, and school performance.[47]

MASS DRUG ADMINISTRATION PHASE 2 (2005): INTEGRATIVE CONTROL WITH THE "RAPID-IMPACT PACKAGE"

Polyparasitism in children is common due to the geographic overlap of soil-transmitted helminths and schistosomiasis globally. Because of this geographic overlap, MDA programs in high-risk communities were administering multiple therapies to control multiple infections. Furthermore, poor efficacy of monotherapy benzimidazoles, specifically for hookworm or whipworm, highlighted the need for an integrative treatment approach.[31] The "rapid-impact" package, the next step in MDA evolution and integration, was a low-cost mechanism proposed in 2005 to distribute multiple drugs to treat multiple parasites simultaneously.[48,49] Implementation of the rapid impact package included 4 drug classes: benzimidazoles (albendazole or mebendazole), ivermectin (or diethylcarbamazine citrate in some areas), praziquantel, and azithromycin, allowing for concurrent treatment of soil-transmitted helminths, filarial diseases, schistosomiasis, and trachoma, respectively.[5,49] In addition, collateral benefits for yaws, scabies, and other neglected tropical diseases were noted.[50] Another advantage of combining albendazole with ivermectin within the medication package was increased drug efficacy for whipworm secondary to cross-reactivity of medications[51] and the possibility of slowing the development of resistance to individual drug classes.[5,52] Although emergence of anthelmintics drug resistance has not yet been proven for human intestinal helminths or schistosomes, veterinary medicine has demonstrated that widespread, frequent, prolonged administration of anthelmintics chemotherapy within a population increases the risk of drug resistance.[53] With this precedent in the veterinary world, the growing evidence of decreased efficacy of mebendazole for whipworm and hookworm[46] as well as decreased efficacy of praziquantel for schistosomiasis after repeated use is of increasing concern.[54]

MASS DRUG ADMINISTRATION PHASE 3 (2012): SCALE-UP PROGRAMS FOR ELIMINATION

Despite private and public efforts, the 2010 goal to provide MDA to at least 75% of school-aged children at risk was not met.[5] By 2010, only 32.6% of children requiring coverage for soil-transmitted helminths and 14.4% of children requiring coverage for schistosomiasis received adequate therapy. Failure to meet these goals was thought to be secondary to cost-prohibitive programs and the intermittent availability of anthelmintics therapies.[52,55] In the early 2010s, the London Declaration of Stakeholders Working Group and the WHO 2020 roadmap advocated for scale-up of MDA programs to not only control infections by providing therapy to 75% of children but also add a new focus on elimination and eradication by interrupting transmission by 2020.[16,42,56,57] Emphasis was placed on collaborative and coordinated efforts by both public and private groups to provide funds for expanded coverage combined with commitments by helminth-endemic countries to focus on improvements in community infrastructure.[16,42,56,57] Programs were expected to place a larger emphasis on national funding and improvements in national health infrastructure to

ensure sustainability.[42] Through such renewed commitments, new estimates by the WHO indicate that globally in 2015 more than 60% and 40% of school-aged children receive benzimidazoles and praziquantel, respectively, on an annual basis.[58]

MASS DRUG ADMINISTRATION AS A PATHWAY TOWARD HELMINTH ELIMINATION

Despite the global commitment to global helminth control and elimination, there are significant hurdles toward achieving these goals solely through current MDA approaches. To date, the Global Burden of Disease 2015 has shown only modest reductions in the global prevalence of intestinal helminth infections since MDA was integrated beginning in 2005, with the greatest reductions in ascariasis (12% reduction in prevalence and 20% reduction in age standardized rates) presumably due to its high sensitivity to single-dose albendazole or mebendazole, whereas the gains have been more modest for trichuriasis and hookworm possibly due to reduced efficacies when these drugs are used in a single dose.[2] Another factor is the finding that, although ascariasis and trichuriasis intensities are highest among school-aged children, it is common to find both high-prevalence and high-intensity hookworm and schistosomiasis infections among adults. Therefore, MDA for preschool- and school-aged children would not be expected to have an impact on elimination for either hookworm or schistosomiasis. Accordingly, there have been calls to expand MDA to treat entire communities in order to simultaneously target both adults and children.[59,60] However, it is unclear whether the concerns highlighted earlier, including paradoxically low drug efficacies or diminished efficacy with increasing use, or even drug resistance would make elimination efforts unattainable even in the setting of community-wide treatments. A survey of several hundred experts in neglected tropical diseases indicated a high degree of uncertainty of achieving elimination targets for intestinal helminth infections or schistosomiasis through MDA alone.[61]

As global MDA efforts continue to expand and reach the 75% to 100% targets adopted by the 54th World Health Assembly in 2001, a parallel program of research and development is needed to not only improve existing anthelmintics drugs to include pediatric formulations but also develop new innovative anthelmintics drug classes, particularly for whipworm and hookworm. Among those under development are tribendimidine, a cholinergic drug that also works against human liver fluke infection,[62] and Cry5B, a *Bacillus thuringiensis*–derived toxin, known to activate the p38 mitogen–activated protein kinase pathway in both hookworm and ascariasis.[63,64] Overall, the pace of human anthelmintics drug development has been slow due to the orphan and neglected status of its disease target. Still another approach has been the development of anthelmintics vaccines, possibly used in combination with existing or new drugs.[65] Toward that goal, a human hookworm vaccine is in phase 1 clinical trials, as are 2 new vaccines for schistosomiasis. Vaccine development programs evaluating the possibility of a multivalent anthelmintics vaccine targeting multiple pathogens would additionally provide significant benefit in areas with helminthic geographic overlap.[65] Unfortunately, global efforts to advance these vaccines through clinical development and ultimately licensure have also been slowed by the absence of prioritization by the global community relative to vaccines for pandemic disease threats such as Ebola and influenza.

SUMMARY

Helminth infections, soil-transmitted helminths and schistosomiasis, adversely affect the lives of millions of children around the world. With the increase in globalization, pediatricians in wealthy nations are increasingly likely to encounter these infections in their clinic. It is imperative to understand the epidemiology, transmission dynamics, and treatment options for these children in order to prevent significant long-term morbidity. The evolution of the MDA movement has progressed from control to integrative elimination programs specifically targeting young children. Scale-up approaches to include whole communities (including adults) have been proposed with the goal to ultimately achieve interruption in transmission. However, the question remains whether these programs will be efficacious and if repeated treatment within the communities will have a lasting impact on drug resistance. As a result of this uncertainty, there remains a significant need for diagnostic innovation, therapeutic development including new drugs and vaccines, as well as drug resistance monitoring to aid in the control and elimination efforts of helminth infections globally.

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KEY POINTS

- Soil-transmitted helminths and schistosomiasis are some of the most common infections found in children and adolescents worldwide and cause significant morbidity and chronic disability.
- Current strategies to reduce morbidity associated with soil-transmitted helminths and schistosomiasis include mass drug administration (MDA) and programs of water, sanitation, and hygiene (WASH).
- Although MDA and WASH are reducing the overall prevalence of helminth infections, global elimination remains elusive because of low drug efficacies and reinfection.
- Alternative strategies, including improved diagnostics, improved worm prevalence and resistance monitoring, new anthelmintics diagnostics, therapies, and vaccines, are required.

Table 1

Prevalence and impact of major helminth infections, soil-transmitted helminths, and schistosomiasis, globally

	Major Human Species	Estimated Prevalence (Cases)	DALYs (Millions)	Deaths	References
Roundworm (Ascariasis)	*Ascaris lumbricoides*	761.9 million	1.075	2700	[2,4,7]
Whipworm (Trichuriasis)	*T trichiura*	463.7 million	0.653	None specified	[2,4,7]
Hookworm	*N americanus* and *Ancylostoma* sp	428.2 million	1.758	None specified	[2,4,7]
Blood Fluke (Schistosomiasis)	*S haematobium*, *S mansoni*	252.3 million	2.613	4400	[2,4,7]
Total		>1.9 billion	6.096	7100	—

Table 2

Transmission, symptoms, and treatment strategies for soil transmitted helminths in children

	Mode of Transmission	Major Symptoms	Treatment	References
Hookworm	Direct percutaneous invasion of larvae in contaminated soil	Growth stunting, cognitive restriction, iron deficiency anemia, and protein losses	Albendazole 400 mg once or mebendazole 100 mg bid × 3 d	8,9,20
Roundworm	Oral ingestion of eggs in contaminated soil	Growth stunting, cognitive restriction, vitamin A malabsorption, intestinal obstruction, asthma	Albendazole 400 mg once or mebendazole 100 mg bid × 3 d	8,9,20
Whipworm	Oral ingestion of eggs in contaminated soil	Growth stunting, cognitive restriction, trichuris colitis, trichuris dysentery syndrome	Albendazole 400 mg po for 3–7 d or mebendazole 100 mg bid for 3–7 d	8,9,20
Schistosomiasis	Direct percutaneous invasion of larvae in fresh water	Growth stunting, cognitive restriction, bladder cancer, liver fibrosis, hematuria, renal failure, female genital schistosomiasis	Praziquantel 20 mg/kg twice a day for 1 d	8,9,20