Review Article

Geohelminths: public health significance

Suvash Chandra Ojha[1], Chayannan Jaide[2], Natini Jinawath[2], Porpon Rotjanapan[2], Pankaj Baral[1]

[1] *Faculty of Science, Mahidol University, Bangkok, Thailand*
[2] *Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

Abstract

The worldwide prevalence of geohelminths and their unique place in evolutionary biology have attracted research focus. These major soil-transmitted intestinal nematodes that cause human diseases are the nematode roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*) and the two hookworms (*Ancylostoma duodenale* and *Necator americanus*), often collectively referred as geohelminths. Studies of geohelminthiasis in poorly nourished children in developing regions report that geohelminths contribute to stunted growth and cognitive impairment. Insights into immunology have shed light on the modulatory role of the parasite on the host immune system and have defined the role of T cells in controlling geohelminthic infection. Recent molecular biological techniques have created an opportunity to analyse the interaction between parasites and their hosts at the molecular level. This paper is a review of the recent literature that examined the prevalence of geohelminthiasis in developing countries, the association between geohelminths in relation to public health, parasitological/diagnostic features, and therapeutic and preventive aspects of these major soil-transmitted helminth (STH) pathogens in humans.

Key words: geohelminths; immune response; pathogenesis; prevalence; treatment; nematodes

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Introduction

Helminths (parasitic worms) are multicellular eukaryotic invertebrates with tube-like or flattened bodies exhibiting bilateral symmetry. The major groups of parasitic helminths include nematohelminths (nematodes) and platyhelminths (flatworms), the latter subdivided into cestodes (tapeworms) and trematodes (flukes). Geohelminths (soil-transmitted helminths, STHs) are a group of intestinal parasites causing human infection through contact with parasite eggs or larvae that thrive in warm and moist soil and belong to the class nematoda, which includes roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*), and two hookworms (*Ancylostoma duodenale* and *Necator americanus*) [1]. The incidence of geohelminthic infections, particularly among poor human populations living in low- and middle-income countries, continues to be a major public health concern [2]. The prevalence of geohelminthic infections has remained at a similar level over the past 50 years [3,4]. Geohelminths usually co-infect the host. Recent global estimates indicate that approximately 3.5 billion people are infected with one or more of the most common of these nematode parasites (STHs) [3,5], which cause more marked morbidity and disability than death (Table 1). The morbidity caused by helminths includes malnutrition, iron deficiency anemia, malabsorption syndrome, intestinal obstruction, chronic dysentery, rectal prolapse, respiratory complications, and poor weight gain [8,9]. Poor weight gain during geohelminthic infections may be due to adult helminth worms residing in the small intestine. This interferes with the host's nutrition and can induce damage to the intestinal mucosa, resulting in the host's reduced ability to extract and absorb nutrients from food. Apart from acute clinical disease, chronic helminthiasis can lead to insidious and debilitating disease, especially in children and women of child-bearing age [8-12]. In addition to their health effects, an intestinal helminth infection impairs cognition in children and hinders economic development [2,13-15]. Infections can be primarily caused by the absence of safe drinking water, lack of hygienic behavior, improper sanitary habits, poor fecal disposal systems, poor socioeconomic status, and wide dispersion of parasites within human communities [16,17].

The magnitude of the burden of geohelminthiasis is grossly underestimated, but it deserves to be given special attention because of its broad geographical

distribution [18], its deleterious effects on nutrition [19], and its impairment of immune functions [20,21]. The important harmful factors in helminth infections include the direct pathogenic effect by the worms and the modulatory role of the parasite on the host immune system, altering the response to other antigens or pathogens and causing additional immunopathology [22]. Chronic helminth infections induce T-cell hyporesponsiveness, which may affect immune responses to other pathogens [23]. STH infections, which are usually found in areas co-endemic to multiple infectious agents, may increase susceptibility to other important tropical diseases such as malaria, human immunodeficiency virus (HIV), and tuberculosis (TB) [24]. Nonetheless, few studies have reported the inverse associations between geohelminth infections and allergic or atopic diseases [25-28]. Advances in genomics, proteomics and molecular biology may lead to improved diagnosis and control of these STHs. We reviewed the current body of literature to gather the latest information about geohelminthic infections, focusing on prevalence, life-cycle, host interaction, treatment, and prevention. The available body of literature focuses on the following developing and emerging countries: Nepal, India, Pakistan, Vietnam, Laos, Malaysia, Nigeria, Cameroon, Brazil, and Thailand (Table 2). We searched PubMed, Embase, Medline, and ISI Web of Science databases for this review up to January 30, 2012.

Host-immune response against geohelminths

Geohelminth infections have been shown to have a significant impact on the occurrence and course of a number of other illnesses. Early exposure of the fetus to maternally derived geohelminth antigens via the placenta, or of the infant through early infection, can induce host tolerance to the nematode parasite (STHs) [39]. Intestinal helminths impair epithelial barrier function, causing increased mucosal permeability and intraluminal fluid accumulation [40]; such effects have been attributed to the upregulation of T helper cell type 2 (Th2) cytokines. Allergens, like helminth antigens, are potent inducers of Th2 responses [41-43]. Resistance to infection in an infected host may be associated with the predominant production of immunoglobulin E (IgE), eosinophilia, mast cells, and the presence of CD4+ T cells preferentially producing different types of interleukin (IL-4, IL-5, IL-9, IL-10, IL-13) [44-47]. However, there is also evidence that these parasites might enhance their own survival by modulating the immune responses of their host by inducing regulatory responses that dampen the activity of effector cells [48]. Increased susceptibility to re-infection or concurrent bacterial infection is associated with cross-regulatory suppression of Th1 immunity by the helminth-driven weak Th2 cytokine responses [49-52]. This may be particularly important in the developing world, where chronic helminth infection coexists commonly with enteric bacterial pathogens. This ability to attenuate Th1-driven inflammatory

Table 1. Characteristics and impact of soil-transmitted helminths

Disease	Causative agents	Size (mm)	Infections (millions)	DALYs (millions)	Death (annual)	References
Ascariasis	*A. lumbricoides*	150-450	807-1221	1.8-10.5	60,000	[6-8]
Trichuriasis	*T. trichiura*	30-50	604-795	1.8-6.4	10,000	[6-8]
Hookworm infection	*N. americanus* *A. duodonale*	7-13 8-13	576-740	1.5-22.1	65,000	[6-8]

Abbreviations: mm, millimetre; DALYs, disability-affected life years

Table 2. Prevalence of soil-transmitted helminths in developing countries according to randomly selected publications

Country	Years isolates obtained	Types of study	% Total of geohelminth	Mixed infection (%)	Geohelminths (%)			References
					AL	**TT**	**HW**	
Nepal	1999-2005	Prospective	9.2	10.1	47.0	24.0	29.0	[29]
India	2000	Cross-sectional	9.0	NS	38.0	43.0	43.0	[30]
Pakistan	2002-2003	Cross-sectional	13.7	NS	1.9	0.6	4.6	[31]
Malaysia	2006	Cross-sectional	98.6	67.7	67.8	95.5	13.4	[32]
Thailand	2002	Cross-sectional	35.2	NS	3.4	2.2	30.5	[33]
Lao	2001-2002	Descriptive	NS	21.4	67.7	3.9	9.7	[34]
Nigeria	2004-2005	Cross-sectional	NS	3.5	34.5	NS	4.5	[35]
Cameroon	2007	Cross-sectional	72.3	33.0	33.0	54.3	26.6	[36]
Brazil	2004	Cross-sectional	12.7	24.5	5.8	2.3	7.7	[37]
Vietnam	2007-2008	Cross-sectional	72.3	NS	13.5	45.2	58.1	[38]

Abbreviations: AL, *Ascaris lumbricoides*; TT, *Trichuris trichiura*; HW, hookworm; NS, not stated

responses [52-54] has prompted the evaluation of helminths as a therapeutic agent for the treatment of some immune-mediated disorders, including certain types of inflammatory bowel diseases [55]. In recent years, several reports have shown the suppressive effect by helminths on the outcomes of diseases such as allergies [25-27,56,57], autoimmunity [58], and inflammatory bowel disease [59]. Therefore, helminths can have a possible beneficial effect in restricting inflammation [28,60]. However, a number of studies have reported either no association [61,62], or a positive association [63,64] between STHs and allergies. Interestingly, few studies have reported that helminth infections might modulate the human immune response to common co-infections such as malaria, TB, and HIV [65-67]. However, in the case of malaria, it has been argued that helminths either exacerbate [68] or reduce [69-71] the severity of malaria. The reasons for conflicting data about the effect of helminth co-infection on the outcomes of malaria or allergic diseases could be due to differences in study design, study groups, and possibly due to the particular helminth species investigated.

Life cycles and pathogenesis of geohelminths

Geohelminthiasis typically evolves through several phases; manifestations of geohelminth infections therefore vary with the infecting parasite species, the age of the host, the presence of risk factors, the specific immune status of the host, and harboring a light or heavy worm burden. The major geohelminthic life history and complications are discussed below.

Trichuriasis

The first-stage larva of *T. trichiura* are liberated from the eggs upon passage into the small intestine. They then undergo multiple moulting processes before maturation. The adult stage usually develops within 30-90 days of infection and mainly inhabits the cecum, where the anterior part of the worm burrows into the mucosal epithelium. The estimated life span of the adult *T. trichiura* is one to two years, and the female worm lays around 2,000-30,000 eggs per day [72]. In heavy infections, adult worms may be present throughout the intestinal tract from the cecum to the rectum. They then remain throughout their parasitic existence in the large intestine, where they survive by creating epithelial tunnels. The tunnels are created by a process of host cell fusion in response to parasite-derived secreted proteins [73]. Eventually, the thickened posterior portion of the worm ruptures out of the epithelial tunnel to protrude into the lumen [74]. Adult worms have the capability to disrupt the normal architecture of the colonic mucosa, which is further affected by host inflammation. Some direct blood loss also occurs at the site of parasite attachment and ulceration.

Although the majority of infected individuals remain asymptomatic, a significant number of trichuriasis patients, especially children with long-standing massive infections, have dysenteric syndrome presenting with chronic mucous diarrhoea, rectal prolapse, anemia from chronic blood loss and iron deficiency, protein-energy malnutrition, and growth retardation [75-78]. The magnitude of these findings is proportional to the intensity of chronic infection. The basis by which whipworms impair physical growth is unknown. Among the mechanisms proposed are direct intestinal protein losses [79-81], anorexia, increased catabolism resulting from host tumour necrosis factor production [82], and reduced host circulating levels of insulin-like growth factor I. Even less well-known are the mechanisms by which *T. trichiura* impairs cognition and school performance.

Hookworm infection (Ancylostomiasis and Necatoriasis)

Human hookworm infection is caused by the nematode parasites *Necator americanus* and *Ancylostoma duodenale*. Both species share a common life cycle. The larva transmission occurs either by direct penetration of the skin, usually through the feet, or by the fecal-oral route [83]. Upon entry into the gastrointestinal tract, the larva moult twice (over approximately two months) to become mature adult worms. Adult worms live with their anterior ends dug deep within the mucosa of the distal duodenum and proximal jejunum. Attachment then is followed by the release of active peptides that downregulate host inflammation, block the clotting of blood, prevent platelet aggregation, and degrade host connective tissue components [84-90], resulting in continuous blood loss from capillaries and arterioles, which the parasite ruptures and degrades. The estimated life span of hookworms is five to seven years, and the female worm lays around 10,000-30,000 eggs per day [8].

The illness is characterized by abdominal pain, nausea, vomiting, anorexia, fatigue, dyspnea, koilonychias, pale sclera, pallor, melena, chlorosis, and poor concentration. During heavy infections, each individual adult hookworm can cause up to 0.2 mL of blood loss per day, which leads to depletion of host iron and protein reserves, causing iron deficiency anemia and protein malnutrition. Plasma protein loss

can impart kwashiorkor-like appearance in children. The processes of growth retardation and deficits in attention and intellectual development that occur during chronic heavy hookworm infections in childhood could be due to the development of a clinical iron deficiency. Iron is considered essential for the biosynthesis of dopaminergic neurons and for the biosynthesis of iron-containing metalloenzymes such as monoamine oxidase [74,91]. However, it is a matter of debate whether iron loss contributes to deficits in growth or whether it has a nutritional basis secondary to plasma protein loss. Infective larvae of *A. duodanale* arrested in pregnant women enter the colostrum and breast milk postpartum, which causes infantile hookworm infection [92]. Pulmonary invasion by hookworm larvae can manifest with cough and transient pulmonary infiltrates. Eosinophilia begins to occur during the extraintestinal migrations of hookworm larvae. Children with chronic infections have an increased susceptibility to recurrent viral illnesses [91]. These children may have profoundly low haemoglobin concentrations.

Ascariasis

The estimated life span of adult *A. lumbricoides* is one to two years. The higher global prevalence of ascariasis is mainly attributed to two reasons. First, the female adult *A. lumbricoides* worm has a remarkable ability to produce offspring. It is estimated that a single worm may release up to 27 million eggs during the course of an infection. Second, the *A. lumbricoides* eggs are quite hardy and have an outer proteinaceous coat and thick egg wall that renders them remarkably resistant to environmental extremes for long periods of time.

After infective eggs have been ingested, the larvae hatch in the small intestine, penetrate blood vessels in the wall of the intestine, and then develop following a heart-lung migration. The larvae grow into adult worms and become sexually mature in six to ten weeks. Unlike whipworms or hookworms, the adult roundworms do not invade the gastrointestinal mucosa. Instead, they can elicit mechanical damage and lumen obstruction if they wander into the biliary tree or become entangled and matted into a bolus of worms. The growth retardation associated with ascariasis may have a nutritional basis [93]. It may be due to the parasite impairing host nutrition by causing malabsorption through a process of villous atrophy. Lactase deficiency also has been described. Although *Ascaris* worms produce a battery of peptide serine protease inhibitors that *in vitro* can block the action of pancreatic trypsin, chymotrypsin, and elastase [94], whether these peptide inhibitors are actually released by the parasite and whether they have a physiologic role in the parasite-host relationship remains unclear. Ascariasis may have a detrimental effect on the host when the worms are abundant, which includes two major types of clinical sequelae: due to migrating larvae and due to adult worms.

Effects due to migrating larvae

Patients may develop Loeffler's pneumonitis, which is characterized by fever, dry cough, mild chest pain, pulmonary infiltrates, dyspnea, and breathlessness on exertion. Hypersensitive people may develop allergic reactions such as urticaria and asthma. Minimal damage is produced by larval intestinal invasion, although some hepatic inflammation and granulomata formation have been described [74]. The extraintestinal migrations in the lungs are associated with a vigorous host inflammatory response that includes elevated serum IgE levels and eosinophilia [83].

Effects due to adult worms

Most infections are light and symptomless, but the presence of even a few *A. lumbricoides* can be potentially pathogenic. The presence of adult worms in the intestine may result in nausea, vomiting, abdominal discomfort, epigastric pain, and in some cases, steatorrhea will occur. Moderate to heavy infections may result in impaired digestion and malabsorption of protein, lactose, and some fat-soluble vitamins [74,95]. *A. lumbrocoides* is the largest of the intestinal nematodes; its size ranges from 15-45 cm long and 2-6 mm in diameter (Table 1). Body fluid of *Ascaris* when absorbed in the blood causes toxic effects and gives rise to typhoid-like fever. The worm masses, especially in children, can cause obstruction or perforation of the intestine and occasionally cause obstruction of the pancreatic duct [96]. Cholecystitis results from worm migrations into the common bile duct, where the worms can cause cystic duct obstruction directly or serve as a nidus for stone formation [97]. Migrating worms may cause liver abscesses and appendicitis and may occasionally enter the stomach and be vomited out.

Diagnosis

Clinical

Diagnostic tools for determining the etiology of helminth-caused diarrhea/dysentery provide useful information for enhanced understanding of the

epidemiology of the disease and for developing infection control policy and measuring its success. Patients presenting with intermittent abdominal pain, loss of appetite, diarrhea, nausea, vomiting, fever, and perianal itching should be highly suspected of having geohelminthiasis. However, the diarrheal stage of the infection cannot be distinguished from other bacterial, viral, and protozoan infections.

Laboratory

Although clinical signs may evoke the suspicion of geohelminthiasis, diagnosis is still dependent upon the isolation and identification of geohelminth from the feces. Adult roundworm can also be demonstrated macroscopically when the adult worm is spontaneously passed in stool or vomitus; administration of an antihelminthic drug may result in expulsion of the worm. The definitive methods usually involve microscopic detection of helminth eggs from fecal preparations via smears or after concentration. Microscopy, however, requires trained experts, has low sensitivity for detection of light and moderate infections, and may result in misdiagnosis leading to delayed or inadequate treatment [98]. Numerous flotation and concentration methods are available, such as the Kato-Katz technique [99], formol ethyl acetate sedimentation [100], modified formol ethyl acetate sedimentation [101], modified Wisconsin flotation [102], simple gravity sedimentation [103], McMaster salt flotation [104], centrifugal-flotation technique in zinc sulphate and sodium nitrate solution [105], and the Harada-Mori filter paper strip technique for detection of geohelminth ova in stool samples. The Harada-Mori filter paper strip technique or charcoal culture method is the method of choice to distinguish the larvae of *A. duodanale* and *N. americanus* on epidemiological ground. However, the usefulness of these techniques may be limited because of their time-consuming nature, labour intensiveness, and low sensitivity. The Kato-Katz quantitative technique, recommended by the World Health Organization (WHO), is suitable for the detection of geohelminth ova [7,106] and is most commonly implemented in human helminth surveys. However, the usefulness of the Kato-Katz method in detecting infections in infants may be limited, because stools of breastfeeding infants tend to be more liquid and have relatively low egg counts. As reported by Richardson *et al.* (2008) [107], a Kato-Katz test will probably pick up only 50% of all low-intensity infections, while a concentration or sedimentation test has much higher sensitivity. Advances in molecular biology, proteomics, and genome-sequencing project data are revolutionizing parasitological research. The applicability of these important tools may lead to improved diagnosis and control of many important pathogens. Antibodies have been developed to identify helminth eggs [108,109], circulating antigen complexes [110], and parasite antigens (coproantigens) released in host feces. Fraser and Craig (1997) [111] hypothesized that helminth coproantigens can be detected by enzyme-linked immunoassays, and such coproantigen enzyme-linked immunosorbent assays (ELISA) have certain advantages over conventional serum antibody assays. Antibody-based methods against geohelminth antigens can be used to detect human immunoglobulins (IgE) [112,113]. Commercial antibody detection tests are available for some STH infections, but because of their low sensitivity and specificity, they are often poorly suited to field conditions and also not able to differentiate current and past infections. More recent alternative methods include detection of antigen and antibodies by ELISA [114], the latex agglutination test [115], the indirect hemagglutination test (IHA), the intradermal test [116], and polymerase chain reaction (PCR) [117] based identification approaches. The PCR-based approaches allow resolution of infection to the genotype level and bring some clarity to the findings of asymptomatic geohelminthiasis. Numerous conventional, real-time PCRs have been designed and proved to be highly sensitive and specific for the detection of microbial agents and enteric pathogens [118-120]. However, although molecular techniques such as luminex-PCR [121] or real-time PCR [122] have proven to be highly specific, sensitive, and reproducible diagnostic methods, their application in lower- and middle-income countries is difficult in view of the elevated cost, instruments, and requirement for a skilled person to perform the test.

Eosinophilia and mild or moderate anemia are also common features of geohelminth infections. Microscopic observations of Charcot-Leyden crystal in fecal or sputum samples of patients may prove beneficial in diagnosing an infection [9,83]. During chronic infection, the occult blood (benzidine) test may show a positive result. The clinical manifestations of geohelminth infections can be varied and depend on the location of the larvae. Colonoscopy is useful for the detection of whipworms in the rectum [123]. Capsule endoscopy may provide substantial benefit for therapeutic studies of geohelminth infections in the treatment of inflammatory diseases.

Table 3. Commonly used drugs against geohelminthiasis: their mechanism of action, recommended dosage, and adverse effects [126,127]

Drugs	Mechanism	Adverse effects	Recommended dosage		Others
			Adults	**Children**	
Benzimidazole compounds					
Mebendazole	Destroys the cytoplasmic microtubules in the worm's intestinal cells. This blocks the uptake of glucose and other nutrients, resulting in death of the helminth.	Generally very well tolerated. Abdominal pain, diarrhea, nausea, vomiting, headache and dizziness. Hypersensitivity reactions such as fever, skin rash, and pruritis.	500 mg as a single dose or 100 mg bid x 3d	500 mg as a single dose or 100 mg bid x 3d	Safe to use in children between 12 and 24 months when given at the same dose as for older children. Distribution: Highly protein bound
Albendazole	Inhibits tubulin polymerization in the parasite and blocks glucose uptake; energy levels are reduced resulting in death of the parasite.	Generally very well tolerated. Nausea, vomiting, and headache. Less common are hypersensitivity reactions.	400 mg as a single dose	400 mg as a single dose	A single 200 mg dose of albendazole has been shown to be both safe and effective in children older than 12 months and younger than 24 months. Children older than 24 months should receive the full 400 mg dose during mass drug administration (MDA) programs. Widely distributed; bile, CSF. Protein-binding: 70%
Thiabendazole	Inhibits fumarate-reductase system of worms, interfering with their source of energy.	One of the more poorly tolerated anthelminthics. Anorexia, diarrhea, nausea, abdominal pain, vomiting, dizziness, fatigue, and headache.	50 mg/kg daily divided into 2 doses, for 2-4 d or 50 mg/kg as a single dose	50 mg/kg daily divided into 2 doses for 2-4 d	The safety and effectiveness of thiabendazole in children weighing less than 13.6 kg are limited.
Triclabendazole	Inhibits fumarate-reductase system of worms, interfering with their source of energy.	Generally well tolerated. Mild and transient abdominal pain, biliary colic, nausea, fever, and hepatomegaly.	25-50 mg/kg daily divided into 2 doses, for 2-3 d or 50 mg/kg as a single dose	10 mg/kg as a single dose or bid x 1d	Uses of triclabendazole in children are limited. Children in fascioliasis and paragonimiasis-endemic regions have been successfully treated with triclabendazole without pediatric-specific adverse reactions.
Other antihelminthic agents					
Pyrantel pamoate	Binds to an ion channel that forms a nicotinic acetylcholine receptor on the body muscle of nematodes which in turn leads to depolarization and spastic paralysis of the nematode muscle.	Generally mild and transient and include diarrhea, abdominal pain, nausea, vomiting, and headache.	11 mg/kg as a single dose	11 mg/kg x 1d (not to exceed 1 g)	Not very effective in treating either trichuriasis or strongyloidiasis.
Levamisole	Binds to an ion channel that forms a nicotinic acetylcholine receptor on the body muscle of nematodes which in turn leads to depolarization and spastic paralysis of the nematode muscle.	Generally well tolerated. Nausea, vomiting, abdominal pain, dizziness, and headache.	150 mg as a single dose	2.5-3 mg/kg as a single dose	No specific adverse effects have been reported.
Praziquantel	Increases cell membrane permeability in susceptible worms, which leads to tegumental damage and paralytic muscular contraction, leading to worm death and elimination.	Dizziness, drowsiness, headache, and malaise, abdominal cramps or pain, and loss of appetite.	25 mg/kg as a single dose	10-25 mg/kg as a single dose, or 40 mg/kg/d in 1-2 doses x 1d, or 60-75 mg/kg/d in 1-3 doses x 1-2d	Very safe drugs. Not recommended for children younger than 4 years. Distributes into CSF, enters breast milk.
Piperazine citrate	Produces a neuromuscular block resulting in muscle paralysis of the worms which are consequently dislodged and expelled in the faeces.	Nausea, vomiting, colic, abdominal pain, diarrhea, urticaria, skin rashes, headache, bronchospasm, dizziness, confusion and blurred vision.	4.5 g as a single dose repeated once after 14 days	As a single dose, repeated once after 14 days. <1 yr: 120 mg/kg (only upon medical advice), 1-3 yr: 1.5 g, 4-5 yr: 2.25 g, 6-8 yr: 3 g, 9-12 yr: 3.75 g	Distributes into breast milk.

Abbreviations: [1]CSF, cerebrospinal fluid; bid, twice daily; x, times; d, days; g, gram; yr, year; mg, milligram; kg, kilogram; [2]mg/kg milligram per kilogram; [3]mg/kg/d milligram per kilogram daily

Treatment

The onset of a geohelminthic infection often prompts patients to seek medical attention. According to the WHO guidelines [124,125], when a presumptive diagnosis of geohelminthiasis is made, all such patients should be treated with an antihelminthic drug. Oral rehydration therapy is an essential first step that can be used to correct dehydration due to diarrheas of any etiology and has markedly reduced the mortality rate caused by diarrhea. The beneficial effect of chemotherapy is to remove the worm burden, which immediately alleviates symptoms and may reduce the rate of transmission. A variety of antihelminthic drugs such as pyrantel pamoate, mebendazole, albendazole, piperazine, and praziquantel have shown effectiveness in the treatment of geohelminthiasis (Table 3), although options are becoming limited due to globally emerging drug resistance.

Hookworm resistance to benzimidazoles was reported from Mali in 1997 [128], and due to its toxicities in laboratory animals [129], this drug is not recommended as an empirical therapy for infants and young children. Benzimidazoles generally are contraindicated in patients with dyscrasias, leukopenia, or liver cirrhosis. Benzimidazole resistance can occur as a consequence of the spread of point mutations in geohelminth tubulin alleles. Tubulin is the target site for mebendazole and albendazole drug action [83]. The drug pyrantel pamoate has also shown resistance against hookworm and whipworm [83,130]. As such, either an alternative drug of choice or oxantel formulated with pyrantel pamoate in combination should be used for the patients affected by these infections.

Few studies have indicated that anthelminthic chemotherapy with a single dose of albendazole (400 mg/day) is a feasible, effective, and low-cost approach to worm control for school-aged children [131]. Some of the growth retardation effects caused by hookworms may be reversible after anthelminthic treatment with albendazole [80,132-135]. Mebendazole 100 mg twice daily for three days, pyrantel pamoate 10-15 mg per kilogram of body weight or levamisole 3-5 mg per kilogram of body weight as a single dose produces cures in most cases [30]. Administration of vitamin B_{12}, folic acid, and iron therapy may be required in heavily infected children. Rarely, blood transfusions are necessary in severe cases of anemia. Anaphylactic shock following therapy is a risk; it may occur due to the death of a large number of worms. When intestinal obstruction is imminent, piperazine citrate is the recommended choice by clinicians, which paralyzes the worms and facilitates relaxation of the bolus. Piperazine and pyrantel pamoate are antagonistic and should not be used together [74]. Surgery may be needed in cases of intestinal obstruction, which requires immediate intervention. Pregnant mothers should be treated after the first trimester to avoid any complications.

Treatment can be administered by doctors or health workers, or by teachers who have been trained to treat children at school. As re-infection is likely to occur [130,136], treatment should take place once a year, or every six months. Numerous studies in developing countries have shown that de-worming benefits the physical growth and fitness of children by partially reversing the effects of stunted growth [80,132,133], improving appetite [137,138], and improving cognitive performance [12]. Treatment of school-age children will also benefit the local community [139], since children not only carry the greatest burdens of worms but can also be a major source of infection. The occurrences of drug failure and possible anthelminthic drug resistance have led to the search for alternative modes of prevention.

Prevention

Health control measures are, at best, long-range strategies for control of geohelminthiasis in tropical countries. The most effective intervention strategies to prevent re-infection and minimize the potential for the development of drug resistance [130,136] in the long term are non-chemotherapeutic-based options. Cure alone is almost useless in stamping out geohelminthic infections, because the patient can easily acquire infections due to lack of sanitation. A systematic review and meta-analysis by Ziegelbauer *et al.* (2012) [140], revealed that providing access to and promoting the use of sanitation facilities is an effective control measure for soil-transmitted helminthiasis. The authors of the Ziegelbauer study stated that to achieve lasting effects in improving sanitation, the community must be involved in the process. This entails creating education and communication strategies that provide information that is specifically targeted at a particular community. This must be done to change the ways that humans behave. The availability of improved sanitation together with chemotherapy and health education could lessen the problem of geohelminthiasis. These measures would improve the quality of life, particularly for children. A change in emphasis to specific community-tailored information would reinforce other programs against helminthiasis

and it would be economically more sustainable. The authors of the Ziegelbauer study also noted that there would be side benefits in reducing susceptibility to other diseases such as schistosomiasis and trachoma and that it would lower the rate of diarrhea. All this would have positive effects on child mortality rates.

Concluding remarks

Geohelminth infection continues to be a significant cause of mortality and morbidity in low- and middle-income countries. Although several hospital-based studies document the relative importance of geohelminthiasis, there have been few studies with a defined population denominator that allows calculation of the incidence rate in the community. There is a need to establish the incidence, prevalence, disease burden, and distribution of particular helminths in many parts of the world so that regional, national, and global estimates can be made. Numerous flotation and concentration methods followed by microscopy are currently being used in many parts of the world for detection of helminth ova/larvae, but they are time consuming, labour intensive and relatively insensitive. Hence, molecular biological approaches which offer speed, sensitivity, and specificity may lead to improved diagnosis and control of many important pathogens in field settings. However, their application as diagnostic or epidemiological tools is difficult in view of the elevated cost, special equipment, and skilled personnel required to perform the test. To overcome the drawbacks of these existing techniques, there is a need to develop a rapid test method which is robust, cost effective, easy to handle, and applicable in clinical and field settings.

Antihelminthic drugs, which vary considerably from place to place and which are in a continuous state of evolution, must be updated. Targeted interventions such as maintaining strict personal hygiene, clean water, sanitation, health education, good sewage management, and improved living conditions have been proven to be effective in reducing geohelminth infection and must be adopted. Advances in molecular biological techniques have created opportunities for the identification of proteins expressed by helminth parasites. This, together with helminth genome sequence information, will allow us to analyze the interaction between parasites and their hosts at the molecular level. Armed with these powerful experimental approaches, we can be optimistic about the control of geohelminth infections in the future.

Geohelminthiasis, which continues to have a global impact, cannot be adequately controlled with the existing prevention and treatment measures. Innovative strategies against the most common geohelminths could provide substantial benefits. This study emphasizes the need for a multi-sectoral approach to reduce the morbidity and mortality associated with geohelminth infections to such levels that these infections are no longer of public health concern.

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Corresponding author

Suvash Chandra Ojha
Molecular Medicine, Faculty of Science
Mahidol University
272 Rama VI Rd, Bangkok, Thailand
Email: suvash2u@gmail.com

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