Soil-transmitted helminth infections

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More than a quarter of the world's population is at risk of infection with the soil-transmitted helminths *Ascaris lumbricoides*, hookworm (*Ancylostoma duodenale* and *Necator americanus*), *Trichuris trichiura*, and *Strongyloides stercoralis*. Infected children and adults present with a range of medical and surgical conditions, and clinicians should consider the possibility of infection in individuals living in, or returning from, endemic regions. Although safe and effective drugs are donated free to endemic countries, only half of at-risk children received treatment in 2016. This Seminar describes the epidemiology, lifecycles, pathophysiology, clinical diagnosis, management, and public health control of soil-transmitted helminths. Previous work has questioned the effect of population-level deworming; however, it remains beyond doubt that treatment reduces the severe consequences of soil-transmitted helminthiasis. We highlight the need for refined diagnostic tools and effective control options to scale up public health interventions and improve clinical detection and management of these infections.

Introduction

Helminthic parasites affect more than a quarter of the world's population and cause substantial disease and disability.[1,2] Because of the role of contaminated soil in their transmission, infections with *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm (*Ancylostoma duodenale* and *Necator americanus*) are, in public health terms, known as soil-transmitted helminthiasis (STH). In this Seminar, we also include the soil-transmitted helminth *Strongyloides stercoralis*, which is an important, but often neglected, cause of severe morbidity.[3]

WHO and partners support STH-endemic countries to implement large-scale anthelmintic treatment of children and women of reproductive age (except in the first trimester of pregnancy). The primary, and most realistic, aim of such mass drug administration is to control STH morbidity by reduction of infection intensity and prevalence.

Search strategy and selection criteria

We searched PubMed, the Cochrane library, MEDLINE, and Embase without restriction of dates or language using "epidemiology", "pathophysiology", "immunology", "genetics", "clinical", "diagnosis", "treatment", "management", and "research" sequentially in combination with each of the following terms "soil-transmitted helminths", "soil-transmitted helminth infections", "soil-transmitted helminthiasis", "soil-transmitted helminthiases", "STH", "*Ascaris lumbricoides*", "*Trichuris trichiura*", "hookworm", "*Ancylostoma duodenale*", "*Necator americanus*", and "*Strongyloides stercoralis*". Titles and abstracts were reviewed, and if found relevant for this Seminar, included for review of full text. Publications presenting strong evidence, or containing information especially relevant for the Seminar were included in the final reference list, prioritising publications from the past 5 years. Reference lists were reviewed and additional references included if not already identified through the main search strategy. Book chapters were included by relevance and importance in the field.

This Seminar provides a state-of-the-art overview of the clinical diagnosis and management of STH. We aim to bring together the evidence base for clinical case management with that of public health control, to inform and leverage both these approaches to control STH (table 1). Furthermore, we discuss reviews that question the effect of population-level deworming, and present the main arguments of the debate that has followed.

Epidemiology

Infections with soil-transmitted helminths are most common in people living in, or coming from, areas with poor access to adequate water, sanitation, and hygiene.[4,5] Although most common in low-income and middle-income countries, STH also occurs in high-income countries in vulnerable populations (figure 1).[6,7] In 2010, WHO estimated that 875 million children needed regular STH treatment. This excludes *S stercoralis*, which also infects up to 100 million people globally.[1,8] Data from the past decade suggest that disability-adjusted life-years (DALYs) associated with STH have declined; however, this reduction has mainly occurred in upper-middle-income countries, with the disease burden becoming more concentrated in low-income and lower-middle-income countries.[9] STH-associated DALYs potentially grossly underestimate the true disease burden, for example, through inadequate attribution of hookworm-induced anaemia.[10]

As of 2013, *A lumbricoides* (roundworm) infects an estimated 804 million people, most commonly children and adolescents.[11,12] Ascaris-associated DALYs have been reduced to around 1 million, a quarter of the disease burden in 1990.[13] Mortality accounts for approximately a sixth of the disease burden; severe morbidity is largely related to wasting.[2] Occasionally, infection with *Ascaris suum* occurs by contact with domestic pigs, including in countries non-endemic for human STH.[14]

T trichiura (whipworm) infects an estimated 477 million individuals, with the highest infection prevalence and intensity in children.[12,15] However, data are scarce and suspicion of infection should not be limited by endemicity maps. Over the past 10 years, with reductions

	Clinical diagnosis and management	Public health control
Diagnosis	Individual	Community level (eg, in selected schools)
Diagnostic criteria	Parasitological	Residence in an area with soil-transmitted helminthiasis prevalence >20%
Treatment approach	Single dose or multiple dose	Single-dose periodic mass treatment
Threshold for treatment	Travel history, symptoms and signs, positive laboratory test	Estimated prevalence of infection in target population
Treatment objective	Parasitological cure	Decreased worm burden; reduction in transmission
Ancillary treatment	Based on clinical signs and symptoms	Typically only if included in mass treatment (eg, vitamin A supplementation)
Follow-up	Parasitological test of cure; improvement in associated health conditions	Not usually done
Health education (sanitation and hygiene)	Recommended	Recommended

Table 1: **Clinical and public health control of soil-transmitted helminthiasis**

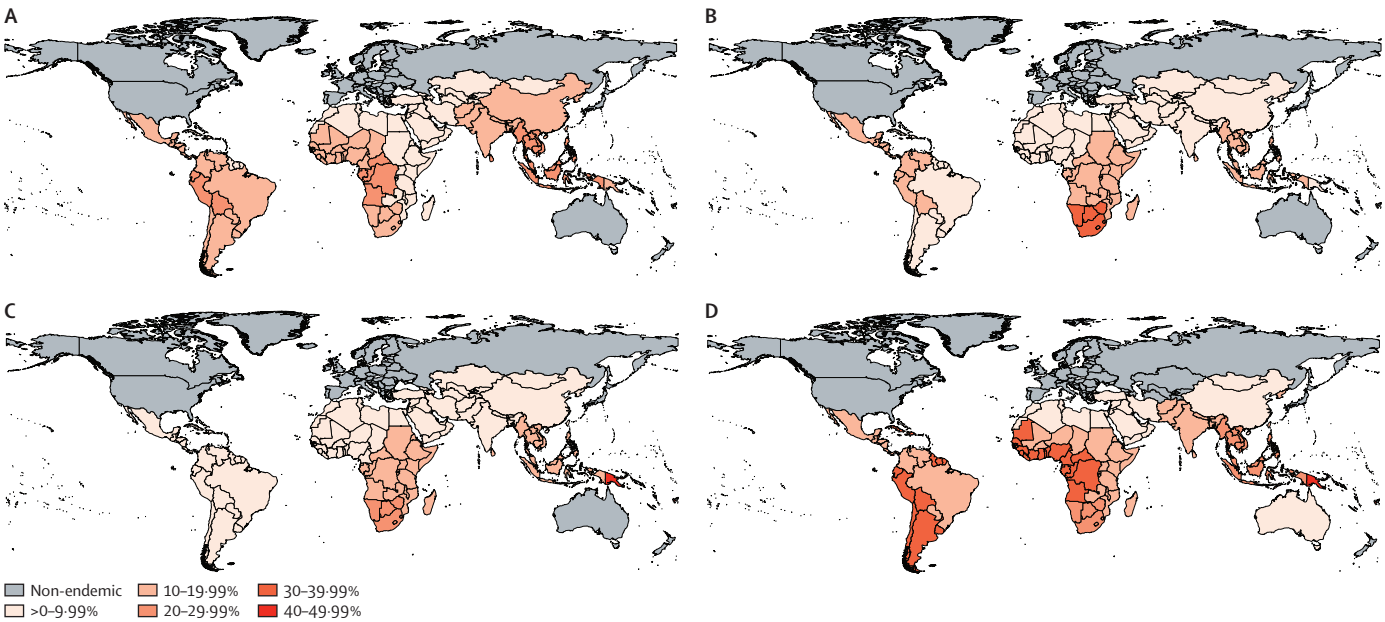

Figure 1: **Prevalence by global regions of (A) *Ascaris lumbricoides* (for 2010), (B) *Trichuris trichiura* (for 2010), (C) hookworm (*Necator americanus* and *Ancylostoma duodenale*; for 2010), and (D) *Strongyloides stercoralis* (for 2011)**

Data for (A), (B), and (C) from Pullan and colleagues.[2] Data for *S stercoralis* are especially scarce and may be associated with strong publication bias; estimates from data by Schär and colleagues.[3] Data from single community-based studies suggest that *S stercoralis* might be present also in Australia, Israel, and Japan (which is marked as non-endemic on the map).

in infection intensity, DALYs due to trichuris have declined to just more than 500 000 in 2010.[13] As for *A suum*, *Trichuris suis* can also infect human beings.[14]

A duodenale and *N americanus* (hookworms) infect an estimated 472 million people.[12] By contrast with ascariasis and trichuriasis, hookworm prevalence and infection intensity are highest in adults, although children are commonly infected.[16] *N americanus* is the most widespread hookworm, found across sub-Saharan Africa, the Americas, and Asia, whereas *A duodenale* is more focal. Both species can coexist in the same area and within the same individuals. Hookworm disease burden is largely due to anaemia, and estimates suggest the burden could be as high as 4 million DALYs, with productivity losses of up to US$139 billion annually.[13,17]

S stercoralis (threadworm) infects up to 100 million people;[1,8] however, data are scarce and suspicion of infection should not be limited by endemicity maps.[3,8] In addition to inadequate sanitation, risk factors for infection include immunosuppression, certain malignancies, human T-cell lymphotropic virus type 1 infection, and alcoholism.[3,8] In central Africa, *Strongyloides fuelleborni*, a non-human primate *Strongyloides* species, can also infect human beings.

Lifecycles

A lumbricoides infects individuals through faecal–oral transmission (figure 2A).[22] After embryonated eggs are swallowed, first-stage larvae (L1) hatch, moult into second-stage larvae (L2), penetrate the intestinal mucosa,

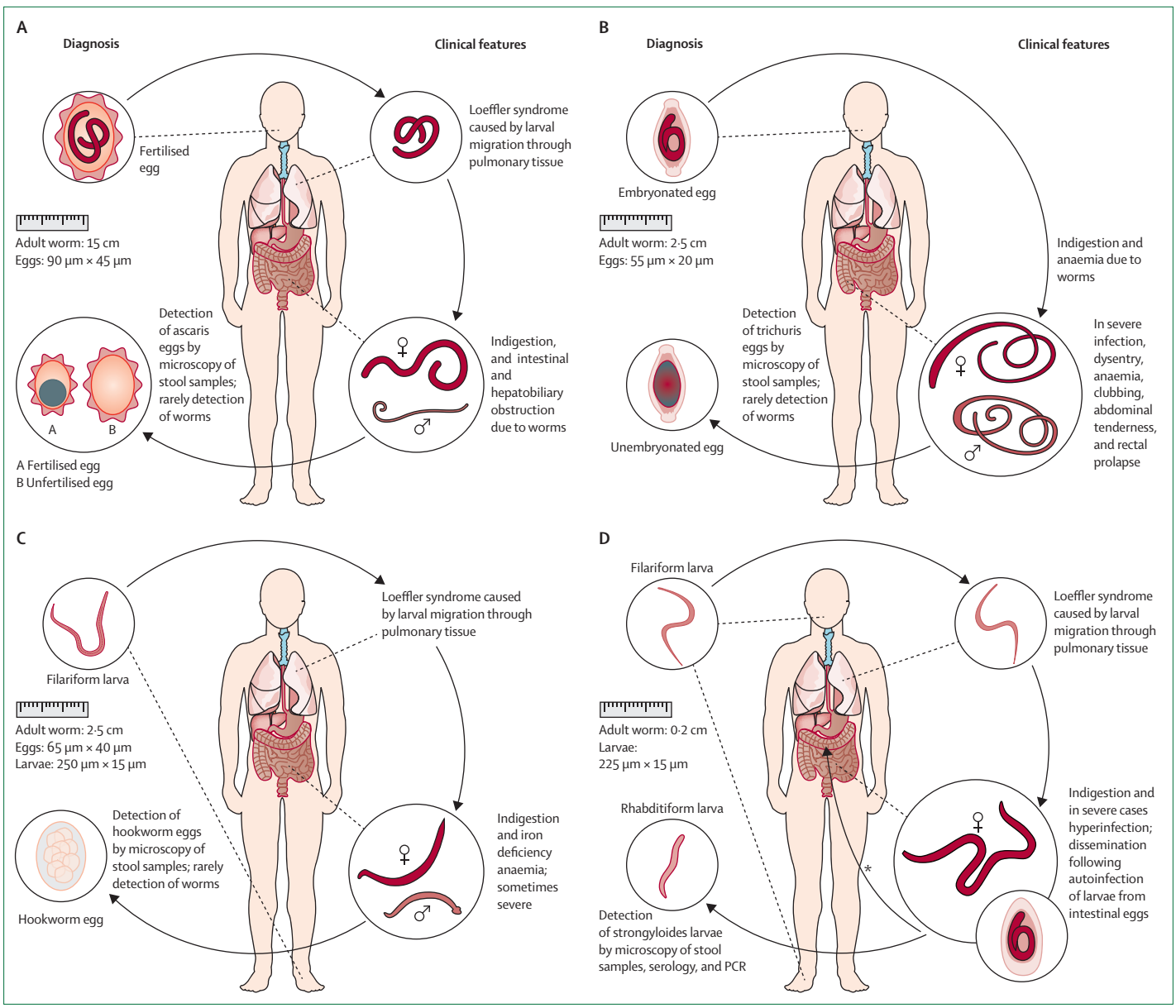

***Figure 2*: Transmission of *Ascaris lumbricoides* (A), *Trichuris trichiura* (B), hookworm (*Ancylostoma duodenale and Necator americanus*; C), and *Strongyloides stercoralis* (D)**
Adapted from previously published data.[18–21] *Arrow indicates autoinfection.

See Online for appendix

and migrate to the pulmonary circulation. Third-stage larvae (L3) migrate across the alveolar wall, as they are too large to pass through capillaries, and traverse the tracheobronchial tree to the larynx and into the small intestine, to moult into fourth-stage larvae (L4) and adult worms. Adult female *A lumbricoides* worms produce thousands of eggs daily that pass in the stool. Egg production occurs 2–3 months after infection, and worms can live for a few years. Eggs can remain viable in warm, moist soil for years.[23]

T trichiura is transmitted through a faecal–oral cycle, with embryonated eggs ingested via food or hands, and hatching into larvae that moult in the small intestine. Unlike ascaris, trichuris does not migrate through the lungs (figure 2B).[24] The larvae attach to the intestinal villi and develop into adult worms, which reside in the caecum and ascending colon. Female worms lay thousands of eggs daily for several years. The eggs pass in the stool and embryonate in warm, moist soil, where they can survive for months.[23,25]

A duodenale and *N americanus* larvae are free-living in the soil, and infect people by penetration of the skin, typically bare feet. Larvae are transported to the pulmonary capillaries, where they penetrate the alveolar wall, pass to the larynx, and are swallowed (figure 2C).[22] Larvae moult and develop into mature worms in the

small intestine over 1–2 months, and can survive for months (*A duodenale*) or years (*N americanus*). A female worm releases thousands of eggs daily into the stool which, after 5–10 days, hatch in warm, moist, sandy soil, or in faeces. Rhabditiform larvae (L1) become infective after moulting to L2 and L3 larvae that survive for several weeks.[23]

In addition to percutaneous infection, *A duodenale* can be orally ingested, potentially resulting in Wakana syndrome (nausea, vomiting, pharyngeal irritation, cough, and dyspnoea). Hookworms can remain dormant in connective tissue or muscle. Zoonotic *Ancylostoma* species also infect people, causing cutaneous larva migrans, a self-limiting skin infection. Data suggest that such species can cause human pathology similar to *A duodenale* and *N americanus*.[26]

S stercoralis follows a complex lifecycle that might take multiple routes, including a complete lifecycle outside the human host. Filariform larvae can infect human beings percutaneously and orally (figure 2D).[27] Following penetration of the skin, typically feet, larvae are transported to the pulmonary capillaries where they penetrate alveoli, pass to the larynx, and enter the small intestine, where they mature into adult worms. Oral infection follows the same cycle after larvae penetrate the intestinal mucosa.

Female adults penetrate the gut wall, lodge in the duodenal and jejunal lamina propria, and lay up to 50 eggs daily. Eggs hatch within the gut wall, and rhabditiform larvae migrate to the lumen and are passed with stool. Larvae might penetrate the colonic wall or perianal skin to enter a new cycle, or disseminate to other organs. This autoinfection enables chronic strongyloidiasis that might last decades, without repeated external exposure.[28] Larvae (or unhatched eggs) in the stool can survive in moist soil for weeks, and develop into infective larvae.[29] *S fuelleborni* follows the same lifecycle.[8]

Pathophysiology

A lumbricoides can cause a type-1 hypersensitivity reaction to larval stages (Loeffler syndrome; appendix), and adult worms can cause intestinal pathology (figure 3A). Adult ascaris can lead to small bowel obstruction, volvulus, or intussusception, especially in children, or can invade orifices leading to appendicitis, cholecystitis, pancreatitis, and gastric ascariasis. Pathology is positively related to worm burden, although non-linearly.[30] *A lumbricoides* might alter nutrition and intestinal microbiota,[31,32] although ascaris can protect against severe enteric

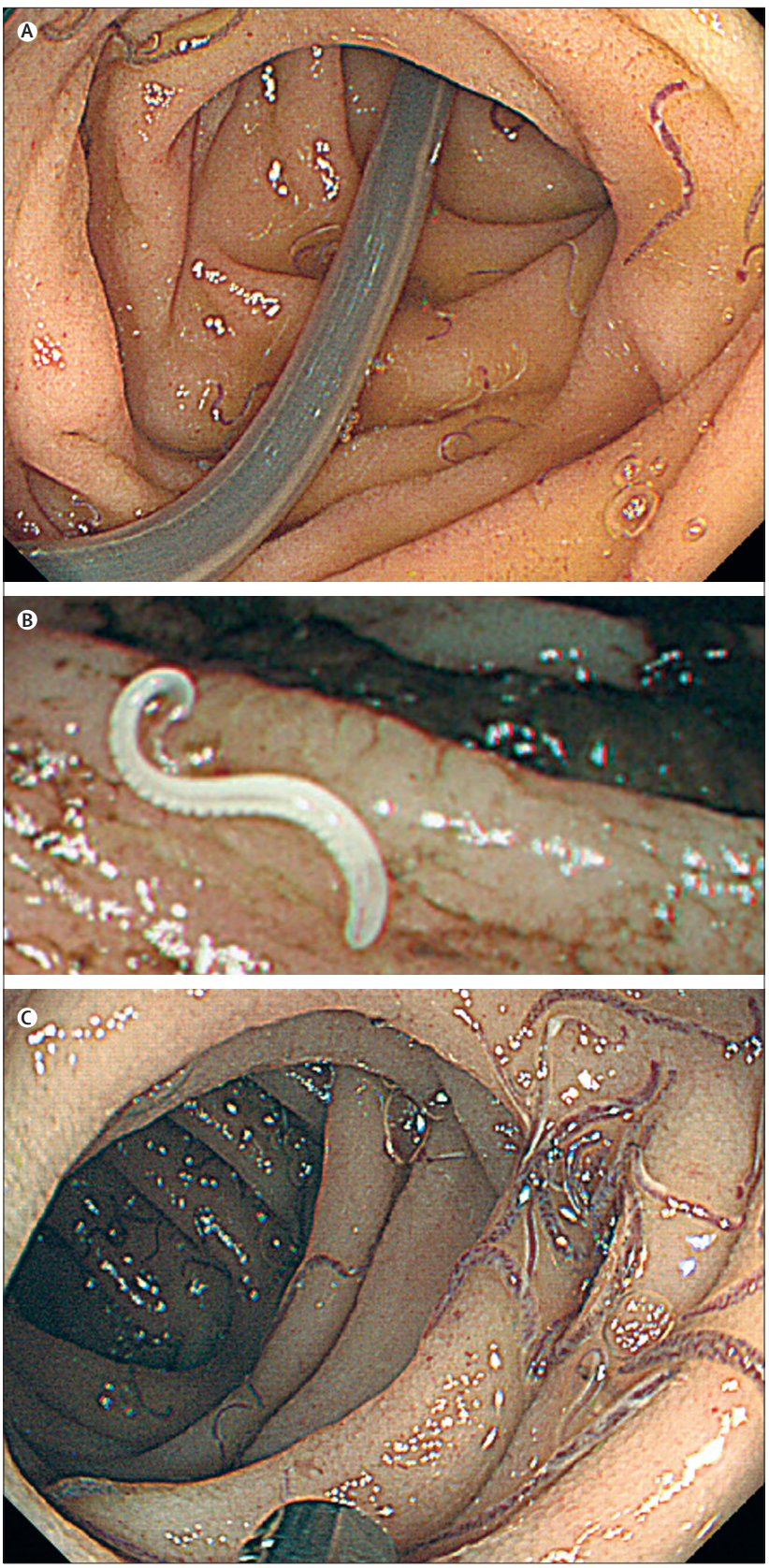

***Figure 3*: Endoscopic images of intestinal *Ascaris lumbricoides* and hookworm co-infection (A), *Trichuris trichiura* infection (B), and hookworm infection (C)**
The partially visible ascaris worm is large in relation to the lumen, and multiple blood-filled hookworms can be visualised (A). The whip-shape part (not visible) of trichuris is burrowed into the mucosa (B), and blood loss associated with the hookworm infection is evident (C). Reproduced with permission by Kunimitsu Inoue.

infections.[33] Anaemia might result from mucosal bleeding in the upper gastrointestinal tract or through generalised inflammation.[34]

Similar to other helminthiases, ascaris induces a predominantly T-helper-2 cell (Th2) immune response.[35] Increased IgE titres and eosinophilia are common in acute infection, and host-protective and parasite evasion features are regulated by interleukin 10 and other cytokines.[36,37] The peak age of infection might shift as partial immunity develops,[38] and host genetic factors play a part in determining disease presentation, including resistance to reinfection.[39] Ascaris-induced immunomodulation might affect co-infections, including HIV, tuberculosis, malaria, and human papillomavirus.[40–43] Ascariasis might also be a risk factor for asthma and atopy, possibly through cross-reaction between parasite, mite, and insect epitopes.[36,44]

T trichiura's slender anterior burrows into the intestinal mucosa (figure 3B), causing petechial lesions, blotchy mucosal haemorrhage, and oozing.[45] Although not consistently apparent on endoscopy,[45] trichuris can cause colonic mucosal inflammation.[17,46,47] Morbidity is associated with infection intensity,[48] and trichuriasis can affect both mucosal and systemic immune responses.[49,50] Anaemia can be severe in vulnerable individuals, such as pregnant women, although not usually as pronounced for trichuris as with hookworm.[45,51]

Eosinophils are typical of acute trichuriasis, and affect local gut pathology.[52] In animal models, trichuris worm expulsion is associated with intestinal epithelial cell turnover, stimulated by cytokine responses.[53] By contrast with ascaris infection, trichuris is not associated with changes in intestinal microbiota,[31] but might protect against diarrhoeal pathogens.[33]

A duodenale and *N americanus* larvae might cause a type-1 hypersensitivity reaction during pulmonary migration (Loeffler syndrome), or, once in the small intestine, adult worms burrow their teeth into the mucosa causing blood loss (figure 3C). Hookworm infection is a major cause of anaemia globally, particularly in children and pregnant women.[54,55]

As with other helminths, hookworm infection is associated with a Th2 cell polarised response, both systemically and in the intestinal mucosa.[56] Elevated IgE titres, interleukin 5, and eosinophilia are common in acute infection.[57] However, unlike other helminth infections, repeated exposure does not seem to stimulate resistance to reinfection, possibly because of immunological down-regulation.[58,59]

S stercoralis larvae might cause a type-1 hypersensitivity reaction (Loeffler syndrome),[60] whereas adult worms cause local inflammation in the intestinal mucosa.[28] A Th2-dominated immune response is a pivotal factor, especially in preventing severe morbidity.[61] Severe infection, whether intestinal and pulmonary or disseminated, appears to be caused by a defective Th2 response that enables larval reproduction to exceed effective host control.[62] Bacterial sepsis is an independent predictor of shock and mortality in disseminated infection.[63] Eosinophils are a prominent feature of strongyloidiasis, and might provide host protection, especially in early-stage infection.[64]

Clinical presentation

The distribution of STH is overdispersed—in other words, relatively few heavily infected individuals harbour almost all of the worms.[15,65] This dispersion might be due to both exposure and host susceptibility.[66] Most individuals with low and moderate infection intensities have limited or non-specific symptoms.

A lumbricoides infection is commonly asymptomatic or produces mild, non-specific symptoms. In patients seeking health care, symptoms depend on the phase of the parasite's lifecycle and infection intensity. Eosinophilic pneumonia (Loeffler syndrome) might occur 10–14 days after infection because of a typically self-limiting inflammatory reaction to larvae migrating through pulmonary tissue.[60,67] Patients present with urticaria, cough, dyspnoea, and haemoptysis, and might have abnormal auscultatory breath sounds. In rare cases, pleuritis or pleural effusion might occur.[68]

Infections with adult ascaris can present as acute abdomen, including upper gastrointestinal bleeding, small bowel obstruction, volvulus and intussusception, peritonitis, and gastric ascariasis, even with perforation.[34,67,69,70] Hepatobiliary and pancreatic ascariasis cause five broad clinical syndromes: biliary colic, acute cholecystitis, acute pancreatitis, acute cholangitis, and hepatic abscess.[71] Hospital-based data from India suggest that ascaris causes about half of biliary disease cases, a third of pancreatitis cases, and 15% of liver abscesses and biliary lithiasis.[72,73] Clinicians in endemic areas should maintain a high suspicion of ascaris infection, as cases might present as surgical emergencies.

Asthenia, lack of appetite, abdominal discomfort, diarrhoea or other altered bowel habits, and weight loss are common in intestinal ascariasis. Anaemia and occult or fresh faecal blood are common with mucosal haemorrhage, and abdominal distension, increased bowel sounds, and abdominal tenderness are typical of intestinal obstruction. Jaundice, fever, or abdominal tenderness might be found in hepatobiliary and pancreatic ascariasis, dependent on the clinical syndrome.[67]

T trichiura infection is commonly asymptomatic. Loeffler syndrome does not occur. Symptomatic individuals complain of asthenia, abdominal pain, and diarrhoea, and severe cases present with trichuris dysentery syndrome; signs include anaemia, digital clubbing, abdominal tenderness, and rectal prolapse.[48] In high-intensity infections, anaemia can be severe.[45]

A duodenale and *N americanus* infections are commonly asymptomatic. So-called ground itch might follow skin penetration with intensely pruritic, tortuous, vesicular

lesions caused by migration of larvae. Although less common than in ascariasis, eosinophilic pneumonia with cough, dyspnoea, and haemoptysis might occur during larval pulmonary migration.[60] In peroral infection, nausea, vomiting, pharyngeal irritation, cough, and dyspnoea can occur (Wakana syndrome).[55]

Once worms are established in the small intestine, symptoms include asthenia, abdominal pain, and diarrhoea, with findings of pallor, tachycardia, tachypnoea, oedema, abdominal tenderness, occult faecal blood, and occasionally melaena.[74] In heavy-intensity infections, blood loss gradually depletes patient erythrocytes and nutrients, and can result in severe anaemia.[75] Individuals prone to undernutrition and malaria, such as children and pregnant women, are especially vulnerable.[54] By contrast with ascaris, the small size of hookworms makes surgical complications uncommon.

S stercoralis infection is commonly asymptomatic in otherwise healthy individuals. Pulmonary migration of larvae presents as eosinophilic pneumonia with cough, dyspnoea, wheezing, and haemoptysis.[60] In hyperinfection, pulmonary infection can become severe and even fatal. Chronic strongyloidiasis might present with asthenia, anorexia, nausea, abdominal pain, diarrhoea, and abdominal tenderness.[76] Larva currens is common in chronic infection, and presents as serpiginous urticaria, typically over the abdomen, torso, buttocks, and groin.[28] Lesions last for a couple of days and can reoccur weeks to months later. Rarely, immune-mediated disease can occur, for example, reactive arthritis.[77]

In immunocompetent hosts, autoinfection produces negligible symptoms. However, in immunosuppressed individuals, autoinfection can lead to strongyloides hyperinfection syndrome, potentially occurring decades after the initial infection.[63] Strongyloides hyperinfection syndrome typically presents as intestinal or pulmonary failure. Cutaneous and intestinal mucosal bleeding can be pronounced. If untreated, strongyloides hyperinfection syndrome has a mortality ratio of nearly 100%. Disseminated strongyloidiasis occurs when large numbers of parasites spread to affect any organ, including hepatic, urogenital, central nervous, musculoskeletal, and cardiovascular systems. High-risk individuals include immunosuppressed patients—individuals on immunosuppressive drugs, especially corticosteroids and vincristine—and patients with hypogammaglobinaemia, haematological malignancies, and human T-cell lymphotropic virus type 1 infection.

Diagnosis

Diagnosis of STH requires knowledge of the parasites' geographical distributions, and an understanding of the varied, and often overlapping, clinical picture of disease. Visitors who return from endemic areas typically present with acute, light-intensity infections. Individuals living in, and emigrants from, endemic areas are prone to repeated exposure and chronic disease, some with very high worm

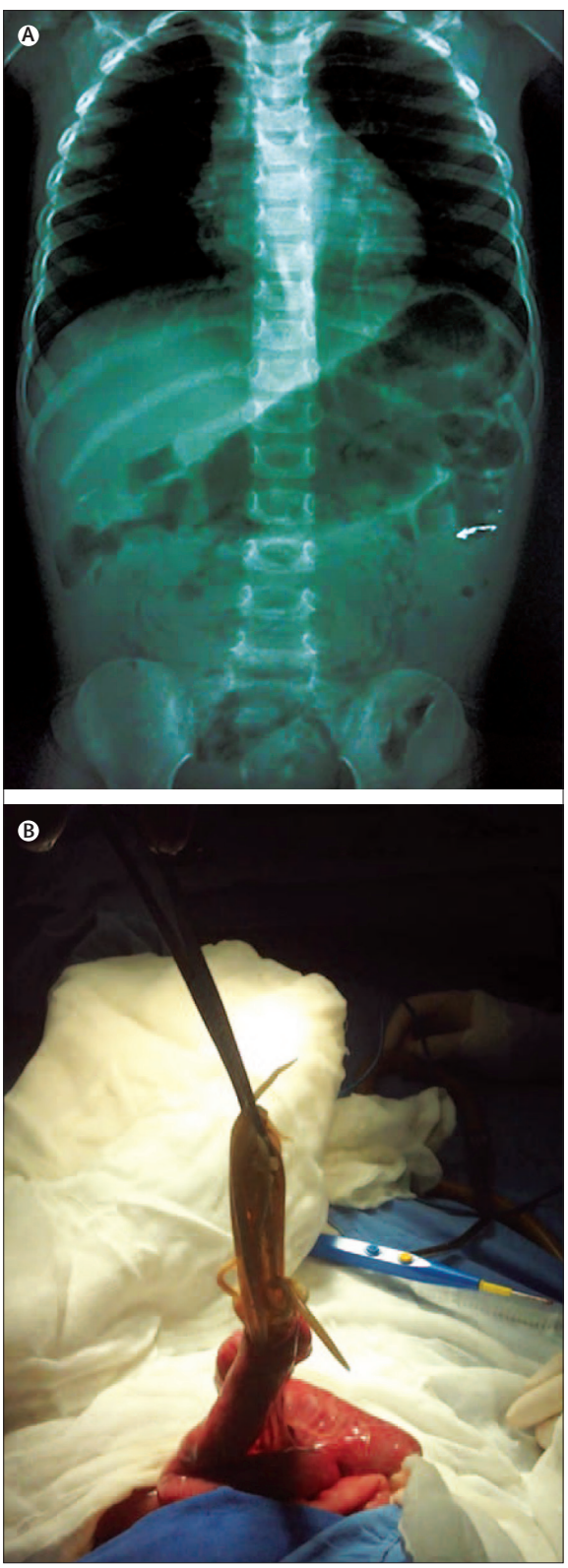

***Figure 4*: Ascaris-induced intestinal obstruction**
Plain abdominal x-ray of 3-year-old girl with ascaris-induced intestinal obstruction showing air-fluid levels, dilated bowel loops, and multiple worm structures (A); and ileum enterotomy with extraction of causative bolus of ascaris worms (B). Reproduced from Andrade and colleagues,[91] by permission of Wolters Kluwer Health.

burdens.[78,79] Besides widely used stool microscopy, antibody assays, although not yet standardised, might aid diagnosis of first-time infections and in stool-negative cases.[80] PCR assays are being developed both for clinical and public health management, although tests are not yet broadly available.[81] Co-infections with multiple parasites are common in endemic areas, making diagnosis challenging (appendix).[82,83]

Diagnosis of *A lumbridoides* requires identification of parasite eggs, larvae, or adult worms. In Loeffler syndrome, chest x-ray can show infiltrates (appendix), and bronchoscopy can show evidence of bronchitis. Examination of sputum, bronchoalveolar lavage, or gastric aspirate might reveal filariform larvae.[60] Eosinophilia and increased titres of IgE are associated with acute larval infections; however, the response is not ascaris-specific and might occur in other conditions, including other parasite infections and allergies.[84]

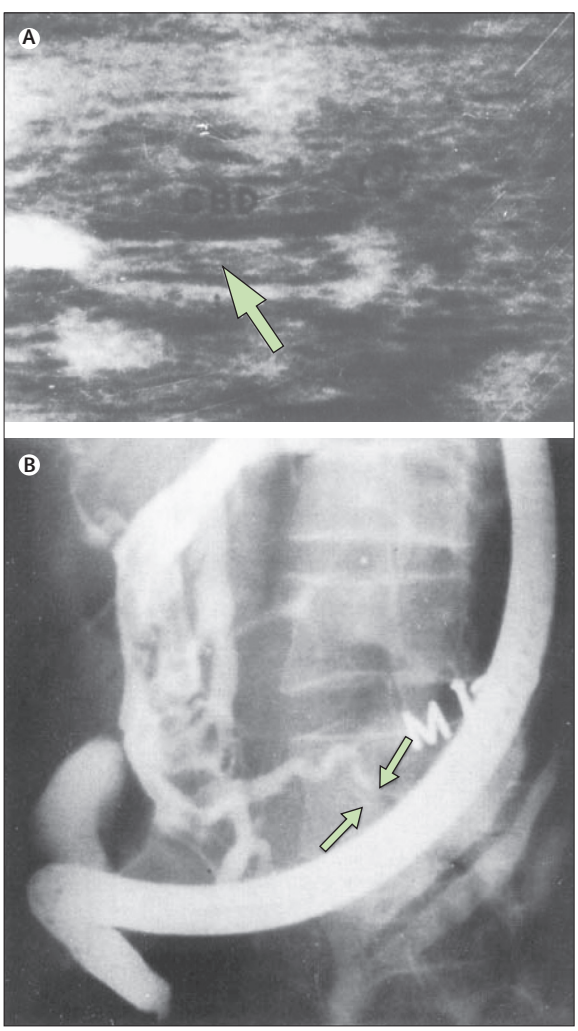

***Figure 5*: Biliary and pancreatic ascariasis**
Abdominal ultrasonography showing the dilated common bile duct containing a thick, long, non-shadowing echogenic strip with a central sonolucent tube (arrow), indicating an ascaris (A); and endoscopic retrograde cholangiopancreatography in ascaris-induced pancreatitis, showing the pancreatic duct containing a filling defect in the distal part (arrows) and the common bile duct containing multiple ascaris worms (B). Reproduced from Khuroo and colleagues,[73] by permission of John Wiley and Sons.

Light microscopy of stool samples remains the mainstay of identification and quantification of *A lumbricoides* eggs (figure 2).[85–87] Hospital-based laboratories commonly use egg concentration techniques, whereas simplified, field-friendly tests, such as the Kato-Katz technique, are used for public health control.[88] Treatment-induced worm expulsion is cumbersome and resource-consuming, and rarely used. Other techniques, including McMaster, FLOTAC, and mini-FLOTAC, concentrate the eggs and can be more sensitive than Kato-Katz.[87]

All techniques are limited by day-to-day variability and uneven distribution of eggs in stool, which might provide false-negative results, especially in low-intensity infection and post treatment.[87–89] In visitors returning from endemic areas, parasite eggs might not appear in stool for months after exposure or symptom onset. An IgG4 assay for detection of *A lumbricoides* haemoglobin might reflect recent exposure; however, the test cross-reacts with other helminths.[90]

In patients with acute abdomen, ultrasonography and plain abdominal x-ray might identify ascaris or signs of obstruction—for example, air–fluid levels, dilated bowel loops, and thickened bowel walls (figure 4).[67,92,93] CT and MRI scans can support the diagnosis.[94]

Ultrasonography remains a diagnostic tool of choice for hepatobiliary and pancreatic ascariasis (figure 5),[67,71] although its sensitivity can be poor.[93] Upper endoscopy might identify duodenal ascaris, and endoscopic retrograde cholangiopancreatography can be used to remove worms from ducts and duodenum (figure 5).[67,71] Case reports[34,95] indicate that capsule endoscopy might be an alternative diagnostic tool for small intestinal ascariasis.

In uncomplicated cases of *T trichuria*, stool microscopy is sufficient (figure 2), with limitations as for ascaris.[88,96] Colonoscopy can detect trichuris in challenging or severe cases (appendix), and biopsies might be needed to confirm diagnosis.[45,97] In trichuris dysentery syndrome, evaluation for iron-deficiency anaemia is essential.

With *A duodenale* and *N americanus*, Loeffler syndrome, although rare, can be diagnosed with chest x-ray (infiltrates), bronchoscopy (bronchitis), or identification of filariform larvae in sputum or bronchoalveolar lavage.[60] In intestinal infection, stool microscopy is the mainstay of diagnosis (figure 2), with limitations as for ascaris.[98] Although rarely used, capsule endoscopy can identify hookworms.[74,99,100] With any hookworm infection, it is essential to determine the degree of anaemia, typically featuring microcytic, hypochromic erythrocytes.

With *S stercoralis*, in Loeffler syndrome chest x-ray facilitates diagnosis and sputum, bronchoalveolar lavage, or lung biopsy might identify larvae. In intestinal infection, a single wet mount stool preparation can reveal filariform larvae,[101] although concentration of fresh stool

might be required. The Baermann method and Koga agar plate culture are more sensitive but less commonly used techniques.[86,102] A coproantigen test for *S stercoralis* has been found to be sensitive and to have low cross-reactivity with other helminths.[103] Duodenoscopy with duodenal biopsies can reveal eggs, larvae and adult worms, and plain abdominal x-ray, contrast-enhanced CT, and MRI can determine gut damage.[101]

Clinical alertness is essential in strongyloides hyperinfection syndrome, as severe infection can occur decades after initial exposure. One of the hallmarks of hyperinfection is a high strongyloides burden in affected organs, and targeted biopsies might identify adult worms, larvae, and eggs (figure 6).[28] Titres of IgE and eosinophils can be either highly elevated or depleted.[63] Serological tests have shown promising results,[105,106] and PCR of blood or CSF samples is available in some well resourced settings.[107,108]

Clinical management and follow-up

In addition to medical interventions (table 2), patients in endemic areas for helminths should be provided with health education on preventive measures, such as the use of footwear and adequate water, sanitation, and hygiene facilities.[110] Furthermore, high-risk individuals, such as children and women, should be made aware of national STH control programmes, which provide preventive chemotherapy as recommended by WHO.[111]

For *A lumbricoides*, albendazole 400 mg or mebendazole 500 mg in a single oral dose, or mebendazole 100 mg twice daily for 3 days is recommended in stable patients older than 12 months with uncomplicated infections.[109] Alternatively, ivermectin can be given in a single dose of 150–200 µg/kg bodyweight. Albendazole might be slightly more efficacious than mebendazole; a single albendazole dose cures 85% of infected individuals, and three doses cure 92% of infected individuals.[112,113]

Patients with intestinal obstruction require intravenous support, anthelmintics, and antibiotic treatment if systemic infection is suspected. In uncomplicated small bowel obstruction, orally swallowed contrast medium may expel worms more rapidly than does conservative treatment.[114]

In cases of small bowel obstruction, volvulus, or intussusception, laparotomy might be necessary to remove worms and resect gangrenous tissue.[67] In unstable cases, anthelmintic treatment should be given once the patient has been stabilised, or should be closely monitored, and supportive treatment given where necessary. Acute abdomen caused by ascaris in pregnancy and in the puerperium might require laparoscopy to exclude other causes; this condition can be treated with benzimidazoles.[115] The effectiveness of treatment should be monitored in cases that require surgery or with high worm burdens, and up to three stool samples should be examined 2 weeks post treatment, unless the clinical condition indicates earlier follow-up.

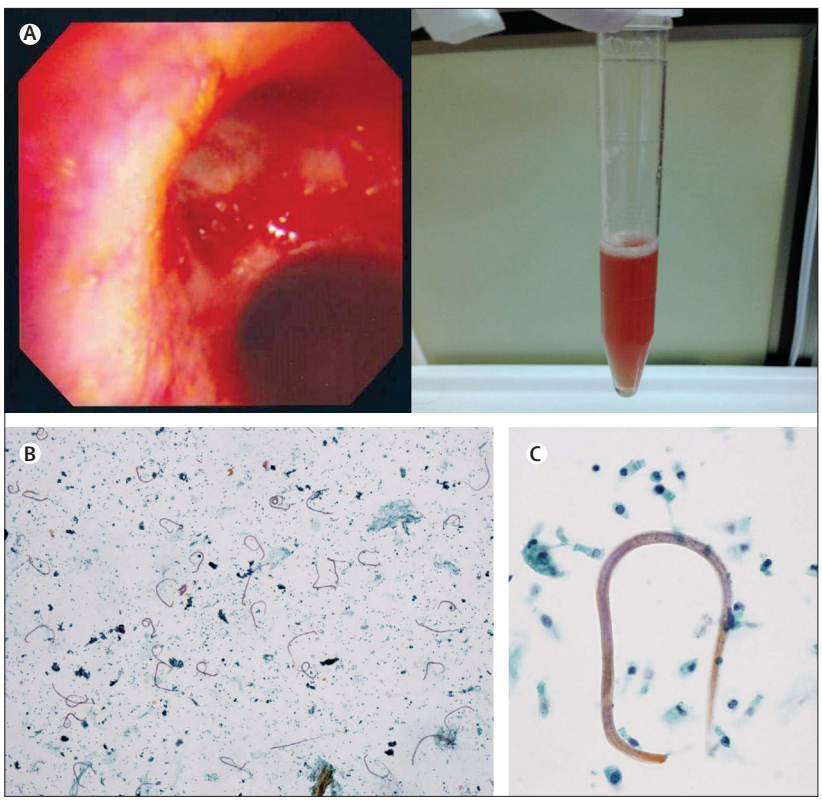

***Figure 6*: Strongyloides hyperinfection syndrome**
Images from a 62-year-old female positive for human T-cell lymphotrophic virus type 1 with acute respiratory distress syndrome following treatment with high-dose corticosteroids during chemotherapy for cervical cancer. Bronchoscopy (A) showed diffuse intrabronchial haemorrhage, and microscopy of Papanicolaou stain of bronchoalveolar lavage fluid (B, C) revealed multiple filariform *Strongyloides stercoralis* larvae (magnification of B × 20, of C × 400). Reproduced from Kinjo and colleagues,[104] by permission of the Japanese Society of Internal Medicine.

Hepatobiliary ascariasis can normally be treated with drug therapy alone.[69] If conservative treatment is unsuccessful, worm extraction and biliary drainage can be done using a duodenoscopic basket or endoscopic retrograde cholangiopancreatography and nasobiliary catheter.[67,71,116] Follow-up should be ensured through relevant imaging, for example, ultrasonography.

For *T trichiura*, 3 days of albendazole 400 mg or mebendazole 500 mg, or mebendazole 100 mg twice daily is recommended for treatment.[109] Alternative treatment options are ivermectin 200 µg/kg once daily for 3 days, or pyrantel embonate 11 mg/kg (maximum of 1 g) once daily for 3 days. Single albendazole and mebendazole treatments have limited efficacy, especially with high worm burdens, and even three doses of albendazole may cure only 83% of patients.[113] Iron supplementation should be considered in patients with severe or symptomatic anaemia, and supportive treatment is warranted in patients with dysentery.[45,117] Because of the partial efficacy of anthelmintic drugs on *T trichiura* infection, effectiveness of treatment should be monitored.

A case study suggests that colonoscopy can diagnose and potentially treat severe trichuriasis,[97] but it is not

	First choice	Alternative treatment
Ascaris lumbricoides	Albendazole 400 mg single dose; or mebendazole 500 mg single dose; or mebendazole 100 mg twice daily for 3 days	Ivermectin in a single dose of 150–200 µg/kg
Trichuris trichiura	Albendazole 400 mg once daily for 3 days; or mebendazole 500 mg once daily for 3 days; or mebendazole 100 mg twice daily for 3 days	Ivermectin 200 µg/kg once daily for 3 days; or pyrantel embonate 11 mg/kg base (maximum of 1 g) once daily for 3 days
Hookworm	Albendazole 400 mg single dose; or mebendazole 500 mg single dose; or mebendazole 100 mg twice daily for 3 days	No alternative treatment
Strongyloides stercoralis	Ivermectin 200 µg/kg once daily for 2 days	Albendazole 400 mg can be given twice daily for 7 days; or tiabendazole 25 mg/kg every 12 h for 3 days; or parenteral ivermectin

All treatment is oral, except for experimental parenteral treatment in strongyloides hyperinfection syndrome. Additional options might be approved for treatment in humans, including combination therapy of benzimidazoles and ivermectin, and of benzimidazoles and oxantel embonate or milbemycin against in particular *T trichiura*, and tribendimidine for treatment of hookworm. Relative contraindications might include adverse reactions to drugs, first trimester of pregnancy, lactating women, age less than 1 year, anticonvulsant drug therapy (for albendazole and mebendazole), and *Loa loa* co-infection (ivermectin treatment can be fatal). In women with high-intensity infection, treatment with mebendazole in the first trimester might be considered on an individual level, taking into consideration the risk of treatment with a poorly absorbed anthelmintic versus the risk of potential adverse events. Adapted from previously published data.[109]

***Table 2*: Anthelmintic treatment of soil-transmitted helminth infections**

commonly used for this purpose. More efficacious drug treatment options are needed. Trials are underway to assess efficacy of combinations of benzimidazoles and ivermectin, and of benzimidazoles and repurposed veterinary drugs, such as oxantel embonate and milbemycin.[118,119]

For *A duodenale* and *N americanus*, treatment with albendazole or mebendazole is recommended as previously described for uncomplicated ascaris infection,[109] although up to three doses of albendazole may be needed to cure 93% of patients.[112,113] Data for unspecified hookworm infection in southeast Asia suggest that a single dose of either drug might have limited efficacy.[120] Iron supplementation, additional nutritional support, and monitoring of treatment effect should be considered in patients with severe disease.[117] Tribendimidine, a broad-spectrum anthelmintic agent, might prove efficacious against hookworm and other STH.[121]

For *S stercoralis* treatment, ivermectin 200 µg/kg once daily for 2 days is recommended for both asymptomatic and symptomatic individuals.[109] Alternatively, albendazole 400 mg can be given twice daily for 7 days, or tiabendazole 25 mg/kg every 12 h for 3 days.[122] In strongyloides hyperinfection syndrome, ivermectin treatment should continue until stool or sputum samples are negative for 2 weeks. If possible, immunosuppressive treatment should be reduced or discontinued, and analgesics, hydration, nutritional support, and antibiotics should be provided as indicated. Parenteral therapy may be attempted in cases with severe intestinal morbidity, but should be considered on a case-by-case basis.[123,124]

Patients should be followed up with triple stool examinations 2–4 weeks post treatment. Strongyloides serology might be useful for defining cure at 6 months post treatment. Patients with strongyloides hyperinfection syndrome require stringent follow-up, including repeat endoscopy, biopsies, and information on preventive measures to avoid recurrence.[101]

Drug-associated safety precautions

Side-effects of benzimidazoles and ivermectin are rare and mostly mild and self-limiting, although allergic reactions might require specific treatment. Benzimidazoles have been shown to be teratogenic in experimental animal studies and are not recommended for use in the first trimester of pregnancy.[109] However, in individuals with high-intensity infection, treatment with mebendazole in the first trimester can be considered on an individual basis. The safety of benzimidazoles has not been established for children younger than 12 months.

Few studies have investigated drug interactions with benzimidazoles. However, some anti-convulsants might decrease the efficacy of benzimidazoles, and an outbreak investigation suggested an association between Stevens–Johnson syndrome and coadministration of metronidazole and mebendazole.[125,126] The quality of generic benzimidazoles is uneven, and many have inadequate efficacy against STH.[127] Ivermectin is contraindicated in high-intensity *Loa loa* infection, because of potentially fatal side-effects, and is also not recommended for children weighing less than 15 kg or for pregnant or lactating women.[109] In extra-intestinal hookworm and strongyloides infection, anthelmintics can be taken with food to increase their bioavailability.

Public health control

WHO recommends mass drug administration of benzimidazole in areas where *A lumbricoides*, *T trichiura*, or hookworm infection prevalence exceeds 20%, to control morbidity and eliminate STH as a public health problem.[128] School-based deworming has reduced infection intensity and prevalence in some areas;[6,128,129] however, mathematical modelling indicates that treatment of adults is also needed for hookworm control.[129,130] STH elimination is still aspirational in most endemic areas, and effective STH control will probably require expanded mass drug administration to include all risk groups, and improved access to water, sanitation, and hygiene.[131] Reviews[132–134]

have questioned the population level effect of mass deworming, generating a debate that is ongoing.

World Health Assembly resolutions have mobilised member states to scale up STH control programmes. Both mebendazole and albendazole are currently donated free of charge for mass drug administration of at-risk school-age children. For preschool-age children, drugs are purchased by governments or others and are often coadministered with vitamin A during child health days.[135] Periodic mass drug administration with single doses reduces infection intensity and prevalence, although cure rates are suboptimal in people with high burdens of trichuris or hookworm.

Several challenges remain for STH control. First, although 63% of school-age children and almost half of preschool-age children in need of treatment are dewormed for *A lumbricoides*, hookworm, and *T trichiura*,[1] only 30% and 28% of countries where these children live, respectively, have achieved the WHO 75% treatment coverage target.[136] Second, strongyloidiasis is rarely intentionally targeted by STH control programmes, although its sensitivity to ivermectin, provided in mass drug administration for lymphatic filariasis and onchocerciasis, makes a strong case for doing so.[8] Third, scaling back of albendazole administration to entire communities through the Global Programme to Eliminate Lymphatic Filariasis could put some 60 million children and women at risk of STH unless other drug delivery platforms are put in place.[137] Ongoing trials aim to establish the feasibility of breaking STH transmission post-lymphatic filariasis mass drug administration through expanded STH MDA coverage. Finally, population groups commonly left out of mass drug administration programmes, such as non-attending school-age children and women of reproductive age, will require particular attention in both public health control programmes and individual case management.

Controversies

In 2015, a Cochrane review[132] of randomised clinical trials concluded that there was no population-level effect of deworming on a range of child health outcomes, including growth and haemoglobin levels. These findings have stirred a heated debate about the effectiveness of current mass deworming policies and programmes.[133,138] A review[134,139] by the Campbell Collaboration, including data from other trial designs, came to similar conclusions. The authors of these reviews argue there is reasonable evidence of little or no effect of mass deworming on child health outcomes, school performance, or cognitive development, and suggest that additional policy options be considered in STH endemic areas.

Critics of the Cochrane and Campbell reviews argue that no long-term trials have been done to determine the effect of periodic deworming, and that failure to detect diluted, population-level health benefits is an issue of measurement or statistical power and not a lack of benefit of deworming.[138] Furthermore, a 2016 non-peer reviewed meta-analysis[140] by World Bank and Harvard University health economists reported significant weight gain in dewormed children. As such, population-level deworming in STH-endemic areas is warranted, as the health benefits of treating STH infections are well established, and mass drug administration of anthelmintics is safe and the most cost-effective way to reach infected individuals.[138]

Some investigators caution that elimination of STH transmission could increase risk of certain autoimmune diseases, invoking the so-called hygiene hypothesis.[141] However, other data show a positive association between helminth infections and atopy.[142] A 2016 review argues that, regardless of the relevance of the hygiene hypothesis with respect to STH, research should focus on identifying helminth-derived molecules of potential therapeutic benefit.[143]

Finally, some studies suggest that deworming might have beneficial effects on co-infections such as HIV,[144] with further research needed to determine the effect of anthelmintic treatment on malaria.[145]

Outstanding research

Improved, accessible, and affordable diagnostic tools are needed to facilitate detection of soil-transmitted helminths, including antibody tests to assess transmission in areas of low endemicity, and antigen tests for detection of active infections.[15,65,80,146,147] No standardised antigen tests exist for human STH, although assays exist in veterinary medicine for *Trichuris vulpis* and *T suis*.[148,149] Multiplex PCR tests for STH co-infections,[83,150,151] and next-generation PCR and loop-mediated isothermal amplification show promising results, but require validation and adaptation for field use.[152]

Although commonly observed in veterinary practice, drug resistance to anthelmintics in people has not been documented. Enhanced and continued surveillance, and novel drugs and drug combinations are needed to address the inherent concerns of resistance from mass drug administration.[153] Effective vaccines against STH are unlikely to be developed and available for use in large-scale control programmes in the near future, although both hookworm and so-called pan-helminthic (targeting ascariasis, trichuriasis, and hookworm infection) vaccines are being developed for human use.[154,155]

As the global community aims to meet the targets set out in the Sustainable Development Goals, relevant water, sanitation, and hygiene interventions are required to sustain reductions in STH burden.[5] High quality evidence to inform alternative control strategies, such as community-wide mass drug administration and vaccination programmes in conjunction with water, sanitation, and hygiene interventions, are needed to optimise STH control efforts. Finally, increased awareness and knowledge of STH are needed among health-care professionals, community health workers, and the general public to improve

clinical case detection and management, and public health control.

Conclusions

Infections with *A lumbricoides*, *A duodenale*, *N americanus*, *T trichiura*, and *S stercoralis* are highly prevalent, especially where access to water, sanitation, and hygiene is poor. The clinician must consider STH in patients with suspected exposure and who present with a range of medical and surgical conditions. Knowledge of epidemiology and infection-associated morbidity, refined diagnostics, and more effective treatment strategies are needed to strengthen clinical detection and management of STH. Safe and largely effective drugs against ascaris, hookworm, and trichuris are donated free of charge for mass drug administration of school-age children in endemic countries; however, elimination of STH as a public health problem will require deworming of additional risk groups and access to improved water, sanitation, and hygiene facilities.

Contributors

PMJ and PHLL performed all literature searches. PMJ, PHLL, and DGA drafted the original and resubmitted manuscripts. PMJ, PHLL, AF, and DGA critically reviewed and approved the final version of the manuscript. PMJ edited figures 1 and 2.

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